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### ACKNOWLEDGEMENT

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MOHS Micrographic Surgery: The Malaysian Experience and a Review of the Evidence

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Summary:
MOHs micrographic surgery is a technique of microscopic margin control in the surgical management of skin cancers particularly at cosmetically sensitive sites. This review article is aimed at sharing our initial experience of performing MOHs surgery for skin cancers in Malaysia since 2015.

Key words: MOHs micrographic surgery, Skin cancer, Basal cell carcinoma, Squamous cell carcinoma

Introduction
Mohs micrographic surgery (MMS) was first discovered in the early 1930s by Frederic E. Mohs as a medical student in Madison, Wisconsin, United States of America (US). In 1976, Dr. Mohs reported a 99.8% five-year cure rate (3450 of 3466 patients) using the fresh tissue technique, resulting in replacement of the fixed tissue technique (originally described and performed by Frederic Mohs himself initially).1

The fresh tissue technique considerably shortened tissue diagnosis by making MMS an efficient technique to complete within a working day. MMS has been practised in office-based setting in the US since the 1970s. The technique was then taught to any physician who was interested and attended attachments with Frederic Mohs. Eventually a keen interest was taken by dermatologist in training and eventually led to the increasing use across Europe and Australasia where skin cancer rates are high. MMS has always been the gold standard in the management of skin cancers even in the Asia Pacific region, hence the development of Mohs in Singapore and Thailand within the last 10 years.

MMS was pioneered in University Malaya Medical Centre (UMMC) since July 2015.

MMS is indicated where there are skin cancers arising in cosmetically sensitive sites or when the tumour is of “high-risk” histological subtype and especially for cancers recurring after initial treatment with either surgery or radiotherapy. It is most suitable for cancers that exhibit contiguous growth pattern.2 Skin cancers commonly excised using MMS include basal cell carcinoma (BCC) and squamous cell carcinoma (SCC).

MMS should be characterised by having peripheral margins cut at an angle of 45°; frozen section laboratory is near the operating theatre and the surgeon should be the one reading the slides. Unifying the duties of surgeon and pathologist minimises errors when performing clinic-pathological correlation for patients. Quality assurance through interaction with a dermato-pathologist is strongly encouraged.2

The aim of this review article is to share the demographic data on MOHs surgery in Malaysia and comparing it with updated international publications.

Materials and Methods
This review summarises all cases of MOHs micrographic surgery performed in University Malaya Medical Centre for the period of July 2015 until May 2017. The following describes how MMS is performed in UMMC.
Initial biopsy of skin is taken to define the histological subtype of skin cancer. Curettage is preferred over a punch biopsy in order to avoid pushing tumour into deeper histological planes. Subsequent steps of MMS performed in our setting are as described below and shown in Figures 1 (a-e). Clinically visible tumour margins drawn around with a marker pen with additional 1-2 mm lateral margin and clock face positions 12, 3, 6, 9 o’clock margins are drawn. (Figure 1a) Double nick is made at 12 o’clock and single nicks are made at 3, 6 and 9 o’clock positions respectively. The nicks made should be from peripheral to central, cleaning the blade carefully after each nick to avoid dragging tumour into a different histological plane. (Figure 1b)

Local anaesthetic is injected around the skin site at least 4-5 mm lateral to the visible peripheral margin of the tumour to avoid seeding tumour from lateral margins into deep margins in case needle used for injecting passes through the tumour. After scoring the surface with a scalpel gently, the scalpel is then angled at a 45 degree angle with blade facing medially and cut is made down to desired plane. The tissue plane should be down to mid fat for BCC and superficial fascia or muscle for SCC.

Specimen is then brought to lab for preparation of frozen section using Tissue-Tek® optimum cutting temperature compound. The lateral edges of the tissue are flattened against the glass slide such that the central deep margin is on the same histological plane as the lateral ones. The specimen is then left in an aluminum foil molded to a maximum size of 2cm across to match the size of a standard glass slide, and left in a cryostat to freeze at -18°C (Figure 1d).

Once specimen is completely frozen, the specimen is separated from the aluminum foil and mounted with the deep margin exposed first to the cryostat blade. Cryostat slices were set at 8 microns each turn and standard practice is to ensure in excess of 200 microns clearance (Figure 1d).

A hand-drawn MMS map is used to map out location of tumour. Nicks on the specimen corresponds to intersecting lines drawn on the Mohs map to denote 12 o’clock, 3 o’clock, 6 o’clock and 9 o’clock positions. The latter is also colour-coded to secure orientation. Our experience is that of using histology slides analysed (Figure 1e) and coloured, then used to superimpose onto Mohs map, similar to that described by Tiger et al. The latter method has been shown to increase accuracy and specificity compared to conventional Mohs map drawing on its own. Tiger describes using histopathological photographs as the Mohs map.

Defect repair options depend on the site involved. Side to side primary closure is ideal when possible. This is then followed by local flap (Figure 1c), full thickness skin graft, partial thickness skin graft and secondary intention. Secondary intention healing maybe more appropriate than previously understood. Concave surfaces including temporal, periorcular, perinasal, periauricular, scalp and anterior lower extremity, deep wounds and large wounds. Many surgeons elect secondary intention healing in patients with current or previous wound dehiscence, flap necrosis or infection, or when treating high-risk large, recurrent or aggressive tumours.

Key personnel involved with MOHs surgery set up include lab technician experienced in the preparation of good quality frozen sections; pathologist to confirm and sign off specimen reports; dermatological surgeon performing and mapping cancer pre-intra and post-operatively; assistant surgeon who is familiar with haemostasis and is able to react in the event of a patient becoming unwell in minor operating theatre; and last but not least theatre nurses who can assist with patient handling.

A literature review was performed online using PubMed, Google Scholar and Medline using the terms “Mohs micrographic surgery” and “Skin cancer” from 1970 to 2017. Search was performed in April 2017. Best available evidence was shortlisted and presented in this review article aimed to produce a concise up to date guide on appropriate indications for MMS.

Results
The University Malaya Medical Centre’s performed 16 MMS over the last 22-month period. The characteristics of our cohort of patients who have undergone MMS are shown in Table 1. The mean age of patients was 70 years old (range 48-84 years). The Karnofsky performance status scale5 of our patients was > 70 in 88% of our patients. The latter confirms that majority of patients undergoing MMS are highly functioning. There was a male preponderance for MMS in our cohort with a male to female ratio of 7:1.
All cases had the tumour located on the face including nose, periocular, cheek, forehead and ears. Four cases (25%) were histologically cleared within one stage, nine (56%) completed in two stages and three (19%) of cases went on to three stages. Histological clearance was double-checked by further sectioning of remaining “clear” tissue specimens and embedding in paraffin sections. All our 16 cases were finally confirmed histologically clear.

Complications observed included one case of post-op local infection overlying the ear abutting the external auditory meatus and the preauricular site, which resolved with oral antibiotics over 2 weeks leading to an uncomplicated recovery.

Discussion

Initial experience of MMS in Malaysia
MMS was performed for skin tumours in our setting to areas close to cosmetically sensitive sites, when initial histology is more likely to exhibit higher risk of incomplete excision. These include infiltrative BCC, poorly differentiated SCC, SCC in high risk individuals such as in post-transplant patients on immunosuppressive agents, and recurrent skin cancers following previous radiotherapy or surgery.

The number of MMS cases performed in Malaysia is still low due to two main factors. Firstly, MMS is more time consuming than standard excision (SE). There is a limited number of Dermatologists in the country performing MMS. Both experienced Dermato-pathologists and Dermatological surgeons are in short supply in Malaysia. As a result, time pressures from MMS that requires a longer duration than other “routine” cases put on involved parties to have a higher threshold to enlist patients for MMS in our centre.

Secondly, high cost involved with the procedure. Our experience is that of having offered MMS as the gold standard to our patients but eventually compromising with SE due to patients’ decision to prioritize affordability despite being aware of the lower recurrence rates with MMS versus SE. As our nation’s average income rises with time, in line with transformation into a developed nation, our patients will be able to afford gold standard treatment of skin cancers such as MMS.

Due to the listed factors, there is a selection bias towards a more challenging caseload in our centre. The latter is confirmed by the demographics of our MMS cases; 60% of referrals to us for MMS had at least one previous excision (recurrent tumour) and 20% of referrals to us had two previous unsuccessful excisions. All of the patients with recurrent tumours had an initial histopathology report stating clear (complete excision) lateral and deep margins through conventional bread-loafing or cross-sectioning technique. The latter confirms that conventional histological analysis is substandard in the complete assessment of histological clearance of skin tumour. The follow up period for patients who have undergone MMS in our centre is now between 3-23 months with no evidence of recurrence. Our initial follow up post MMS is 6 weekly for the first three months to include scar management if necessary and monitoring for local recurrence. Beyond that, patients are then followed up 6 monthly for up to 5 years.

Our mean number of stages was 1.94, consistent with the published literature where cases selected were appropriate for MMS and our figures were comparable to the site (head and neck area) operated on.6 Our data confirms that MMS performed at our centre produced similar results to existing published literature despite our suspicions that selection bias would have increased the mean number of stages closer to three due to the more complex cases selected for MMS in our centre.

How is MMS different from conventional surgery and histological analysis?
Skin specimen containing suspected cancer can be sliced in several ways. Firstly, bread-loafing or cross-sectioning whereby slices of tissue are cut through the centre (where the tumour is located) and laterally (to confirm tumour absence at the peripheral margin (figure 2a). Secondly, peripheral sectioning method whereby lateral and deep edges of tumour are cut to rule out any residual tumour (figure 2b). Thirdly MMS sectioning method such that 100% of the tissue can be analysed (both lateral and deep margins) on the same plane concurrently, making it the only technique with complete histological margin control (figure 2c). It is important to note that the first two methods of sectioning only allow examination of less than 0.1% of the entire specimen, hence the risk of missed tumour of unsectioned areas account for a higher 5-year recurrence rate for conventional histological analysis compared to MMS.
In a multi-centre published case series involving 20,821 cases in 23 centers, there were 149 adverse events, 4 serious events and no deaths. Common adverse events reported were infections (61.1%), wound dehiscence, partial or full necrosis (20.1%), and bleeding and haematoma (15.4%). The latter was predominantly associated with patients receiving anticoagulation therapy.7

Mosterd et al in 2008 performed a prospective randomised controlled trial to compare the cost-effectiveness of MMS compared to SE for the treatment of primary and recurrent facial BCC.8 The difference in the number of recurrences between treatments was in favour of MMS for recurrent facial BCC but was not significant for primary BCC. In primary BCC the total treatment costs were €1248 for MMS and €990 for surgical excision. For recurrent BCC, the total treatment costs were €1284 for MMS and €1043 for SE.

The estimated cost of MMS in our setting is RM3625 (€754). The cost includes procedural cost (RM500) for the use of minor operating theatre, dermatological surgeon’s time, supporting staff including theatre nurses, and physician assistants. The laboratory and histo-pathologist fees are subsidized by the University Malaya Medical Centre up to an approximate value of 50% for MMS (mean of 2 stages). The cost for a SE including pathology charges (excluding indirect financial, time and psychosocial costs to patient associated with re-attendance to hospital for further surgical procedure and medication) is RM 500 (€106.70).

Due to the significant cost difference, SE is still the first choice for most patients. MMS should be strongly recommended to patients by doctors and dermatologists when there are “high risk” patient or tumour characteristics present. The characteristics include locally recurrent skin cancers following either SE or radiotherapy, immunocompromised individuals on long term immune-suppressives, aggressive histological subtypes such as perineural and/or perivascular invasion and micronodular/infiltrative histological subtype. Secondary factors include occurrence at cosmetically sensitive sites where tissue sparing is crucial to optimize the final cosmetic outcome post-surgery.

When discussing cost of MMS versus SE, one should consider extra hospital visits for close monitoring and the potential need for subsequent MMS if SE does not successfully clear the skin tumour the first time round.

Evidence favouring Mohs Micrographic Surgery (MMS) over Standard Excision (SE) for Basal Cell Carcinoma (BCC)

It is well established in numerous publications that the 5-year recurrence rates of BCC using MMS is superior to that of standard excision (SE). Five year recurrence rates of BCC when SE was performed ranges from 5-40% whilst the equivalent for MMS ranges from 3-8%.9,10,11,12

MMS is strongly recommended for recurrent facial BCC, especially with poor prognostic factors. Smeets and colleagues specifically studied MMS in the setting of facial BCC. The study comprised a retrospective study of 720 BCCs reporting an estimated 5-year recurrence rate of 3.2% for primary BCC and 6.7% for recurrent BCC13. Predictive factors for recurrence include aggressive histopathological subtype, greater than four MMS stages, a large defect size and a recurrent BCC.

Smeets et al in a randomised controlled trial in 2004 concluded that the recurrence rates over a follow-up period of 5 years for facial primary basal cell carcinoma (BCC) were lower when excised by MMS (2.5%) compared to surgical excision (4.1%) albeit not statistically significant.14 Due to the limitations of the study, no recommendation could be made for the management of primary facial BCCs. The limitations of this above include 3mm lateral margins of excision taken in both SE and MMS groups. In addition, there was reluctance for a significant number of patients to participate, potentially introducing population and selection bias. Furthermore, there were a large number of subjects lost to follow up. Even with the intention-to-treat analysis, attrition bias might lead to underestimation of recurrence rates. With a cross-over design of the trial, there were patients crossing over from one treatment arm to the other, namely 3.7% in the primary BCC group and 17% in the recurrent BCC group. Therefore, carry-over effect could lead to bias tending to favour lower recurrence rates in the recurrent BCC group.

Interestingly, the 10-year follow-up data from the same cohort, 5 years later, published recently in the European Journal of Cancer strongly favoured MMS against SE with fewer recurrences; 4.4% vs 12.2% for primary BCC, and 3.9% vs 13.5% for recurrent BCC15. A substantial proportion of recurrences occurred after more than 5 years post-treatment: 56% for primary BCC and 14% for recurrent BCC. This is important as we can now better decide on
what age group of patients we should be offering MMS to. The authors suggest that patients expected to live beyond 5 years after MMS would be deemed as having the benefits of MMS outweigh the time and expertise cost.

A large prospective multicentre case series by Leibovitch and colleagues in 2005 reported on the clinical findings of all patients with BCC treated with MMS. A total of 11,127 patients were included in the study (47% females and 53% males) with a mean age of 62 years (range, 15-98 years). Most of the BCCs (98.3%) were on the head and neck area. Sites on the head and neck in decreasing frequency include the nose, cheek and maxilla, periocular area, and auricular region. The most common histological subtypes were infiltrating (30.7%) and nodulocystic (24.2%). Recurrent BCC accounted for 43.8% of cases suggesting that standard excision of basal cell carcinomas on the head and neck area should be planned with caution. However, in reality it is difficult due to the fact that a generous margin would consistently result in lower recurrence rates but would be offset against a larger defect and likely an inferior cosmetic outcome. Conversely an inadequate margin around the skin cancer would lead to higher recurrence rates.

Further details from Leibovitch were that recurrent tumours were larger than primary tumors ($p < 0.001$), had a larger post-excision defect and a more subclinical extension, and required more levels of excision ($p < 0.001$). High-risk tumours dominated the case load for MMS in this series. Most tumours were located in the mid-facial area and the histologic subtype was mainly infiltrating or nodulocystic. Recurrent tumours were larger and demonstrated a more extensive subclinical extension compared with primary tumours, emphasising the importance of initial tumour eradication with margin control.

A Cochrane review performed in 2014 comparing MMS versus SE for periorificial basal cell carcinoma by Narayanan et al.16 concluded that there was insufficient randomised controlled trials (RCTs) to make a comparison on the recurrence rates, complications, cost effectiveness and acceptability of either technique. Good quality RCTs are desperately needed in this field. However, we are aware that randomised controlled trials for surgery can be challenging as there are numerous variables to control for, with differences such as surgical techniques and different levels of experience in reading the MMS histopathology slides. It is therefore premature to make any conclusions that MMS is not useful for periorificial BCC in the absence of RCTs.

Our experience of performing MMS on two periorificial cases between 2015 and 2017 involved an average of 2.5 stages (excising 2 mm lateral to the macroscopically visible margins of BCC each time). We also observed that infiltrative BCCs were likely to invade into orbicularis oculi. Unlike SE, MMS is essential prior to a complex closure of the eyelid to avoid difficulties with tracking a future cancer recurrence. Recurrent cancers within complex closure sites pose two major challenges. Firstly, they tend to be aggressive histological subtypes that are more difficult to interpret. Secondly, residual tumour recurrence tends to proliferate along the wound-closure scar lines during the healing process from the initial surgery. We therefore strongly recommend MMS for infiltrative or recurrent skin cancers in the periorificial region.

**Evidence supporting MMS for squamous cell carcinoma**

Evidence for MMS in the management of squamous cell carcinoma (SCC) has been reported in a large retrospective review by Pugliano et al in 2010 involving 260 high risk squamous cell carcinoma (SCC) in 215 patients. A recurrence rate of 1% was detected following MMS for squamous cell carcinoma over a mean follow up period of 3.9 years. The latter suggests that MMS is an effective treatment for high risk SCC as the comparable rates for SE in current literature is much higher, closer to 10%, as previously reported by Rowe et al.19

We would recommend that in Malaysia, any SCC that has been reported as being close to the excision margin or with aggressive histological features including perineural/perivascular invasion or with equal to or greater than 6mm Breslow thickness should have the histology slides reviewed. MMS should be considered to ensure a complete local disease control is achieved in addition to further appropriate imaging to obtain accurate staging of the disease.

**Evidence supporting MMS for rarer skin tumours**

A systematic review of 23 non-randomised trials (4 comparative, 19 non-comparative) as per Cochrane Handbook for Systematic Reviews of Interventions was performed on MMS for the treatment of Dermatofibrosarcoma Protuberans. MMS was
given a weak recommendation based on the following recurrence rates. MMS (1.11%; 95% CI: 0.02%-6.03%) versus wide local excision (6.32%, 95% CI: 3.19%-11.02%).

Thomas and colleagues (2007) conducted a retrospective review to evaluate the effectiveness of MMS in the treatment of six rare aggressive cutaneous malignancies as seen by Mohs surgeons working at a referral centre. Retrospective chart review of 26,000 cases treated with MMS at the Geisinger Medical Center Department of Dermatology during a 16-year period with the following diagnoses: poorly differentiated squamous cell carcinoma (PDSCC), dermatofibrosarcoma protuberans (DFSP), microcystic adnexal carcinoma (MAC), extramammary Paget’s disease (EMPD), Merkel cell carcinoma (MCC), and sebaceous carcinoma (SEB CA). Patient demographic data, tumour measurements, treatment characteristics, and marginal recurrence rates were compiled and evaluated. The mean numbers of cases identified per year for each tumor type were as follows: PDSCC, 6.19; DFSP, 2.44; MAC, 1.63; and EMPD, 0.63. For PDSCC, 85 cases were available for follow-up with a local recurrence rate of 6% at a mean follow-up time of 45 months. For DFSP, there were 35 cases with no local recurrence at a mean follow-up of 39 months. For MAC, there were 25 cases with a local recurrence rate of 12% at a mean follow-up of 39 months. For EMPD, there were 10 cases with no local recurrences at a mean follow-up of 34 months. The authors concluded that the data on PDSCC, DFSP, MAC, and EMPD, combined with other studies in the literature, showed that MMS is the most effective therapy for these rare aggressive cutaneous malignancies.21

A further large case series recently published adds support to MMS as an appropriate treatment for rare cutaneous tumours with a recurrence rate of less than 3%. This case series comprised 27 DFSP, 22 AFX, 8 MCC, 9 MAC, 6 Sebaceous carcinoma, 2 EMPD.22

MMS can be considered for rarer skin tumours in Malaysia provided MMS continues to advance further to a subspecialty with good support of resources and sufficient workforce.

**Slow MOHs for melanoma**

Bene and colleagues published the results of a prospective study in 2008, evaluating if margins determined to be cleared by MMS were confirmed by subsequent paraffin-embedded sections (gold standard for determining margins) and to compare the cure rate with available data for MMS versus SE. A total of 167 patients with melanoma in-situ participated in the study and were treated by MMS with subsequent evaluation over a period of 12 years. Overall, the authors reported of 167 cases of melanoma in-situ, eight cases had a positive margin on paraffin-embedded sections after margins on MMS frozen sections were called “clear”, resulting in a 95.1% clearance rate. However, after one re-excision, all eight tumors had clear margins on paraffin-embedded sections. Cure rates reported for mean follow-up of 50 months and of 63 months were 98.6% and 98.2%, respectively.23

Bricca and colleagues conducted a prospective case series in 2005, consisting of 625 patients with primary cutaneous melanoma or melanoma in situ of the head and neck treated with MMS technique. Follow-up was conducted biannually for the majority of cases with invasive melanoma, and annually for patients with melanoma in situ. The mean follow-up for the group was 58 months. The results of their study suggest that MMS achieved a five-year local recurrence rates, metastasis rates, and disease-specific survival rates comparable to or better than historical controls after Breslow thickness stratification. The size of the surgical margin required for a complete excision was significantly related to the tumour thickness but not the tumour size or the specific location.24

McKenna and colleagues in 2006 conducted a review evaluating the clinical features, histopathology and various treatments for lentigo maligna, a subtype of melanoma in situ that develops on sun-damaged skin. In the authors’ opinion, standard excision using a 5 mm margins is insufficient in many cases, and the recurrence rates with standard excision ranges from 8 to 20%. MMS and staged excision may offer improved margin control and lower recurrence rates.25

We would recommend that melanoma in situ can be managed with slow Mohs. However, invasive melanoma extending deeper than the epidermis should be managed with wide excision and consideration of sentinel lymph node biopsy, as well as appropriate staging through computed tomography (CT) or positron emission tomography CT (PET-CT) scans.
MMS is a tissue sparing treatment
Muller et al. in a blinded assessor observational study in 2009, reported that the median area of MMS defect size is significantly lower than the SE group for small nodular BCCs. Therefore, there is an additional tissue sparing role for MMS, beyond achieving lower recurrence rates. The above observation is not comparable to our dataset because our current criteria for MMS are stringent with recurrent tumour, clinically ill-defined tumour or aggressive histological subtypes. The size of such defects are certainly larger than excising small nodular BCCs based on our observation that out of our total of 16 cases, 25% were closed side-to-side with the majority (75%) needing a complex closure.

MMS improves quality of life
One would wonder about whether there is a difference between different surgical treatment options for non-melanoma skin cancer. Chren and colleagues in 2007 reported an improvement in quality of life Skindex Symptom scores by 9.7 (95% CI: 6.9,12.5) after SE, 10.2 (95% CI: 7.4,12.9) after MMS, and 3.4 (CI: -0.9,7.6) after electrodessication and cautery. Quality of life improvements were not statistically different comparing SE and MMS. However, it is notable that the latter two approaches were better than electrodessication and cautery.

MMS have been criticized as a lengthy procedure, tolerated poorly by elderly patients. Both our experience and that in the United Kingdom is that almost all patients had their MMS procedure completed within 4 hours after arriving. Secondly, there have been concerns about overall safety of MMS and reconstruction. These were mainly reported in the United States where such surgery occurs in office-based setting. However, recent work has demonstrated that MMS is very safe in this context. In our centre, we have a set up as a day-case or outpatient operating rooms rather than an aseptic, main theatre environment just like in the United Kingdom, with an acceptable complication rate.

There are, however, notable risk factors for types of surgical repairs associated with higher risk of complications such as infection, wound dehiscence, flap or graft failure. The risk factors are firstly, composite location of defects, secondly, interpolated flaps with cartilage grafting and thirdly, delayed reconstruction of more than two days.

Recurrence rate in MMS
The 5-year recurrence rate is reported to be 1%. Histo-pathological pitfalls of MMS could result in inaccuracies and hence higher recurrence rates. Our recurrence rate so far at 23 months is nil, however, we would of course have to continue monitoring and resubmit further data in due course.

The future of MMS in Malaysia
As our caseload increases, we will be keen to report on the recurrence rate after 5 years. The authors’ recommendation is that frozen section MMS should be performed in the following situations in Malaysia for primary skin cancers. This includes commonly BCC and SCC, in cosmetically sensitive sites, with histological features that portend poorer prognosis, with patient being financially able to enjoy the lower recurrence rates offset against any potential financial hardship that may arise and finally in an age category where the likelihood of enjoying a recurrence-free five-year is highly relevant to the patient’s quality of life. The latter would ultimately differ from one patient to another and would have to be decided on a case-to-case basis.

For rarer skin cancers such as dermatofibrosarcoma protuberans (DFSP), microcystic adnexal carcinoma (MAC), extramammary Paget’s disease (EMPD), Merkel cell carcinoma (MCC), and sebaceous carcinoma (SEB CA), it is not possible for us to comment as there is no local data or experience available yet.

The same is true for malignant melanoma. However, based on current literature, slow MOHs should be considered for better histological margin evaluation in cases where wider excisions are necessary following histological confirmation of malignant melanoma. Frozen section MMS is not recommended due to a significant number of cases reported as clear on frozen Mohs sectioning, subsequently found to be positive for melanoma on paraffin-embedded specimens. As a 5mm lateral margin is associated with a 20% local recurrence rate, the first slow MOHs stage should be taken with a 5mm lateral margin around the first scar, followed by smaller 2-3 mm lateral margins for subsequent stages. Due to the fatal nature of melanoma, it is even more challenging to design an ethical trial that answers our many unanswered questions on MMS for melanoma.

Mohs surgical reconstruction education would spur interest in Dermatological surgery in Malaysia.
and develop this subspecialty within Dermatology further. Hands-on courses and reconstruction educational activity can be utilised to increase Dermatology trainee’s confidence in complex repairs.  

Conclusion
Based on the current observations of MMS cases at our centre, we are pleased to report that despite the higher threshold (hence selection bias towards complicated cases) at which MMS is considered and subsequently performed, we have comparable mean number of stages compared to existing publication. This review summarises the current up-to-date experience in the first centre in Malaysia performing MMS. It is hoped that this technique can be adopted by other centres in Malaysia to cover the entire geography of Malaysia. As MMS training is offered to future Dermatology trainees, it is hoped that this technique will be more widely available and hence there would be sufficient manpower to conduct collaborative data collection and clinical studies on MMS to enhance this technique further in Malaysia.

Conflict of Interest Declaration
The authors have no conflict of interest to declare.

Acknowledgement
The authors would like to thank the lab technicians in University Malaya Medical Centre for their patience and perseverance with perfecting the technique of Mohs tissue preparation. The authors are also thankful to the Board of Directors of University Malaya Medical Centre for approving and supporting the procedure in the hospital ethics committee in 2015.
Figure 1. The steps of MMS done in UMMC.

a. Patient with Mohs map drawn on site of excision; b. Final defect after 3 stages; c. Process of reconstruction with an O-to-T bilateral advancement flap by dermatological surgeon; d. Skin with tumour flattened and submerged in optimum cutting temperature gel in aluminium foil prior to freezing in cryostat; e. Multi-headed microscope discussion between dermatologist, pathologist and lab technician.

Figure 2. The method of histological sectioning in MMS as compared to conventional methods.

- Cross-sectioning:
  - a) 8-10 micron slices
  - Analysed once

- Peripheral sectioning:
  - b) 8-10 micron slices
  - Analysed once

- MOHs sectioning:
  - c) 8 micron slices
  - Analysed progressively until >200 microns clear
### Table 1. Characteristics of patients who underwent Mohs micrographic surgery in UMMC between July 2015-May 2017

<table>
<thead>
<tr>
<th>No</th>
<th>Sex</th>
<th>Age</th>
<th>Fitzpatrick skin type</th>
<th>Karnofsky performance scale (%)</th>
<th>Indication for MMS</th>
<th>Site</th>
<th>No of stages</th>
<th>Final histological diagnosis</th>
<th>Margin clearance (microns)</th>
<th>Complications</th>
<th>Closure</th>
<th>Total cost (RM)</th>
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<tbody>
<tr>
<td>1</td>
<td>F</td>
<td>72</td>
<td>III</td>
<td>100</td>
<td>Ill-defined BCC</td>
<td>Right ala nasi</td>
<td>2</td>
<td>Infiltrative BCC</td>
<td>246</td>
<td>Nil</td>
<td>Local flap</td>
<td>3600</td>
</tr>
<tr>
<td>2</td>
<td>F</td>
<td>77</td>
<td>III</td>
<td>90</td>
<td>Incompletely excised BCC</td>
<td>Bridge of nose</td>
<td>2</td>
<td>Infiltrative BCC</td>
<td>250</td>
<td>Nil</td>
<td>Side to side</td>
<td>4000</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>84</td>
<td>IV</td>
<td>70</td>
<td>Deep margin close and perineural invasion</td>
<td>Right temple</td>
<td>1</td>
<td>SCC</td>
<td>292</td>
<td>Nil</td>
<td>Side to side</td>
<td>2500</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>72</td>
<td>IV</td>
<td>90</td>
<td>Cosmetically sensitive site</td>
<td>Left lower eyelid</td>
<td>2</td>
<td>Infiltrative BCC</td>
<td>240</td>
<td>Nil</td>
<td>Local flap</td>
<td>3500</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>62</td>
<td>IV</td>
<td>90</td>
<td>Incompletely excised BCC</td>
<td>Left side of nose</td>
<td>1</td>
<td>Nodular BCC - local tissue reaction</td>
<td>288</td>
<td>Nil</td>
<td>Local flap</td>
<td>1500</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>87</td>
<td>IV</td>
<td>70</td>
<td>Poorly defined BCC</td>
<td>Right ear</td>
<td>3</td>
<td>Infiltrative BCC</td>
<td>388</td>
<td>Post-op infection under flap</td>
<td>Flap and full thickness skin graft</td>
<td>5000</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>64</td>
<td>II</td>
<td>90</td>
<td>Poorly defined BCC</td>
<td>Left nasolabial fold</td>
<td>2</td>
<td>Infiltrative BCC</td>
<td>292</td>
<td>Nil</td>
<td>Local flap</td>
<td>4500</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>67</td>
<td>IV</td>
<td>80</td>
<td>Incompletely excised nodular BCC</td>
<td>Left upper cutaneous lip</td>
<td>1</td>
<td>No residual tumour seen</td>
<td>292</td>
<td>Nil</td>
<td>Side to side</td>
<td>1500</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>75</td>
<td>IV</td>
<td>80</td>
<td>Cosmetically sensitive site</td>
<td>Left upper eyelid</td>
<td>2</td>
<td>Infiltrative BCC</td>
<td>280</td>
<td>Nil</td>
<td>Local flap</td>
<td>5800</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>48</td>
<td>V</td>
<td>100</td>
<td>Ill defined margins</td>
<td>Right nasolabial fold</td>
<td>2</td>
<td>Infiltrative BCC</td>
<td>242</td>
<td>Nil</td>
<td>Local flap</td>
<td>3800</td>
</tr>
<tr>
<td>11</td>
<td>M</td>
<td>67</td>
<td>III</td>
<td>90</td>
<td>Immuno-compromised-renal transplant patient</td>
<td>Left cheek</td>
<td>3</td>
<td>Infiltrative BCC</td>
<td>242</td>
<td>Nil</td>
<td>Local flap</td>
<td>4800</td>
</tr>
<tr>
<td>12</td>
<td>M</td>
<td>72</td>
<td>II</td>
<td>90</td>
<td>Cosmetically sensitive site</td>
<td>Tip of nose</td>
<td>3</td>
<td>Infiltrative BCC</td>
<td>242</td>
<td>Nil</td>
<td>Full thickness skin graft</td>
<td>5000</td>
</tr>
<tr>
<td>13</td>
<td>M</td>
<td>74</td>
<td>II</td>
<td>90</td>
<td>Incompletely excised BCC</td>
<td>Right cheek</td>
<td>1</td>
<td>No residual tumour</td>
<td>240</td>
<td>Nil</td>
<td>Side to side</td>
<td>1000</td>
</tr>
<tr>
<td>14</td>
<td>M</td>
<td>77</td>
<td>III</td>
<td>90</td>
<td>Ill-defined BCC</td>
<td>Forehead</td>
<td>2</td>
<td>Infiltrative BCC</td>
<td>242</td>
<td>Nil</td>
<td>Local flap</td>
<td>3500</td>
</tr>
<tr>
<td>15</td>
<td>M</td>
<td>74</td>
<td>IV</td>
<td>90</td>
<td>Cosmetically sensitive site</td>
<td>Right ala nasi</td>
<td>2</td>
<td>Nodular BCC</td>
<td>292</td>
<td>Nil</td>
<td>Local flap</td>
<td>3000</td>
</tr>
<tr>
<td>16</td>
<td>M</td>
<td>51</td>
<td>II</td>
<td>100</td>
<td>Ill defined tumour</td>
<td>Right ala nasi</td>
<td>2</td>
<td>Infiltrative BCC</td>
<td>288</td>
<td>Nil</td>
<td>Local flap</td>
<td>5000</td>
</tr>
</tbody>
</table>
References


**Microbiological Profile and Antibiotic Susceptibility Patterns of Isolates of Skin Specimens from the Department of Dermatology, Hospital Kuala Lumpur: A 3-Year Audit**

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**Abstract**

**Introduction:**
Due to the emergence of antibiotic resistance worldwide, the bacterial pathogens and susceptibility patterns causing skin infections should be monitored periodically to alert early intervention. This study aimed to analyse the bacterial profile and their antibiotic susceptibility patterns among the patients with cutaneous infections at Department of Dermatology, Hospital Kuala Lumpur (HKL).

**Methods:**
This retrospective analysis analysed the bacterial profile and the antibiotic susceptibility patterns of 1221 positive cultures obtained from skin swabs and biopsy specimens sent from the Department of Dermatology Hospital Kuala Lumpur (HKL) from 2013-2015.

**Results:**
*Staphylococcus aureus* (2/3 methicillin-sensitive, 1/3 methicillin-resistant) was the most frequent isolate (44%), followed by *Pseudomonas aeruginosa* (17.4%); *Acinetobacter* sp. (6.7%); *Proteus* sp. (6.1%); *Klebsiella* sp. (5.7%); *Enterobacter* sp. (3.0%), *Escherichia coli* (2.8%) and others. About 45% and 10% of MRSA was resistant to fucidic acid and mupirocin respectively. About 15% of *Pseudomonas aeruginosa* was resistant to ciprofloxacin. Majority of *Acinetobacter* sp. were resistant to most of the common antibiotics used.

**Conclusion:**
*Staphylococcus aureus* remained the main microorganisms isolated from patients with cutaneous bacterial infections. Empirical use of antibiotics prior to availability of culture sensitivity should be avoided for prevention of multi-resistant micro-organisms. We advocate judicious use of antibiotics based on results of the culture sensitivity and strict adherence to infection control measures to prevent development of antibiotic resistance.

**Key words:** Microbiological profile, antibiotic susceptibility, *Staphylococcus aureus*, *Pseudomonas aeruginosa*

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infections and the antibiotic susceptibility patterns among the patients presented to the Department of Dermatology, Hospital Kuala Lumpur (HKL).

**Materials and Methods**
This is a retrospective analysis conducted in the Department of Dermatology, HKL from January 2013 to December 2015. All positive cultures obtained from skin swabs and biopsy specimens sent from the dermatology clinic and ward were analysed.

**Results**
There were a total of 1221 positive cultures isolated from skin specimens with predominantly gram positive organisms (54%). Nearly 99% of the microorganisms were aerobic bacteria. *Staphylococcus aureus* (537, 44.0%) was the most frequent isolate; followed by *Pseudomonas aeruginosa* (213, 17.4%); *Acinetobacter* sp. (82, 6.7%); *Proteus* sp. (75, 6.1%); *Klebsiella* sp. (69, 5.7%); *Enterobacter* sp. (37, 3.0%); *Escherichia coli* (34, 2.8%), Group B *Streptococcus* (30, 2.5%), *Streptococcal pyogenes* (28, 2.3%), *Pseudomonas sp.* (28, 2.3%), *Enterococcus* sp. (13, 1.1%), *Staphylococcus coagulase negative* (12, 1.0%) and others. About 80% of methicillin-sensitive *Staphylococcus aureus* (MSSA) was resistant to penicillin G (Figure 1).

A third of *Staphylococcus aureus* (34.3%) was methicillin-resistant (MRSA). 62.5% of MRSA were resistant to clindamycin while 47.8% were resistant to co-trimoxazole. About 45% and 10% of MRSA were resistant to fucidic acid and mupirocin respectively. About 14% of *Pseudomonas aeruginosa* was resistant to ciprofloxacin. Figure 2 demonstrated the antibiotic sensitivity pattern of *Pseudomonas aeruginosa*. Majority of *Acinetobacter* sp. were resistant to most of the antibiotics tested including piperacillin/tazobactam, carbapenem and tigecycline (52.4-64.6%). About 67 to 100% of gram negative organisms such as *Proteus sp.*, *Klebsiella sp.*, *Enterobacter sp.* and *Escherichia coli* were resistant to ampicillin. The susceptibility rates of *Proteus sp.*, *Klebsiella sp.*, *Enterobacter sp.* and *Escherichia coli* to ciprofloxacin were 73.3%, 49.3%, 86.5% and 67.6% respectively.

**Figure 1.** Antibiotic resistance pattern of *Staphylococcus aureus* cultured from skin specimens sent from the Department of Dermatology, HKL from January 2013 to December 2015.
About 44% of the isolates in this study cohort was *Staphylococcus aureus*. It was much higher than previous local studies as shown in Table 1. Previous reports studied on patients with diabetic foot infections mainly. Different types of infections and the patients’ underlying immune status could have contributed to different types of microorganisms isolated as shown in various studies. We propose proper prospective studies in the future addressing bacteriological pattern of cutaneous infections with important factors such as comorbidities; sites of specimens obtained; types of specimens (swab versus biopsy samples) together with proper sampling methodology.

When compared to the results being reported by a recent study conducted in UMMC on patients on non-infected atopic dermatitis, we reported a higher resistance rate of *Staphylococcal aureus* to various antibiotics; i.e. penicillin (86.6% versus 82.1%), fusidic acid (37.2% versus 17.9%), erythromycin (35.4% versus 7.7%), clindamycin (24.6% versus 7.7%) and co-trimoxazole (17.3% versus 2.6%).

About a third (34.3%) of *Staphylococcus aureus* isolated was MRSA; which was comparable to a report published in 1994 in HKL where 35.4% of *Staphylococcus aureus* was MRSA. In that report, *Staphylococcus aureus* were cultured from skin, blood, cerebral spinal fluid, peritoneal fluid and throat swabs; but the highest yield was from wounds, ulcers and skin swabs. However, the resistance rate to rifampicin and fusidic acid had increased from 4.5% and 2% in 1994 to 32.6% and 45.7% respectively in our audit. Interestingly, the resistance rate to co-trimoxazole; erythromycin and gentamicin had reduced from 71.0%; 97.0%; and 98.7% to 47.8%; 85.3% and 56.0% respectively. In another study published in 2000, the rate of mupirocin resistant MRSA was 2.8% in HKL but it has increased to 10.3% in this audit.

The resistance rate of *Staphylococcus aureus* to fusidic acid was 37% generally and 45% among MRSA in present study. This is far higher than the previously reported local data which showed 3.6% resistance generally and 3.2% among MRSA. When compared with other countries, the resistance rate to fusidic acid in our study is much higher than European countries such as 0.4-1.0% in Denmark from 1967 to 1987, 1.2-1.7% in England between 1969 and 1983 and 0.7% in Germany in 1970. The widely availability of topical fusidic acid is a
contributing factor for its increasing resistance rate. We therefore advocate topical fusidic acid to be used selectively in indicated cases of skin infections such as localised impetigo in outpatient setting.

Different amino acid alterations were shown to be responsible for rifampicin and fusidic acid resistance among Malaysian MRSA strains.\(^7\) Both rifampicin and fusidic resistance were associated with mutation at \(rpo\beta\) and \(fusA\) respectively.\(^7\) The high rifampicin and fusidic acid resistance rates against MRSA in our cohort indicate that the use of combination of oral fusidic acid and rifampicin in the management of MRSA infection in skin may not be as effective as previously thought.

The fact that the development of rifampicin resistance is prevented by combination with other antibiotic such as fusidic acid is disputed by a systematic review that concluded that in vitro results of interactions between rifampicin and other antibiotics are method dependent and do not correlate with in vivo findings.\(^8\) Combination of oral fusidic acid and rifampicin may be considered only if the strain is susceptible in cases of recurrent active MRSA skin and soft tissue infections despite optimisation of wound care and hygiene measures, nasal and topical decolonization.\(^9\) A retrospective cohort study showed that early initiation of rifampicin combination treatment within 7 days of positive blood culture for at least 14 days in \(Staphylococcus aureus\) bacteraemia patients with a deep infection focus improved survival.\(^10\)

The use of mupirocin should be reserved for culture-proven MRSA. Appropriate infection control measures and use of antiseptics such as chlorhexidine and potassium permanganate should be practised.

Our analysis reported an important finding of high resistance rate of MRSA towards co-trimoxazole (47.8%) and clindamycin (62.5%) which are common antibiotics employed to treat MRSA. This should serve as a warning sign to call for a strict policy on the usage of these antibiotics in Malaysian hospitals. Judicious and controlled use of these antibiotics in indicated cases of culture-proven MRSA infections is essential.

\(Pseudomonas aeruginosa\) exhibited the lowest susceptibility to piperacillin/tazobactam and ciprofloxacin in this audit. The resistant rate to ciprofloxacin of 14% was slightly reduced from the previous study done in HKL i.e. 16.5% in 2009.\(^11\) Nevertheless, the susceptibility rate to piperacillin/tazobactam had reduced from 92.8% to 83.6%. The susceptibility rate to amikacin was the highest in this audit i.e. 97.2% followed by cefepime (96.2%). Judicious use of ciprofloxacin in outpatient and piperacillin/tazobactam in inpatient setting is important to reduce their resistance rate.

It is attention-grabbing to the findings that most important gram-negative bacteria cultivated were resistant to ampicillin. The widely use of ampicillin, ampicillin/sulbactam and amoxicillin/clavulanic acid at primary care level due to the easy availability and convenient dosing frequencies may not be very effective in treating gram-negative bacteria cutaneous infections, which contributed 46% of cutaneous infections in this audit. Similarly, ciprofloxacin which is available in oral form and widely prescribed at primary care setting demonstrated significant reduction in the effectiveness towards many gram-negative bacteria cutaneous infection especially \(Klebsiella\) sp.
**Conclusion**

Staphylococcus aureus remained the main microorganisms isolated from patients with cutaneous bacterial infections. Gram negative bacteria demonstrated lower sensitivity rate to most of the common oral antibiotics used in the clinical setting. This analysis served as an important reference for the construction of local antibiotic usage guideline specifically on cutaneous infections. Empirical use of antibiotics prior to availability of culture sensitivity should be avoided for prevention of multi-resistant micro-organisms. We advocate judicious use of antibiotics based on results of the culture sensitivity and strict adherence to infection control measures to prevent development of antibiotic resistance.

**Conflict of Interest Declaration**

The authors have no conflict of interest to declare.

**Acknowledgement**

We would like to extend our gratitude to the Department of Microbiology HKL who provided us the data. We would also like to thank the Director General of Health, Malaysia for permission to present this report.

**References**


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**Table 1. Comparison of top 5 microorganisms isolated among present and other local studies.**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>n</th>
<th>Type of patients</th>
<th>Top 5 microorganisms (%)</th>
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<tr>
<td>Nadeem Sajjad Raja, 2007</td>
<td>194</td>
<td>Diabetic foot infections</td>
<td>1. Staphylococcus aureus (17%)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>2. Proteus sp. (15%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Pseudomonas aeruginosa (13%)</td>
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<tr>
<td></td>
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<td></td>
<td>4. Group B Streptococcus (11%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>5. Bactensides sp. (1%)</td>
</tr>
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<td>SD Balakrishnan et al 2014</td>
<td>96</td>
<td>Diabetic foot infections</td>
<td>1. Staphylococcus aureus (27.0%)</td>
</tr>
<tr>
<td></td>
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<td>2. Klebsiella pneumoniae (22.0%)</td>
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<td>3. Streptococcus sp. (15.0%)</td>
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<td>4. Pseudomonas sp. (12.0%)</td>
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<td>5. Enterobacter sp. (10.0%), Proteus mirabilis (10.0%)</td>
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<td>Nur Hilda Hanina Abd Wahab et al 2015</td>
<td>77</td>
<td>Diabetic foot ulcers</td>
<td>1. Proteus mirabilis (20.5%)</td>
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<td>3. Staphylococcus aureus (13.3%)</td>
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<tr>
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<td></td>
<td></td>
<td>4. Klebsiella pneumoniae (13.3%)</td>
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<td>5. Group B Streptococcus (8.4%)</td>
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<td>6. Escherichia coli (7.2%)</td>
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<td>SL. Vijaya Kumar et al 2016</td>
<td>122</td>
<td>Diabetic foot infections</td>
<td>1. Klebsiella sp. (14.7%)</td>
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<td>2. Pseudomonas sp. (12.3%)</td>
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<td>3. Staphylococcus sp. (14.9%)</td>
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<td>4. Bacter group (Citrobacter, Enterobacter, Acinetobacter, etc) (11.7%)</td>
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<td>Present study, 2016</td>
<td>1221</td>
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<td>1. Staphylococcus aureus (44.0%)</td>
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<td>3. Acinetobacter sp. (6.7%)</td>
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<td>4. Proteus sp. (6.1%)</td>
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<td>5. Klebsiella sp. (5.7%)</td>
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ORIGINAL ARTICLE

Prevalence of Skin Diseases in Dermatology Outpatient Clinic, Hospital Kuala Lumpur

Swee Kuan Heah, MD, Noorlaily Mohd Noor, AdvMDerm, Asmah Johar, MMed

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Abstract

Introduction:
Cases referred to a tertiary hospital tend to be more difficult to manage. Therefore, the demographic pattern may differ and changes with time. To determine the prevalence and changing trend of skin diseases according to age, gender and ethnicity in Hospital Kuala Lumpur.

Methods:
This retrospective, cross sectional study was conducted in the Department of Dermatology, Hospital Kuala Lumpur from 1st January 2008 to 31st December 2014.

Results:
The top five skin diseases in descending order of frequency were eczema, infection, acne and acneiform disorders, psoriasis and urticaria/angioedema. Eczema is now the most common skin disease as compared to an earlier study from 1995 to 1999 where infection was the most common. A total of 58,252 clinic attendees consist of Malays (61.0%), followed by Indians (20.1%) and Chinese (18.9%). Out of these, 51.6% were females and 48.4% were males. Majority of patients were 20-29 years old (n = 11546, 24.6%) followed by 30-39 (n= 6621, 14.1%) and 10-19 years old (n= 6335, 13.5%).

Conclusion:
As eczema is now the most common skin disease encountered, the management of each patient need to be tailored according to the different type of eczema. Training for eczema and other skin diseases can be provided by primary care health providers as treatment for these cases are available at primary care level.

Key words: Prevalence, skin diseases, Malaysia

Introduction

Skin diseases are common in the community and the more difficult patients will be referred to a hospital for further investigation and treatment. The most common skin diseases encountered in the Department of Dermatology Hospital Kuala Lumpur for the year 1995 to 1999 in descending order of frequency were infection, eczema, acne, psoriasis and tumours.1

The pattern of skin diseases may be influenced by external factors such as personal lifestyle, educational background and socioeconomic status.

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as well as internal factors such as age, gender, and ethnicity. Malaysia is a developing country with three major ethnicities namely Malay, Chinese and Indian. However, there is no recent study to determine the prevalence and changing trend of skin diseases in our centre.

The aim of this study was to determine the prevalence of skin diseases among patients attending the dermatology clinic HKL, which is a tertiary referral centre. We were also interested to look at the distribution of skin diseases according to age, gender and ethnicity.

Materials and Methods
This retrospective, cross sectional study was conducted in the Department of Dermatology, Hospital Kuala Lumpur. Data was collected and retrieved from electronic database for all patients seen in the dermatology outpatient clinic from 1st January 2008 to 31st December 2014. Most of the diagnoses were made based on clinical history and physical examination. In some cases, the diagnoses were supported by laboratory tests and histopathological examination. Diagnoses were captured in accordance to the International Classification of Diseases, version 10 (ICD -10). Data were analyzed using Microsoft Office Excel (version 2013).

Patients with Sexually Transmitted Infections under the care of Genitourinary Medicine Clinic were not included in the study as they are not captured in the database. Benign tumours were excluded in this study as the scope was too wide to be analysed from the database.

Results
The top 5 skin diseases were eczema, infection, acne and acneiform disorders, psoriasis and urticaria and angioedema as shown in table 1.

Table 1. Prevalence of common skin diseases among clinic attendees.

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Number, n</th>
<th>Percentage, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Eczema</td>
<td>23429</td>
<td>39.07</td>
</tr>
<tr>
<td>2 Infection</td>
<td>13957</td>
<td>23.27</td>
</tr>
<tr>
<td>3 Acne and acneiform disorders</td>
<td>6241</td>
<td>10.41</td>
</tr>
<tr>
<td>4 Psoriasis</td>
<td>5719</td>
<td>9.54</td>
</tr>
<tr>
<td>5 Urticaria and angioedema</td>
<td>2478</td>
<td>4.13</td>
</tr>
<tr>
<td>6 Pigmentary disorders</td>
<td>2365</td>
<td>3.94</td>
</tr>
<tr>
<td>7 Alopecia</td>
<td>1080</td>
<td>1.8</td>
</tr>
<tr>
<td>8 Drug allergy</td>
<td>591</td>
<td>0.99</td>
</tr>
<tr>
<td>9 Melanoma &amp; Non melanoma skin cancer</td>
<td>328</td>
<td>0.55</td>
</tr>
<tr>
<td>10 Autoimmune bullous diseases</td>
<td>286</td>
<td>0.48</td>
</tr>
<tr>
<td>Others</td>
<td>3493</td>
<td>5.82</td>
</tr>
<tr>
<td>Total</td>
<td>59967</td>
<td>100</td>
</tr>
</tbody>
</table>

A total of 58,252 patients in the 3 main ethnic groups attended the skin clinic over a period of seven years for which the majority were Malays (n=35509, 61.0%), followed by Indians (n=11728, 20.1%) and Chinese (n=10652, 18.9%). Out of these 51.6% were females and 48.4% were males. The majority were 20-29 years old, (n = 11546, 24.6%) followed by 30-39 (n= 6621, 14.1%) and 10-19 age groups (n= 6335, 13.5%).

The Malaysian main ethnic group, gender and age group are shown in figure 1. The top 10 skin disease groups by ethnicity are shown in table 2. Almost two third of the cases were eczema and infections.
Figure 1. The distribution of clinic attendance according to age, gender and ethnicity.
Table 2. Prevalence of top ten skin disease groups according to ethnicity and specific diagnoses.

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Malay</th>
<th>Chinese</th>
<th>Indian</th>
<th>Others</th>
<th>Total number of patients</th>
<th>Percentage, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1) Eczema</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contact dermatitis</td>
<td>3526</td>
<td>1339</td>
<td>992</td>
<td>173</td>
<td>6030</td>
<td>10.06</td>
</tr>
<tr>
<td>Atopic eczema</td>
<td>2617</td>
<td>789</td>
<td>643</td>
<td>54</td>
<td>4103</td>
<td>6.84</td>
</tr>
<tr>
<td>Hand &amp; feet eczema</td>
<td>1619</td>
<td>671</td>
<td>607</td>
<td>52</td>
<td>2949</td>
<td>4.92</td>
</tr>
<tr>
<td>Seborrheic dermatitis</td>
<td>1465</td>
<td>690</td>
<td>553</td>
<td>59</td>
<td>2767</td>
<td>4.61</td>
</tr>
<tr>
<td>Discoid eczema</td>
<td>1452</td>
<td>421</td>
<td>322</td>
<td>28</td>
<td>2223</td>
<td>3.7</td>
</tr>
<tr>
<td>Phototoxic dermatitis</td>
<td>743</td>
<td>559</td>
<td>264</td>
<td>25</td>
<td>1591</td>
<td>2.65</td>
</tr>
<tr>
<td>Stasis eczema</td>
<td>498</td>
<td>268</td>
<td>511</td>
<td>14</td>
<td>1291</td>
<td>2.15</td>
</tr>
<tr>
<td>Lichen simplex chronicus</td>
<td>670</td>
<td>188</td>
<td>364</td>
<td>10</td>
<td>1232</td>
<td>2.05</td>
</tr>
<tr>
<td>Others</td>
<td>644</td>
<td>309</td>
<td>273</td>
<td>17</td>
<td>1243</td>
<td>2.07</td>
</tr>
</tbody>
</table>

| **2) Infectious diseases**            |       |         |        |        |                          |               |
| **i) Viral infection**                |       |         |        |        |                          |               |
| Viral wart                            | 1055  | 330     | 342    | 57     | 1784                     | 2.97          |
| Herpes zoster                         | 875   | 195     | 110    | 41     | 1221                     | 2.04          |
| Herpes simplex                        | 149   | 69      | 32     | 27     | 285                      | 0.43          |

| **ii) Bacterial infection**           |       |         |        |        |                          |               |
| Impetigo                              | 272   | 29      | 42     | 8      | 351                      | 0.59          |
| Cellulitis                            | 130   | 50      | 68     | 4      | 252                      | 0.42          |
| Folliculitis                          | 121   | 56      | 52     | 5      | 234                      | 0.39          |
| Leprosy                               | 53    | 32      | 7      | 75     | 167                      | 0.28          |
| Cutaneous TB                          | 17    | 10      | 2      | 1      | 30                       | 0.05          |

| **iii) Fungal infection**             |       |         |        |        |                          |               |
| Tinea corporis                        | 1483  | 307     | 449    | 26     | 2265                     | 3.78          |
| Tinea cruris                          | 656   | 198     | 310    | 11     | 1175                     | 1.96          |
| Tinea pedis                           | 475   | 138     | 263    | 15     | 891                      | 1.49          |
| Tinea capitis                         | 276   | 33      | 67     | 10     | 386                      | 0.64          |
| Pityriasis versicolor                 | 301   | 59      | 134    | 16     | 510                      | 0.85          |
| Onychomycosis                         | 613   | 287     | 490    | 33     | 1423                     | 2.37          |
| Sporotrichosis, lymphocutaneous       | 40    | 7       | 2      | 1      | 50                       | 0.08          |
| Intertrigo                            | 593   | 136     | 400    | 7      | 1126                     | 1.88          |
| Others                                | 1147  | 296     | 285    | 77     | 1807                     | 3.05          |

| **3) Acne and acneiform disorders**   |       |         |        |        |                          |               |
| Acne vulgaris                         | 3900  | 841     | 903    | 102    | 5746                     | 9.58          |
| Acne cystic                           | 179   | 28      | 27     | 4      | 238                      | 0.4           |
| Rosacea                               | 54    | 38      | 24     | 10     | 126                      | 0.21          |
| Hidradenitis suppurativa              | 24    | 10      | 18     | 3      | 55                       | 0.09          |
| Others                                | 57    | 9       | 5      | 3      | 76                       | 0.13          |

| **4) Psoriasis**                      |       |         |        |        |                          |               |
| Psoriasis vulgaris                    | 3084  | 908     | 1569   | 158    | 5719                     | 9.54          |
| Erythrodermic psoriasis               | 2910  | 848     | 1504   | 145    | 5407                     | 9.02          |
| Guttate psoriasis                    | 53    | 29      | 13     | 4      | 99                       | 0.17          |
| Generalised pustular psoriasis       | 49    | 9       | 14     | 3      | 75                       | 0.13          |
| Others                                | 65    | 18      | 37     | 5      | 88                       | 0.15          |

| **5) Urticaria and angioedema**       |       |         |        |        |                          |               |
| Urticaria                             | 1473  | 531     | 417    | 57     | 2478                     | 4.13          |

| **6) Pigmentary disorder**            |       |         |        |        |                          |               |
| Vitiligo                              | 1191  | 366     | 695    | 113    | 2365                     | 3.94          |
| Melasma                               | 711   | 199     | 412    | 76     | 1398                     | 2.33          |
| Post inflammatory hypermelanosis     | 234   | 91      | 152    | 20     | 497                      | 0.83          |
| Naevus of Ota                         | 185   | 42      | 126    | 13     | 366                      | 0.61          |
| Hori ’s spot                          | 30    | 20      | 2      | 2      | 54                       | 0.09          |
| Others                                | 31    | 14      | 3      | 2      | 50                       | 0.08          |
Discussion
The top five skin diseases in the Department of Dermatology from 1st January 2008 to 31st December 2014 in descending order of frequency were eczema, infection, acne and acneiform disorders, psoriasis and urticaria/angioedema. This was almost similar to an earlier study in the department for the year 1995 to 1999 which showed that the top five skin diseases were infection (30.9%), eczema (29.5%), acne (6.1%), psoriasis (5.2%) and tumours (4.1%). There is a changing trend as eczema appeared to be the most common skin disease.

Looking into more specific diagnosis, contact dermatitis (10.06%) was the commonest followed by acne vulgaris (9.58%), psoriasis vulgaris (9.02%), atopic eczema (8.84%), hands & feet eczema (4.92), seborrhoeic dermatitis 4.61% and urticaria/angioedema (4.13%). Allergy related diseases such as contact dermatitis, atopic eczema and urticaria/angioedema were on the rise, as compared to previous study for the year 1995-1999, as the data showed the following: contact dermatitis (6.19%), atopic eczema (4.01%) and urticaria (4.0%). This might be due to various environmental and genetic factors causing the population at risk to be more susceptible to allergy related diseases.

Amongst the infections, fungal was the commonest, followed by viral and bacterial infections. This may not represent the actual figure as skin infections are also managed by primary care doctors. Only those with more serious infections are referred to dermatologists.

Although leprosy has reached elimination phase in Malaysia (0.7:100,000 population: data from Ministry of Health 2015), new cases are still being detected mainly among the foreigners, Sabahan, Sarawakian and indigenous groups. Malaysia has a large influx of foreign workers from countries, which are still endemic with leprosy. The public health still needs to continue addressing this issue to prevent the spread of disease.

Acne still contributed to the bulk of consultation. Lyn DD et al noted that acne was the top three most prevalent skin conditions in the general population as found in large studies within UK, France, and USA. Throughout the world, similar numbers were found among young adults in various countries. This prevalence of about 10% in our center was not
reflective of the actual burden in the community as many tried over the counter or on-line products and sought treatment in primary care and private dermatologist.

We were also seeing a large number of patients with psoriasis. According to the Malaysian Psoriasis Registry from March 2007 to December 2014, 12462 new patients were registered. In our study there were more Indians (27.4%) with psoriasis as compared to Chinese (15.9%) despite the clinic being attended by almost similar numbers of Indians and Chinese.

There were more Indian patients with pigmentary disorders as compared to Chinese and Malays with a ratio of 2:1:1. The pigmentary problems seen were mainly vitiligo, melasma and post inflammatory hypermelanosis. Due to the significant contrast in skin colour among Indians with vitiligo, they sought further treatment in hospitals with phototherapy services.

As expected, both melanoma and non-melanoma skin cancers (NMSC) were not very common. They only constituted 0.55% and majority was Chinese (0.24%, n=143). Chinese were at higher risk of getting skin cancers, probably due to the fair skin phototype. Basal cell carcinoma (n=205) was commoner than squamous cell carcinoma (n=90). However, there may be cases that are being treated by surgeons. Melanoma appeared to be uncommon.

As this is a retrospective study, there may be errors in data entry and missing data in the system. There may be recall or misclassification bias, as the diagnosis may change in the subsequent visits but the latest diagnosis may not be updated in the system.

Based on these data, we plan to train and educate the general practitioners and family medicine specialists to manage the more prevalent diseases in the community. We may further assess the factors which may be specific to a certain ethnic group that put them at higher risk for certain skin diseases.

However, we do acknowledge that this study was conducted in a tertiary centre in the heart of Kuala Lumpur. Thus, it may not be representative of the actual epidemiology of the whole country. Similar studies should be done in the rural areas as well as Sabah and Sarawak to look at the prevalence of common skin diseases.

**Conclusion**

From this study, as eczema was now the most common skin disease encountered, the management of each patient needs to be tailored according to the different types of eczema. Training for eczema and other skin diseases can be provided by primary care health providers as treatment for these cases are available at primary care level. It is also important for us to train health care providers to recognize certain diseases such as leprosy and skin cancers so that treatment can be instituted earlier.

**Conflict of Interest Declaration**
The authors have no conflict of interest to declare.

**Acknowledgement**

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**References**

ORIGINAL ARTICLE

Cardiac Abnormalities in Psoriasis

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Abstract

Introduction:
Psoriasis is considered an independent cardiovascular risk factor. This study aims to determine and describe the cardiac abnormalities using echocardiography and electrocardiography in patients with plaque psoriasis.

Methods:
This is a case control study of psoriasis patients with no previous history of cardiac disease. One hundred and thirty-five patients attending the Dermatology Clinic, Hospital Kuala Lumpur were recruited over one year. A full history, physical examination, echocardiogram and electrocardiogram were done. The controls were 135 age and sex matched healthy individuals.

Results:
The psoriasis group had a significantly higher body mass index and blood pressure. The echocardiogram showed that the mean left ventricular wall diastolic thickness, aortic annulus diameter and isovolumetric relaxation time of the left ventricle was significantly prolonged, and a higher prevalence of tricuspid regurgitation in psoriasis. On the electrocardiogram, more psoriasis patients had left ventricular hypertrophy, ischaemia and right bundle branch block. The QRS interval was significantly shorter in these patients. The tricuspid valve E/A ratio was significantly lower in patients with psoriatic arthropathy. The mitral valve early filling velocity deceleration time, tricuspid valve E/A ratio and QRS interval were significantly higher among systemic therapy naïve patients. The mean mitral and tricuspid valve E/A ratio were significantly lower; and the mean ascending aorta diameter larger, in those with psoriasis for more than ten years.

Conclusion:
Psoriasis may be associated with an increased risk of cardiac abnormalities suggesting diastolic dysfunction and tricuspid regurgitation. These abnormalities appear to be related to disease duration. Further studies employing newer echocardiographic and cardiac imaging techniques are needed to validate this.

Key words: Psoriasis, cardiovascular disease, cardiac abnormalities, echocardiogram, electrocardiogram

Introduction
Psoriasis is one of the commonest chronic skin diseases worldwide. It is an immune mediated inflammatory, papulo-squamous, immune disease with cutaneous and skeletal manifestations.¹
which is characterized by cycles of remission and exacerbations. Before the 1980s, psoriasis was defined as an inflammatory cutaneous disorder. In recent years; substantial advances have been made in elucidating the molecular mechanisms of psoriasis. The concept of an inflammatory autoimmune component has recently emerged based on the observation of psoriasis association with diseases like Crohn’s, ulcerative colitis and giant cell arthritis. The association of psoriasis with cardiovascular disease has been well established and received much attention over the last 40 years or so. Possible risk factors and relative mechanisms responsible for the epidemiological associations between CV disease and psoriasis include the concomitant traditional CV risk factors e.g. hypertension, diabetes mellitus, obesity and dyslipidaemia, which are part of the metabolic syndromes that place the patient at a higher risk for CV disease. Interestingly, there is an increased prevalence of metabolic syndrome in psoriasis patients that is independent of psoriasis severity. Epidemiological data from large population based studies found an increase in the prevalence of both conventional and non conventional cardiovascular risk factors in patients with psoriasis. However, in a patient with psoriasis and no known cardiovascular disease, are other cardiac abnormalities and cardiac conduction defects present? To date, very scant data is found regarding myocardial, valvular and conduction pathologies in psoriasis with no available data in Asian patients. This study hopes to shed some light in this aspect. Thus, we aim to study the cardiac abnormalities in patients with psoriasis.

Materials and Methods

This is a case control study conducted in Hospital Kuala Lumpur that compares cardiac abnormalities in patients with plaque psoriasis versus healthy controls from August 2010 to August 2011. We recruited patients aged 18 years and above with plaque psoriasis diagnosed by dermatologists. Pregnant patients, smokers and patients with any form of pre-existing diagnosed cardiac diseases, diabetes mellitus, thyroid disorders, obesity, connective tissue disease, hepatic disorders, renal failure and dyslipidaemia were excluded. Controls were age-and-sex matched subjects with no personal or family history (in a 1st degree relative) of psoriasis. After obtaining consent, recruited patients and controls were interviewed; followed by physical examination. The severity of psoriasis was assessed using body surface area (BSA) affected by psoriasis; Psoriasis area and severity index (PASI) and Physician Global Assessment (PGA). The capillary blood sugar was measured, and 12-lead electrocardiogram and an echocardiogram were done.

All data was analyzed using SPSS version 16.0. Normality was tested using the Kolmogorov-Smirnov test. Parametric data are expressed as mean ± SD. Non-parametric data are expressed as median + tertiles. Precision of measurement is calculated as 1.96 times the standard deviation of repeated measurements (expressed as percentage of the sample mean value). Descriptive statistics are provided for the numerical and categorical variables using mean ± SD and percentage distribution where appropriate. Sub-group analyses used the Mann-Whitney U-test; for normal distribution, the Student’s t-test were used to compare numerical variables across groups. The chi-squared test and Fisher’s test were used to compare percentage distributions across levels of nominal variables. The Pearson correlation was used to assess the relationship between numerical variables, and the Spearman correlation was used to measure the relationship between categorical variables. Comparison of the accuracy and precision of each method is calculated using the Student’s t test. A p value < 0.05 is considered as significant.

Results

The study population consisted of 135 patients with psoriasis and 135 control subjects with no known medical problems. The control subjects who fulfilled the inclusion and exclusion criteria were invited to participate in the study after they were matched for age and gender with the enrolled psoriasis patients. The demographic data and clinical characteristics of both groups are shown in Table 1. The majority of the subjects were males (55.5%). The mean age was 40.24 ± 12.9, range 20-80 years in the psoriasis group and 40.55 ± 12.7, with range 20-79 years in the control group. The highest number of subjects was in the younger age group of less than 40 (56.3%),
followed by the middle age group of between 41-60 years old (36.3%) and the least number of patients (7.4%) were more than 61 years old. The majority ethnic groups in both the psoriasis and control groups were Malays. There was no significant difference in the random capillary blood sugar between the psoriasis patients and the control group. However, the psoriasis group had a significantly higher body mass index, systolic blood pressure and diastolic blood pressure compared to controls (p = 0.01, 0.02 and 0.00 respectively).

Table 2 summarizes the management of the 135 patients with psoriasis. At the time of recruitment, 108 (80%) of patients were on topical treatment alone and the other 27 patients were on the combination of topical treatment with either phototherapy or a systemic agent. One patient was on a combination of two systemic agents (Leflunomide and Etanercept) and one patient was on Ustekinumab. In the past, 37% of patients (50 patients) had been on systemic treatment. Of these 50 patients, 13 patients had been on more than one systemic treatment. The systemic agents used in these patients included methotrexate, cyclosporine, sulphasalazine, adalimumab, etanercept and acitretin.

The electrocardiogram and echocardiogram findings of the study populations are shown in Table 3 and 4. There were no abnormalities in terms of rhythm in either group. All patients were in sinus rhythm with no statistically significant difference noted between the two groups in term of the prevalence of atrial or ventricular premature beats. The QRS interval was significantly shorter in the patient group. The prevalence of left ventricular hypertrophy, ischemic changes and right bundle branch block was significantly higher in the psoriasis group. In this study, ischemic changes on ECG were defined as ST elevation, ST depression or T wave inversion in contiguous leads with or without the presence of Q waves.

The mean left ventricular posterior wall diastolic thickness was significantly longer in the psoriasis group as was the aortic annulus diameter. The isovolumetric relaxation time of the left ventricle was also significantly prolonged in the psoriasis group compared to controls. There was no statistically significant difference in the prevalence of right or left ventricular diastolic dysfunction between the two groups. Similarly, there was no statistically difference in the E/A ratio of both the mitral and tricuspid valves between the two groups. There was no pulmonary valve pathology noted in either group. The prevalence of tricuspid valve regurgitation was significantly higher in the psoriasis group. Otherwise, no other statistically significant differences were noted in terms of valvular pathology between the psoriasis and control group.

The study population was then divided into three groups based on age (≤ 40, 41-60 and ≥ 61) and the above analysis of the electrocardiogram and echocardiogram modalities was carried out. This was to ascertain if a particular age group of psoriasis patients was more at risk for cardiac abnormalities. As age is an independent risk factor for cardiac disease especially ischemic heart disease, the cases and controls are matched in terms of age. In the study population aged ≤ 40, there is a statistically significant higher prevalence of tricuspid regurgitation in the psoriasis group. The prevalence of mitral regurgitation and aortic regurgitation was not significantly different between the two groups. The only ECG parameter to note is the QRS interval. This was significantly higher in the control group.

In the study population aged 41-60, diastolic dysfunction of the right ventricle was significantly more prevalent in the psoriasis group compared to controls. The aortic annulus diameter was significantly larger in the psoriasis group as well. The prevalence of all other echocardiogram parameters was not significantly different between psoriasis patients and the control population in this age group. No significant difference in the prevalence of valvular pathologies was found between patients and controls too. The only statistically significant parameter on the ECG of this age group was the prevalence of ischaemic changes. The prevalence of ischemic changes was higher in the patient group.

In the study population aged 60 years and above, there was no difference in term of the ECG findings. However, it was noted that patients with psoriasis had significant higher posterior wall diastolic thickness, longer mitral valve early filling velocity deceleration time, longer mitral valve isovolumetric relaxation time and a larger aortic annulus diameter. The other echocardiographic parameters were not significantly different from the controls.

With regards to disease severity, there was no statistically significant difference between the BSA (affected by psoriasis) and PASI of patients with any ECG and echocardiographic abnormalities as shown
in Table 5. Nevertheless, there was a weak positive correlation between the BSA (affected by psoriasis) and the left atrial diameter and the posterior wall thickness on echocardiogram. The coefficients of determinations ($R^2$) were 0.039 (Pearson product-moment correlation test) and 0.040 respectively. There was a weak positive correlation between the PASI score and the left atrial diameter together with left ventricular posterior wall thickness on echocardiogram ($R^2=0.067$ and 0.037 respectively). There was also a weak negative correlation between the PASI score and the ejection fraction ($R^2=0.029$).

There was a weak positive correlation between the disease duration and PR interval on the ECG ($R^2=0.03$); isovolumetric relaxation time of the left ventricle ($R^2=0.031$); and ascending aorta diameter ($R^2=0.044$) on echocardiogram. Nevertheless, there was a weak negative correlation between the disease duration and mitral E/A ratio ($R^2=0.03$); isovolumetric relaxation time of the left atrium ($R^2=0.03$); and ascending aorta diameter ($R^2=0.044$) on echocardiogram. Nevertheless, there was a weak negative correlation between the disease duration and mitral E/A ratio ($R^2=0.053$). The mean mitral valve early filling velocity ($E$); mean mitral E/A ratio; and mean tricuspid E/A ratio were significantly longer in patients with a disease duration of ≤ 10 years [0.72 (SD 0.16) cm/s vs 0.65(SD 0.18) cm/s, $p = 0.01$; 1.51(0.46) vs 1.29(0.45), $p=0.01$; and 1.54(0.43) vs 1.37(0.44), $p=0.02$ respectively]. However, the ascending aorta diameter was significantly longer in the group with a disease duration > 10 years [25.5(3.3) mm vs 24.1(3.1) mm, $p=0.01$] (Table 6).

There were 50 patients (37%) who had received oral systemic therapy for psoriasis in the current cohort. The only statistically significant finding on the ECG was the mean QRS interval which was longer in the patients who had never received systemic therapy (76.2ms vs 68.0ms; $p=0.04$). The mean mitral valve early filling velocity deceleration time was significantly higher (193.9ms vs 167.0ms; $p=0.03$) and the tricuspid valve E/A ratio was significantly lower (1.4 vs 1.5; $p=0.03$) in group that never received systemic therapy. The other echocardiogram parameters did not show a significant difference between the two groups.

Of the 135 patients with psoriasis, 40 patients had some form of psoriatic arthropathy. No statistically significant difference was seen between patients with and without arthropathy in terms of echocardiogram parameters. The tricuspid valve E/A was significantly lower in the patients with arthropathy (1.3 vs 1.5; $p=0.03$). No other echocardiogram parameters significantly differed between the two groups of psoriasis patients.

Discussion
Psoriasis is now viewed as a systemic inflammatory process that may increase the prevalence of other co-morbidities in this patient population. A considerable body of evidence supports the association between psoriasis and cardiovascular disease. However, the data on cardiac abnormalities is limited. The studies that have been done so far have been in Western and Far Eastern populations like the Jewish, Turkish and Europeans. This study aims to explore the association between psoriasis and cardiac abnormalities in a multi ethnic Asian population. Limitations of the studies so far have been in terms of; patient number whereby most studies have less than 100 patients with psoriasis, or no control group. One study was retrospective. Some of the studies only included patients less than 60 years old whereas our study includes those from age 18 to 80. To minimize bias, our patient population was matched in terms of age and sex.

Interestingly, although obese patients were excluded, the mean BMI of the psoriasis group is significantly higher than the control group in this study. This is consistent with many other studies that have shown that, compared to the general population; patients with psoriasis are more frequently overweight and obese. Both the systolic and diastolic blood pressure was noted to be significantly higher in the psoriasis group. This was in keeping with several epidemiologic studies that have shown hypertension to be a common co-morbidity in patients with psoriasis. The higher the blood pressure, the greater is the risk of stroke, myocardial infarction, heart failure and kidney failure. Cohen et al in their large scale study that looked at more than 12,000 patients; attributed the association between psoriasis and hypertension to angiotensin II, a product of angiotensin-converting enzyme (ACE) that regulates vascular tone and stimulates the release of pro-inflammatory cytokines. They also discussed the possible role of oxidative stress, which is present in all acute and inflammatory states including psoriasis. Oxidative stress may play a role in hypertension by destructive effects of reactive oxygen species, damaging endothelium-dependent vasodilatation. The association between psoriasis and hypertension may also be attributed to the production of endothelin-1, which is produced by keratinocytes as an autocrine growth factor. Endothelin-1 is a potent vasoconstrictor and may contribute to hypertension in psoriasis patients.
Bonifati et al.\textsuperscript{28} reported that endothelin-1 was increased in both sera and lesional skin of patients with psoriasis, compared with controls.

The left ventricular posterior wall diastolic thickness refers to the thickness of the left posterior wall at the end of diastole and it normally ranges from 7-11mm. This parameter positively correlates to left ventricular mass and left ventricular hypertrophy (LVH).\textsuperscript{29} Although the value of this parameter was within normal range for both groups in our study, it was significantly higher in the psoriasis group. This differs from the study by Biyik et al\textsuperscript{18} that showed no significant difference between their psoriasis patient and control groups. This could be due to the fact that all the patients in Biyik’s study\textsuperscript{18} were younger with the oldest patient being 55 years old. In our study, we further analyzed this parameter based on age groups and found that more specifically, in the ≥ 61 age group, the mean left ventricular posterior wall diastolic thickness was significantly higher in the psoriasis group compared to controls. Grossman et al\textsuperscript{30} demonstrated that the left posterior wall diastolic thickness is an important determinant of left ventricular diastolic stiffness and pressure, and that wall thickness appears to predict diastolic stiffness independent of the presence or absence of LVH. Hence, this suggests that psoriasis patients have increased diastolic stiffness of the left ventricle compared to controls. This may possibly be explained the higher incidence of myocardial fibrosis (due to systemic inflammation) or higher blood pressure amongst patients with psoriasis (as demonstrated in our study and also by Biyik et al\textsuperscript{18} in keeping with Akkoc et al.\textsuperscript{31} who demonstrated that left posterior wall diastolic thickness is increased in hypertensives compared to controls. Therefore, the author postulates that the positive correlation between the left ventricular wall diastolic thickness & the severity of disease study may be related to inflammation. In our current study, a weakly positive correlation between the PASI/BSA and the left ventricular wall diastolic thickness was demonstrated. A higher PASI score and a higher percentage of BSA affected by psoriasis suggest more extensive disease that possibly translates to more inflammation; hence the presence of larger amounts of inflammatory mediators that contribute to diastolic stiffness of the left ventricle.

The principal method to diagnose LVH is echocardiography, where the thickness of the heart muscle can be measured. The ECG often shows signs of increased voltage from the heart in individuals with LVH, but has high sensitivity and low specificity. This is because the ECG criteria for LVH, particularly those that are heavily reliant on voltage criteria may result from abnormal thickening of the LV free wall or ventricular septum, LV chamber dilatation or increased LV wall tension.\textsuperscript{32} Feld et al\textsuperscript{33} noted a higher prevalence of LVH on the ECG among patients with psoriatic arthritis compared to controls in their study but this difference was not statistically significant. The large scales study by Biyik et al\textsuperscript{18} also showed a statistically significant higher prevalence of LVH among psoriasis patients compared to controls. The prevalence of left ventricular hypertrophy demonstrated by ECG in this study was significantly higher in the psoriasis group compared to control group. One may argue that these could be false positive findings. Nevertheless, this ECG finding may reflect early LVH that is not yet visible on the echocardiogram. Moreover, the fact that left ventricular posterior wall diastolic thickness as mentioned above positively correlates to left ventricular mass and left ventricular hypertrophy (LVH) supports our theory that the ECG finding of a higher prevalence of left ventricular hypertrophy in psoriasis patients was not merely a false positive. This may be associated with the higher blood pressures found in psoriasis patients than in controls. Whether high blood pressure levels in patients with psoriasis predisposes them to develop hypertension and left ventricular hypertrophy requires further investigation. The Framingham study, published in 1991, states that hypertension predisposes to sudden death caused by left ventricular hypertrophy. The presence of left ventricular hypertrophy was associated with a 5-year mortality rate of 33\% in men and 21\% in women.\textsuperscript{33} The risk of sudden death in the presence of left ventricular hypertrophy was comparable to that of coronary artery disease or heart failure.\textsuperscript{34} Left ventricular hypertrophy identified by echocardiography (or features suggestive of early left ventricular hypertrophy) may increase the risk of sudden cardiac death and pose an additional risk for patients with psoriasis.\textsuperscript{18}

Diastolic heart failure is defined as a condition caused by increased resistance to the filling of one or both ventricles; this leads to symptoms of congestion from the inappropriate upward shift of the diastolic pressure volume relation. Diastolic dysfunction results in a decline in the performance of one or both ventricles during the time phase of diastole. It is characterized by elevated diastolic pressure in the left or right ventricle despite essentially
normal systolic function and ejection fraction.\textsuperscript{35} On echocardiography, the peak velocity of blood flow across the mitral valve during early diastolic filling corresponds to the $E$ wave. Similarly, atrial contraction corresponds to the $A$ wave. From these findings, the $E/A$ ratio is calculated. Under normal conditions, $E$ is greater than $A$ and the $E/A$ ratio is approximately 1.5. In early diastolic dysfunction, the ventricular relaxation is impaired and, with vigorous atrial contraction; the $E/A$ ratio decreases to less than 1.0. As the disease progresses, left ventricular compliance is reduced, which increases left atrial pressure and, in turn, increases early left ventricular filling despite impaired relaxation. This paradoxical normalization of the $E/A$ ratio is called pseudonormalization. In patients with severe diastolic dysfunction, left ventricular filling occurs primarily in early diastole, creating an $E/A$ ratio greater than 2.\textsuperscript{20,36} The isovolumetric relaxation (IVRT) time is measured as the time between the closure of the aortic valve and the opening of the mitral valve. Normally in adults, it is less than 100ms. The left ventricular early filling velocity deceleration time (DT) is the time taken from the maximum $E$ point to baseline and is normally less than 200ms in adults.\textsuperscript{36,37} In early diastolic dysfunction, a lengthening of the deceleration time and isovolumetric time may be seen, without changes in early and late ventricular filling velocities.\textsuperscript{38} This is an extremely important point to guide prognostic stratification and treatment in these groups of patients.

Biyik et al\textsuperscript{18} revealed that left ventricular diastolic dysfunction was significantly more common in patients with psoriasis than control subjects. In a smaller study, Guven et al\textsuperscript{10} showed that the incidences of left ventricular diastolic dysfunction and was higher in 62 psoriasis cases compared with healthy controls. Gunes et al\textsuperscript{8} also found a higher prevalence of diastolic dysfunction among psoriasis patients compared to controls. In 1991, Rowe and coworkers reported the presence of diastolic dysfunction in 7 of 11 patients with psoriatic arthropathy\textsuperscript{15}. Saricaoglu et al\textsuperscript{45} have suggested that mild left ventricular diastolic dysfunction may be seen in patients with psoriatic arthropathy.

In our study, the overall prevalence of left ventricular diastolic dysfunction was higher among the psoriasis group compared to controls although not statistically significant. However, our results do suggest the presence of possible early left ventricular diastolic dysfunction which has a statistically significant higher prevalence in the psoriasis group. This is supported by a few of our results. Firstly, in our cohort of patients as a whole, the mean isovolumetric relaxation time is significantly longer in the psoriasis group. Secondly, in the older age group of $\geq$ 61 years old, the mean IVRT was not only significantly longer in the psoriasis group, but abnormal as well ($>100$ms). This suggests Grade 1 left ventricular diastolic dysfunction.\textsuperscript{36} A similar result in the DT was noted in this age group as well. The mean DT was not only significantly longer in the psoriasis group, but abnormal as well ($>200$ms), again suggesting Grade 1 left ventricular diastolic dysfunction.\textsuperscript{36}

Hypertension and cardiac ischaemia are known to be the most common causes of left ventricular diastolic heart failure.\textsuperscript{35} As mentioned previously, the mean blood pressure among the psoriasis patients in our study was higher than the controls. This may explain the higher prevalence of left ventricular diastolic dysfunction in our psoriasis patients, concurring with Biyik et al.\textsuperscript{18} They suggested that the significantly higher blood pressure levels in their group of psoriasis patients might partly explain the significantly higher incidence of left ventricular diastolic dysfunction detected. The other significant factor in our cohort that may be contributing to left ventricular diastolic dysfunction is ischaemia. We found a significantly higher prevalence of ischemic changes on the ECGs of our psoriasis patients compared to controls. This is not surprising as it is a well-established fact that psoriasis is associated with both macrovascular and microvascular disease, both of which contribute to myocardial ischaemia.\textsuperscript{5,20,21,23,39,41} This was seen looking at the patient cohort as a whole and more specifically, in the 41-60 age group. In our study subjects of $\geq$ 61 years of age, although 4 out of 10 individuals in each group had left ventricular diastolic dysfunction, none had ischemic changes on the electrocardiograms. This could be due to the fairly small number of subjects (only 20) aged $\geq$ 61 in our study. The other possibility is that hypertension or other factors may contribute more to diastolic dysfunction in this age group rather than ischaemia. However, more studies that look at this age group specifically are needed to support or refute this theory.

There have been reports of secondary amyloid deposits in the myocardial interstitium, intramyocardial small vessels, cardiac conduction system and other heart structures in patients with psoriasis.\textsuperscript{42-45} These changes might also partly explain the frequently observed echocardiographic
abnormalities in patients with psoriasis, such as left ventricular hypertrophy and left ventricular diastolic dysfunction. This aspect was not studied by us but may be a contributing factor to bear in mind. Further studies looking at this aspect will be helpful.

In terms of valvular disturbances, we found that patients with psoriasis had a higher prevalence of mitral valve prolapse, tricuspid regurgitation and aortic regurgitation compared to controls. The only statistically significant result was that of tricuspid regurgitation; the prevalence of which was significantly higher among psoriasis patients compared to controls. This was noted more specifically in patients≤ 40 years old. However, the prevalence of tricuspid regurgitation was higher in all age groups of the psoriasis group compared to controls. Gunes et al. noted that 31.9% of patients with psoriasis in their study had tricuspid regurgitation as well but this was not statistically significant compared to controls. This is most likely due to the fact that the number of controls in the study was less than half of the subjects. In 2005, Gonzalez-Juanetey and colleagues also noted a higher prevalence of tricuspid regurgitation among patients with psoriatic arthritis compared to controls.

We postulate that the higher prevalence of tricuspid regurgitation in this study may be a surrogate to higher pulmonary artery pressure among psoriasis patients. The Bernoulli equation applied to tricuspid regurgitation suggests that tricuspid regurgitation is a reflection of increased pulmonary artery pressure. Nevertheless no patient in our study had pulmonary hypertension (PH) based on the Doppler echocardiogram. On the echocardiogram, the presence of pulmonary valve regurgitation in combination with a tricuspid valve regurgitation flow of less than 25 mmHg/sec indicates PH. The actual pulmonary artery systolic pressure is measured by an invasive procedure using a Swan-Ganz catheter that is beyond the scope of this study. Gunes et al found an increased frequency of mild pulmonary hypertension in otherwise healthy, asymptomatic psoriasis patients to controls, suggesting that patients with psoriasis may have a mean pulmonary artery pressure that is higher than controls, albeit not reaching the stage of pulmonary hypertension yet. However, further studies that measure the actual pulmonary artery pressure are needed to confirm this hypothesis. This is further supported by the finding in our study of a statistically significant higher prevalence of right ventricular diastolic dysfunction among psoriasis patients aged 41-60 compared to controls. Faludi et al demonstrated that diastolic dysfunction of the right ventricle may be a sign of stress-induced (or latent) pulmonary hypertension. This means that patients with psoriasis may have this form of pulmonary hypertension that was not detected at rest on routine echocardiography but may account for the findings of tricuspid regurgitation and right ventricular diastolic dysfunction as mentioned. This may also explain in part why the prevalence of tricuspid regurgitation was statistically significant compared to controls among the youngest group of patients studied (≤ 40 years old) whereas right ventricular diastolic dysfunction showed up as statistically significant later on; in the middle aged patient group studied, suggesting that tricuspid regurgitation may be an early sign preceding right ventricular diastolic dysfunction and pulmonary hypertension.

It has been proposed that inflammatory mechanisms could play a part in the genesis or progression of pulmonary hypertension (PH). Pulmonary hypertension is an increasingly recognized complication of rheumatic diseases, including rheumatoid arthritis and an inflammatory/autoimmune pathogenesis has been suggested. Similar mechanisms may be responsible for the finding of increased frequency of pulmonary hypertension in psoriasis patients. The systemic nature of the inflammatory processes underlying the pathogenesis of psoriasis may potentially result in systemic involvement. Increased antigen presentation, increased cutaneous T lymphocyte activity, interleukins and tumor necrosis factor-α in the pathophysiology of psoriasis also cause endothelial dysfunction, an important mechanism in pathophysiology of PH. Increased procoagulant activity and platelet activation in psoriasis are also potential mechanisms for PH Gunes et al.

The valvular disturbances found in other studies differed from our slightly. Biyik et al found a statistically significant more common prevalence of mitral valve prolapse and tricuspid valve prolapse in their study. These findings may be due to the higher number of patients in their study i.e. 216 in each arm, allowing for perhaps a higher pick up rate of these anomalies; and the phenotype of their population compared to ours. There is a possibility that valvular anomalies associated with psoriasis may differ among different populations. Guven et al noted a higher prevalence of mitral valve regurgitation among psoriasis patients in their
study but this was not statistically significant.\textsuperscript{10}
More studies looking at various populations and phenotype are needed to confirm this postulation.

The aortic annulus is a complex fibrous ring in the wall of the root of the aorta. The normal absolute diameter of the aortic annulus is 17-25cm.\textsuperscript{48}
Enlargement of the aortic root (due to any cause) will result in enlargement of the aortic annulus, and in severe cases, lead to aortic regurgitation. We found that although still within normal limits, the aortic annulus diameter was significantly larger in the psoriasis group compared to controls. This was noted looking at the study population as a whole; and in the 41-60-year-old age group as well as those more than 61 years old i.e. in patients those above 41 years old. This may be due to the significantly higher blood pressure found in the psoriasis patients compared to controls or it may be a common non specific finding of psoriasis as chronic inflammatory disease; or a combination of both factors. It is interesting to note the prevalence of aortic regurgitation was higher in the psoriasis group (9 patients) compared to only 3 control subjects. Aortic regurgitation is related to abnormalities in the ascending aorta which in our study is reflected by the higher mean aortic annulus diameter among psoriasis patients. To the best of the author’s knowledge, no other studies regarding psoriasis and cardiac abnormalities have commented on the aortic annulus diameter. There is a need for further studies involving larger case series to clarify the results of our study.

There is scarcity of data on heart rate abnormalities and conduction disturbances in psoriatic patients, despite quite a clear connection between these parameters and chronic inflammatory processes.\textsuperscript{49,50} Markuszeski et al found a mean faster heart rate of 73 \pm 6 beats /min in their psoriasis patients compared to 63 \pm 4 beats per minute in the control group.\textsuperscript{7} This difference was statistically significant. The sample size of only 64 patients in total was probably a limiting factor in their study. All patients in our study, however, were in sinus rhythm and mean heart rate was similar in both the groups. Feld et al\textsuperscript{15} noted similar findings in their cohort of 92 patients with psoriatic arthritis and 92 controls as did Gunes et al in their study.\textsuperscript{8}

There were twice as many patients with right bundle branch block (RBBB) compared to controls in the study by Feld et al\textsuperscript{15} but this difference was not statistically significant. This was perhaps due to their smaller sample size of 184 compared to 270 subjects in our study. One can argue that RBBB could be considered a normal variant based on 12-lead ECG when there were no other significant differences in conduction abnormalities between the groups in our study. RBBB occurs when the electrical impulse from the bundle of His does not conduct along the right bundle branch. The right bundle branch is vulnerable to disturbance for two thirds of its course when it is near the sub-endocardial surface and can be compromised by myocardial ischaemia, myocardial inflammation, high blood pressure and increased right ventricular pressure. In the author’s opinion, these contributing factors could account for the significantly higher prevalence of RBBB among the psoriasis group in our study. In the group of 22 patients with psoriatic arthritis, Carvalho et al reported a higher incidence of premature atrial beats; however, this group observed both atrial tachy- and bradycardia in the examined group of patients.\textsuperscript{6} Markuszeski et al did not note a higher prevalence of conduction disturbances in their 32 psoriasis patients compared to controls.\textsuperscript{7} Ozturkan et al noted an unspecified intra-ventricular conduction disorder on the ECG of one of their 36 psoriasis patients compared to none in the control group.\textsuperscript{11}

The QRS complex corresponds to the depolarization of the right and left ventricles. Shortening of the QRS complex occurs either in tachycardia or presence of an accessory conduction pathway in the ventricles.\textsuperscript{51} Although within normal range, the QRS complex duration was significantly shorter in the psoriasis group compared to controls in the current study, particularly those younger than 40 years old. This finding could be explained easily by a higher mean pulse rate among the psoriasis patients, especially those less than 40 years of age. The mean pulse rate of patients aged 41-60 was similar in both groups i.e. around 72 and hence no difference was seen in the QRS complex duration. In the oldest cohort of patients (\geq 61 years old), the mean pulse rate was higher in the psoriasis group but there was no statistical difference noted in the QRS complex duration between groups. Further research that encompasses 24 hour ambulatory electrocardiogram holter monitoring and electrophysiological studies may shed more light on this matter and would certainly be very interesting. To the best of the author’s knowledge, no other similar study to date has noted a shorter QRS duration among psoriasis patients. Feld et al found no statistically significant difference with respect to the QRS interval among their cohort of 92 psoriatic arthritis patients.
The inflammatory character of psoriatic abnormalities leads to excessive Th-1 type cytokines that exert systemic effects and thus could induce arrhythmias, conduction disturbances and tachycardia, which are regarded as non-specific response to inflammatory processes. Laboratory data revealed pro-arrhythmic effect of some cytokines (IL-1, IL-2, and IL-3) and TNF-α. It should be stressed that the innate inflammatory cytokine TNF-α is of prime importance as an inducer of psoriasis. TNF-α and its receptors exert toxic effects on cardiomyocytes. Up regulation of TNF-α together with down regulation of its receptors is observed in cardiac insufficiency. Patients with cardiac disease have increased TNF-α levels in the circulation. Animal studies have confirmed a relationship between TNF-α and supraventricular arrhythmias. Some researchers demonstrated a correlation between C-reactive protein level, IL-1 and TNF-α and atrial fibrillation incidence. It could be speculated that our observation of increased incidence of atrial premature beats in psoriatic patients could predispose to further atrial fibrillation development. An inflammatory background of ventricular arrhythmias was reported by Kowalewski et al. This group demonstrated a positive correlation between TNF-α levels and ventricular arrhythmias. This may explain the increased prevalence of ventricular premature beats in our psoriasis population compared to controls.

The authors are not surprised to find no complex forms of arrhythmia in psoriasis patients in our study. This is because a special group of patients was selected i.e. relatively young (mean age 40 years) and with negative personal history of cardiovascular diseases. Based on the obtained results, it seems important to include in further studies a higher number of the older population of psoriatic patients and carrying out a 24-hours ambulatory electrocardiogram holter monitoring or a rhythm card monitoring.

The electrocardiogram results noted in our study do strongly suggest that the active inflammatory processes observed in psoriasis seem to exert their influence on increased heart rate and cardiac conduction abnormality development in psoriatic patients. However, to confirm the above findings, further studies on larger groups of psoriatic patients presenting different types of the disease are mandatory.

Biyik et al found no associations between the clinical and echocardiographic abnormalities and the PASI scores of the patients. On the other hand, Marcuszeski et al found a positive correlation between the PASI and heart rate in their small cohort of 32 patients. Unlike their study, there was no correlation noted between the heart rate and PASI scores or BSA affected in our study. This is probably due to the much higher number of patients (more than four times) in the current study. Our study found a weakly positive correlation between the PASI scores with the left atrial diameter and the left ventricular posterior wall diastolic thickness on the echocardiogram. A similar correlation was noted for the affected BSA as well. Thus, it could be regarded as a useful measure of the systemic inflammatory process intensity. So, the positive correlations described above could result from the above extrapolation. There was a negative correlation of PASI with the ejection fraction, suggesting that a higher severity of inflammation may result in the compromise of both the structural and functional components of the left side of the heart. The author postulates that the reason for this may be due to the thicker muscle layer of the left heart, rendering it more susceptible to insult. The other contributing factor could be that increased inflammation may lead an increase afterload and increased systemic vascular resistance, resulting in increased diastolic ventricular stiffness and a compromised ejection fraction. To overcome the increased diastolic stiffness, there is compensatory dilatation of the left atrium. However, further studies should be encouraged to confirm that. The correlation between the PASI/BSA and the above discussed abnormalities is weak. Therefore, clinicians must not rely on the PASI or BSA alone as a tool to identify the psoriasis patient group at a higher risk of developing cardiac abnormalities.

About a third of our patients (37%) had received systemic therapy over the course of their disease. The prescription of systemic therapy in psoriasis is usually reserved for more severe disease. Hence,
we would extrapolate that the patients who received systemic therapy had more severe disease and more systemic inflammation; resulting in a worse cardiac abnormality profile compared to those who have never been on systemic therapy. Surprisingly, our results revealed otherwise. The mitral valve early filling velocity deceleration time was significantly longer in the subgroup that had never been on systemic therapy, suggesting possible very early diastolic dysfunction among these patients. Moreover, there was not a single case of diastolic dysfunction reported on the echocardiogram of patients who had been on systemic therapy. In the group that had never been on systemic therapy, diastolic dysfunction was seen in 5 patients. We could not explain this result; perhaps another study with higher number of psoriasis patients on systemic therapy will answer better. Further studies are also needed to ascertain if perhaps, commencing systemic therapy reverts cardiac abnormalities.

Similarly, the results suggest that patients who have never been on systemic treatment may also have a higher risk of right ventricular diastolic dysfunction. The mean tricuspid valve E/A ratio in this group of patients was significantly lower at 1.4 compared to 1.5 in the other group. Although the clinical relevance of this finding is questionable since the absolute difference was small, the importance of the observation is the implication of possible right ventricular dysfunction should the E/A ratio become less than 1 in the future. Therefore, long term follow up is very important in these patients. Interestingly, the percentage of patients with right ventricular dysfunction detected on echocardiography is the same for both groups. Lastly, the QRS interval was significantly longer in the systemic treatment naïve group although in both groups, it was within normal range. The simplest explanation for this finding would be the mean lower pulse rate in the treatment naïve group. Our results suggest that diastolic dysfunction (both left and right sided) may have a higher prevalence in systemic treatment naïve patients. This is probably because of the anti-inflammatory property of the systemic agents to the pericardium, myocardium, cardiac conducting system and both the macro and micro vasculature of the cardiovascular system as well. The most common systemic treatment used in our setting is methotrexate which is known to be a potent anti inflammatory agent. Methotrexate has been associated with reduced risk of cardiovascular disease events in patients with rheumatoid arthritis by reducing disease specific outcomes and collateral damage such as atherosclerosis. Prodanowich et al showed that methotrexate therapy reduced the incidence of vascular disease in veterans with psoriasis or rheumatoid arthritis, most likely due to its anti inflammatory effect. The resultant of other therapies as protection against cardiac disease has not been fully investigated yet, but the author assumes that side effects like hypertension (seen with cyclosporine) or dyslipidaemia (seen with acitretin) will be negatively influencing the anti-inflammatory effects.

Only about 30% of patients with psoriasis in our cohort had psoriatic arthropathy (PsA). The only parameter with a statistically significant difference between those with arthropathy and without was the tricuspid valve E/A ratio. The mean tricuspid valve E/A ratio in patients with arthritis is significantly lower i.e. 1.3 compared to 1.5 in the other group. This may not be clinically significant as the absolute value is very small, but it may also represent very early right ventricular dysfunction in this group of patients. An E/A ratio of less than 1 is consistent with grade 1 diastolic dysfunction. Whether or not these patients will progress to grade 1 diastolic dysfunction cannot be predicted at this stage. Interestingly, 10% of patients with PsA had right ventricular diastolic dysfunction noted on the echocardiogram compared to 5% of patients without PsA, but this difference was not statistically significant. To the best of the author’s knowledge, there have been no previous studies that have compared the tricuspid valve E/A ratio between patients with and without joint manifestations of psoriasis. However, clinicians managing PsA patients should be aware of the above results. Symptoms suggestive of “pre” right heart failure warrant an early cardiology referral.

The small study by Saricaoglu et al consisting of 21 patients with psoriatic arthropathy found that mild left ventricular diastolic dysfunction may accompany PsA and was related to the duration of psoriasis. No mention was made about right ventricular diastolic dysfunction. Rowe et al also reported lower mitral E/A ratios consistent with diastolic dysfunction in 11 PsA subjects compared to controls. They postulated that the most likely cause of these abnormalities was an increased connective tissue deposition in the myocardium. Gonzalez-Juanetey et al assessed the prevalence of echocardiographic and Doppler abnormalities in 50 PsA patients without clinically evident cardiovascular manifestations or classic atherosclerosis risk factors and compared them to controls. There were no significant differences
between both groups.

As mentioned above, in our study, the overall prevalence of left ventricular diastolic dysfunction was higher among the psoriasis group, with or without PsA; compared to controls. Our results also suggest the presence of possible early left ventricular diastolic dysfunction which has a statistically significant higher prevalence in the psoriasis group compared to controls. Hence, indirectly perhaps, our results do somewhat concur with previous studies by Saricaoglu et al12 and Rowe et al.13 The patient selection by Gonzalez-Juanetey et al might have contributed to their results.9 They selected patients with PsA who were actively being treated by the rheumatology team in their hospital for the disease. As we know, most DMARDs and NSAIDs result in reduced inflammation which is believed to be the main culprit in the pathogenesis of cardiac abnormalities in psoriasis. The active management of the arthritis most likely led to reduced systemic as well as cardiac inflammation which then resulted in no significant findings on the echocardiogram between the two groups.

Another study with a similar design to the current study i.e. looking at a small cohort of patients with psoriasis and comparing those with and without arthropathy was done by Pines et al.14 Most of their 25 PsA patients had peripheral joint disease, similar to our cohort. Axial disease was present in 12% of their cohort and 10% of ours. They found that 56% of their patients with PsA had mitral valve prolapse (MVP). In our study however, no PsA patient had mitral valve prolapse compared to 2.1% of patients without PsA. MVP was present in 6.4% of their psoriatic patients without arthritis. These findings suggest that in their population as a whole, the prevalence of mitral prolapse is higher. Some studies have estimated the prevalence of MVP in the general population at 5-15% or even higher59,60 but most of these studies have been done in Caucasian populations with a different geno-phenotype compared to our population. In addition, no aortic valve lesion were detected in their cohort of patients where as we found aortic regurgitation in 10% of PsA patients and 5.3% of patients without PsA. This further leads the author to postulate that there may be a geno-phenotypic element that influences the development of valvular problems; in addition to the chronic inflammatory state of psoriasis.

Patients with PsA have increased HLA-B locus antigens, including B27. The presence of HLA-B27 correlates best with axial arthritis involvement. The cardiac manifestations of the prototypical B27 arthropathy include aortitis and conduction system disorders.15 Bergfeldt et al61 postulated that the HLA-B27 antigen itself may be pathogenic to the development of conduction system abnormalities. Feld et al, in their study of cardiac conduction disturbances of psoriasis arthritis patients; noted a significantly longer PR interval in patients with PsA compared to controls15. The study has identified the possible subtle AV node involvement in PsA as observed by the prolonged PR interval. The mean PR interval of the PsA patients in our study was noted to be longer than the patients without PsA but this was not statistically significant. Biyik et al18 noted that longer disease duration was significantly associated with (i) a higher incidence of left ventricular diastolic dysfunction; (ii) a higher systolic blood pressure and (iii) a higher diastolic blood pressure. There were no other significant associations between psoriasis disease duration and other echocardiographic or clinical abnormalities in their study. Saricaoglu et al also showed that the incidence of left ventricular diastolic dysfunction was significantly related to the duration of the disease.12 Gunes et al on the other hand did not observe any significant correlations between the disease duration and abnormalities noted on the echocardiogram or 24 hour ambulatory holter monitoring in their study.8 Gonzalez-Juanetey et al found no correlation between disease duration and diastolic dysfunction in their study either.9 Again, the findings were limited by the small patient numbers. Markuszeski et al commented that there was no correlation between psoriasis duration and arrhythmia incidence in their study.7 Feld et al found no correlation between the PR intervals on the ECG with disease duration in their cohort of 92 patients with psoriatic arthritis.15 Our study identified a weak positive correlation between the duration of disease and the PR interval on the ECG, the left ventricular IVRT and the ascending aorta diameter. The weak correlation suggests that the etiology of the prolonged PR interval is multifactorial and heterogeneous. Disease duration is most likely is minor contributing factor only.

The positive correlation between the ascending aorta diameter and disease duration can most likely be explained by the chronic inflammatory state as well. Aortic dilatation, seen in aortitis is a known complication of chronic inflammation. However, other causes of aortic dilatation in patients with psoriasis include atherosclerotic disease and degenerative dilatation.51 Degenerative dilatation
occurs with age and it is a well-established fact that psoriasis is associated with accelerated atherosclerosis as well as macrovascular and microvascular endothelial dysfunction. The presence of this other factors may be the reason that the correlation between disease duration and ascending aorta diameter is weak.

Left ventricular IVRT and mitral valve E/A are markers of left ventricular diastolic dysfunction. The increase of left ventricular IVRT and decrease of the mitral valve E/A as the duration of psoriasis increases in our study is in keeping with the studies done by Biyik et al and Saricaoglu et al. Both noted that disease duration significantly correlates with left ventricular diastolic dysfunction. However, the weak correlation found in our study again suggests a multifactorial etiology of diastolic dysfunction in patients with psoriasis that includes high blood pressure, ischaemia and atherosclerosis.

Looking at the actual duration of the disease, we found a statistically significant difference of a few echocardiogram parameters between patients who had psoriasis for duration of > 10 years compared to patients who had the disease for ≤ 10 years. Our results suggest that after >10 years of disease, the risk of left and right diastolic dysfunction and aortic abnormalities is higher. Therefore, the author strongly recommends that the attending dermatologists or clinicians screen their patients who have had psoriasis for more than ten years for cardiac abnormalities, even if symptoms are absent.

We acknowledge a few limitations in our study. Although the power of the study was achieved, this study still had a relatively small number of subjects, particularly in the > 60-year-old age group. There is no assessment of cardiac abnormalities in patients less than 18 years old.

Inflammation indices were not measured and thus no direct correlation based on disease activity could be imputed. Regrettably the QT intervals were not studied in this study. QT intervals represent global ventricular electrical repolarization. Any slightest change in QT interval signifies subtle subclinical cardiac manifestation in various conditions. A 24-hours holter measurement or a rhythm card would be a preferred method of assessing conduction abnormalities rather than an electrocardiogram. The use of E and A wave measurement in echocardiogram is one of many techniques in determining diastolic function. Newer techniques such as Tissue Doppler Imaging (TDI) or Strain and Strain rate are shown to be more accurate, either used on its own or in combination. However, due to logistic reasons and limited resources, these could not be done for this study but are excellent starting points for similar future research.

Conclusion
Our study supports that the view psoriasis affects the heart not only from an increased cardiovascular risk point of view, but also in terms of structural and conduction abnormalities. Psoriasis may be associated with high blood pressure, increased risk of cardiac abnormalities suggesting diastolic dysfunction and tricuspid regurgitation. These abnormalities appear to be related to disease duration. There may an association between the PASI and BSA scores with the left atrial diameter and the left ventricular posterior wall diastolic thickness on the echocardiogram, perhaps suggesting that the higher degree of inflammation in more severe disease may contribute to the development of early diastolic dysfunction. Further studies employing newer echocardiographic and cardiac imaging techniques are needed to validate this.

The findings of this study regarding cardiac abnormalities in psoriasis and previous studies that have established that psoriasis is an independent risk factor for cardiovascular disease suggest to us that cardiac disease is a source of mortality and morbidity in patients with psoriasis. Therefore, dermatologists and physicians must be aware of the cardiac and cardiovascular manifestations of psoriasis. History taking and a physical examination related to the cardiovascular system must be incorporated into consultations and follow up appointments with psoriasis patients including a simple ECG. In addition, the authors recommend that the attending dermatologists or clinicians screen their patients who have had psoriasis for more than ten years for cardiac abnormalities, even if symptoms are absent.

Conflict of Interest Declaration
The authors hereby certify that, to the best of our knowledge, the work which is reported on in said manuscript has not received financial support from any pharmaceutical company or other commercial source and neither us nor any first degree relatives have any special financial interest in the subject matter discussed in said manuscript.
Acknowledgement
The author would like to thank the Deputy Director General of Health, Malaysia (Datu Dr Jeyaindran Tan Sri Sinnadurai) for all his guidance and support. The author would also like to thank the Director General of Health, Malaysia for permission to publish this paper.

Table 1. Demographic data and clinical characteristics of the study population.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patients n=135</th>
<th>Controls n=135</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean age in years (SD)</td>
<td>40.24± 12.9</td>
<td>40.55 ± 12.7</td>
<td>0.52</td>
</tr>
<tr>
<td>Age group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤40</td>
<td>76 (56.3%)</td>
<td>76(56.3%)</td>
<td>1.0</td>
</tr>
<tr>
<td>41-60</td>
<td>49 (36.3%)</td>
<td>49(36.3%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 61</td>
<td>10 (7.4%)</td>
<td>10(7.4%)</td>
<td></td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>75(55.5%)</td>
<td>75(55.5%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Female</td>
<td>60(44.5%)</td>
<td>60(44.5%)</td>
<td></td>
</tr>
<tr>
<td>Body Mass Index, (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>25.7(3.5)</td>
<td>24.5(3.6)</td>
<td>0.01</td>
</tr>
<tr>
<td>Random capillary blood sugar,(mmol/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5.8(1.9)</td>
<td>5.6(1.6)</td>
<td>0.51</td>
</tr>
<tr>
<td>Mean blood pressure in mmHg (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>128.8(16.5)</td>
<td>124.2(15.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Diastolic</td>
<td>80.4(10.9)</td>
<td>74.6(9.5)</td>
<td>0.00</td>
</tr>
<tr>
<td>Mean heart rate in beats per minute (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>76(13.0)</td>
<td>73(10.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>Mean duration of disease in years (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.1(8.0)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean body surface area involvement in % (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>12.3(18.4)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Mean PASI (SD)</td>
<td>7.6(7.2)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Presence of nail psoriasis,n (%)</td>
<td>105 (77.7%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Presence of psoriatic arthropathy, n(%)</td>
<td>40 (29.6%)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A: not applicable
Mean values between psoriasis and controls were compared using independent samples t-test. Comparison of categorical variables was performed using Chi-square test for independence. p value <0.05.

Table 2. Management of the psoriasis patients (n=135).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Current therapy n (%)</th>
<th>Previous therapy n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Topical only</td>
<td>108(80.0)</td>
<td>85(63.0)</td>
</tr>
<tr>
<td>Systemic/Phototherapy &amp; topical</td>
<td>27 (20.0)</td>
<td>50(37.0)</td>
</tr>
<tr>
<td>Systemic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methotrexate</td>
<td>18(13.3)</td>
<td>19 (14.0)</td>
</tr>
<tr>
<td>Acitretin</td>
<td>5 (3.7)</td>
<td>(1.0)</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>0</td>
<td>(0.7)</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Biologics</td>
<td>2 (1.5)</td>
<td>0</td>
</tr>
<tr>
<td>Phototherapy</td>
<td>2 (1.5)</td>
<td>16 (11.9)</td>
</tr>
<tr>
<td>Various (patients who have received more than one systemic agent in the past, with and without phototherapy)</td>
<td>13(9.7)</td>
<td></td>
</tr>
</tbody>
</table>
Table 3. Electrocardiogram findings in patients with psoriasis and control subjects.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Psoriasis n=135</th>
<th>Controls n=135</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhythm: Sinus, n(%)</td>
<td>135</td>
<td>135</td>
<td>1.00</td>
</tr>
<tr>
<td>Atrial conduction:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial premature beats, n(%)</td>
<td>2 (1.5)</td>
<td>0</td>
<td>0.25</td>
</tr>
<tr>
<td>Left ventricular hypertrophy, n(%)</td>
<td>5 (3.7)</td>
<td>0</td>
<td>0.02</td>
</tr>
<tr>
<td>Right ventricular hypertrophy, n(%)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Left atrial enlargement, n(%)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Right atrial enlargement, n(%)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>RBBB, n(%)</td>
<td>9 (6.7)</td>
<td>2 (1.5)</td>
<td>0.03</td>
</tr>
<tr>
<td>LBBB, n(%)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Left anterior hemiblock, n(%)</td>
<td>1 (0.7)</td>
<td>0</td>
<td>0.32</td>
</tr>
<tr>
<td>Left posterior hemiblock, n(%)</td>
<td>0</td>
<td>0</td>
<td>0.16</td>
</tr>
<tr>
<td>Ventricular Conduction:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ventricular premature beats, n(%)</td>
<td>2 (1.5)</td>
<td>0</td>
<td>1.56</td>
</tr>
<tr>
<td>Ischaemic changes, n(%)</td>
<td>10 (7.4)</td>
<td>1 (0.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Pulse Rate, (Mean, SD)</td>
<td>76 (13.0)</td>
<td>73 (10.0)</td>
<td>0.07</td>
</tr>
<tr>
<td>AV conduction:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PR interval, ms (Mean, SD)</td>
<td>149.2 (22.2)</td>
<td>148.4 (22.1)</td>
<td>0.78</td>
</tr>
<tr>
<td>Ventricular Conduction:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QRS interval, ms (Mean, SD)</td>
<td>73.2 (16.8)</td>
<td>78.0 (14.3)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Mean values between groups were compared using independent samples t-test. Comparison of categorical variables was performed using Chi-square test for independence. p value <0.05 is significant.

Table 4. Two Dimensional and Doppler echocardiogram measurements of patients with psoriasis and control subjects.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Psoriasis n=135</th>
<th>Controls n=135</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left atrial measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial diameter, mm (SD)</td>
<td>30.3 (5.1)</td>
<td>29.6 (4.7)</td>
<td>0.19</td>
</tr>
<tr>
<td>Left ventricular measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End systolic diameter, mm (SD)</td>
<td>27.1 (3.8)</td>
<td>27.2 (3.3)</td>
<td>0.79</td>
</tr>
<tr>
<td>End diastolic diameter, mm (SD)</td>
<td>43.2 (5.8)</td>
<td>44.3 (5.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>Interventricular septum diastolic thickness, mm (SD)</td>
<td>8.7 (1.6)</td>
<td>8.6 (1.4)</td>
<td>0.81</td>
</tr>
<tr>
<td>Posterior wall diastolic thickness, mm (SD)</td>
<td>8.6 (1.7)</td>
<td>8.1 (1.5)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ejection fraction, (%)</td>
<td>66.8 (5.8)</td>
<td>67.4 (5.0)</td>
<td>0.37</td>
</tr>
<tr>
<td>Hypertrophy (n, %)</td>
<td>3 (2.2)</td>
<td>5 (3.7)</td>
<td>0.47</td>
</tr>
<tr>
<td>Wall motion abnormalities (n, %)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>-</td>
</tr>
<tr>
<td>Mitral valve inflow measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early filling velocity (E), cm/s (SD)</td>
<td>0.7 (0.2)</td>
<td>0.7 (0.2)</td>
<td>0.54</td>
</tr>
<tr>
<td>Late filling velocity (A), cm/s (SD)</td>
<td>0.5 (0.2)</td>
<td>0.5 (0.2)</td>
<td>0.19</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.40 (0.5)</td>
<td>1.50 (0.5)</td>
<td>0.30</td>
</tr>
<tr>
<td>Early filling velocity deceleration time, ms (SD)</td>
<td>187.9 (44.2)</td>
<td>185.2 (41.8)</td>
<td>0.60</td>
</tr>
<tr>
<td>Isovolumetric relaxation time, ms (SD)</td>
<td>93.2 (20.8)</td>
<td>87.9 (18.9)</td>
<td>0.03</td>
</tr>
<tr>
<td>Diastolic dysfunction of the left ventricle (n, %)</td>
<td>7 (5.2)</td>
<td>5 (3.7)</td>
<td>0.56</td>
</tr>
<tr>
<td>Tricuspid valve inflow measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early filling velocity (E), cm/s (SD)</td>
<td>0.5 (0.5)</td>
<td>0.5 (0.1)</td>
<td>0.57</td>
</tr>
<tr>
<td>Late filling velocity (A), cm/s (SD)</td>
<td>0.4 (0.1)</td>
<td>0.4 (0.1)</td>
<td>0.73</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.5 (0.4)</td>
<td>1.5 (0.5)</td>
<td>0.39</td>
</tr>
<tr>
<td>Pressure half time, ms (SD)</td>
<td>63.7 (22.8)</td>
<td>57.6 (13.8)</td>
<td>0.20</td>
</tr>
<tr>
<td>Diastolic dysfunction of the right ventricle (n, %)</td>
<td>7 (5.2)</td>
<td>3 (2.2)</td>
<td>0.19</td>
</tr>
<tr>
<td>Aortic measurements</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annulus, mm (SD)</td>
<td>19.2 (2.3)</td>
<td>18.5 (2.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Ascending aorta, mm (SD)</td>
<td>24.8 (3.2)</td>
<td>24.3 (3.0)</td>
<td>0.27</td>
</tr>
</tbody>
</table>
Mean values between groups were compared using independent samples t-test. Comparison of categorical variables was performed using Chi-square test for independence. p value <0.05 is significant.

Table 5. The association of electrocardiographic and echocardiogram parameters with BSA and PASI in psoriasis patients, n=135.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>BSA (Mean, SD)</th>
<th>p-value</th>
<th>PASI (Mean, SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Electrocardiographic findings</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11.6(8.1)</td>
<td>0.89</td>
<td>8.8(5.7)</td>
<td>0.53</td>
</tr>
<tr>
<td>No</td>
<td>12.4(19.0)</td>
<td></td>
<td>7.5(7.3)</td>
<td></td>
</tr>
<tr>
<td>Ventricular premature beats</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12.0(11.3)</td>
<td>0.90</td>
<td>9.5(7.7)</td>
<td>0.79</td>
</tr>
<tr>
<td>No</td>
<td>12.3(18.5)</td>
<td></td>
<td>7.6(7.2)</td>
<td></td>
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<tr>
<td>Atrial premature beats</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>41.5(54.4)</td>
<td>0.58</td>
<td>14.0(15.6)</td>
<td>0.66</td>
</tr>
<tr>
<td>No</td>
<td>11.9(17.5)</td>
<td></td>
<td>7.5(7.1)</td>
<td></td>
</tr>
<tr>
<td>Left ventricular hypertrophy</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10.2(7.5)</td>
<td>0.79</td>
<td>8.1(3.4)</td>
<td>0.78</td>
</tr>
<tr>
<td>No</td>
<td>12.4(18.7)</td>
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<td>7.7(7.3)</td>
<td></td>
</tr>
<tr>
<td>Right bundle branch block</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>17.7(26.3)</td>
<td>0.37</td>
<td>9.5(7.8)</td>
<td>0.41</td>
</tr>
<tr>
<td>No</td>
<td>11.9(17.8)</td>
<td></td>
<td>7.5(7.1)</td>
<td></td>
</tr>
<tr>
<td>Left anterior hemiblock</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6</td>
<td>0.73</td>
<td>4.8</td>
<td>0.69</td>
</tr>
<tr>
<td>No</td>
<td>12(18.4)</td>
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<td>7.6(7.2)</td>
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</tr>
<tr>
<td><strong>Echocardiographic findings</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Left ventricular hypertrophy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4.2(2.1)</td>
<td>0.45</td>
<td>4.1(0.7)</td>
<td>0.39</td>
</tr>
<tr>
<td>No</td>
<td>12.5(18.6)</td>
<td></td>
<td>7.7(7.2)</td>
<td></td>
</tr>
<tr>
<td>Diastolic dysfunction of the left ventricle</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3.5(4.4)</td>
<td>0.93</td>
<td>3.2(0.5)</td>
<td>0.17</td>
</tr>
<tr>
<td>No</td>
<td>1</td>
<td></td>
<td>7.8(7.3)</td>
<td></td>
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<tr>
<td>Diastolic dysfunction of the right ventricle</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>4.9(2.9)</td>
<td>0.27</td>
<td>4.4(1.7)</td>
<td>0.23</td>
</tr>
<tr>
<td>No</td>
<td>12.8(18.8)</td>
<td></td>
<td>7.8(7.3)</td>
<td></td>
</tr>
<tr>
<td>Mitral valve prolapse</td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Yes</td>
<td>2.5(0.7)</td>
<td>0.44</td>
<td>4.8(1.6)</td>
<td>0.57</td>
</tr>
<tr>
<td>No</td>
<td>12.5(18.5)</td>
<td></td>
<td>7.6(7.2)</td>
<td></td>
</tr>
<tr>
<td>Mitral valve regurgitation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>18.9(23.2)</td>
<td>0.30</td>
<td>12.2(11.9)</td>
<td>0.06</td>
</tr>
<tr>
<td>No</td>
<td>11.9(18.1)</td>
<td></td>
<td>7.3(6.7)</td>
<td></td>
</tr>
<tr>
<td>Tricuspid regurgitation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>14.0(28.6)</td>
<td>0.78</td>
<td>7.6(6.8)</td>
<td>0.88</td>
</tr>
<tr>
<td>No</td>
<td>12.2(17.6)</td>
<td></td>
<td>7.6(6.9)</td>
<td></td>
</tr>
<tr>
<td>Aortic regurgitation</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>6(5.6)</td>
<td>0.29</td>
<td>5.5(3.8)</td>
<td>0.36</td>
</tr>
<tr>
<td>No</td>
<td>12.8(18.9)</td>
<td></td>
<td>7.7(7.3)</td>
<td></td>
</tr>
</tbody>
</table>
Table 6. Two Dimensional and Doppler echocardiogram measurements of psoriasis patients based on disease duration of ≤ 10 years and > 10 years

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Duration≤10 years, N=69 (Mean, SD)</th>
<th>Duration&gt;10 years, N=66 (Mean, SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left atrial measurements:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left atrial diameter, mm</td>
<td>29.9(4.7)</td>
<td>30.7(5.4)</td>
<td>0.38</td>
</tr>
<tr>
<td><strong>Left ventricular measurements:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>End systolic diameter, mm</td>
<td>27.2(2)</td>
<td>26.9(3.8)</td>
<td>0.76</td>
</tr>
<tr>
<td>End diastolic diameter, mm</td>
<td>43.5(6.3)</td>
<td>42.9(5.3)</td>
<td>0.59</td>
</tr>
<tr>
<td>Interventricular septum diastolic thickness, mm</td>
<td>8.7(1.6)</td>
<td>8.7(1.6)</td>
<td>0.93</td>
</tr>
<tr>
<td>Posterior wall diastolic thickness, mm</td>
<td>8.6(1.8)</td>
<td>8.7(1.6)</td>
<td>0.72</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>67.2(6.0)</td>
<td>66.5(5.7)</td>
<td>0.48</td>
</tr>
<tr>
<td>Hypertrophy (n, %)</td>
<td>2(2.9)</td>
<td>1(1.5)</td>
<td>1.00</td>
</tr>
<tr>
<td>Wall motion abnormalities (n, %)</td>
<td>0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td><strong>Mitral valve inflow measurements:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early filling velocity (E), cm/s</td>
<td>0.7(0.2)</td>
<td>0.6(0.2)</td>
<td>0.01</td>
</tr>
<tr>
<td>Late filling velocity (A), cm/s</td>
<td>0.5(0.1)</td>
<td>0.5(0.2)</td>
<td>0.25</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.5(0.5)</td>
<td>1.3(0.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Early filling velocity deceleration time, ms</td>
<td>190.6(47.8)</td>
<td>185.2(40.2)</td>
<td>0.49</td>
</tr>
<tr>
<td>Isovolumetric relaxation time, ms</td>
<td>91.2(21.7)</td>
<td>95.4(19.4)</td>
<td>0.24</td>
</tr>
<tr>
<td><strong>Diastolic dysfunction of the left ventricle (n, %)</strong></td>
<td>4(5.8)</td>
<td>1(1.5)</td>
<td>0.37</td>
</tr>
<tr>
<td><strong>Tricuspid valve inflow measurements:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early filling velocity (E), cm/s</td>
<td>0.5(0.1)</td>
<td>0.6(0.7)</td>
<td>0.52</td>
</tr>
<tr>
<td>Late filling velocity (A), cm/s</td>
<td>0.3(0.1)</td>
<td>0.3(0.2)</td>
<td>0.11</td>
</tr>
<tr>
<td>E/A ratio</td>
<td>1.5(0.4)</td>
<td>1.49(0.4)</td>
<td>0.02</td>
</tr>
<tr>
<td>Pressure half time, ms</td>
<td>62.2(23.6)</td>
<td>63.1(22.1)</td>
<td>0.82</td>
</tr>
<tr>
<td><strong>Diastolic dysfunction of the right ventricle (n, %)</strong></td>
<td>3(4.3)</td>
<td>4(6.1)</td>
<td>0.71</td>
</tr>
<tr>
<td><strong>Aortic measurements:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Annulus, mm</td>
<td>18.9(2.3)</td>
<td>19.5(2.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Ascending aorta, mm</td>
<td>24.1(3.1)</td>
<td>25.5(3.3)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Mean values between groups were compared using independent samples t-test. Comparison of categorical variables was performed using Chi-square test for independence. p value <0.05 is significant.

References


63. Suran D, Sinkovic A, Naji F. Tissue Doppler imaging is a sensitive echocardiographic technique to detect subclinical systolic and diastolic dysfunction of both ventricles in type 1 diabetes mellitus. BMC Cardiovasc Disord 2016;16:72-81.
ORIGINAL ARTICLE

Liquid Nitrogen Cryotherapy Versus 20% Salicylic Acid Ointment for the Treatment of Plantar Warts – A Randomized Trial

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Abstract

Introduction:
Cryotherapy and salicylic acid ointment are the two most common treatments used for treating plantar warts. The aim of this study is to compare the clearance rate of plantar warts at 12 weeks between liquid nitrogen cryotherapy and 20% salicylic acid ointment.

Methods:
Patients with plantar warts were randomized into cryotherapy and 20% salicylic acid groups. Patients assigned into cryotherapy group received a maximum of four treatments given two weeks apart. Patients recruited into 20% salicylic acid group were instructed to apply the salicylic acid ointment onto the wart nightly and to cover the treated area with a hypoallergenic plaster. Both groups were also provided with a personal foot file to thin out the surrounding callus daily at home. Digital pictures were taken at first visit and 12 weeks after enrolment to assess the resolution of plantar wart.

Results:
Eighty patients with plantar warts were included. Thirty-nine patients were randomized into cryotherapy group and forty-one patients were randomized into 20% salicylic acid ointment group. Thirteen (33.3%) patients had a complete clearance of the warts with cryotherapy whereas eleven (26.8%) patients had a complete clearance of the warts with topical 20% salicylic acid ointment (p=0.526). Nine patients were lost to follow-up. With cryotherapy, two patients reported blister formation and one patient developed hyperpigmentation. No side effects were reported with 20% salicylic acid ointment.

Conclusion:
There is no difference in effectiveness between cryotherapy and 20% salicylic acid ointment in the treatment of plantar wart.

Key words: Plantar wart, Cryotherapy, salicylic acid

Introduction
Cutaneous warts are caused by human papilloma virus (HPV). Over 200 types of papillomaviruses have been identified and have been completely sequenced, including more than 150 types of HPV. An incubation period of 3 weeks to 8 months can occur before lesions become apparent, depending on inoculation. Inoculations are more common if there is a break in the skin barrier such as in atopic dermatitis and also at sites where there is regular
frictions and traumas such as on the palms and soles.\(^4\)

A plantar wart has the typical appearance of a sharply demarcated, rounded lesion, with a rough, keratotic surface surrounded by a smooth collar of thickened horn. The small tortuous capillary loops in the most superficial layer of papillary dermis can also become damaged and thrombosed in the presence of cutaneous HPV infection and paring of the surface will reveal small bleeding points. This feature distinguishes warts from calluses, which may present with hyperkeratotic stratum corneum but lacks the appearance of these small bleeding points. With localized spread of the infection, there may be satellite lesions, which are lesions erupting near the site of a longstanding wart. Multiple lesions may also coalesce to form a single mosaic wart, which is often resistant to treatment.

HPV1 and 4 are frequently the cause of plantar warts, although HPV57, 60, 63, 65, and 66 can also be involved.\(^5\) HPV1 is more commonly associated with a painful lesion that manifests as a keratotic plug surrounded by a hyperkeratotic rim.\(^5\) HPV4 on the other hand causes mosaic warts, which are more superficial lesions that occur in a confluent cobblestone pattern and are usually painless.\(^6\)

Salicylic acid and cryotherapy have been used to treat plantar warts for more than 20 years and these are the two most commonly prescribed treatments for plantar warts.\(^7\) This study aims to determine whether 20% salicylic acid would have the same efficacy as cryotherapy in treating plantar warts.

Materials and Methods
This is an open label, prospective, two-arm, randomized study. This study was conducted at the Dermatology Day Care Unit, Hospital Selayang and Dermatology Clinic, Hospital Kuala Lumpur from February 2014 to August 2015. The target population was patients aged 12 years and above with plantar warts attending the Dermatology Day Care Unit, Hospital Selayang and the Dermatology Clinic, Hospital Kuala Lumpur during the study period.

Inclusion criteria are patients above 12 years of age, plantar warts must have been present for at least 2 months and patients must be able to read and sign the informed consent. Exclusion criteria are patients with diabetes mellitus and peripheral vascular disease, patients who are immunosuppressed, patients with previous history of salicylate sensitivity and patients who are unable to give informed consent. Patients who were already undergoing treatment were given a 1-month wash-out period before being included in the study.

This study was funded by Department of Dermatology, Hospital Selayang and Department of Dermatology, Hospital Kuala Lumpur. Randomization was performed by assessing an online randomization programme (www.randomizer.org)

For cryotherapy, topical anaesthetic EMLA (lidocaine 2.5% and prilocaine 2.5% cream) was first applied onto the warts and left for 60 minutes. Paring was then performed with a No.10 curved blade before cryotherapy. The liquid nitrogen was applied with a cryospray (Brymill) and the size of the plantar wart determined the size of probe tip to be used. Specifically, size A probe tip was used for large lesion more than 1.0cm, size B probe tip for lesions between 0.5 and 1.0cm, and size C probe tip was used for small lesion measuring less than 0.5cm. The cryospray was directed from a 90-degree angle at a distance of 1 to 2cm from the wart and liquid nitrogen was applied to the wart until there was a 2mm halo around the wart. Two freeze-thaw cycles were used.

Patients randomized into cryotherapy group with liquid nitrogen received a maximum of four treatments given two weeks apart by the same health care professional. Patients in the cryotherapy group were also given a foot file so that they could file down the callosity surrounding the plantar wart after soaking the plantar wart in water for about 5 minutes. Filing of the callosity surrounding the warts was performed daily at home during the intervals between the cryotherapy sessions. Patients were seen during the two weekly cryotherapy sessions and at 12 weeks.

Patients randomized into self-treatment with 20% salicylic acid ointment (Xorlyx 20, manufacturer: Xorix Sdn Bhd) were taught on how to apply the treatment by a designated health care professional. The wart was soaked in water for about 5 minutes to soften the skin. A foot file was supplied to each patient and the patient was instructed to file down any callus surrounding the plantar wart every night after soaking. 20% salicylic acid ointment was then applied with their finger directly onto the wart until it covered the entire wart. After application
of the salicylic acid ointment, the treated area was completely covered with a non-medicated, waterproof and hypoallergenic plaster (Tegaderm). Treatment was left overnight for 8 hours before patient was allowed to remove the plaster and salicylic acid the next morning. The treatment regime was repeated every night for 12 weeks. Patients were seen at the beginning of the study and at 12 weeks.

Primary end point of this study was to determine the complete clearance of all plantar warts at 12 weeks after randomization. Clearance of plantar warts was defined as the restoration of normal skin on close inspection. Digital photographs of the plantar warts were taken at baseline and at the outcome assessment at week 12. The photographs taken at baseline and at week 12 were compared and assessed by two independent dermatology clinical specialists who were blinded to treatment allocation in order to determine whether the plantar wart has cleared. Should any discrepancies occur, the digital photographs were referred to a third assessor. The secondary end-point is to determine complete clearance of all plantar warts after controlling for age, duration of warts, type of warts, and whether the plantar wart had been treated before. We also sought to determine any adverse events for each of the intervention groups and to compare the number of plantar warts at 12 weeks between the two treatment groups with adjustment for the number of plantar warts at baseline.

All analyses were conducted on an intention-to-treat basis. Analyses were conducted using the SPSS version 22, using two-sided significance tests at 5% significance level. Independent T-test was used to compare the mean age between cryotherapy and salicylic acid ointment groups. Chi-square test was used to compare the clearance rate between cryotherapy and salicylic acid ointment groups. Fisher’s exact test was used when the frequency of one or more of the cells were less than five. Mann-Whitney U test was used to compare the number of plantar warts at baseline between cryotherapy and salicylic acid ointment groups. Cohen’s kappa was used to assess the agreement between the two assessors of the photographs, to indicate whether patient had complete or incomplete response. Logistic regression analysis was used to look for associated factors that could influence the rate of clearance between the cryotherapy and salicylic acid ointment groups.

Comparison between the mean number of warts at 12 weeks between the two treatment groups before and after adjusting for the mean number of warts at baseline was performed. Analysis of covariance (ANCOVA) was used to allow comparison between the mean numbers of warts at 12 weeks after taking into account of the number of warts at baseline.

Results

This study was conducted from February 2014 to August 2015. Eighty five patients were diagnosed with plantar warts; with 80 patients fulfilling the inclusion and the exclusion criteria defined by the study. These 80 patients were randomly allocated to cryotherapy (n=39) and 20% salicylic acid ointment (n=41). Five patients with plantar warts were excluded from the study. One of the patients excluded had underlying systemic lupus erythematosus and was taking oral prednisolone, 3 of the patients have diabetes mellitus and 1 patient refused to join the study.

Demographic and baseline characteristics of the patients are shown in Table 1. There was no statistically significant difference between the two treatment groups in terms of their mean age, gender and ethnicity. Overall, 46% of patients had sought treatment prior to participating in this study. More patients in the cryotherapy group had previous treatment for their plantar warts (59%) compared to those in the salicylic acid group (34.1%) and this difference is statistically significant (p=0.026). Prior treatments consisted of topical salicylic acid of various concentrations (2% to 20%) and cryotherapy.

For the topical salicylic acid, treatments were obtained from retail pharmacy, primary care clinic and from hospital setting and they were in the form of wart paint, ointment and plaster impregnated with salicylic acid. Previous cryotherapy sessions were performed in hospital setting and the intervals between cryotherapy sessions varied between 2 weeks interval to 8 weeks interval.
Table 1. Demographic and baseline characteristics between patients presented with plantar warts randomized to either cryotherapy or salicylic acid treatment

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Overall (n=80)</th>
<th>Salicylic acid (n=41)</th>
<th>Cryotherapy (n=39)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (SD)</td>
<td>36.11 (17.39)</td>
<td>34.44 (17.13)</td>
<td>37.87 (17.72)</td>
<td>0.381a</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>35 (43.8%)</td>
<td>18 (43.9%)</td>
<td>17 (43.6%)</td>
<td>0.978b</td>
</tr>
<tr>
<td>Female</td>
<td>45 (56.2%)</td>
<td>23 (56.1%)</td>
<td>22 (56.4%)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>57 (71.2%)</td>
<td>28 (68.3%)</td>
<td>29 (74.4%)</td>
<td>0.822c</td>
</tr>
<tr>
<td>Chinese</td>
<td>11 (13.8%)</td>
<td>6 (14.6%)</td>
<td>5 (12.8%)</td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>12 (15.0%)</td>
<td>7 (17.1%)</td>
<td>5 (12.8%)</td>
<td></td>
</tr>
<tr>
<td>Number of plantar warts per participant</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.63 (4.36)</td>
<td>3.95 (5.16)</td>
<td>3.28 (3.36)</td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td>2 (1-24)</td>
<td>2 (1-24)</td>
<td>2 (1-17)</td>
<td>0.657c</td>
</tr>
<tr>
<td>Duration of warts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>33 (41.2%)</td>
<td>20 (48.8%)</td>
<td>13 (33.3%)</td>
<td>0.372e</td>
</tr>
<tr>
<td>1-2 years</td>
<td>31 (38.8%)</td>
<td>14 (34.1%)</td>
<td>17 (43.6%)</td>
<td></td>
</tr>
<tr>
<td>&gt;2 years</td>
<td>16 (20%)</td>
<td>7 (17.1%)</td>
<td>9 (23.1%)</td>
<td></td>
</tr>
<tr>
<td>Predominant types of plantar warts, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mosaic</td>
<td>15 (18.8%)</td>
<td>5 (12.2%)</td>
<td>10 (25.6%)</td>
<td>0.124f</td>
</tr>
<tr>
<td>Non mosaic</td>
<td>65 (81.2%)</td>
<td>36 (87.8%)</td>
<td>29 (74.4%)</td>
<td></td>
</tr>
<tr>
<td>Previous treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.026f</td>
</tr>
<tr>
<td>Yes</td>
<td>37 (46.2%)</td>
<td>14 (34.1%)</td>
<td>23 (59.0%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>43 (53.8%)</td>
<td>27 (65.9%)</td>
<td>16 (41.0%)</td>
<td></td>
</tr>
<tr>
<td>Reason for seeking plantar warts treatment, n (%)</td>
<td></td>
<td></td>
<td></td>
<td>0.941f</td>
</tr>
<tr>
<td>Pain</td>
<td>72 (90%)</td>
<td>37 (90.2%)</td>
<td>35 (89.7%)</td>
<td></td>
</tr>
<tr>
<td>Cosmetic &amp; others</td>
<td>8 (10%)</td>
<td>4 (9.8%)</td>
<td>4 (10.3%)</td>
<td></td>
</tr>
</tbody>
</table>

aIndependent T-test   b Chi Square test   c Mann Whitney U test   d Fisher’s exact test SD standard deviation.

The unit of analysis for clearance is taken as the patient rather than the individual wart. A participant was considered cured when all warts present at baseline were gone at follow-up. This outcome is shown in Figure 1. Overall, 24 of the 80 (30.0%) patients had complete clearance of their plantar warts at 12-weeks. There were 13 (33.3%) patients with completely cleared plantar warts in the cryotherapy group as compared to 11 (26.8%) patients from the topical 20% salicylic acid ointment. This difference was not statistically significant (P = 0.526).

Figure 1. Response to treatments at 12-weeks
Cohen’s kappa is an index that measures inter-rater agreement for categorical items. In this study, it was used to assess the agreement between the two assessors of the photographs, to indicate whether patient had complete or incomplete response. The agreement was estimated to be 0.76 (95% confidence interval 0.61 to 0.91; p<0.001), which indicates a good level of agreement.

A logistic regression model was used to adjust the primary analysis for important prognostic variables (Table 2). These variables include age, duration of warts, whether the plantar warts had been previously treated (yes or no) and the type of plantar warts (mosaic or non-mosaic). For secondary analysis, patients were divided into 2 categories; age of 12 years to 19 years, and age of 20 years or more. This study found no difference in the rate of clearance of plantar warts between the two age categories, duration of warts, type of warts, and whether patients had received prior treatment for their plantar warts.

Both treatments were well-tolerated with only 3 patients developing adverse events while having treatment with cryotherapy. Two patients had blisters after cryotherapy. The blisters were already ruptured by the time patient came back for a review. One patient developed post inflammatory hyperpigmentation after cryotherapy. The adverse events were not categorized as serious and did not warrant withdrawal from the study. There was no reported severe adverse event with cryotherapy. There was no reported adverse event with salicylic acid such as maceration.

When the comparison of the number of warts at week 12 was made without controlling for number of warts at baseline, there was no significance difference in the mean number of warts at week 12 between the two treatment groups (p=0.751). Similar finding was reported after controlling for the number of warts at baseline (p=0.550).

### Table 2. Factors associated with complete clearance of plantar warts between the two treatment groups

<table>
<thead>
<tr>
<th>Factors</th>
<th>Simple Logistic Regression</th>
<th>Multiple Logistic Regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Crude OR*</td>
<td>95% CI*</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-19</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>≥20</td>
<td>1.04</td>
<td>0.32,3.35</td>
</tr>
<tr>
<td>Duration of warts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1 year</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>1-2 years</td>
<td>0.51</td>
<td>0.17,1.54</td>
</tr>
<tr>
<td>≥2 years</td>
<td>0.80</td>
<td>0.22,2.84</td>
</tr>
<tr>
<td>Predominant types of warts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non mosaic</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Mosaic</td>
<td>0.13</td>
<td>0.02,1.06</td>
</tr>
<tr>
<td>Previous treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>No</td>
<td>0.64</td>
<td>0.24,1.66</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>0.73</td>
<td>0.28,1.91</td>
</tr>
</tbody>
</table>

*Odd Ratio  *Confidence Interval Constant=0.223.

Overall, 9 patients were lost to follow-up in this study and efforts were made to contact these patients via the telephone. 2 (4.9%) patients from the salicylic acid group were lost to follow-up. One of the patients complained about difficulty in adhering to the treatment regime whereas the other one was not contactable. 7 (17.9%) patients did not come for their follow-up from the cryotherapy group. 4 of these patients cited inability to come for the two-weekly follow-up because of their work schedule; with one of them already relocated to another state. 1 patient cited difficulty in paying the treatment fee. 2 of the other patients were not contactable. The difference between the drop-out rates is not statistically significant (p=0.084).

**Discussion**

There are numerous treatments for plantar warts and they can be divided into destructive, virucidal, antiproliferative agents and immunotherapy.\(^8\) Destructive therapy include the usage of salicylic acid, cryotherapy, laser and photodynamic therapy. Virucidal therapy includes usage of formaldehyde and glutaraldehyde. Antiproliferative agents include...
dithranol, podophyllotoxin and 5-fluorouracil. Immunotherapy includes imiquimod and contact immunotherapy with diphenylcyclopropenone/diphenocryprone (DPC) or squaric acid dibutyl ester (SADBE). The cure rates for these treatments are shown in the table below:

<table>
<thead>
<tr>
<th>Treatment modalities</th>
<th>Cure rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Salicylic acid (all preparations)</td>
<td>0-69%</td>
</tr>
<tr>
<td>Cryotherapy</td>
<td>0-69%</td>
</tr>
<tr>
<td>Pulsed dye laser</td>
<td>74%</td>
</tr>
<tr>
<td>Nd YAG laser</td>
<td>70%</td>
</tr>
<tr>
<td>Photodynamic therapy</td>
<td>75%</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>80%</td>
</tr>
<tr>
<td>Glutaraldehyde</td>
<td>72%</td>
</tr>
<tr>
<td>Dithranol</td>
<td>71%</td>
</tr>
<tr>
<td>Podophyllotoxin</td>
<td>67%</td>
</tr>
<tr>
<td>5-fluorouracil</td>
<td>95%</td>
</tr>
<tr>
<td>Diphenylcyclopropenone/diphenocryprone (DPC)</td>
<td>88%</td>
</tr>
<tr>
<td>Squaric acid dibutyl ester (SADBE)</td>
<td>58%</td>
</tr>
</tbody>
</table>

Our study found cryotherapy and 20% salicylic acid ointment were equally effective in treating plantar warts. Our results confirm the findings of three other published studies comparing cryotherapy and salicylic acid for the treatment of plantar warts.19-21

Our cure rate was 33.3% (13/39) for cryotherapy and 26.8% (11/41) for 20% salicylic acid ointment and this was found to be almost similar to Bruggink et al,20 which found that cure rates for all patients with plantar warts were 30% and 33% for cryotherapy and salicylic acid respectively.20 However, our study differed from the two other previous studies in terms of the cure rate.19, 21 Our overall cure rate is less when compared to an earlier study showing clearance rate of 58% and 41% for cryotherapy and salicylic acid, respectively.19 This difference could be attributed to the different populations recruited to the study. This previous study excluded patients with mosaic warts, patients with more than five warts and lesions outside an average diameter of 3-9mm. There were 18.8% of patients in our study patients with mosaic warts and 21.2% had more than five warts; and mosaic warts are generally regarded as more resistant to treatment. However, when compared to Cockayne et al,21 which showed 14% clearance for both cryotherapy and salicylic acid, we found our cure rate was higher. This difference could be due to the cryotherapy regime employed by our study.

Our study used two freeze-thaw cycles for each treatment, whereas cryotherapy in the study by Cockayne et al21 was not standardized. In the study by Cockayne et al,21 each centre was allowed to deliver the cryotherapy according to the site’s usual practice and the median number of cryotherapy applied was 1.5, which is lower compared to the two freeze-thaw cycles used in our study. Plantar wart is typically surrounded by callus and this callus can act as a good thermal insulator and may prevent the cellular destruction from cryotherapy. Two freeze-thaw cycles may help to alleviate this.22

Our study found that there is no difference in the complete clearance rate between the two treatments after taking into consideration their age, duration of warts, type of warts, and previous therapy. Our study recruited patients who were adolescents and adults whereby adolescent was taken as 19 and below and adults were taken as the age of 20 and above. Using World Health Organization definition, adolescence age is defined as between the ages of 10 to 19 years. We did not include patients below the age of 12 as previous study had shown that even without treatment, patients who are less than 12 years old have a 43% chance of clearing their plantar wart without treatment.20 Cockayne21 et al only included patients aged 12 years or older but this study however did not delineate further whether there is a difference in the rate of clearance between adolescent and adult patients.21

Our study found that there is no difference in the clearance rate of plantar wart between adolescent and adult patients when they were treated with 20% salicylic acid ointment and cryotherapy. Most adolescents are in the school-going age and choosing salicylic acid ointment over cryotherapy for these patients would allow for administration of treatment at home and therefore avoid disruption of their education because of the need to come to hospital for cryotherapy sessions at regular intervals.

Overall, the rate of clearance for both treatments were about 30%, which means that majority of patients (about 70%) were still not cleared of their plantar warts at 12 weeks. The response to treatment may be related to the types of warts. HPV types have been shown to influence the natural course and treatment response. Warts containing HPV 1 have shown the most distinct clinical profile, being related to children aged <12 years, plantar location, duration <6 months and to patients with < 4 warts.23 HPV 27 and HPV 57 were related to patients aged more than 12 years old, and especially to patients...
aged more than 21 years old. For plantar warts, the subgroup with HPV 1 had a favourable natural course compared to those with HPV 2, 27 and 57; with 58% spontaneously cured in patients with HPV 1 versus 7% in patients with HPV 2, 27 and 57. The higher prevalence of HPV 1 in younger patients might explain why younger patients have a higher rate of spontaneous clearance compared to adolescents and adults. This study was conducted in the Netherlands so the application of these findings to Malaysian population is still unknown. Our study only involves patient above the age of 12 years and the higher percentage of incomplete response compared to complete response (70% vs 30%) could be caused by the predominance of HPV 2, 27 and 57 in the plantar warts of our patients. However, further study is needed to confirm this.

Seventy percent of patients in our study did not have complete clearance at 12 weeks and it is important to identify which of these patients are classified as having recalcitrant warts. Recalcitrant warts can be defined as warts of more than 2 years duration and had persisted despite treatment with at least 2 different treatment modalities. In terms of availability of treatment at our local setting a more aggressive approach of cryotherapy may be employed for treating recalcitrant warts and mosaic plantar warts. Cryotherapy techniques can vary in application mode, freeze times and intervals between treatments. Freeze times for warts are defined as traditional or aggressive. Traditionally, cryotherapy is applied until the wart has a 2mm white halo around it. An aggressive or longer freeze maintains a white halo for 5-20 seconds. In a comparison between traditional freeze versus 10 seconds freeze, the longer freeze was more effective than the traditional method, although the incidence of pain and blistering is significantly greater. After thawing, a second freeze cycle has been shown to improve the cure rate in plantar warts. Paring can also improve the efficacy of cryotherapy in treating plantar warts. Standard practice is to repeat the treatment every 2-3 weeks until clearance of the warts.

Our study uses the traditional method of cryotherapy, whereby the application of cryotherapy is stopped once there is a 2mm halo around the wart. Efficacy might be improved if we adopt a more aggressive method of cryotherapy by applying the cryotherapy for 10 seconds for each cycle, as evidenced by the study done by Connolly et al. Apart from this, a combination of cryotherapy and salicylic acid may also be considered for patients presenting with recalcitrant or mosaic plantar warts and a combination of cryotherapy and 70% salicylic acid have been tried before, with a cure rate of 86%. Prophylactic quadrivalent HPV vaccine (types 6, 11, 16 and 18) has been proven to be effective in preventing HPV-associated precancerous and cancerous lesions. Specifically for plantar wart, there was a reported case of complete regression of recalcitrant plantar wart after treatment with a recombinant quadrivalent human papillomavirus vaccine, and in this case the patient had already received treatment with cryotherapy, 40% salicylic acid, topical imiquimod 5%, intralesional bleomycin, pulsed dye laser, and oral cimetidine; with no success. HPV vaccines have been proven to show cross-protection against other strains, and it is postulated that this may have caused the complete clearance of wart in this patient. Malaysia started its national HPV vaccination programme in 2010 and it is interesting to see whether this has affected the epidemiology of cutaneous HPV infection in Malaysia.

Cryotherapy and 20% salicylic acid ointment were generally well tolerated by the patients and there were only 3 patients who reported side effects to cryotherapy. Two of these patients developed blisters and 1 patient developed hyperpigmentation. There was no reported adverse event with 20% salicylic acid ointment such as maceration. These findings are similar to two previous studies, which also found that more side effects were related to cryotherapy. 20% salicylic acid ointment has been shown to be painless and maybe more cosmetically acceptable compared to cryotherapy as it does not cause side effects such as hyperpigmentation. Cryotherapy is associated with a higher cost. For the hospital, there is a higher cost associated with the healthcare professional’s time for treatment administration and the cost of the treatment itself, which included the cost of equipment and liquid nitrogen. For the patient, the cost of travelling to the hospital, parking fees and registration fees also need to be taken into consideration. Since both treatments were shown to be equally effective, the safety profile of salicylic acid and the fact that cryotherapy is more expensive makes salicylic acid a more attractive treatment for plantar warts.

There are several limitations in this study. This study did not have an arm for placebo so natural resolution
of the warts cannot be elucidated. A better designed study would include a wait-and-see treatment arm as this would allow for a control group for the study. There is also no blinding for the patients and the health care provider who administered the treatment as the two treatments used different modalities and realistic blinding cannot be achieved. Salicylic acid ointment were applied by the patients themselves so there is bound to be some variations between each individual including compliant issue with this self-applied topical treatment. We did not evaluate the effectiveness of salicylic acid treatment if it is delivered by a health care professional as this would mean a daily visit to hospital by the patient and therefore would be impractical.

Conclusion
This study showed that cryotherapy is as effective as 20% salicylic acid ointment in the treatment of plantar warts. Cryotherapy is associated with more side effects including pain, blisters and hyperpigmentation. The cost of treatment for cryotherapy is also higher for the hospital and the patient. Salicylic acid ointment on the other hand did not have any reported side effects in this study and can be applied at home.

Conflict of Interest Declaration
The authors have no conflict of interest to declare.

Acknowledgement
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24. Bruggink SC, Gusseklojo J, de Koning MN, Feltkamp MC, Bavinck JN, Quint WG et al. HPV type in plantar warts influences natural course and treatment response:


ORIGINAL ARTICLE

An Epidemiological Study of Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN) overlap in University Malaya Medical Centre

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Abstract

Introduction:
Steven-Johnson syndrome and Toxic Epidermal Necrolysis are rare but life threatening severe cutaneous adverse reactions to drugs. To determine the epidemiology of SJS, TEN and SJS/TEN overlap in University Malaya Medical Centre (UMMC).

Methods:
All patients admitted to UMMC from year 2013-2015 for SJS, SJS/TEN, TEN were recruited. The classification of SJS, SJS/TEN overlap and TEN was made based on the criteria laid down by Bastuji et al.²

Results:
A total of 32 patients were recorded to have SJS, SJS/TEN overlap and TEN from 2013 to 2015. Drugs (n=32, 86.49%) remained the most common aetiology of SJS and TEN. The top three commonest drugs are allopurinol (n=6), followed by carbamazepine (n=5) and bactrim (n=3).

Conclusion:
This study demonstrates that drugs were the most common cause of SJS/TEN. Antibiotics were the most common drug group that caused SJS/TEN. Awareness of the common etiology such as drug is important and high index of suspicion of SJS and TEN is needed if patients were on the above medications.

Key words: Severe Cutaneous Adverse Reactions (SCAR), Stevens-Johnson Syndrome (SJS), Toxic epidermal necrolysis (TEN)

Introduction

Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are severe cutaneous adverse reactions (SCAR) to drugs. Previous conceptions on the SJS and TEN as two individual reactions with differing pathogenesis had been replaced by SJS and TEN being a continuum that differs by the extent of skin detachment.¹ The classification depends on the extent of body surface area affected by epidermal detachment and the
extent of mucosal involvement (at least 2 mucosal surface comprising ocular, oral and genital). SJS is characterized by the presence of flat, atypical target lesions with epidermal detachment of less than 10% of the total body surface area. As for TEN, TEN with spots involves detachment above 30% of the body surface area plus widespread purpuric macules or flat atypical targets while toxic epidermal necrolysis without spots involves detachment above 10% of the body surface area with large epidermal sheets and without any purpuric macule or target. In the SJS/TEN overlap, epidermal detachment of 10-30% of the total body surface area is observed.1 The study is to determine the epidemiology of SJS, TEN and SJS/TEN overlap in University Malaya Medical Centre (UMMC).

Materials and Methods
This is a single centre study of SJS, SJS/TEN overlap and TEN cases done on patients admitted to UMMC from year 2013-2015. Patients who refused to participate in the study were excluded.

The classification of SJS, SJS/TEN overlap and TEN was made based on the criteria laid down by Bastuji et al.2 No skin biopsies were done. The diagnoses were achieved by dermatologists on clinical grounds. Drug(s) taken within and up to eight weeks preceding the onset of symptoms were considered as the causative drugs. If more than one drug were taken, they were all considered as causative drugs. Blood investigations were taken to assess for organ involvement and to exclude other severe cutaneous adverse drug reactions like Drug Hypersensitivity Syndrome.

Patients who had not taken any drugs regularly or prior to the onset of symptoms and did not have any noticeable cause of their symptoms were categorized as unknown.

The data collected were all compiled on a Microsoft Excel spreadsheet. Descriptive statistical analysis was performed.

Results
A total of 32 patients were recorded to have SJS, SJS/TEN overlap and TEN from 2013 to 2015. Drugs (n=32, 86.49%) remained the most common aetiology of SJS and TEN. In the other 5 patients (n=5, 13.51%) the aetiology was not identified. Antibiotics (n=15, 46.88%) turned out to be the most common type of drug that led to SJS and TEN followed by anti-gout medication (n=6, 18.75%), antiepileptics (n=5, 15.63%) and then NSAIDS (n=3, 9.38%) and others (n=3, 9.38%). Penicillins group accounted for most of the cases caused by antibiotics with 7 cases (n=7, 21.88%) followed by sulphonamides with a total of 3 cases (n=3, 9.38%). The only antiepileptic that was recorded to cause SJS was carbamazepine.

The drug most frequently associated with the cases in this study was allopurinol (6 cases, 18.75%) followed by carbamazepine (5 cases, 15.63%) and Sulfamethoxazole and trimethoprim (Bactrim) (3 cases, 9.38%).

Table 1. Causes of SJS, SJS/TEN overlap and TEN

<table>
<thead>
<tr>
<th>Causes</th>
<th>SJS, n</th>
<th>TEN, n</th>
<th>SJS/TEN, n</th>
<th>No. of cases, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td>30</td>
<td>2</td>
<td>0</td>
<td>32 (86.49)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>5 (13.51)</td>
</tr>
</tbody>
</table>

Out of the 32 patients, 4 patients (12.5%) had more than one drug being the suspected aetiological agents. The initial age of presentation ranges from 15 to 85 years old with the mean age of 50. Out of 32 patients, the majority affected is male (n=22, 68.75%). 21.4% (6 out of 28 patients) has renal impairment and only 7% (2 out of 28 patients) has liver impairment.
Table 2. Drugs implicated in SJS, SJS/TEN overlap and TEN

<table>
<thead>
<tr>
<th>Category</th>
<th>SJS, n</th>
<th>TEN, n</th>
<th>SJS/TEN, n</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibiotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulphonamides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sulfamethoxazole+trimethoprim (Bactrim)</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3 (9.38)</td>
</tr>
<tr>
<td>Penicillins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2 (6.25)</td>
</tr>
<tr>
<td>Amoxicillin+Clavulanic acid (Augmentin)</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2 (6.25)</td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (3.13)</td>
</tr>
<tr>
<td>Penicillin</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (3.13)</td>
</tr>
<tr>
<td>Bacampicillin</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (3.13)</td>
</tr>
</tbody>
</table>

Total: 7 (21.88)

- **Tetracycline**
  - Doxycycline: 1 case (3.13%)

- **Macrolides**
  - Azithromycin: 1 case (3.13%)

- **Cephalosporins**
  - Cefuroxime (Zinnat): 1 case (3.13%)

- **Others**
  - Vancomycin: 1 case (3.13%)
  - Rifampicin+Isoniazid (Akurit): 1 case (3.13%)

<table>
<thead>
<tr>
<th>Category</th>
<th>SJS, n</th>
<th>TEN, n</th>
<th>SJS/TEN, n</th>
<th>Total, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-epileptics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>5 (15.63)</td>
</tr>
<tr>
<td><strong>NSAIDS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etoricoxib (Arcodia)</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>1 (3.13)</td>
</tr>
<tr>
<td>Mefenamic acid(Ponstan)</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>2 (6.25)</td>
</tr>
<tr>
<td><strong>Anti-gout</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allopurinol</td>
<td>5</td>
<td>1</td>
<td>0</td>
<td>6 (18.75)</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (3.13)</td>
</tr>
<tr>
<td>Telmisartan(Micardis)</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (3.13)</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>1 (3.13)</td>
</tr>
</tbody>
</table>

Total: 3 (9.38) (362 cases)

Table 3. Demographic of SJS, SJS/TEN overlap and TEN

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Mean age of initial presentation (years)</th>
<th>No. of cases, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>50.00</td>
<td>22 (68.75)</td>
</tr>
<tr>
<td>Male</td>
<td>47.95</td>
<td>10 (31.25)</td>
</tr>
<tr>
<td>Female</td>
<td>55.12</td>
<td>6 (21.40)</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>63.83</td>
<td>2 (7.00)</td>
</tr>
<tr>
<td>Liver impairment</td>
<td>65.50</td>
<td>22 (68.75)</td>
</tr>
</tbody>
</table>

Discussion

The most commonly implicated drugs were allopurinol (6 cases, 18.75%) followed by carbamazepine (5 cases, 15.63%), possibly due to common usage of both drugs and the genetic susceptibility to SJS, SJS/TEN and TEN in this region. No previous epidemiological studies on SJS, SJS/TEN and TEN had been done in University Malaya and surrounding regions. However, there had been studies on SJS, SJS/TEN and TEN done on other regions in Malaysia that showed drugs, mainly antibiotics and antiepileptics as the most common culprit. These results are also consistent with other studies done in Thailand, Singapore and Korea.

A study done by Ding et al. in Johor showed that allopurinol, carbamazepine, phenytoin and cotrimoxazole were the main culprit for adverse drug reactions with allopurinol 39 (13.9%), carbamazepine in 29 (10.3%), phenytoin in 27 (9.6%) and cotrimoxazole in 26 (9.3%) cases. Choon et al also has done a study in Johor, out of 362 cases of cutaneous adverse drug reactions, 144 cases were severe cutaneous adverse reaction to drugs. Carbamazepine, allopurinol and cotrimoxazole were the top three etiology of SJS/TEN. In 2015, Sasidharanpillai et al had conducted a study on drug eruption and severe cutaneous adverse reaction which included 14 patients. The culprit...
drugs identified were anticonvulsants, antibiotics and NSAIDs. This is consistent with our study. However, phenytoin is not the causative drug in our study. This finding is surprising and was not consistent with other countries. Phenytoin has been a common causative agent for SJS, SJS/TEN and TEN up to 13% in a study involving 127 patients. Our study showed that carbamazepine was second commonest agent associated with SJS and TEN in our population.

This is difficult to explain as phenytoin is still one of the first line antiepileptics used in this region especially for status epilepticus. On top of that, HLA1502 testing is available in University Malaya Molecular laboratory and is routinely carried out before initiating treatment of carbamazepine but not for phenytoin and allopurinol. This explained the high incidence of allopurinol induced SJS but not for the lack of phenytoin induced SJS. Phenytoin is not the preferred 1st line for maintenance therapy for epilepsy in University Malaya may be because chronic phenytoin user is associated with high incidence of side effects such as sedation, gum hypertrophy, lymphadenopathy, chorea and ataxia. Among those, there are a few reports on cerebellar atrophy and degeneration. However, the usage of phenytoin is still high in this university due to compliance and financial issues.

The correlation between human leukocyte antigen (HLA) genotype and SJS/TEN had been observed in many studies. An association between the HLA-B*5801 allele and allopurinol-induced SJS/TEN can be found in some studies, including one done in Europe. There are currently no studies published in Malaysia regarding this.

Studies have also suggested that Han Chinese and other Asian populations, including Malaysia are more susceptible to carbamazepine-induced SJS/TEN due to the HLA-B*1502 gene. However, studies done in Europe have so far failed to prove this correlation.

Conclusion
This study demonstrates that drugs were the most common cause of SJS/TEN. Antibiotics were the most common drug group that caused SJS/TEN. Other common drug groups that caused SJS/TEN includes anti-gout medication, antiepileptics and non-steroidal anti-inflammatory drugs (NSAIDS). The most commonly implicated individual drug was allopurinol, followed by carbamazepine. Our study showed that drugs that were implicated in the aetiology of SJS and TEN in our population are commonly used drugs in the clinical setting. We support the need for HLA testing prior to the commencement of carbamazepine. Obtaining an allergy history prior to prescribing antibiotics and NSAIDs may be useful to reduce the incidence of SCARs as prescribers can then avoid using possibly implicated drugs for patients with known allergies while maintaining a high index of clinical suspicion for any patients who report adverse reactions in order to commence necessary treatment at an early stage.

Conflict of Interest Declaration
The authors have no conflict of interest to declare.

Acknowledgement
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References
ORIGINAL ARTICLE

Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS): A Review of 21 Cases over 7 years Period from Selayang Hospital

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Abstract

Introduction:
DRESS is an uncommon severe cutaneous adverse drug reaction, which is under recognized. In this review, we aim to study the clinical characteristics of patients with DRESS that presented to our hospital.

Methods:
We conducted a retrospective analysis on the data of all the patients with DRESS from January 2006 to December 2012 in Selayang Hospital.

Results:
Twenty-one patients were included with median age of 33 and male to female ratio of 1:1. Allopurinol was the most frequent causative drug followed by anti-tuberculous drugs. The mean latency period was 28.6 days. All patients had macula-papular rash of which 6 progressed to erythroderma. Liver was the most frequent extra cutaneous organ involvement with median peak alanine transaminase of 746 iu/l, (range 45-3677) and median peak aspartate transaminase of 632 iu/l (range 30-3136). Six patients (28.5%) had acute liver failure. The mainstay of treatment was systemic corticosteroid. Mortality rate was 23.8%.

Conclusion:
DRESS is a severe cutaneous adverse drug reaction with a myriad of clinical presentation and is associated with mortality. Our series has higher mortality compared to most other reported studies, most probably due to referral bias. Early recognition is crucial.

Key words: severe cutaneous adverse drug reaction, maculo-papular rash, acute liver failure, eosinophilia

Introduction
DRESS (Drug reaction with eosinophilia and systemic symptoms) or otherwise also known as Drug induced hypersensitivity syndrome (DIHS) is an uncommon but severe idiosyncratic cutaneous adverse drug reaction, which carries a mortality rate of up to 10%. It is characterized by fever, skin rash, lymphadenopathy and multi-organ involvement. The incidence of this adverse drug
reaction ranges between 1:1000 to 1:10,000. The onset of symptoms usually occurs 2-8 weeks after drug ingestion, which is delayed when compared to other types of cutaneous drug reactions. There is also possible persistence or worsening of DRESS despite withdrawal of the offending drug. The diagnosis is a challenge as it mimics other clinical diseases such as sepsis and connective tissue disease. Currently, there is no specific markers for the diagnosis of DRESS and the clinical features are not pathognomonic therefore it is a diagnosis of exclusion, however awareness of the condition will help.

Recently with the increasing awareness about this severe cutaneous adverse drug reaction, there is an increased in the number of published reports from overseas on DRESS. Some studied the clinic-pathological features while others attempted to look for prognostic factors or long term outcome. However local data is scarce. Hence the objective of this study is to report on the clinical features, disease course and outcome in patients with DRESS.

Materials and Methods

A retrospective medical records review was conducted on Adverse Drug Reaction Registry in Selayang Hospital, Malaysia from January 2006 to December 2012. Patients recruited were either diagnosed to have DRESS by a consultant dermatologist or had drug rash and eosinophilia. All cases also had to fulfill the criteria proposed by the European Registry of Severe Cutaneous Adverse Drug Reaction (RegiSCAR). (Table 1)

The definitions of extra cutaneous involvement were as from previous studies. Liver involvement was defined as increased in transaminases of more than two times upper limit of normal (Upper limit normal of aminotransferase for male = 43iu/l, female = 30iu/l) or patient’s baseline and other common causes of hepatitis were excluded. Acute liver failure was defined as evidence of coagulation abnormality with International Normalized Ratio (INR) ≥1.5 and any degree of mental alteration (encephalopathy) in a patient without preexisting cirrhosis of less than 26 weeks’ duration.

Renal involvement was defined as unexplained increased in creatinine level of more than twice from baseline or new onset proteinuria or hematuria. Pulmonary involvement was defined as unexplained abnormal chest radiograph findings. Cardiac involvement was defined by unexplained elevation of cardiac enzymes. Blood culture and sensitivity, Hepatitis surface antigen, anti–Hepatitis C antibody and anti-nuclear antibodies were performed to exclude septicemia, connective tissue diseases and other common liver diseases. In cases of acute liver failure, ultrasound liver was also done.

Patients whom fulfill the inclusion criteria were further divided into possible, probable or definite based on RegiSCAR’s scoring system. A final score of 4-5 is probable case whereas final score of more than 5 is definite case. Only the probable and definite cases were analyzed.

Any drug(s), including prescribed medications, over the counter self medications, supplements and herbal products consumed within the 2-months period before the onset of symptoms were recorded. A criteria set by Naranjo et al was used to assign causality of each potential agent. The offending agent(s) was categorized as uncertain if more than one drug were implicated.

Statistical analysis

SPSS version 20 was used to analyze the data collected. Chi square test was adopted for 2-sample comparison for allopurinol or anti-tuberculosis induced DRESS with other drug induced DRESS for categorical variables. The results were expressed as means or medians. P value of less than 0.05 is considered to be statistically significant.

Results

There were 21 patients with equal proportion of males and females whom were diagnosed with
DRESS and fulfilled the inclusion criteria during the study period, yielding a frequency of 0.024% among the reported adverse drug reactions in our hospital. The median age of the patients in years was 33 (IQR 27; range 20-73). There were 9 Malay patients, 6 Chinese patients, 2 Indian patients and 4 foreigners (3 from Indonesia and 1 from Pakistan). The clinical data of the patients are summarized in Table 2.

**Culprit Drugs**
The offending agents in order of decreasing frequencies were: allopurinol (n=6, 28.5%), anti-tuberculous drugs (n=5, 23.8%), anti-infectives namely minocycline, ceftriaxone, doxycycline and dapsone (n=4, 19.0%), anti-epileptics (n=3, 14.3%), herbal medications (n=2, 9.5%) and anti-rheumatics (n=1, 4.7%) (Figure 1).

![Pie chart showing drug groups causing DRESS.](image)

**Clinical Features**
The mean latency period from ingestion of drug to onset of rash was 29 days with median of 28 days (range 12–60). The anti-tuberculous groups had the longest latency period of 33.8 days compared to all the other groups but this was not statistically significant (p =0.431). Fever was reported in 13 out of 21 patients (61.9%).

All of our patients had maculo-papular rash, of these 6 patients (28.5%) progressed to erythroderma. Eight patients had facial oedema, two of these had allopurinol as the culprit agent who also developed concomitant pustules. One patient had Steven Johnson Syndrome like presentation with mucosal involvement.

![A DRESS patient with macula-papular rash and facial edema.](image)

**Laboratory Investigations and other organ involvements**
Twenty of our patients (95.2%) had liver involvement with peak median alanine transaminase of 746 iu/l, (IQR 1236; range 45-3677), peak median aspartate transaminase of 632 iu/l (IQR1099; range 30-3136), median bilirubin of 74 umol/l (range 10-803) and median INR of 1.5 (IQR 4.6; range 1.09-30.7). Six patients had acute liver failure. All of these acute liver failure patients had poor prognostic criteria as defined by the King’s College Criteria. Renal impairment was present in 23.8% of our patients. No renal impairment was detected in the antiepileptic group.

In 12 patients with peripheral blood film performed, 54.5% had atypical lymphocytes. Eosinophilia was present in 85.7% of the study group (18 out of 21) and the highest median eosinophil count was 2.4 (range 0.0 -16.6).

**Liver Histopathological Findings**
Patients 12 and 15 had liver biopsy performed during liver transplant and post mortem respectively. The liver tissue of patient 15 showed widespread
degeneration and necrosis of hepatocytes with extensive intra-acinar fibrosis and inflammation. Portal tracts were expanded and infiltrated by lymphocytes, plasma cells and also significant number of eosinophils. There was also evidence of cholestasis.

Treatment/Management
The causative drug(s) was discontinued in all patients. Sixteen patients (76.2%) received systemic corticosteroids (intravenous hydrocortisone or oral prednisolone) and the remaining 5 patients received topical corticosteroids and other supportive therapies, which included oral antihistamines and emollients. Of the patients whom did not receive systemic steroids, one patient (patient 18) had mild DRESS while 4 patients were not recognized to have DRESS (patients 11, 12, 15, 19). Out of the 16 patients who received systemic corticosteroid of an average duration of one month, 4 patients (25%) experienced cutaneous flare during tapering of prednisolone.

Outcome
Sixteen of the 21 patients recovered. One patient with acute liver failure and poor prognostic criteria received cadaveric organ liver transplantation and remained well at 5 years post transplant. Five patients died within median of 7 days of admission (range 4 -12) to our hospital. The causes of death were acute liver failure and sepsis (n=3) and multi-organ failure (n=2). The offending agents in those who died were allopurinol (n=2), traditional medications (n=1), carbamazepine (n=1) and anti-tuberculous therapy (n=1).

Discussion
In this cohort of patients with DRESS, we found that the common presentations were macula-papular rash, liver involvement, peripheral eosinophilia and fever. The in-hospital mortality rate was high at 23.8% which was much higher than the 5.9 -10% reported in other published literature. The Taiwanese1,11 and European9 studies report a mortality rate of 10% (Table 3) whereas an earlier Malaysian study reported a lower mortality rate of 5.9%.10 The higher mortality rate in the present study could be due to referral bias as our hospital is a tertiary referral center for hepatology services. All of the cases that died had preceding acute liver failure. Five out of the 6 patients with acute liver failure were referred from other government or private hospitals for further management of drug induced liver injury. The period between the onset of rash and diagnosis of DRESS were almost similar between those that died (mean 16.4 days) and those that recovered (15.8 days).

The most frequent causative drug in our study was allopurinol. This finding is consistent with findings from the Taiwanese studies.1,11 However, studies from Europe,12 Brazil,13 Thailand14,18 and Korea15 reported anticonvulsant as the most frequent causative drug. This could be due to the difference in the prevalence of genetic susceptibility such as HLA-B*5801 in different populations.19,20 While prescribing allopurinol for asymptomatic hyperuricemia is probably more common in Taiwan,1 only one of the six patients in our cohort was prescribed allopurinol for this reason. It is worth noting that the Malaysian Adverse Drug Reaction Advisory Committee has taken several risk minimization measures to ensure proper allopurinol prescription among health care providers, including restricting the prescription of this drug to specialist only.21

In the present study, patients’ median age was 39, which is similar to other studies.1, 12, 13 The anti-tuberculosis medications had higher mean latency time of 33.8 days (range 28 – 60 days) compared to the overall mean of 28 days. It is important for the health care providers to take note of the delayed presentation of this adverse drug reaction related to anti-tuberculosis drugs. On a further note, it is commendable that the Malaysia Clinical Practice Guidelines 201222 has recommended an earlier follow-up with liver function test monitoring within one month (2-4 weeks) after starting anti-tuberculosis medications instead of 2 months as in the 2002 version.

The most common skin presentation was macula-papular rash. 38.1% of the patients had facial edema (Fig 2). This finding is lower compared to other studies probably because of incomplete physical examination. Walsh et al12 and Wongkitisophon et al14 found 85.1% and 74.1% of their DRESS patients respectively had facial edema. Patient that presents with facial edema along with macula-papular or exanthematous rash should alert the healthcare provider the possibility of DRESS. In addition, DRESS is known to be associated with vesicles, bullae, atypical targetoid plaque, purpura and pustules.13 Hence it is prudent for clinicians to be aware of the various manifestations in order not to miss the diagnosis of DRESS.

In this study, liver is the most common extra
cutaneous involvement, as with findings from most other studies.\textsuperscript{1,11,12,13,14} Lin et al\textsuperscript{2} who studied pattern of liver injury in patients with DRESS found most of their patients had cholestatic type of liver injury followed by mixed and hepatocellular type. However, we did not study this. One third of our patients with hepatic involvement had acute liver failure. One had liver transplant, whereas the others died. Walsh S et al\textsuperscript{12} reported in their cohort of 27 cases of DRESS, one out of the three patients with severe hepatic impairment died following rejection of a liver transplant. In a case report,\textsuperscript{24} a patient with sulphasalazine induced DRESS had fatal recurrence after given vancomycin post liver transplant.

About one fifth of our patients had renal involvement. As with the previous Taiwanese studies\textsuperscript{1,11} our cohort of patients had higher rate of renal involvement compared to European studies.\textsuperscript{8,11} Chen YC et al\textsuperscript{1} postulated that the high rate of renal involvement of 40\% in their study might be related to the large proportion of allopurinol induced DRESS as they found statistical significance in renal involvement rate compared with other drugs. In the present study among those with renal involvement, half was due to allopurinol induced DRESS whereas the other half was due to anti-tuberculosis therapies.

Early recognition of this cutaneous adverse drug reaction and withdrawal of the causative agent are crucial in the management of DRESS.\textsuperscript{5,25} Systemic corticosteroid is the mainstay of treatment. However it may not be required in the management of mild forms of DRESS.\textsuperscript{26} Near to a third of our patients who received systemic steroid had relapse of the rash demonstrating the importance of gradual tapering of systemic corticosteroids and careful frequent assessment during that process. Prospective studies are needed to evaluate optimal pharmacological management.

The limitation of this study is the small number of patients and its retrospective nature. Wei CH et al\textsuperscript{16} in their cohort of 91 patients found tachycardia, leukocytosis, tachypnea, coagulopathy, gastrointestinal bleed and systemic inflammatory response syndrome (SIRS) were associated with poor outcome in DRESS patients, which we did not study. It would be utmost useful to study the prognostic factors as we have higher mortality however we are unable to do so in this study due to its small sample size. We also did not look at the long-term outcome of these patients. Another interesting area to be studied is human herpes virus 6 reactivation, which is considered to be part of a diagnostic marker of DRESS.\textsuperscript{27}

**Conclusion**

DRESS presents with a variety of cutaneous as well as extra cutaneous manifestations and is associated with mortality. Our series had higher mortality, which is contributed by referral bias. Awareness and recognition of this adverse drug reaction by front-line clinicians is pertinent especially when patient is on allopurinol, anti-tuberculosis therapies and even traditional medication.

**Conflict of Interest Declaration**

The authors have no conflict of interest to declare.

**Acknowledgement**

We would like to thank the Director General of Health Malaysia for permission to publish this paper.
Table 2. Clinical data of the patients.

<table>
<thead>
<tr>
<th>No</th>
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<th>Offending drug(s)</th>
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<th>Liver involvement</th>
<th>Renal involvement</th>
<th>Outcome</th>
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M- Malay, C- Chinese, I- Indian

RegiSCAR*: Final score<2: no case; final score 2-3: possible case; final score 4-5: probable case; final score> 5: definite case
Table 3. Comparison with other studies

<table>
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<tr>
<th></th>
<th>Roujeau &amp; Stern*</th>
<th>Walsh S et al12</th>
<th>Chen YC et al13</th>
<th>Wongkitisophon et al44</th>
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<td>Mortality (%)</td>
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<td>11</td>
<td>10</td>
<td>3.7</td>
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References


Low Dermatitis Potential of a Powder-Free, “Accelerator-Free” Non Natural Rubber Latex Gloves Using Modified Draize Study

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Abstract

Introduction:
The escalated demand for protective rubber glove in the healthcare industries has resulted in increased prevalence of glove related skin problem, irritant and allergic contact dermatitis and latex sensitivity. The industry has recently introduced a new nitrile glove product using a novel patented non-sulphur system to effect co-valent bond crosslinking to provide the desired elasticity of the gloves. This glove also has ionic crosslinking provided by the zinc oxide used in the formulation and the carboxylic group of the nitrile latex. The main objective of this study is to prove that residual chemical additives at a level that may induce Type IV allergy in the unsensitized general user population are not present in this rubber glove and to compare it with a powder free latex examination glove.

Methods:
In collaboration with the Islamic University of Gaza, we conduct modified test on a specially formulated and powder free, accelerator free LOW DERMA™ enhanced nitrile rubber glove that has physical properties and barrier integrity similar to that of NRL gloves. This glove does not contain sulphur or sulphur related compound. Two sets of Powder free, accelerator free LOW DERMA™ Nitrile Patient Examination Gloves*, white and blue colour were tested using the modified draize-95’ test. Filter paper soaked in normal saline and powder free latex examination glove were used as control.

Results:
A total of 209 subjects, 149 subjects, Caucasian (71.29%), 30 subjects, Afro Caribbean (14.35%) and 30 subjects, Asiatic (14.35%) were recruited. All 209 subjects had a final patch testing scoring of not more than 1.5 during both the induction phase and the challenge phase for both types of Powder Free Nitrile Patient Examination Gloves (white and blue) and to the negative control, normal filter paper and the powder free NRL control glove.
Conclusion:
The skin sensitization test (‘Modified Draize-95’ Test) of Powder Free Nitrile Patient Examination Gloves (white and blue) and the powder free NRL examination glove were negative. There was no clinical evidence on the presence of residual chemical additives at the level that may induce Type IV allergy in unsensitized general user population for both Powder Free Nitrile Patient Examination Gloves, blue and white colored, non-sterile. Both gloves qualify for “Low dermatitis Claim”.

Key words: Latex, Allergy, Nitrile, Glove

Introduction
With the practice of universal precaution in response to the AIDS epidemic and the worldwide emergence of fatal influenza A(H1N1), A(H5N1), MERS-CoV, the sporadic epidermic of the deadly ebola virus and many other fatal transmissible diseases, the use of protective glove has become an absolute necessity not only among healthcare professionals but also caregivers.

Consequent to this, there is an exponential increase in the demand and usage of protective rubber gloves, both natural and synthetic. This inevitably resulted in the increased prevalence of rubber glove related skin problem mostly contributed by three constituents of rubber gloves, namely the latex protein, chemical accelerators and the powder that is used to ease donning of these gloves.

Three major cutaneous effect of rubber gloves are irritant contact dermatitis, type I allergic reactions and type IV allergic reactions namely allergic contact dermatitis.1 Irritant contact dermatitis which is non-allergenic in nature is most common, affecting any individual and can occur with gloves made from any form of materials.

Type I allergy is an IgE immune-mediated response triggered by exposure to allergenic proteins or polypeptides that occur in latex products. The reaction is immediate and presents typically as direct contact urticaria, less commonly rhinoconjunctivitis and asthma or rarely, systemic in nature, most severe of which is anaphylactic reaction.2 Chronic occupational exposure to latex results in higher incidence of latex allergy (type I hypersensitivity)3 affecting 4.32% to 12% of healthcare workers3-4 and even higher among atopics with chronic occupational exposure, 43% when compared a prevalence is only 1.4% in the general population.5

Type IV reaction is a delayed type hypersensitivity reaction that occurs in response to rubber
chemicals, manifesting also as contact dermatitis which is illicit following usage of rubber glove (24 to 48 hours) in an already sensitised individual. Common causes are residual chemical additives, rubber as accelerators such as dithiocarbamate, tetramethylthiuram disulphide or mercaptobenzothiazoles and antioxidant that was added during the manufacturing of NRL gloves to facilitate cross linking, which is a fundamental process that provide the excellent elastic nature of NRL glove with effective barrier property which can hardly be challenged by synthetic rubber.

Starch powder used to ease donning of rubber glove, increases the allergenic nature of rubber glove as it has the capacity to bind with protein antigens (NRL) and released into the air when the gloves are donned or removed which through inhalation or ingestion can lead to the sensitisation and allergic reactions to NRL. Most powdered gloves, powdered surgeon’s gloves, powdered patient examination gloves in Germany (1990’s) and the United States. Latex sensitisation which heightened in the 1980s and 1990s has declined dramatically with the combination of safety regulation imposed on latex products, improved education and awareness and with the shift from the use of NRL powdered examination and surgical gloves to the use of powder-free NRL gloves with reduced protein levels and synthetic gloves.

Several types of latex-free gloves such as vinyl and nitrile have since been invented to overcome the situation as the demand for glove wearing increased and to provide suitable alternative to individuals with latex allergy. Compared to vinyl, nitrile glove serves greater protective barrier, almost comparable to that offered by latex gloves. However, these synthetic gloves also use the similar cross-linking agent and vulcanisation accelerator with that of NRL glove. Hence, the shift from NRL to synthetic rubber glove did not solve rubber glove related problem. Reports of allergic contact dermatitis to non-latex gloves like nitrile gloves, that used to be far less prevalent than those to NRL gloves, have become more common in recent years.

In order to avoid type IV allergy, it is crucial that synthetic gloves adopt a different formulation or using a different cross-linking system that eliminates the use of chemicals that may cause allergic reactions. The industry has recently introduced a new nitrile glove product using a novel patented non-sulphur system to effect co-valent bond cross linking to provide the desired elasticity of the gloves. This glove also has ionic cross linking provided by the zinc oxide used in the formulation and the carboxylic group of the nitrile latex.

The main objective of this study is to prove that residual chemical additives at a level that may induce Type IV allergy in the unsensitized general user population are not present in this rubber glove and to compare it with a powder free latex examination glove. This study is also designed to meet the requirements for claim, “where this product must demonstrate reduced potential for sensitizing users to chemical additives as described in “Guidance for Industry and FDA Staff - Medical Glove Guidance Manual. Supporting Test Data: A negative skin sensitization test (Modified Draize-95 Test)” on a minimum of 200 non-sensitized human subjects.

Materials and Methods
In collaboration with Islamic University of Gaza, we conducted a modified test on a specially formulated and powder free, accelerator free LOW DERMA™ enhanced nitrile rubber glove that has physical properties and barrier integrity similar to that of NRL gloves, made from acrylonitrile-butadiene. This glove does not contain sulphur or sulphur related compound.

Ethical Consideration
This study was conducted in compliance with the Helsinki Declaration and a written informed consent from the subject was obtained prior to recruitment and filed with the subject’s records. The ethical approval were obtained from Islamic University of Gaza (Ethics approval number: PHRC/HC/46/14) and Healthmedic Research Ethics Committee (HMREC) (Ethics approval number: HMREC-HMR-12-2016-B).

Materials
Two sets of Powder free, accelerator free LOW DERMA™ Nitrile Patient Examination Gloves, white and blue colored that have undergone primary skin irritation test and guinea pig sensitisation studies and have been tested negative for rubber chemical accelerators using chemical analytical technique were tested. Filter paper soaked in normal saline were used as negative control and powder free latex examination glove were used as control. The nitrile gloves are produced from a patented
manufacturing process No. US 2013/0198933 A1 and are provided by the sponsor (Kossan International Sdn. Bhd.).

Selection and recruitment of study subjects
A total of 209 non-sensitized healthy adult human subjects with no skin problem or previous type 1 or type IV allergy, aged between 18 to 65 years were recruited into the study.

The study comprised of 3 weeks induction phase, 2 weeks rest period followed by challenge phase. During the induction phase, a total of 10 test patches that consists of 2cm by 2cm of tests and control materials were patched onto the skin on each working day. The test patches were removed and replaced with a new one at the same site every 48 hours, for a total of 10 changes. Patches applied before the weekend were removed the next working day, i.e. 72 hours later.

During the challenge phase, two samples of the same test material were applied consecutively to a virgin site for 48 hours each. The test sites are evaluated for cutaneous reaction at the time of each patch removal and for the challenge patch, the test sites are again evaluated 2 to 4 days after removal of the second patch.

Scoring Criteria
Patch Testing Scoring criteria are based on standard scoring of the North American Contact Dermatitis Research Group (NACDRG).\(^{19}\) The intensity of reactions were scored as basic and supplemental score according to the criteria listed in table 1a and 1b.

### Table 1a. Scoring Criteria (Basic Score)

<table>
<thead>
<tr>
<th>Basic Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No visible reaction</td>
</tr>
<tr>
<td>0.5</td>
<td>Doubtful or negligible erythema reaction</td>
</tr>
<tr>
<td>1.0</td>
<td>Mild or just perceptible macular erythema reaction in a speckled/follicular, patchy or confluent pattern (slight pinking)</td>
</tr>
<tr>
<td>2.0</td>
<td>Moderate erythema reaction in a confluent pattern (definite redness)</td>
</tr>
<tr>
<td>3.0</td>
<td>Strong or brisk erythema reaction that may spread beyond the test site</td>
</tr>
</tbody>
</table>

### Table 1b. Scoring Criteria (Supplemental Score)

<table>
<thead>
<tr>
<th>Supplemental scores</th>
<th>Description</th>
<th>Label</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>Edema</td>
<td>E</td>
</tr>
<tr>
<td>0.5</td>
<td>Papules</td>
<td>P</td>
</tr>
<tr>
<td>0.5</td>
<td>Vesicles</td>
<td>V</td>
</tr>
<tr>
<td>0.5</td>
<td>Bullae</td>
<td>B</td>
</tr>
</tbody>
</table>

Skin reaction during the patch testing were observed and labelled using the scoring criteria provided. For skin reactions (basic score) that occur together with the described signs (supplemental score), both of the scores were added to produce the final score as the final result.

In order to qualify for the claim of a reduced sensitization potential, all the subjects completing the study should exhibit score value of no more than 1.5 based on the scoring criteria describe above.

### Results
A total of 209 subjects, 149 Caucasian subjects (71.29%), 30 Afro Caribbean subjects (14.35%) and 30 Asiatic subjects (14.35%) were recruited and completed the study. Age range of the study subjects were between 18 – 58 years (25.29± 9.13). One hundred and five subjects were females (50.24%) and 104 subjects were males (49.76%).

All 209 subjects had a final score of not more than 1.5 during both the induction phase and the challenge phase for both types of Powder Free Nitrile Patient Examination Gloves (white and blue) and to the negative control, normal filter paper and the powder free NRL glove. The results of the final score are summarized in the table 2 while table 3 summarizes the percentage of positive reaction in the duration of induction and challenge test.
Table 2. Final Score of the skin reaction induced by the test patches during the challenge phase for non-sensitized subjects for inner surface of both types of Powder Free Nitrile Patient Examination Gloves (white and blue).

<table>
<thead>
<tr>
<th>Sample</th>
<th>Total Score</th>
<th>Number of Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Powder Free Nitrile Patient Examination Gloves, White Colored,</strong></td>
<td>Score less than 1.5</td>
<td>209</td>
</tr>
<tr>
<td><strong>Non-sterile, Low Dermatitis Potential Claim (inner surface).</strong></td>
<td>Score more than 1.5</td>
<td>0</td>
</tr>
<tr>
<td><strong>Powder Free Nitrile Patient Examination Gloves, Blue Colored,</strong></td>
<td>Score less than 1.5</td>
<td>209</td>
</tr>
<tr>
<td><strong>Non-sterile, Low Dermatitis Potential Claim (inner surface).</strong></td>
<td>Score more than 1.5</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 3. Summary of percentage of positive reaction during the induction phase and the challenge phase for the test material and the control sample.

<table>
<thead>
<tr>
<th>Description</th>
<th>Number of subject</th>
<th>Percentage of positive reaction in non sensitized subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test material:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Powder Free Nitrile Patient Examination Gloves, White Colored,</td>
<td>209</td>
<td></td>
</tr>
<tr>
<td>Non-sterile, Low Dermatitis Potential Claim (inner surface).</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Challenge</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Powder Free Nitrile Patient Examination Gloves, Blue Colored,</td>
<td>209</td>
<td></td>
</tr>
<tr>
<td>Non-sterile, Low Dermatitis Potential Claim (inner surface).</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Challenge</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td><strong>Negative control:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Filter paper</td>
<td>209</td>
<td>0%</td>
</tr>
<tr>
<td>Challenge</td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td><strong>Control glove:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRL glove</td>
<td>209</td>
<td>0%</td>
</tr>
<tr>
<td>Challenge</td>
<td></td>
<td>0%</td>
</tr>
</tbody>
</table>

**Discussion**

These nitrile gloves are manufactured from a co-polymer of acrylonitrile and butadiene synthetic latex, (carboxilic nitrile rubber latex) instead of NRL, using a patented method. It is the best alternative and to a certain extent almost equal to latex glove, in terms of performance. The patented method eliminates the usage of sulfur as crosslinking agent and sulfur containing compound as crosslinking accelerator, specifically, dithiocarbamate, tetramethylthiuram-disulfide (TMTD) or mercaptobenzothiazole (MBT) which are among the commonest sensitizers detected in patients with contact dermatitis (Type IV) and suspected glove allergy. It serves as one of the best option for synthetic rubber latex and does not contain latex protein, which is a known cause of Type I allergy.

Patch testing, chosen for this study to evaluate the presence of and the potential effects of the sensitizers is universally regarded as the best method to identify these allergens. It is used to simulate and exaggerate the everyday situations of product application on the skin. None of the volunteers showed positive reaction towards the gloves sample. The results can be interpreted as the non-existence of allergen causative agent or perhaps it exists in a very low amount that has no clinical effects on the skin of the study subjects, thus, provides more than 95% confidence that the chemical sensitization potential in the user population is expected to be less than 1.5%.

NRL glove which uses the chemical accelerators that was used as control in this study also gave similar result. In this case the chemical accelerators in this NRL gloves maybe present in very small quantity that is lower than the threshold for sensitisation hence also qualify for claim of low dermatitis potential.

Changes in glove technology and a dramatic decrease in the prevalence of NRL allergies after interventions, technological advances and education justify the revisit of glove restriction policies of the use of devices made of NRL in healthcare that has been practised as precautionary measures against the perceived risk of NRL allergy.

The introduction of powder-free gloves has been associated with reductions in protein content and associated allergies. The use of low-protein, low-allergenic, powder-free gloves is associated with a significant decrease in the prevalence of type I
allergic reactions to NRL among healthcare workers. Given the excellent barrier properties and physical characteristics, dramatically reduced incidences of allergic reactions, competitive costs, biodegradable in nature and naturally derived environmental friendly material, the usage of type II reactions without clinical sequelae, major allergy may prevent them from pursuing certain careers, using many household and workplace objects, and seeking timely medical care. Moreover, those with underlying atopy and workplace objects, and seeking timely medical care. Furthermore, low-protein, low-allergenic, powder-free gloves does totally eliminate sequelae, major allergy may prevent them from pursuing certain careers, using many household and workplace objects, and seeking timely medical care. Moreover, those with underlying atopy and those who are high risk of latex sensitisation. There is still a need for non-nitrile gloves especially among high risk individuals.

Although most patients can be treated effectively for type IV and type I reactions without clinical sequelae, major allergy may prevent them from pursuing certain careers, using many household and workplace objects, and seeking timely medical care. Moreover, those with underlying atopy and those who are high risk of latex sensitisation. There is still a need for non-nitrile gloves especially among high risk individuals.

This powder free, accelerator free LOW DERMA™ rubber glove provides reasonable alternative to NRL rubber glove and further advantage over NRL rubber glove among atopic individuals, high risk group and latex sensitised individuals and elimination of possible future latex sensitisation even though both meets the criteria of low dermatitis potential.

**Conclusion**

The skin sensitization test (‘Modified Draize-95’ Test) of Powder Free Nitrile Patient Examination Gloves (white and blue) and the powder free NRL examination glove is negative. There was no clinical evidence of the presence of residual chemical additives at the level that may induce Type IV allergy in the unsensitized general user population in the Powder Free Nitrile Patient Examination Gloves, Blue and white Colored, Non-sterile, Low Dermatitis Potential Claim. Powder free, accelerator free LOW DERMA™ provides for the continuing requirement for synthetic gloves with low dermatitis potential for known latex-allergic patients and staff and those who are high risk of latex sensitisation.

**Conflict of Interest Declaration**

Authors declare no affiliation or significant financial involvement in any organizations or entity with a direct financial interest in the subject matter or materials discussed in the manuscript on this page. Kossan International Sdn. Bhd sponsored the study material - nitrile gloves (US 2013/0198933 A1).

**Acknowledgement**

The authors would also like to thank the Director General of Health, Malaysia for permission to publish this paper.

**References**

CASE REPORT

Behçet’s Disease: A Case Series of 5 Patients in the Department of Dermatology, Hospital Kuala Lumpur, Malaysia

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²Department of Dermatology, Hospital Kuala Lumpur, Kuala Lumpur, Malaysia

Summary
Behçet’s disease (BD) is a variant of systemic vasculitides characterized by recurrent oral aphthous ulcers, recurrent genital ulcers with eyes, cutaneous, gastrointestinal, joints, neurological and others organ involvement. Here we aim to describe the demography, clinical patterns and the treatment of 5 cases of BD presented to the Department of Dermatology Hospital Kuala Lumpur between 2002 and 2016. All the patients had a delay in their diagnosis. The clinical characteristics and the choices of treatment in our patients did not differ greatly compared to the reports from other countries. BD could be under-diagnosed in Malaysia as the presenting symptoms are non-specific. Therefore, a high index of suspicion is needed.

Key words: Behçet’s disease, systemic vasculitides, neurological manifestation

Introduction
Originally described in 1937, Behçet’s disease was defined as a disease with a triad of recurrent oral aphthous ulcer, genital ulcer and uveitis by Professor Hulusi Behçet, a Turkish Dermatologist.¹ In 2012, BD was classified under the Variable Vessel Vasculitis group in the Revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides.² Unlike other forms of autoimmune diseases, BD has a distinctive clinical progress. It affects vessels of variable sizes at one or more different organs with unpredictable duration of active diseases and remissions.³

In Malaysia, scarce reports of BD had been described by vascular surgeons, ophthalmologists and neurologists.⁴⁵ Here we aim to describe the demography, clinical patterns and the treatment of BD managed in the Department of Dermatology, Hospital Kuala Lumpur between 2002 and 2016.

Case Reports
There were a total of five cases diagnosed to have BD during this period, involving three male and two female patients. The characteristics of these patients were shown in Table 1. All were Malay patients except one with mixed ethnicity (Bajau, Philippine and Chinese). The median age of these patients at
The latest clinic review was 36 years old (range: 27-57). The median age when their first symptoms developed was 24 years old (range: 15 - 40). All patients presented with recurrent oral aphthous ulcers while four patients had recurrent genital ulcers. Four patients had eye involvement which included uveitis, scleritis, chorioretinitis and optic neuritis. Both female patients had history of unusual papulopustular eruptions and ulcerated papules or plaques over the face (Figure 1a). Presence of pathergy reactions (Figure 1b) were documented in three patients. Erythema nodosum (Figure 1c) was present in 4 patients. Severe ulceration in small and large intestines was reported in one patient whom subsequently underwent right hemicolecotomy. Transient acute arthritis was observed in three patients.

One patient presented with neurological manifestations. This Malay gentleman who was positive for HLA-B51 first presented with recurrent oral and genital ulcers associated with erythema nodosum at the age of 15 years old. He subsequently had blurring of vision of the right eye at 20 years old. Two years later, he presented with bilateral optic neuritis and superior sagittal sinus thrombosis. He was treated with warfarin for 6 months duration for the superior sagittal sinus thrombosis. Unfortunately, he became completely blind. Since the age of 26 years old he started to experience recurrent epilepsy with intermittent status epilepticus. His electroencephalography showed cerebral dysfunction with focal pathology over the left fronto-temporal lobe. The diagnosis of BD was only made after 11 years of the first presentation of oral ulcers. His magnetic resonance imaging of brain at the age of 29 years old revealed patchy, nodular and linear contrast enhanced changes in the parenchymal of both frontal lobes with ongoing cerebral atrophy. At the age of 31 years old, this unfortunate gentleman succumbed to status epilepticus.

Due to the non-specific presentation, all the patients had a delay in diagnosis, with a mean duration from initial presentation to diagnosis of 5.9 years (range: 1.5 to 12 years). They were misdiagnosed as having a recurrent genital herpes in two patients, recurrent simple oral aphthosis in one, systemic lupus erythematosus in another and demyelinating disease prior to the final diagnosis of Behcet’s disease. Histopathology examination of the erythema nodosum-like lesions revealed nodular vasculitis (Figure 1d) in one patient and septal panniculitis with vasculitis in another. Laboratory investigations during initial presentations revealed hypochromic microcytic anaemia in one patient and raised erythrocyte sedimentation rate (less than 80mm/hr) in four patients. Anti-nuclear antibodies (ANA) and anti-neutrophil cytoplasmic antibodies (ANCA) were negative in the three patients tested.

All the patients received systemic corticosteroids initially and during disease exacerbations (intravenous methylprednisolone, intravenous hydrocortisone and oral prednisolone). The steroid sparing immunosuppressive agents used included methotrexate, cyclosporine, colchicine, dapsone and azathioprine. The longest disease free duration ranged from five to eight months while on treatment.

Discussion
Behçet’s disease is a multi-system vasculitis of variable vessel sizes with the disease most active at young adulthood. It was classically described to be most frequently seen in countries along the historical Silk Road such as Turkey, Iran, Saudi Arabia, Iraq, Italy, Israel, China, Japan etc. In South East Asia, case series of BD has been reported in Singapore and Thailand; while a few case reports had been published in Malaysia.

Till date, the aetio-pathogenesis of the disease remains unidentified; however patients’ genetic make-up, infectious agents and immunological abnormalities have been implicated. The major histocompatibility complex (MHC)-related human leukocyte antigens (HLA)-B51 or HLA-B5 is found to be carried by a third to two third of patients with BD. The presence of these HLA significantly increases the risk of BD development. More predominant in males, these HLA carriers are associated with a higher prevalence of genital ulcer, ocular and skin manifestations but with lower prevalence of gastrointestinal involvement. Interestingly the male patient with neuro-BD in our cohort was identified to carry this HLA-B51 and he had the worst prognosis among the 5 patients. Regrettably HLA-typing was not able to be arranged for the other four patients. More recently, the imbalances in the expression of innate immunity together with T helper1 (Th1) and Th17-related cytokines have been shown to play an important role in the pathogenesis and the disease severity of BD.

Lacking of a universally recognized pathognomonic test, BD diagnosis is primarily based on clinical
criteria. The diagnosis of BD is often delayed as it imposes great challenges to clinicians to recognize the non-specific disease pattern. We had a mean duration of 5.9 years prior to the diagnosis, comparable to East Africa14 which was 5.5 years. Interestingly, even in Turkey, a country with one of the highest prevalence rate of BD in the world, Alpsoy et al15 reported that the duration taken to fulfill the diagnostic criteria was 2.83 years. There are many diagnostic criteria available for BD of which the most important ones include the International Study Group criteria (ISG) 1990 and the International Criteria for Behcet’s Disease (ICBD) 2014.16-18 The original ICBD was created in 2006, with the collaboration of 27 countries. It was then revised and then published in 201419 as shown in Table 2. As compared to the ISG 1990, the ICBD 2014 has been shown to have a higher sensitivity and equivalent specificity.3 Therefore the accuracy of BD diagnosis is expected to be better with the use of ICBD 2014.3

The disease presentations may vary in different ethnic groups and countries19-22 as shown in Table 3. Our patients had a high prevalence of oral ulcers, skin lesions, and eye manifestations. Aside from Korea20 cutaneous manifestations are not very common in the other countries and pathergy test particularly has a low prevalence. Although relatively rare, the central nervous system involvement which frequently develops late is associated with significant morbidity and mortality.

In our cohort of patients, pathergy reactions were demonstrated in 3 patients when papules on an erythematous base were noted at branula insertion sites and venipuncture sites during disease flares. However in another 2 patients, pathergy tests were performed when the patients were on high dose prednisolone and as a result they were negative. Pathergy is the term used to describe hyper-reactivity of the skin or development of new skin lesions or aggravation of existing skin lesions in response to trauma.23 It has been reported positive not only in BD but in pyoderma gangrenosum, erythema elevatum diutinum and Sweet’s syndrome.23 The method to perform a pathergy test is not standardized globally. Different techniques have been reported.7 As a result, the rates of positive pathergy tests in BD are inconsistently reported in different countries.3 Literature reviews have shown that patients with BD duration of less than 5 years24 and patients who did not take the medications for the BD at the time of testing25 had a higher rate of positive pathergy reactions.

Neurological manifestation of BD (Neuro-BD) is among the most aggressive forms of BD with high mortality.26 According to the 2014 International Consensus Recommendation of diagnosis and management of Neuro-BD, there are two main subtypes of Neuro-BD i.e. parenchymal and non-parenchymal.27 Our only neuro-BD patient suffered from both the subtypes at different occasions. Being a potentially treatable disease, clinicians need to consider Neuro-BD as a differential diagnosis of other central nervous system disorders. Correlation of variable neurological manifestations with other clinical presentations through a thorough history taking is vital to reach the diagnosis of Neuro-BD.

The main goal of therapy in patients with BD is to induce and maintain remission and improve patients’ quality of life. There were similarities in terms of the types of immunosuppressive agents used between our centre and a rheumatology centre in Singapore.8 Systemic corticosteroids, azathioprine and methotrexate were commonly used in these regions. We have used dapsone, pentoxiphylline and colchicine in our cohort of patients. The use of other immune-modulating agents such as cyclophosphamide and sulphasalazine had been reported as well.8

Over the last decade, a considerable amount of literature has been published regarding the use of tumor necrosis factor (TNF) inhibitors in BD with beneficial effects noted with infliximab, etanercept and adalimumab.28 As Interleukin-1β (IL-1β) is intimately involved in the pathogenesis of BD,29 biologics that inhibit this cytokine are also being evaluated. Gevokizumab, a recombinant humanized anti-IL-1β antibody, was associated with rapid and durable clinical response in seven patients with acute posterior or panuveitis, or retinal vasculitis who failed to respond to azathioprine or cyclosporine A.30 Meanwhile canakinumab, a fully human anti-IL-1β antibody, was efficacious in achieving a prompt and complete disease response in one patient with resistant fevers, oral and genital aphthosis, arthritis and ileocolic ulcers, who was unresponsive other agents.31 In addition, anti-CD52 antibody (alemtuzumab) has been described to be able to induce remission in majority of patients with difficult-to-treat BD. Nevertheless, relapses were common and it may cause new autoimmunity.32
Conclusion
In conclusion, we reported 5 cases of Behcet’s disease managed in Hospital Kuala Lumpur Malaysia. All of the patients had recurrent oral ulcers and 4 of them had recurrent genital ulcers, ocular involvement and cutaneous manifestations. Although it is a rare disease, Behçet’s disease is likely to be under-diagnosed in Malaysia. Perhaps it is more commonly managed by the rheumatologists than the dermatologists. In addition, patients may be evaluated by ophthalmologists, neurologists, gastroenterologist or other medical specialties. Early diagnosis which enables prompt and appropriate treatment is vital to prevent morbidity in BD. A high degree of awareness among physicians is important to diagnose BD especially in the context of recurrent aphthous ulcerations that present with other organs involvement.

Conflict of Interest Declaration
The authors have no conflict of interest to declare

Acknowledgement
The authors would like to thank the Department of Neurology, Hospital Kuala Lumpur for the contribution of part of the data of this paper. The authors would like to acknowledge the Department of Pathology, Hospital Kuala Lumpur who had contributed the slide of skin biopsy in one of the patients. The authors would also like to thank the Director General of Health, Malaysia for permission to publish this paper.

Figure 1. (a) Papulopustular eruptions with ulcers around the nose, nasal ala, philtrum, above the left eyebrow; (b) Positive pathergy reactions with papulopustular eruptions at the branula insertion side; (c) erythema nosodium at right anterior shin; (d) lobular panniculitis with vasculitis (H&E x400)
Table 1. Characteristics of five patients with Behçet’s disease (BD).

<table>
<thead>
<tr>
<th>Patient No</th>
<th>Age at latest review in years/ Ethnicity/Gender</th>
<th>Age of first symptoms in years</th>
<th>Duration from first symptoms to the diagnosis of BD (years)</th>
<th>Clinical presentations</th>
<th>Medications given</th>
<th>Complications due to BD</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36/Multinacial (Bajau, Philippine, Chinese)/ Male</td>
<td>18</td>
<td>12</td>
<td>Recurrent oral ulcers, ulcers at large &amp; small intestines, pangastritis, genital ulcers, erythema nodosum, positive pathergy reaction, uveitis</td>
<td>Prednisolone, methotrexate, cyclosporine, colchicine</td>
<td>Right hemicolectomy</td>
<td>Alive</td>
</tr>
<tr>
<td>2</td>
<td>57/Malay/Male</td>
<td>40</td>
<td>3</td>
<td>Recurrent oral ulcers, genital ulcers, chorioretinitis</td>
<td>Prednisolone, colchicine, pentoxifylline, azathioprine</td>
<td>-</td>
<td>Alive</td>
</tr>
<tr>
<td>3</td>
<td>46/Malay/Female</td>
<td>30</td>
<td>2</td>
<td>Recurrent genital ulcers, recurrent oral ulcers, erythema nodosum, papulopustular lesions, positive pathergy reaction, arthritis</td>
<td>Prednisolone, colchicine, dapsone</td>
<td>-</td>
<td>Alive</td>
</tr>
<tr>
<td>4</td>
<td>27/Malay/Female</td>
<td>24</td>
<td>1.5</td>
<td>Recurrent oral ulcers, erythema nodosum, arthritis, ulcerated papules and plaques, scleritis, positive pathergy reaction</td>
<td>Prednisolone</td>
<td>Abortion during a flare</td>
<td>Alive</td>
</tr>
<tr>
<td>5</td>
<td>31/Malay/Male</td>
<td>15</td>
<td>11</td>
<td>Recurrent oral ulcers, genital ulcers, erythema nodosum, optic neuritis, central retinal vein obstruction, superior sagittal sinus thrombosis, recurrent headache, epilepsy</td>
<td>Prednisolone, methylprednisolone, methotrexate</td>
<td>Blindness, epilepsy</td>
<td>Died at 31 years old</td>
</tr>
</tbody>
</table>

*age when patient died

Table 2. Revised International Criteria for Behçet’s disease (adapted from Davatchi et al 2014)

<table>
<thead>
<tr>
<th>Sign / Symptom</th>
<th>Description</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ocular lesions</td>
<td>Anterior uveitis, posterior uveitis, retinal vasculitis</td>
<td>2</td>
</tr>
<tr>
<td>Genital Aphthosis</td>
<td>Ulcers are usually larger, deeper than the oral aphthosis. In female they are mainly localized on the vulva, rarely in the vagina and exceptionally on the cervix. In males, ulcers are mainly seen on the scrotum but can be seen on the shaft of the penis and on the meatus</td>
<td>2</td>
</tr>
<tr>
<td>Oral Aphthosis</td>
<td>Aphthous oral ulceration at least 3 times in a 12-month period</td>
<td>2</td>
</tr>
<tr>
<td>Skin manifestations</td>
<td>Pseudofolliculitis, erythema nodosum, skin aphthosis</td>
<td>1</td>
</tr>
<tr>
<td>Neurological Manifestations</td>
<td>Central (Parenchymal and non-parenchymal) and peripheral</td>
<td>1</td>
</tr>
<tr>
<td>Vascular Manifestations</td>
<td>Arterial thrombosis, large vein thrombosis, phlebitis, superficial phlebitis</td>
<td>1</td>
</tr>
<tr>
<td>Positive Pathergy Test**</td>
<td>Pathergy test was done by 3 needle pricks. One with a 21 gauge needle, the second with a 25 gauge needle, and the third with a 25 gauge needle and the injection of drops of a normal saline solution. The results were read 24 hours later. A test was considered positive, if at the site of the needle puncture a papule or a pustule was formed, and it was surrounded by an erythema.</td>
<td>1</td>
</tr>
</tbody>
</table>

*Point score system: scoring ≥ 4 indicates Behçet’s disease diagnosis.
**Pathergy test is optional. However, where pathergy testing is conducted one extra point may be assigned for a positive result.
Table 3. Comparison of baseline clinical characteristics and treatment modalities of various countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Mean age of onset (years)</th>
<th>Male:Female ratio</th>
<th>Oral ulcers</th>
<th>Genital ulcers</th>
<th>Skin lesions</th>
<th>Ocular lesions</th>
<th>Articular lesions</th>
<th>GI lesions</th>
<th>Epididymitis</th>
<th>Vascular lesions</th>
<th>Neurologic lesions</th>
<th>Pathergy</th>
<th>Cardiac</th>
<th>Pulmonary</th>
<th>Treatment modalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Japan19 1993</td>
<td>35.7</td>
<td>0.98:1</td>
<td>98%</td>
<td>65%</td>
<td>65%</td>
<td>57%</td>
<td>37%</td>
<td>16%</td>
<td>6%</td>
<td>9%</td>
<td>3.8%</td>
<td>44%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A - not available; GI- gastrointestinal</td>
</tr>
<tr>
<td>Korea20 2001</td>
<td>33</td>
<td>1:1.75</td>
<td>98.8%</td>
<td>83.2%</td>
<td>84.3%</td>
<td>50.9%</td>
<td>38.4%</td>
<td>7.3%</td>
<td>0.6%</td>
<td>1.8%</td>
<td>4.6%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>Corticosteroids Azathioprine Methotrexate Cyclophosphamide Sulfasalazine</td>
</tr>
<tr>
<td>Turkey21 2003</td>
<td>32.7</td>
<td>1:1:1</td>
<td>100%</td>
<td>85.6%</td>
<td>38.0%</td>
<td>45.5%</td>
<td>11.3%</td>
<td>1.4%</td>
<td>N/A</td>
<td>11.7%</td>
<td>3.3%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A - not available; GI- gastrointestinal</td>
</tr>
<tr>
<td>Singapore22 2004</td>
<td>1.56:1</td>
<td>1:1.1</td>
<td>100%</td>
<td>64.9%</td>
<td>48.6%</td>
<td>35.1%</td>
<td>43.2%</td>
<td>40.5%</td>
<td>0%</td>
<td>5.4%</td>
<td>5.4%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A - not available; GI- gastrointestinal</td>
</tr>
<tr>
<td>Thailand23 2006</td>
<td>1.2:1</td>
<td>1:1.1</td>
<td>100%</td>
<td>69.6%</td>
<td>60.9%</td>
<td>52.2%</td>
<td>34.8%</td>
<td>8.7%</td>
<td>4.3%</td>
<td>8.7%</td>
<td>8.7%</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A - not available; GI- gastrointestinal</td>
</tr>
<tr>
<td>Iran24 2010</td>
<td>26</td>
<td>1:1.75</td>
<td>97.3%</td>
<td>64.6%</td>
<td>64.9%</td>
<td>56.8%</td>
<td>37.4%</td>
<td>7.4%</td>
<td>4.7%</td>
<td>8.3%</td>
<td>3.8%</td>
<td>52.3%</td>
<td>0.6%</td>
<td>0.9%</td>
<td>N/A - not available; GI- gastrointestinal</td>
</tr>
<tr>
<td>Current study</td>
<td>24</td>
<td>1.5:1</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>80%</td>
<td>80%</td>
<td>20%</td>
<td>0%</td>
<td>20%</td>
<td>60%</td>
<td>0.6%</td>
<td>N/A</td>
<td>N/A</td>
<td>Corticosteroids Azathioprine Methotrexate Dapsone Colchicine pentoxiphylline</td>
</tr>
</tbody>
</table>

N/A – not available; GI- gastrointestinal
References


CASE REPORT

Acitretin an Additional Treatment Option for Elephantiasis Nostras Verrucosa: A Case Report

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Summary
Elephantiasis nostras verrucosa occurs due to chronic lymphedema, characterized by cutaneous changes consisting of papillomatous, verrucous, and hyperkerototic lesions. Treatment of elephantiasis nostras verrucosa is challenging and results are often disappointing. We report our experience with a patient who was successfully treated with oral acitretin.

Key words: Elephantiasis nostras verrucosa, elephantiasis, acitretin

Introduction
Elephantiasis nostras verrucosa occurs due to chronic non-filarial lymphedema.1 It is characterized by cutaneous changes consisting of papillomatous, verrucous, and hyperkerototic lesions.1 This condition has been reported under a variety of other names, including elephantiasis nostras, elephantiasis verrucosa, elephantiasis crurum papillaris et verrucosa, lymphostatic papillomatosis cutis, pachydermia vegetans, lymphostatic verrucosa, papillomatosis cutis verrucosa and mossy foot.2 Treatment of elephantiasis nostras verrucosa is challenging and results are often disappointing. Conservative therapies aim to reduce edema and infection using manual or mechanical massages, elastic bandages, pneumatic stockings, diuretics, topical agents, antibiotics and surgical debridement.3-5 The beneficial effects of systemic retinoid for elephantiasis nostras verrucosa have been described.6 We report our experience with a patient who was successfully treated with oral acitretin.

Case report
A 67-year-old man with hypertension presented with fever and right leg pain of 4 days duration. In addition, he has chronic right lower limb swelling for past 15-years and diagnosed as elephantiasis nostras verrucosa secondary to recurrent cellulitis. He was treated conservatively with elastic bandages and hydrocolloid dressings with not much improvement.

On examination, the right leg was enlarged from the foot up to the knee. There were mossy,
cobblestone-like verrucous papules, nodules and plaques noted on the skin surface. These lesions were also malodorous, macerated and covered with slough in few areas (Figure 1a & b). The leg was warm and tender on palpation. He was diagnosed as chronic lymphedema with cellulitis and treated with intravenous ampicillin/sulbactam and potassium permanganate wet dressing. Once the cellulitis resolved, oral acitretin (0.6 mg/kg/day) was introduced and the dose was increased to 0.9 mg/kg/day after 6 weeks of therapy.

Acitretin treatment resulted in disappearance of the verrucous masses and remarkable flattening of hyperkeratotic lesions (Figure 1c & d). Clinical response was measured by the reduction in calf and ankle circumferences. Calf and ankle circumference were 40 cm and 32 cm pre-treatment and following 16 weeks of therapy were 30 cm and 31 cm respectively. There were no more episode of cellulitis during the course of oral Acitretin therapy. Liver function tests and serum cholesterol remained normal. Treatment was discontinued after 12 months due to minor side effects of dry skin with eczema craquele, sticky skin and brittle nails. And unfortunately, he developed recurrent cellulitis.

Figure 1. Clinical presentations of patient with elephantiasis verrucosa nostrae; (a&b) Enlarged left lower limb with mossy and cobblestone-like verrucous plaques and nodules affecting the foot, ankle and lower leg; (c&d). The left lower limb after 16 weeks of acitretin therapy. Calf circumference was reduced by 10 cm while ankle circumference was reduced by 2 cm. There was marked improvement of the skin with disappearance of the cobblestoned verrucous plaques.
Discussion
Lymphatic vessels are the main drainage channel for interstitial proteins and fluid that regulates cell hydration and osmosis. In elephantiasis nostras verrucosa, lymphatic obstruction causes accumulation of protein rich fluid which stimulates proliferation of keratinocytes, fibroblasts and adipocytes. The epidermal, dermal layers and subcutaneous tissue became hardened due to excessive fibroblast activity. Lymph stasis results in a localised immune deficiency as immune cells fail to circulate through the affected tissue predisposing it to bacterial infection. Lymph leaks on the skin surface and fissures in the skin increase the susceptibility of the area to infection. Chronic peripheral oedema due to lymph stasis produce thickened skin with hyperkeratotic, verrucous and papillomatous lesions. Mixed venous/lymphatic oedema caused by recurrent infection further induces or promotes elephantiasis as seen in this patient.

Acitretin had markedly improved the papillomatous nodules, verrucous lesions, hyperkeratosis, and lymphedema in our patient and he has no further episodes of cellulitis. However, treatment was withheld due to mucocutaneous side-effects. Despite being a good treatment option for this condition, the optimal dose and duration of treatment is still unclear. Improvement has been shown with doses as low as 0.3mg/kg and eight weeks of therapy seemed adequate to achieve satisfactory response nevertheless, there is a high probability for relapse upon its discontinuation. Hence, long term maintenance therapy at a lower dose is required to minimize relapses and side effects.

Conclusion
Acitretin is a useful alternative treatment for elephantiasis nostras verrucosa. But the optimal dose and duration of treatment is still unclear. Long term maintenance therapy at a lower dose is needed.

Conflict of Interest Declaration
The authors have no conflict of interest to declare.

Acknowledgement
The authors would also like to thank the Director General of Health, Malaysia for permission to publish this paper.

References
CASE REPORT

Toxic Epidermal Necrolysis as the First Presentation of Systemic Lupus Erythematosus

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2Department of Medicine, Hospital Tuanku Fauziah, Kangar, Perlis

Summary
Toxic epidermal necrolysis (TEN) is a severe mucocutaneous disease characterized by extensive epidermal detachment with drugs as the most probable cause. We describe a unique case of TEN where systemic lupus erythematosus (SLE) was found to be the precipitating underlying disease. Our patient was managed in ICU, however succumbed one month after her diagnosis due to overwhelming sepsis and multiorgan failure.

Key words: TEN and SLE, TEN like SLE, Acute cutaneous lupus

Introduction
Toxic epidermal necrolysis is a severe mucocutaneous disease characterized by more than 30% of body surface involvement of epidermal detachment. This disease may also have oral, ocular, pulmonary and genitourinary complications. The initial presentation of the rash maybe nonspecific, together with prodromal symptoms of fever. However, the cutaneous lesions are rapidly progressing and lead to desloughing of the epidermis with extensive mucosal lesions. The involvement of the oral and genital mucosa can lead to ulcerations and mucositis. Most TEN can be attributed to drug ingestion. Here, our patient presented a case of rapid progressing TEN which surprisingly was the rare variant of TEN like acute cutaneous SLE confirmed by skin biopsy.

Case Report
A 33-year-old Chinese female with underlying bipolar disorder presented with a history of generalised maculopapular rash of a rapid onset of one week. History revealed no drug consumption or over the counter medication, including supplements and traditional medicines prior to developing cutaneous lesions. She had defaulted her psychiatric medications for the past few years. She was spiking a high temperature of 40 degrees Celsius and her other vital signs were within normal range.

Cutaneous examination revealed a generalised maculopapular rash with 6% body surface area (BSA)
of epidermal detachment, positive Nikolsky’s sign with severe oral and genital ulcerations. Within days she progressed to full blown TEN with BSA >30% (Figure 1) and also required intubation for respiratory distress. Further blood investigations fulfilled the Systemic Lupus International Collaborating Clinics (SLICC) criteria for Systemic Lupus Erythematosus (SLE) consisting of thrombocytopenia, leukopenia, lymphopenia, proteinuria (24 hour urine protein 1273 mg/24 hours, urine protein creatinine index =3.8g/mmol), positive ANA titres 1: 160, positive SSA antibodies at 1:640 and low c3 levels(0.51mg/dL). Also, other pertinent investigations like mycoplasma pneumonia, chlamydia psittaci, chlamydia trachomatis and chlamydia pneumonia serologies were negative.

Histology showed an atrophic epidermis, marked parakeratosis, presence of civatte bodies and basal cell vacuolar degeneration (Figure 2 and 3). There was scanty perivascular lymphocytic infiltrates seen in the upper dermis with lymphocyte exocytosis. Alcian blue stain was positive for copious amounts of mucin deposition. However the specimen was unsuitable for immunofluorescence study. These findings of interface dermatitis are consistent with lupus erythematosus. A diagnosis of TEN like SLE was made from her clinical presentation, skin histology findings and laboratory and autoimmune markers.

**Figure 1.** The clinical presentation of the patient showing extensive epidermal detachment

**Figure 2.** The histopathological examination of the skin biopsy; (a) parakeratosis with vacuolar degeneration of the basement membrane (H&E x40); (b) presence of civette bodies within the epidermis (H&E x100).
She was treated with IV hydrocortisone and intensive skin nursing with bactigrass dressing for the erosions. Her condition was complicated with severe sepsis and acute kidney failure for which active treatment was instituted comprising of IV antibiotics and haemodialysis. She succumbed to her disease after one month of admission due to overwhelming sepsis and multiorgan failure.

Discussion

TEN is considered to be a T cell mediated disease which causes extensive keratinocyte apoptosis in the epidermis which further leads to the blister and bullae formation with epidermal detachment being the end result. Increased levels of soluble Fas ligand detected in the serum of TEN and granulysin detected in blister fluid have both been implicated in the pathogenesis of TEN as the cause of massive keratinocyte cell death.2, 3

Drugs are believed to be the most common precipitant while there have been other suggested aetiologies like mycoplasma pneumonia and herpes simples virus infections. As this disease carries a high mortality rate of 25%-30%, it is pertinent to consider other underlying aetiologies. This clinical scenario previously referred to as acute syndrome of apoptotic pan-epidermolysis (ASAP) by Ting et al covers the spectrum of TEN to include the drug induced TEN (drugs as the cause) and other diseases such as graft versus host disease (GVHD) and pseudoporphyria which may present similarly.4 The association between SLE and TEN has been well documented in the literature. In most reported cases, the diagnosis of SLE had been established well before the onset of TEN. The classical TEN and SLE induced TEN is a difficult one to distinguish.

In our case, the cutaneous lesions were the presenting manifestation of florid SLE. Prior to this, she had not displayed any systemic symptoms suggestive of lupus. The progression of the rash in this patient from a generalised maculopapular rash to extensive epidermal detachment of >30% occurred in a very short span of time, is similarly seen in drug induced TEN. Despite detailed history taking, we were unable to demonstrate any drug ingestion that may have led to TEN, thus making the possibility of other aetiologies plausible. We had also excluded underlying infections like mycoplasma and chlamydia in our search of underlying aetiology. Albeit rare, there should be a high index of suspicion for SLE in cases where the treating physician has difficulty establishing a causal drug.

The fact that our patient presented with “fulminant TEN” contradicts previous case reports of SLE-associated TEN which have a very gradual slow progression. The histopathology findings from the skin biopsy help strengthen our diagnosis of SLE as the probable underlying cause.

TEN being a potentially fatal disease is a medical emergency necessitating ICU admission. Severity of Illness Score for Toxic Epidermal Necrolysis (SCORTEN) should be used in the initial assessment of TEN as it assists in prognosis.3 Treatment instituted is centred on supportive care to the skin and other vital organs. As large areas of skin are denuded, wound care is critical for the prevention of acute skin failure and the complications that may arise such as electrolyte imbalance, hypoalbuminemia, hypo/hyperthermia and fulminating sepsis.

Preventive trends with IVIG and systemic corticosteroids although used extensively, has not been consistently beneficial for TEN.6 In a review by Kirchhof et al there was benefit shown with the administration of cyclosporine when compared to the use of IVIG.7 In this case, short course of Methylprednisolone followed by IV Hydrocortisone was prescribed, and showed some initial improvements. Single dose of etanercept has also induced re-epithelisation with success in patients where SLE was the cause.8 In our patient, the development of TEN and SLE synchronously contributed to her being severely immunocompromised, which led to her demise.

Conclusion

SLE-associated TEN is a potentially fatal disease, a dermatological emergency. A multidisciplinary team comprising of dermatologist, rheumatologist, intensivist and infectious disease specialist should be managing the patient for better clinical outcomes.

Conflict of Interest Declaration

The authors have no conflict of interest to declare

Acknowledgement

The authors would also like to thank the Director General of Health, Malaysia for permission to publish this paper.
References


A Case Report of Acne Agminata

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2Department of Pathology, Hospital Sultanah Aminah, Johor Bahru, Malaysia

Summary
Granulomatous facial skin lesions are a rare and challenging clinical problem. Differential diagnoses include cutaneous tuberculosis, sarcoidosis, granulomatous rosacea and acne agnimata. We reported a case of acne agminata presented with granulomatous facial papules.

Key words: Acne agminata, granulomatous facial papules

Introduction
Granulomatous facial skin lesions are a rare and challenging clinical problem. Differential diagnoses include cutaneous tuberculosis, sarcoidosis, granulomatous rosacea and acne agnimata. We reported a case of acne agminata presented with granulomatous facial papules.

Case Report
A 51 years old Indian lady presented with multiple brown-coloured, non-pruritic painless papules over her face and neck since June 2015. The skin lesions initially started on the lateral side of nose and perioral region, which later spread to the periorbital region. No history of facial flushing or worsening upon sun exposure. She had no constitutional symptoms and no history of steroid consumption. Examination revealed multiple discrete brownish coloured papules on the forehead, periorbital and perioral region. (Figure 1a, 1b)

Systemic examination was normal. Laboratory indices were normal except for a positive antinuclear antibody (ANA) with a titre of 1:256. Mantoux test was negative. Her chest x-ray and CT brain revealed no abnormal findings.

Skin histology revealed numerous epitheloid granulomas (Langerhan’s type giant cell) within the dermis and peri-appendageal areas. These granulomas are formed by collection of epitheloid histiocytes, with some showing evidence of necrosis (Fig 2a, 2b, 2c). Patchy infiltrates of lymphocytes and plasma cells were seen in peri-vascular and peri-appendageal areas. There was no evidence of
malignancy. No fungal bodies were seen on PAS and GMS stains. No acid fast bacilli were detected on Ziehl-Neelsen (ZN) and Wade Fite stains.

The clinical presentation and histological findings were consistent with acne agminata. She was treated with dapsone but showed minimal improvement. She was then started on prednisolone which resulted in significant improvement of her skin lesions. However upon tapering down the prednisolone dosage to 15mg OD, her condition worsened. She was then commenced on oral isotretinoin 20mg OD and her lesions improved greatly. Her prednisolone was tapered off after one month.

Discussion

Acne agminata or lupus miliaris disseminates faciei (LMDF) was first described by Fox in 1878 as “disseminated follicular lupus”. Its pathogenesis is still much unclear. It is a rare condition which was initially thought to be associated with tuberculosis. It is seen often in young adults of both sexes though it can affect at any age groups. In 2000, Skowron et al proposed a name change from LMDF to FIGURE (facial idiopathic granulomas with regressive evolution).

In our patient, her presentation is similar to those described in previous reports of acne agminata. The skin lesions are characterised by multiple, 1 – 3 mm, discrete, smooth, brown/red to yellowish dome-shaped papules. Typically, the lesions appeared on central and lateral side of the face, particularly on and around eyelids and often extend onto the neck and chin. Diascopy examination may reveal apple-jelly nodules like those seen in lupus vulgaris. Histologically, there are typical changes seen in the skin biopsy of our patient. This includes epithelioid granulomas within the dermis, which may be caseating even in the absence of tubercle bacilli. There were no acid fast bacilli detected on ZN and Wade Fite stains in the histology of our patient. These changes are conforming to those seen in acne agminata.

Acne agminata is classified into 3 stages based on age of the lesions, which are early (developing), fully developed and late lesions. In the early (developing) stage, the lesions developed within 1 month and usually less than 2 mm diameter. The histology will show superficial peri-vascular and peri-appendegal cellular infiltrate composed of lymphocytes, a few histiocytes and occasional neutrophils. In the fully developed stage (which usually occurs 3 – 6 months later), the lesions will enlarged to 3 – 4 mm in size. Histologically it will show ruptured follicular wall involving one or more hair follicles with peri-follicular epithelioid cell granuloma. Late stage usually appears after 8 months and biopsy will show extensive fibrosis at peri-follicular areas with scattered lymphocytes, histiocytes and neutrophils within fibrotic area. In this case, our patient’s histology is likely to be in the fully developed stage.

Our initial differential diagnosis include cutaneous tuberculosis, nodular sarcoidosis, granulomatous-rosacea, steroid dermatitis-resembling rosacea, acne vulgaris, eruptive syringomas and multiple trichoepithelioma. However, there was no significant lymphadenopathy or other systemic involvement suggestive of tuberculosis or sarcoidosis. Chest radiograph and CT scans were normal. Our patient also did not have any history suggestive of rosacea such as flushing of the face or lesions being aggravated by sun exposure. Histologically the lesions were not suggestive of multiple trichoepithelioma or eruptive syringoma.

The management of acne agminata is often difficult. The disease itself is self-limiting with spontaneous resolution seen within 2 years. However, it often heals with scarring. Several modalities have been tried and found to be effective which include dapsone, doxycycline, minocycline, isotretinoin, clofazimine, isoniazid and even oral corticosteroids. Topical steroids and psoralen-UVA, erythromycin, and metronidazole have also been used.

Our patient showed no response to dapsone. However she responded well to a course of oral prednisolone. Good response to prednisolone was also seen in a study done by Uesugie et al, whereby 3 out of 4 of his patients showed dramatic improvement with prednisolone.

Our patient developed new lesions while on tapering dose of prednisolone. Hence, we decided to start her on isotretinoin. She responded very well and we were able to taper off her prednisolone after one month. Isotretinoin is known to have effects on the pilosebaceous apparatus and inflammatory processes. Maryam et al reported good response in 2 patients treated with isotretinoin on doses as low as 0.5mg/kg/day.
Conclusion
Acne agminata is a rare condition whereby its pathogenesis is still unclear. Typically, it presented with brown / red to yellowish papules over the facial region. Diagnosis is via clinical and histological examination. We should always bear in mind of the possibility of cutaneous tuberculosis or sarcoidosis upon encountering similar skin lesions. Current modalities of treatment showed variable results. A number of case studies have been reported on the efficacy of different treatments for acne agminata, but no control studies have been done to establish standard-of-care treatment.

Conflict of Interest Declaration
The authors have no conflict of interest to declare

Acknowledgement
The authors would also like to thank the Director General of Health, Malaysia for permission to publish this paper.

Figure 1 (a&b). The clinical presentation of the patient showing multiple discrete brownish papules over the forehead, periorbital, along the nasolabial fold, nose and perioral region.

Figure 2. The histopathological examination of the skin biopsy; (a) Numerous epitheloid granuloma with areas of necrosis (H&E x 40); (b) Numerous epitheloid granuloma with areas of necrosis (H&E x 100); (c) Epitheloid granuloma (H&E x 400)
References


CASE REPORT

Pseudolymphoma due to Hair Dye on Background of Chronic Actinic Dermatitis Responding to Intra-lesional Triamcinolone

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National Skin Centre, Singapore

Summary
Cutaneous pseudolymphoma refers to a heterogenous group of benign T-cell or B-cell lymphoproliferative processes that mimic cutaneous lymphoma clinically and sometimes histologically. The causes of cutaneous pseudolymphoma are diverse, including lymphomatoid drug eruptions, lymphomatoid contact dermatitis, arthropod-bite reactions, chronic actinic dermatitis (CAD). Here we describe a case of pseudolymphoma due to hair dye on background of CAD.

Key words: Pseudolymphoma; hair dye, chronic actinic dermatitis

Introduction
Cutaneous pseudolymphoma refers to a heterogenous group of benign T-cell or B-cell lymphoproliferative processes that mimic cutaneous lymphoma clinically and sometimes histologically.1 The causes of cutaneous pseudolymphoma are diverse. It can occur in patients with chronic actinic dermatitis (CAD). Here we describe a case of pseudolymphoma due to hair dye on background of CAD.

Case Report
A 76-year-old first was diagnosed with CAD following a year of photo-distributed erythematous, scaly plaques affecting the face, V-neck, extensor aspects of his forearms. His MED to UVB was 30mJ/cm2 on phototests. Workup for his photo-distributed rash included showed undetectable levels of plasma porphyrins, creatine kinase levels of 228u/L (normal range 30-350u/L), negative anti-nuclear antibody and extractable nuclear antigen antibody (ENA), with marginally raised aldolase levels (6.60u/L; normal range 1.3-6.3u/L). His retroviral, hepatitis B and C screens were negative. Skin biopsy demonstrated superficial and deep perivascular dermatitis with eosinophils.

The dermatitis was well-controlled with methotrexate (cumulative dose: 835mg) and topical steroids. However, he had a persistent facial plaque despite multiple changes to his topical therapy. He denied
any preceding insect bites, trauma, or contactants, though he had used hair dye regularly for many years. He claims to be compliant to photoprotection. A one-month trial of oral doxycycline 100mg twice daily was unhelpful.

The facial lesions were only responsive to intralesional triamcinolone and oral prednisolone, though recurrence occurred upon cessation of therapy. Clinically, the patient has an indurated, erythematous plaque on the forehead (Figure 1). There was no palpable cervical lymphadenopathy. He declined to undergo patch-tests. Skin biopsy from the forehead lesion showed a superficial and deep lymphocytic infiltrate admixed with eosinophils and plasma cells. A lymphoid follicle was present in the upper reticular dermis with reactive germinal centre containing tingible-body macrophages (Figure 2). Direct immunofluorescence was negative. No light chain restriction was detected on kappa and lambda immune-histochemical stains. The clinical picture and presence of lymphoid follicle on skin biopsy was suggestive of B-cell pseudolymphoma on background of CAD.

The patient currently remains on follow-up and is on a tapering dose of prednisolone for his facial lesion.

Discussion

Cutaneous pseudolymphoma refers to a group of benign T-cell or B-cell lymphoproliferative processes that clinically or histologically mimic cutaneous lymphoma. Cutaneous T-cell pseudolymphoma (CTPL) may be classified into distinct entities such as lymphomatoid drug eruptions, lymphomatoid contact dermatitis, arthropod-bite reactions, and actinic reticuloid. Cutaneous B-cell pseudolymphoma (CBPL) may be idiopathic, or triggered by Borrelia Burgdoferi tick bite, trauma, tattoos. Clinically CBCL usually present as red or skin-coloured dermal and subcutaneous nodules and plaques, mimicking cutaneous B-cell lymphomas.

A constellation of histological findings may help distinguish CBPL from cutaneous B-cell lymphoma. CBPL typically shows a predominantly nodular or diffuse infiltrate of lymphocytes, admixed with histiocytes, eosinophils and plasma cells, which tend to favour the papillary dermis ("top-heavy"). This is contrast to cutaneous B-cell lymphoma where the infiltrate is more intense in the deep dermis ("bottom-heavy"). Germinal centres in CBPL can be divided in to small-cell nodular forms that show typical germinal centre formation with no cellular pleomorphism; and large-cell nodular forms which show large pleomorphic lymphocytes with mitotic figures. Immunohistochemical studies may then be employed to help distinguish between CBPL from cutaneous lymphoma. CBPL typically demonstrate a mixture of κ and λ light chains in B cells, in contrast to cutaneous B-cell lymphoma which usually expresses either κ or λ light chains. However, the expression of monotypic light-chains is only useful diagnostically when there is clear-cut restriction of light chains with κ/λ ratio of more than 10:1 or less than 0.5:1. Other useful markers include MT2/CD45RA which stains very intensely in B-cell lymphoma compared to CBPL, and anti-bcl-2 protein monoclonal antibodies, which stain positive in cutaneous B-cell lymphoma within germinal centres. In general, histological features that favour CBPL over cutaneous B-cell lymphoma include acanthosis, top-heavy infiltrate, mixed cellular infiltrate, presence of germinal centres, presence of tangible bodies, vascular proliferation, preservation of adnexal structures.

The mainstay of treatment of cutaneous pseudolymphoma is removal of the causative agent. However, cutaneous pseudolymphoma can have a chronic and indolent course. Localized persistent lesions may be treated with topical or intralesional corticosteroids, cryosurgery and surgical excision, with varying success. There have been reports of CBPL transforming to cutaneous lymphoma, and therefore long-term follow-up may be required. However, whether these cases represent a misdiagnosis of lymphoma or true malignant transformation remains to be seen.

We believe our patient had B-cell pseudolymphoma, and not actinic reticuloid given the histological findings of a lymphoid follicle with a reactive germinal centre, which is suggestive of a B-cell lymphocytic infiltrate. In contrast, actinic reticuloid is characterized by a predominantly T-cell infiltrate. Histological features that point to cutaneous pseudolymphoma rather than cutaneous lymphoma in this patient include a mixed cellular infiltrate, presence of germinal centres, and tingible bodies, with negative light-chain restriction studies. Contact allergy is frequently reported in CAD. A more recent study of 50 patients with CAD reported a significant increase in contact allergy to p-phenylenediamine, a marker of hair dye sensitivity, reflecting the increased popularity of hair-dyeing practices in recent years. His ongoing use of hair dye and possible underlying contact allergy to P- paraphenylenediamine may
contribute to the persistence of the lesion despite photoprotection, topical and systemic therapy. Unfortunately, he declined patch-tests and wishes to maintain his hair-dyeing practices.

**Figure 1.** An indurated, erythematous plaque on patient’s forehead (arrow)

**Figure 2.** Photomicrograph showing reactive lymphoid hyperplasia in the (arrow) and superficial and deep lymphocytic infiltrate admixed with eosinophils and plasma cells (H&E, x200)

**Conclusion**
Cutaneous pseudolymphoma can mimic cutaneous B-cell lymphoma. A constellation of histological findings may help to distinguish CBPL from cutaneous B-cell lymphoma. The mainstay of treatment of CBPL is removal of the causative agent.

**Conflict of Interest Declaration**
The authors have no conflict of interest to declare.

**References**

CORRESPONDENCE

Malaysia Urticaria Expert Group (MARTEG) Meeting Outcomes


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Key words: Chronic urticaria, Chronic spontaneous urticaria, antihistamines

Dear Editor,

Malaysia Urticaria Expert Group (MARTEG) met on the 7th May 2017. The meeting was jointly held by the Dermatological Society of Malaysia and the Malaysian Society of Allergy and Immunology. MARTEG comprised twelve dermatologists and three allergists. It has four main objectives:

1) To optimise efficacy and safety of management of urticaria in Malaysia
2) To promote awareness of urticaria among healthcare professionals and patients
3) To adapt management of urticaria to the local setting
4) To identify knowledge gaps that impact the management of urticaria in Malaysia.

During this meeting, key international urticaria guidelines, including the European (EAACI)¹, British (BSACI)², American (AAAAI)³ and Asian (AADV)⁴, were discussed. MARTEG achieved consensus on treatment recommendations for Malaysian primary care practitioners and pharmacists managing acute and chronic urticaria. Overall, the EAACI 2013 was the most referenced. Urticaria is defined as wheals with or without angioedema. Acute urticaria is defined as urticaria

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lasting shorter than 6 weeks and chronic urticaria is defined as urticaria lasting longer than 6 weeks.\textsuperscript{3} Chronic urticaria is an umbrella term to include chronic spontaneous urticaria, physical/inducible urticaria and autoimmune urticaria. Refractory chronic spontaneous urticaria is defined as cases who fail to achieve urticaria activity scores of less than 3 despite second generation non-sedating antihistamines (nsAH) at four-fold licensed dose.

The first-line treatment for chronic urticaria is nsAH at licensed once daily dosing. If symptoms remain after 2 weeks,\textsuperscript{5} nsAHs dose may be increased up to four-fold. If symptoms are still not adequately controlled after another 2 weeks, referral to an urticaria specialist (adult and pediatric dermatologists, and allergists/immunologists) should be made. In the absence of a prescription, pharmacists should dispense antihistamines at licensed doses. Only doctors, not pharmacists, should be permitted to up-dose nsAHs by four-fold to ensure proper safety monitoring.

First generation, sedating antihistamines should be avoided in the treatment of urticaria due to their sedating and anticholinergic side effects.\textsuperscript{5} MARTEG recognises that montelukast may be useful as a third line add-on therapy for some patients, hence further research is required to identify this subset of patients in Malaysia. Ciclosporin is an effective treatment for urticaria but patients should be closely monitored by an urticaria specialist for side effects.\textsuperscript{3} Omalizumab is effective and useful in patients who do not respond adequately to high-dose nsAHs\textsuperscript{1}. Short-course oral prednisolone 0.5mg/kg/day for 3-7 days can be useful in the management of urticaria exacerbations in addition to nsAHs.\textsuperscript{1} MARTEG strongly discourages frequent or prolonged courses of oral, intramuscular or intravenous steroids in any form due to potential serious systemic side effects. MARTEG recommends that updosing of antihistamines in paediatric patients should only be done under supervision of an urticaria specialist. MARTEG recommends using standard doses only in children due to the lack of evidence in terms of long term safety.

MARTEG proposes the following research questions in decreasing order of importance:

1. Epidemiology of chronic urticaria in the Malaysian adult and paediatric populations.
2. Efficacy and safety of montelukast as an add-on therapy to nsAHs in the treatment of refractory chronic spontaneous urticaria. (Refractory chronic spontaneous urticaria is defined as Urticaria Activity Score (UAS) of greater than 3 despite four-fold dosing of nsAHs.)
3. The efficacy and safety of dual combination nsAHs at doses up to four-fold in patients who are not controlled on a single nsAHs at increase dosage up to four-fold.

The second MARTEG meeting will take place during the 42nd Annual Dermatology Conference in August 2017.

**Conflict of Interest Declaration**
MARTEG has received support to hold the meeting from Menarini Asia Pacific Pte Ltd. This manuscript has been written by MARTEG members with no involvement of MENARINI employees.

**Acknowledgement**
MARTEG would like to thank A/Prof Mokhtar Nor from Hospital University Sains Malaysia, Kelantan for his contribution during this meeting.
No | Recommendations
--- | ---
1 | *nsAHs is the first-line treatment of urticaria and up to four-fold licensed dose may be used.
2 | Use of *sAHs are not recommended due to sedation and anti-cholinergic side effects.
3 | General practitioners are advised to refer to specialists for further management if four-fold updosing of antihistamines fails to adequately control urticaria.
4 | Pharmacists should advise the use of *nsAHs at standard licensed doses and refer to general practitioners or specialists if standard doses fail to control urticaria.
5 | Montelukast remains a potential add-on for resistant urticaria after four-fold updosing of *nsAHs.
6 | Ciclosporin and Omalizumab are effective third-line treatment options for urticaria, which should be used under specialist supervision.
7 | Short courses of oral prednisolone 0.5mg/kg/day for 3-7 days can be used for acute urticaria and exacerbation of chronic urticaria. However, frequent or prolonged courses of oral, intramuscular or intravenous steroids in any form are strongly discouraged due to potential serious systemic side effects.
8 | Updosing of *nsAHs in children should be done under close supervision and caution by specialist due to the lack of available evidence on safety.

*sAHs: first generation sedating antihistamines, *nsAHs: second generation non-sedating antihistamines

References

CORRESPONDENCE

A Rare Case of Cutaneous Infection of *Mycobacterium fortuitum*

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²Department of Dermatology, National Skin Centre, Singapore

**Key words:** *Mycobacterium fortuitum; non-tuberculous mycobacteria, cutaneous infections*

Dear Sir,

Cutaneous infections caused by non-tuberculous mycobacteria (NTM) are rare, though there has been an increasing trend noted over the past decade.¹ It is usually suspected in the immunocompromised, and diagnosis can be delayed in immunocompetent patients. A high degree of clinical suspicion is often required. We present an unusual case of cutaneous *M. fortuitum* infection in an adult male.

A 77-year-old Chinese gentleman presented with a four-month history of occasional pruritic papular rash over his right forearm (Fig. 1). He had a background history of metabolic syndrome, coronary artery disease, type two diabetes mellitus (HbA1c 6.4%), gout and benign prostatic hyperplasia. He did not have any prior gardening or soil exposure nor was he on any immunosuppressants. Initial impression was that of a granulomatous rash secondary to atypical infection. Skin biopsies were performed. Histology revealed mild compact hyperkeratosis, acanthosis with marked elastotic background with perivascular aggregates of lymphocytes. There were no granulomas detected. Fungal spores were noted on direct microscopy in 10% potassium hydroxide. He was treated for possible pityrosporum folliculitis with miconazole cream 2 times per day, without much improvement.

The patient subsequently defaulted follow up. Five-months later, he was hospitalized for worsening right forearm cellulitis, with expansion of his verrucous plaques. Clinical impression was deep fungal infection or NTM infection, and repeat histology and cultures were performed. Initial gram stain, fungal and acid-fast bacilli (AFB) smears were negative. Fungal culture later revealed incidental scanty growth of *M. fortuitum*, which was confirmed on mycobacteria culture. The histology findings were consistent with granulomatous infection, with

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compact hyperkeratosis, focal parakeratosis, lower dermal fibrosis, and infiltrates of predominantly neutrophils forming an abscess, admixed with collections of histiocytes, lymphocytes and plasma cells (Fig. 2). He was treated with ciprofloxacin and clarithromycin, with good response.

*M. fortuitum* is usually found in immunocompromised individuals, such as those with diabetes, and in association with trauma or clinical procedures. Diabetics may predispose patients to *M. fortuitum* infection due to the impairment of the antimycobacterial function of their macrophages, leading to poorer outcomes. Therefore, in addition to appropriate antibiotic treatment, tighter control of diabetes is necessary to achieve treatment objectives.

Our patient’s diagnosis was delayed due to a non-representative biopsy with positive fungal scrape presenting as a red herring. Cutaneous *M. fortuitum* was only confirmed after repeat biopsy and cultures. Histological findings for rapidly-growing mycobacteria may be non-representative, depending on the immune status of the patient as well as the disease duration. Therefore, the chance of false-negative investigations can be high, especially in immunocompetent individuals. If there is a high degree of clinical suspicion and when lesions are unresolved despite prior treatment, repeat microbiological investigations with histology are warranted to allow for timely and effective treatment of patients.

The diagnosis of NTM is often made on clinical, microbiological and pathological grounds. Confirmatory microbiology testing with isolation of the causative species on tissue cultures remain as the gold standard. Polymerase chain reaction with the detection of mycobacterial deoxyribonucleic acid, when available, may provide a faster alternative. Histopathology of skin biopsies demonstrate inflammatory granulomatous infiltrate with granuloma formation, abscesses or histiocytic infiltration to the dermis and subcutaneous tissue. Empirical treatment with antibiotics such as macrolides or quinolones may be initiated while results from susceptibility testing are pending. Conventional anti-tuberculosis treatment is ineffective for *M. fortuitum*. The antibiotic treatment of choice include ciprofloxacin, sulfonamides, clarithromycin, amikacin, doxycycline and imipenem for three to six months. Dual-drug therapies are recommended to reduce the risk for antimicrobial resistance, and success rate varies depending on patient and microbial factors. If antibiotics are given timely, surgical debridement or drainage can be avoided. Surgical excision is an option for patients who are recalcitrant to dual antibiotic therapy.

**Conflict of Interest Declaration**
The authors have no conflict of interest to declare

**Acknowledgement**
We thank the National Skin Centre, Singapore, for providing us with the support and resources for this case report.

Figure 1. Right forearm verrucous plaques

Figure 2. Higher power revealed an infiltrate of histiocytes admixed with Langhans-type giant cells and surrounded by numerous lymphocytes, plasma cells and neutrophils (H&E, original magnification 100x)
References


CORRESPONDENCE

A Case of Senescent Actinic Depigmentation

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2National Skin Centre, Singapore

Key words: leukoderma, hypopigmentation, senescent actinic depigmentation, pigmentary disorders

Dear Sir,

A 68 years old diabetic Sri Lankan man with extensive androgenic alopecia and seborrheic dermatitis presented to the National Skin Centre in Singapore with hypopigmented patches on the scalp of a few months’ duration. The patches are not pruritic nor painful. He reports occasional sun exposure with no protection. There is no history of application of cosmetic products or medication on the scalp. On examination, there is extensive alopecia with multiple patches and macules of hypo-pigmentation involving the entire scalp (Fig. 1). There are no other areas of hypopigmentation. There were solar lentigines and ephelides on his face and other sun exposed areas. Skin scraping and microscopy revealed no fungus. A skin biopsy was offered, but the patient declined. A diagnosis of senescent actinic depigmentation was made.

Senescent actinic depigmentation is a relatively new pigmentary disorder of the scalp introduced by Verma et. al.1 The condition was first described in a case series of 10 dark skinned patients who had androgenic alopecia and subsequently developed asymptomatic hypo-pigmented macules which were limited to areas affected by androgenic alopecia. It is uncommon in light skinned individuals, which present with hypermelanosis.1 No association of this condition with other forms of alopecia was found in English literature.

Senescent actinic depigmentation occurs in older patients with androgenic alopecia.2 It is postulated that an excess of pro-oxidants, formed due to the loss of UV protection caused by alopecia, induce melanocyte apoptosis in the pigmentary unit of the aging hair follicles.3 It usually presents as asymptomatic, well defined patches and macules of hypo-pigmentation which are limited within the hair margins. An important differential diagnosis

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to consider is vitiligo – however, unlike vitiligo, senescent actinic depigmentation is limited only to the scalp area. There is also no personal or family history of vitiligo or other autoimmune disorders. Other differential diagnoses, such as drug induced pigmentary disorders, chemical induced leukoderma or post-inflammatory hypopigmentation can be excluded based on the history. A skin scraping for microscopy should be done to look for Malassezia.

Senescent actinic depigmentation is thought to be a benign condition. However, it is important for clinicians to recognize this condition to avoid unnecessary investigations and inappropriate treatment. Reassurance should be given to patients, especially in patient populations where pigmentary disorders have sociocultural implications. Although this condition is not thought to be pre-malignant, it must be noted that oxidative stress has been implicated in cutaneous carcinogenesis and hence patients with actinic depigmentation should be checked and followed up for the development of any suspicious skin lesions.

The management of senescent actinic depigmentation is not well established. As it is a benign and asymptomatic condition, our patient was educated on the importance of sun avoidance and protection. 3 years since presentation, he has not returned with any issues.

In summary, senescent actinic depigmentation of the scalp can occur in dark skinned individuals with a history of androgenic alopecia and should not be confused with other conditions.

Conflict of Interest Declaration
The authors have no conflict of interest to declare

Figure 1. A 68 years old Sri Lankan man with extensive androgenic alopecia presents with asymptomatic hypopigmented macules and patches on his scalp.

References
CORRESPONDENCE

The Night is Darkest Just Before the Dawn

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Summary
This short essay comments on three inflammatory skin reactions that present following the treatment of infectious diseases.

Key words: IRIS, Jarisch-Herxheimer, Mazzotti

Dear Editor,

“The night is darkest just before the dawn,” Harvey Dent declares in the 2008 cult classic The Dark Knight. It is a proclamation that resonates with the human condition, and is a sentiment oft-expressed by doctors to their patients; to persevere, and that all hope is not lost. Here, we discuss three conditions where the initiation of treatment results in a worsening before a turn for the better.

The immune reconstitution inflammatory syndrome (IRIS) is the first condition that mirrors the spirit of the quote. It occurs in HIV patients who have just been diagnosed and initiated on treatment. This is characterized by the paradoxical worsening of pre-existing infections [1], as the previously suppressed immune system reactivates and starts an inflammatory reaction against the infection. Generally, this happens within one to three months of starting HAART. An example includes CMV retinitis resulting in visual impairment. Many dermatoses that are exacerbated by HIV such as seborrheic dermatitis, psoriasis and eosinophilic folliculitis can also worsen in the initial stage of treatment.

The second condition is the Jarisch-Herxheimer reaction- a sequelae of treating syphilis, particularly in the acute phase occurring in patients with high rapid plasma reagin (RPR) titres [2]. While this is generally self-limiting, patients should be forewarned about the systemic symptoms that come on soon after the first dose of penicillin. This most commonly manifests as oedema or pain in the primary ulcer and a macular eruption. Severe

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cases may require admission to be monitored for complications such as shock.

The third condition, the Mazzotti reaction, is less well-known. It is a response to the treatment of onchocerciasis using diethylcarbamazine (DEC). As with the J-H reaction, the severity of the Mazzotti response correlates with the severity of the infection, with the corresponding symptoms of fever, hypotension, pruritus and adenitis [3]. Interestingly, this reaction is so common that it can be used to confirm the diagnosis of river blindness by using DEC in a patch test of patients.

The effect of these syndromes has only served to complicate treatment outcomes for these patients as it can be difficult to demand patients place their faith in something that will eventually make them better. “You’ll get more sick at first,” does not inspire confidence. It was not very long ago that being HIV+ meant a death sentence; today, advances in our understanding of the disease has added years to the prognosis. To those patients who waited and suffered, mostly in silence, the quality of life experienced by HIV+ patients now would have seemed like a pipe dream. I hope someone was there to express the second half of the quote, in sentiment if not in exact wording, “— and I promise you, the dawn is coming.”

Conflict of Interest Declaration
The authors have no conflict of interest to declare

References
OBITUARY NOTICES

Dr Noorlaily binti Mohd Noor
Consultant Dermatologist
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2nd April 1974 – 3rd March 2017

How do you say goodbye to someone so young and full of life? That’s our Laily, the sweet and gentle person with a smiling face. Laily succumbed to multiple myeloma the Friday evening of March 3rd 2017 when the sun was setting and the sky was a glorious array of all the colours that she would have liked. She was in the comforts of her own home, in her own room and surrounded by her close family and friends. It feels like only yesterday that as we discussed our cases along the corridors of the hospital that she started facing one adversity after another. Though her illness was non-forgiving and raging on, she faced it with such grace and strong will, that she actually won the battle in her soul though not in her body. Laily was also a person who found comfort in God’s grace and was always surrounded by people she loved. Her family especially her sisters were her pillars of strength.

Laily served as a dermatologist in Hospital Kuala Lumpur from July 2009. She obtained her MRCP in 2005 and worked as a physician in Hospital Kuala Lumpur from 2005-2006. She went on to pursue her degree in Advanced Masters in Dermatology and graduated as a dermatologist in July 2009. She then did her fellowship in infectious dermatology at the St John’s Institute of Dermatology in 2010. Her contribution in the field of dermatology especially in Hansen’s disease will be remembered. She wanted to continue her work and contributed as much as she could and did so with dedication and passion until the end. Laily contributed to the nation through her involvements in the society and the field of dermatology. It was through her lectures and presentations that most of the dermatologists in the country came to know her better.

We remember her for her quietness, her gentleness, her grace and her soft-spoken ways. We have lost not only a dermatologist but a friend and comrade. Memories of the good times will carry us on.

Rest sweet Laily, rest in peace. Your journey has ended and your pain and struggles have ceased. We will miss you always. May Allah bless your soul and place you among the pious.

Alfatihah.

Dawn Ambrose
Noor Zalmy Azizan
Azura Mohd Affandi
Erratum for Malaysian Journal of Dermatology
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In the Contents, there are errors in authorship of 2 Case Reports:
• “The wrath of the Rengas: A Report of Severe Contact Dermatitis and Implications for Public Health in Rural Areas”
  The authors should be – Xavier G, Yong KY, Pubalan M
• Maxillary Oral Cutaneous Fistula in Diabetes Mellitus Patient: A Case Report
  The authors should be – Tan ST, Gunawan L, Reginata G

In the original article “Correlation Between Cumulative Dose of Methotrexate and Methotrexate Induced Hepatotoxicity in Psoriasis Patients Undergoing Liver Biopsy – A 15 Years Retrospective Study”
A printing error for the first sentence under the Results in the abstract: “Skin areas treated with AEBritening Complex-01 showed significant degree of lightening effect (+1”’. This sentence does not belong to the abstract but was mistakenly printed there.
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