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An editorial 700-1200 words in length with approximately five references. The author may express his or her opinion without complete documentation.

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Letters to the editor and short notes. Contributions should not exceed 600 words, two figures, and 10 references.

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Refer to patients by number or letters; names or initials should not be used.

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Send illustrations as tiff or jpeg files. In the case of photomicrographs, the stain type and original magnification should be stated. Each figure should bear a reference number corresponding to a similar number in the text.

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Letter to Editor

A PATIENT WITH AN UNEXPLAINED OILY PANNICULITIS THAT RESPONDED TO DOXYCYCLINE

Su P, Ng SK

Sir,

In some cases of panniculitis, an oily discharge may be seen. The important causes of this oily panniculitis are pancreatic panniculitis and Alpha-1-antitrypsin (AAT) deficiency panniculitis. We report a 51 year old Chinese lady who presented with a painful plaque over her left axilla. On biopsy, a film of oil was noted to be coming from the panniculus. Investigations were negative for pancreatic panniculitis and AAT deficiency panniculitis. She responded promptly to doxycycline.

A 52 year old female presented to the Accident and Emergency (A&E) department with pain and redness over her left axilla. There was no history of trauma. She was treated initially for cellulitis and concomitant herpes zoster with cloxacillin and acyclovir.

However, a week later, there was still persistent pain and the patient was referred to us. On examination, a tender erythematous plaque was seen over her left axilla (Fig. 1). A biopsy was scheduled. During the biopsy, an oily film was seen coming from the panniculus (Fig. 2). Histology was consistent with a neutrophilic panniculitis. Investigations to rule out pancreatic disease were negative [amylase 37u/L (0-110u/L); lipase 9u/L (8-55u/L)]. Investigations to rule out AAT deficiency were also negative [AAT levels measured on two occasions: 141mg/dL and 132mg/mL (70-180mg/dL)]. Other investigations that were negative were bacterial and fungal cultures. A Computed Tomography (CT) scan of the thorax and abdomen showed non-specific ground glass changes and spirometry was also unremarkable. She was prescribed doxycycline and the response was significant, with a 50% improvement after one week.

Figure 1. An erythematous indurated plaque over the left axilla.

Figure 2. Oily droplets (arrow) seen during the incisional biopsy.

We report a case of an oily panniculitis, with no obvious preceding cause, and which responded well to doxycycline. Initial differentials included pancreatic panniculitis, AAT deficiency panniculitis and infective panniculitis. However, serum lipase, amylase, AAT levels and infective cultures were normal. 25% of patients with AAT panniculitis,
however, may have normal serum AAT levels. In addition, lesions may be induced by low intensity trauma or simply physical activity of the affected area in 35% of cases with AAT panniculitis so a negative history for trauma does not exclude the diagnosis. Other differentials of a neutrophilic panniculitis might include factitious, Sweet’s syndrome or neutrophilic panniculitis associated with rheumatoid arthritis but features of these were histologically and clinically absent in our patient.

It was interesting to note that our patient has a good response to doxycycline as this has been used as a treatment for AAT associated panniculitis. It is possible that the anti-inflammatory effect of doxycycline contributed to the patient’s improvement rather than its antimicrobial activity.

In conclusion, our case represents an idiopathic oily panniculitis which showed good response to doxycycline. Fortunately for the patient, there was no evidence of pancreatic panniculitis or AAT deficiency panniculitis which may otherwise be associated with a less desirable prognosis.

References

Letter to Editor

GEFITINIB-INDUCED ACNEIFORM ERUPTION

Long V

Sir,

A 70-year-old Asian female with advanced non-small-cell lung adenocarcinoma with metastasis receiving gefitinib 250mg daily presented with a progressively worsening pruritic and painful erythematous rash after 1 month of therapy. She denied any drug allergy nor usage of traditional Chinese medications.

On examination, there were widespread erythematous papules, erosions and crusts on her upper limbs and trunk (Figure 1). There were 3 pustules located on her abdomen (Figure 1, arrows), with an area of maceration and pustulation at the left inguinal region (Figure 2). There was no scalp, face, nail involvement nor mucositis. Nikolsky’s sign was negative.

She was afebrile. Full blood count, liver, renal function tests were all within normal limits. C-reactive protein was slightly elevated. Cultures obtained from the pustule and KOH test of the inguinal region were negative.

Gefitinib is a selective EGFR inhibitor. The most common dermatological side effect is an acneiform eruption. Although the pathogenesis of EGFR-induced skin rash is not well clarified, the inhibition of EGFR tyrosine kinase activity seems to be responsible. Lichtenberger et al.1 showed that EGFR is expressed in the basal layer of the epidermis. In papulopustular rash, the main target is the epidermal keratinocyte and not the cutaneous adnexa. The inhibition of EGFR in keratinocytes induces apoptosis, arrests cell growth, reduces cell migration, and increases cell adhesivity and cell differentiation. All these processes induce keratinocytes to release inflammatory chemokines (such as chemokine (C-C motif) ligand 2 (CCL2), chemokine (C-C motif) ligand 5 (CCL5)). Hence, cellular growth arrest and inflammation cause xerosis and the most common appearance of a papulopustular acneiform rash.

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Figure 1. Erythematous patches with 3 non-follicular pustules, erosions and crusts over abdomen (arrows).

Figure 2. Linear pustulation in left inguinal region.
Other side effects include xerosis, telangiectasia, hair changes and paronychia with pyogenic granuloma. In patients presenting with dozens to hundreds of pustules, the differential diagnosis of AGEP must be considered. However, this patient had insufficient pustules to qualify.

Gefitinib was withdrawn temporarily and her skin lesions resolved without treatment. Gefitinib was then restarted without further development of rashes. The dose of EGFR TKI should generally be maintained through mild-moderate acneiform rash (i.e. grade 2 where affected body surface area is between 10%-30%). Even if the rash progresses to stage 3 (>30% body surface area affected), studies have shown that the drug may be temporarily discontinued (2-4 weeks) and reintroduced at physician’s discretion. A “treat-through” approach is commonly employed for EGFR TKI induced rash.

References

Letter to Editor

EYELID THROMBUS - AN UNUSUAL LOCATION, AN UNUSUAL DIFFERENTIAL

Long V\textsuperscript{1}, Liau MM\textsuperscript{2}, Huma J\textsuperscript{2}

Dear Sir,

We describe an unusual case of an asymptomatic papule found on the eyelid of an otherwise healthy male, with an interesting subsequent diagnosis.

A 30-year-old male with no past medical history presents with an asymptomatic papule on the left upper eyelid that has been growing gradually over 4 months. It is mobile, not tethered to the skin and is slightly bluish-tinged. He requested for excision as it was not cosmetically pleasing. Histological examination of the lesion revealed a thrombus composed predominantly of fibrin and admixed with some red blood cells mostly in the periphery of the lesion. Coagulation studies were normal. Antinuclear antibody (ANA) was also within normal limits.

Eyelid lesions prompt several considerations - whether there is skeletal involvement, anatomically “bad” locations, the existence of perineural spread, or otherwise aggressive behaviour of “benign tumors”. Many trials\textsuperscript{1,2} have studied the incidence of eyelid tumors with different histopathological types, citing that up to 86\% of lesions were benign, including squamous cell papilloma, seborrheic keratosis, melanocytic nevi, hidrocystoma and xanthoma. Malignant lesions included basal cell carcinoma, Meibomian gland carcinoma, squamous cell carcinoma.

It is therefore highly unusual that this lesion turned out to be a thrombus, without the patient having any history of thrombotic or connective tissue disorders. The patient did not sustain any injury or trauma to the eyelid area.

\textbf{Figure 1.} Clinical image of asymptomatic left upper eyelid papule with slight bluish-tinge.

\textbf{Figure 2.} Histological image of a thrombus composed predominantly of fibrin and admixed with some red blood cells mostly in the periphery of the lesion.

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Eyelid tumors must be taken seriously as there is a chance that they could malignant. Amongst benign eyelid tumors, squamous cell papillomas are most common. Eyelid thrombus is a rarely reported, but benign lesion. One should not consider an eyelid thrombus in initial generation of differential diagnoses. Rather, practitioners should first take into consideration the possibility of benign and malignant eyelid skin tumors arising from adnexal structures. It is likely that an isolated eyelid thrombus does not signify underlying thrombotic/coagulation/connective tissue disorders, however, it must prompt consideration of these disorders.

References


MULTICLEAR™ TREATMENT FOR STRIAE DISTENSIAE

Su P, Heng JK, Yang SSY, Aw DCW

Abstract

Introduction: Striae distensiae (SD) are common cosmetic complaints. Treatment of SD remains difficult and topical therapies are often disappointing. This study attempts to evaluate the efficacy of ultraviolet light (UVB/UVA1) therapy using the MultiClear™ (Curelight Ltd, Israel) machine in the treatment of SD.

Materials and Methods: Eighteen participants were enrolled into a six-week trial of twice-weekly treatments. Fourteen completed the study. Pre-and post-treatment measurements of the width and length of striae over the abdomen or thighs were taken. Pre- and post-treatment photographs were assessed by a blinded investigator and any improvements were rated on a 4-point scale.

Results: Six participants (42.9%) had reductions in the width of their SD (Mean reduction 0.54mm, p= 0.0038). Four participants (28.6%) had reductions in the length of their SD (Mean reduction=4.57mm, p= 0.069). Nine participants (64.3%) did not have any noticeable improvement in the appearance of their SD. Ten participants (71.4%) developed tanning as a consequence of treatment. No patients experienced any pain.

Conclusion: Ultraviolet light (UVB/UVA1) therapy may help reduce the width of SD in skin phototypes IV-V but tanning is a common side-effect.

Introduction

Striae distensae (SD) or stretch marks are common cutaneous lesions, most prevalent amongst adolescents, pregnant women and in individuals of body mass index (BMI) greater than 27. Up to 88% of adolescence may be affected. In addition, the anatomical locations affected may vary between different patient population groups. The abdomen and breasts are the most common sites for SD in pregnant women. Although they do not pose any threats to internal health, these dermal scars can cause significant psychological burden for patients.

Two forms of SD have been described: striae rubrae and striae albae. The former appears initially as linear erythematous plaques which then progress to become hypopigmented atrophic scars (striae albae). Several factors are thought to contribute to the pathogenesis of SD. These include mechanical stretching of the skin (e.g. in pregnancy, during the adolescent growth spurt), hormonal imbalance (hypercortisolic states such as Cushing syndrome) and hereditary influence. Striae distensiae can be cosmetically distressing and various treatment strategies have been tried.

Unfortunately, treatment of SD is both frustrating and disappointing. Studies evaluating the efficacy of topical agents have been conflicting. Furthermore, the therapeutic outcome may vary according to the type of SD. Tretinoin appears to be more efficacious in the treatment of striae rubrae than striae albae. It may also be beneficial in preventing or reducing the severity of striae gravidarum. Some of these topical agents may have a beneficial effect on SD through collagen stimulation. Ud-Din et al demonstrated significantly higher collagen levels in patients with SD treated with silicone gels.
In recent years, other treatment modalities have been tried. These include chemical/mechanical debridement techniques, ablative and nonablative lasers, fractional resurfacing, light therapy, radiofrequency devices and microneedling therapy. Pulsed dye laser and intense pulsed light are thought to improve the appearance of SD through the stimulation of collagen production\(^{14,15}\). Fractional carbon dioxide laser was shown to be more effective than topical treatment with 10% glycolic acid+0.05% tretinoin cream in reducing the mean striae area in patients with striae alba\(^{16}\). Microdermabrasion has been reported to activate a dermal remodeling and wound healing cascade via the elevation of transcription factors, primary cytokines, matrix metalloproteinases and procollagen\(^{17}\).

The MultiClear™ machine is a multi-wavelength medical device which can be adjusted to optimal narrow band emission spectra in the UV A and UVB range. Specifically, it emits three different ranges of narrow-band light-UVB (296-315nm), UVA-1(360-370nm), and blue light (405-420nm) or blend of UVB and UVA1. Thus, it is able to selectively target many skin conditions including psoriasis, acne and vitiligo\(^{18,19,20}\). In addition, it may help repigment hypopigmented scars and striae alba. To our knowledge, only one study using the MultiClear™ device has been used in the treatment of SD and it demonstrated a greater than 50% improvement in repigmentation of stretch marks of 67% of participants at 8 weeks and 56% of participants at 12 weeks after the last treatment\(^{21}\).

In the present study, we evaluate the efficacy and safety of 12 twice-weekly treatments of UVB/UVA1 for the treatment of SD in patients of skin phototypes IV-V. The study was approved by National Healthcare Group (NHG) Domain Specific Review Board.

### Materials and Methods

The study was conducted at the National University Hospital (NUH) in Singapore with the aim of assessing the efficacy of UVB/UVA1 therapy for the treatment of striae alba. Thirty participants were consecutively assessed for eligibility and recruited accordingly into the study. Patients with other co-existing dermatoses, who were pregnant, previously intolerable to light treatment or treated with light in the last six months and patients with skin type III and below were excluded. Eligible patients were those of either gender aged 21 and above who had striae alba, able to attend treatment sessions regularly and not currently using any topical treatment for their striae alba. Eighteen participants were enrolled and twelve excluded. During the first visit, the width and length of the widest striae over the abdomen or thighs were measured and a baseline photograph was taken. Participants were treated according to the MultiClear™ (Curelight Ltd, Israel) manufacturer’s protocol for striae alba with the UVB/UVA1 mode. All treatments started with a minimal erythema dose (MED) of 75mJ/cm\(^2\) which was increased by 0.5MED for subsequent treatments. All subjects received twice-weekly treatments over a period of 6 weeks. Normal skin surrounding the striae distensiae was shielded with a UV-blocking stencil. Each treated area was a one-inch square which was added up to cover the intended area of treatment.

Upon completion the course of treatment, participants were assessed by a doctor and measurements over the reference stria were repeated. The same doctor performed pre- and post-treatment measurements. Any change in pre- and post-treatment measurements was calculated as a percentage of the pre-treatment measurement. Pre and post-treatment photographs (with the participants in standing position) were evaluated by a blinded investigator. The improvement in striae

### Table 1. 4-point scale used to grade participant’s striae distensiae (SD) after treatment.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Minimal to no improvement; &lt;25% (stretch marks hardly changed or no obvious change)</td>
</tr>
<tr>
<td>2</td>
<td>Moderate improvement; 26-50% (stretch marks show some improvement in size only)</td>
</tr>
<tr>
<td>3</td>
<td>Good improvement; 51-75% (stretch marks substantially diminished in size)</td>
</tr>
<tr>
<td>4</td>
<td>Very good to excellent improvement; &gt;75% (stretch marks disappeared or almost disappeared)</td>
</tr>
</tbody>
</table>
was graded on a 4 point scale (Table 1). Presence of tanning was recorded. A post-treatment feedback form was also distributed to the participants.

Pre- and post-treatment results were analysed using a one-tailed T test.

Results

Eighteen participants were enrolled for the study. Fourteen participants completed the study. Four dropped out due to unsightly pigmentation from tanning and inability to comply with the treatment schedule. Those who dropped out were not included in the final analysis of the study.

(i) Patient demographics

All participants were female. The median age was 28 years (Range: 26- 52 years). All but two were of skin phototype IV (Table 2). 50% of the participants were Chinese, the remaining were either of Malay, Filipino or Indian race.

(ii) Pre- and Post-treatment measurements

Six participants (42.9%) had reductions in the width of their SD varying 10-40% (Mean reduction 0.54mm, p= 0.0038), the remaining eight participants showed no change (Table 3). Four participants (28.6%) had reductions in the length of their SD (Mean reduction 4.57mm, p= 0.069) whilst ten participants had no difference.

(iii) Pre- and Post-treatment appearance of SD

Most participants (64.3%) did not have any noticeable improvement in the appearance of their SD (Graph 1, Figures 1-3). Ten participants (71.4%) were noted to develop tanning as a consequence of treatment. Four patients developed marked tanning that took the form of the stencil shape that was exposed to the UV light (Figure 4).

(iv) Patient Feedback

Close to half (42.9%) of participants felt that there was no improvement in their stretch marks after treatment. Only four participants (28.6%) perceived some improvement. When asked on aspects of improvement, half of the patients felt that there was improvement in colour. Ten (71.4%) participants felt warmth during treatment but none experienced any pain. The only reported side-effect was tanning in eight (57.1%) of the participants. Only four participants (28.6%) would recommend the treatment to others.

Table 2. Patient demographics.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age</th>
<th>Race</th>
<th>Skin phototype*</th>
<th>Site of striae distensae</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27</td>
<td>Malay</td>
<td>IV</td>
<td>R lower abdomen</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>Chinese</td>
<td>IV</td>
<td>L thigh</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>Malay</td>
<td>IV</td>
<td>R thigh</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>Chinese</td>
<td>IV</td>
<td>L abdomen</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>Malay</td>
<td>V</td>
<td>L abdomen</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>Chinese</td>
<td>IV</td>
<td>R thigh</td>
</tr>
<tr>
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<td>Malay</td>
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<td>8</td>
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<tr>
<td>14</td>
<td>37</td>
<td>Chinese</td>
<td>IV</td>
<td>R abdomen</td>
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</table>
Table 3. A summary of the pre- and post- treatment measurements of the width and length of the widest striae. The numbers in bold represent the percentage (%) change in measurements.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Width of widest striae (pre-treatment mm)</th>
<th>Width of widest striae (post-treatment mm)</th>
<th>% change</th>
<th>Length of widest striae (pre-treatment mm)</th>
<th>Length of widest striae (post-treatment mm)</th>
<th>% change</th>
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</table>

Graph 1. Improvement in striae distensiae (SD) appearance as scored by the investigator post-treatment.

Figure 1. Pre- (A) and post-treatment (B) photographs of a patient rated to have a grade 2 improvement. This patient also had a 33.3% reduction in the width of the reference SD and a 10% decrease in the length of the longest SD.

Figure 2. Pre- (A) and post-treatment (B) photographs of a patient rated to have a grade 1 improvement. The patient had a 25% reduction in the width but no change in the length of the SD.
help improve the appearance of hypopigmented striae alba through increased melanin pigment, melanocyte hypertrophy and an increase in the number of melanocytes.

Although our study demonstrated a minute but statistically significant improvement in the width of SD after MultiClear™ treatment, the results could be confounded by the small sample size and drop-out bias. Objective scoring of SD is difficult and no scales have been validated. We attempted to objectively measure the width and length of the widest striae but we may have missed significant improvement over the other striae.

The management of SD remains challenging. Only a small proportion of our participants showed satisfactory improvement following treatment. Unsightly patterned pigmentation from tanning was a common outcome. Less intensive treatment regimens may thus be considered in future studies involving laser/light-treatment of SD in Asian patients.

Darker skin types are prone to post-inflammatory skin pigmentation which may be evident after skin resurfacing treatments. Ablative laser treatment using the ablative 10 600-nm carbon dioxide (CO₂) laser may have some benefit in SD treatment but may result in persistent erythema and post-inflammatory pigmentation in patients with skin types IV and VI. Notably, more than half our participants developed tanning as a result of the ultraviolet treatment. Indeed, light sources emitting UVB may help improve the appearance of hypopigmented striae alba through increased melanin pigment, melanocyte hypertrophy and an increase in the number of melanocytes.

Although our study demonstrated a minute but statistically significant improvement in the width of SD after MultiClear™ treatment, the results could be confounded by the small sample size and drop-out bias. Objective scoring of SD is difficult and no scales have been validated. We attempted to objectively measure the width and length of the widest striae but we may have missed significant improvement over the other striae.

The management of SD remains challenging. Only a small proportion of our participants showed satisfactory improvement following treatment. Unsightly patterned pigmentation from tanning was a common outcome. Less intensive treatment regimens may thus be considered in future studies involving laser/light-treatment of SD in Asian patients.

Acknowledgments
The authors would like to thank Madam Peh Bee Eng for her contribution to the study.

Discussion
Only 35.7% of our participants were assessed to have an improvement after comparing pre and post-treatment clinical photos. Moreover, our participants were reviewed within 2 weeks after the last treatment. Different treatment regimens may have contributed to the difference observed. Our participants completed 12 treatment sessions over six weeks whereas in the study by Sadick et al. study, participants completed a maximum of 10 treatments over a longer duration of 22 weeks. In addition, their study focused on repigmentation of striae alba in Fitzpatrick skin types II to IV whereas we evaluated the change in width and length of striae alba in participants of skin types IV and V only.

Figure 3. Pre- (A) and post-treatment (B) photographs of a patient who did not show any noticeable improvement in the appearance of her striae distensae (SD). There was no change in SD measurements after treatment.

Figure 4. Tanning in a patient who completed 12-weeks of twice weekly treatment.
References

EVALUATION OF SERUM BIOTIN AND SERUM FERRITIN IN WOMEN WITH DIFFUSE HAIR Loss

Nagesh TS, Misquith A, Silvia WD

Abstract

Introduction: Diffuse hair loss is a very common problem in women. The condition has several causes. Anything that interrupts the normal hair cycle can trigger diffuse hair loss. Various studies have shown reduced levels of haemoglobin, serum ferritin, biotin, and thyroid abnormalities to be triggering factors for diffuse hair loss. Supplements of biotin and iron are commonly used in the management of diffuse hair loss in females. However, contradictory observational data have so far failed to establish a conclusive evidence about the serum levels of biotin and ferritin.

Materials and Methods: This study has been planned to evaluate the role of hemoglobin, thyroid hormones, serum levels of Biotin and Ferritin in female patients with diffuse hair loss of different types. 80 female patients presenting with diffuse hair loss were included in the study after considering the inclusion and exclusion criteria. Ethical clearance was taken from the institutional ethics committee before starting the study. Serum ferritin and serum biotin were estimated using ELISA method. Haemoglobin was estimated using an auto analyzer. Thyroid function test were evaluated using chemiluminescence method.

Results: Reduced haemoglobin was seen in 35 patients. However, serum ferritin was reduced in only one patient. Hypothyroidism was detected in 8 patients. Serum biotin was normal in all the patients. However, serum biotin was towards the lower limit of normal in many patients.

Conclusion: From findings of our study, association of serum ferritin with hair loss is not conclusive and also the role of biotin in hair loss has to be evaluated with further larger studies.

Keywords: Diffuse hair loss, Serum Ferritin, Serum Biotin, Thyroid Profile

Introduction

Diffuse hair loss is a very common problem in women. The condition has several causes. Anything that interrupts the normal hair cycle can trigger diffuse hair loss. The common causes include telogen effluvium (acute and chronic) followed by female pattern hair loss, anagen effluvium, loose anagen hair syndrome, and diffuse type of alopecia areata1,2.

Various studies have shown reduced levels of haemoglobin, serum ferritin, biotin, and thyroid abnormalities to be triggering factors for diffuse hair loss. Supplements of biotin and iron are commonly used in the management of diffuse hair loss in females. However, contradictory observational data have so far failed to establish a conclusive evidence about the serum levels of biotin and ferritin3. Hence this study has been planned to evaluate the role of hemoglobin, thyroid hormones, serum levels of ferritin and biotin in female patients with diffuse hair loss of different types.
**Materials and Methods**

This was a prospective cross sectional study. The study included 80 female patients aged 18 to 60 years presenting with diffuse hair loss. Ethical clearance was taken from the institutional ethics committee before starting the study. The duration of study extended for a period of 1 year.

A detailed history was taken about the onset, duration and severity of hair loss. Any precipitating factors were ruled out by taking history suggestive of anaemia, thyroid abnormalities, hormonal abnormalities, fever, surgery, pregnancy, emotional stress and crash dieting. The patients were also asked for any drug intake or administration of chemotherapy and hair grooming practices (brushing wet hair, using hair drier, straightening). Patients who were taking iron or multivitamin supplements, any products which influence hair growth or having thyroid abnormalities were excluded from the study. After considering the inclusion and exclusion criterion, the eligible patients were asked to sign a written informed consent. A thorough clinical examination was done to look for any evidence of scarring or patchy hair loss.

**Inclusion criteria :**

- Female patients
- Patients between 18 - 60 yrs
- Non scarring hair loss patients

**Exclusion criteria:**

- Patients on iron or multivitamin supplements for at least 3 months
- History of illness lasting longer than 7 days over past 3 months
- Post partum women within 3 months
- Patients who have applied products known to influence hair growth for 6 months
- Scarring alopecia
- Patient already on treatment for hypo-or hyperthyroidism

**Hair shaft abnormalities**

5ml of blood sample was collected. Serum ferritin and serum biotin were estimated using ELISA method. Haemoglobin was estimated using an auto analyzer. Thyroid function test were evaluated using chemiluminiscence method.

**Results**

Most of the patients in our study were in the age group of 18 to 30 years (60%) followed by 31 to 40 years (27.5%), 41 to 50 years (8.75%) and 51 to 60 years (3.75%) (Table 1). The average duration of hair loss was around 1 year. Reduced haemoglobin was seen in 43.75% of patients. However serum ferritin was reduced in only five patients (6.25%). Hypothyroidism was detected in 8 (10%) patients. Serum biotin was normal in all the patients. However serum biotin was towards the lower limit of normal in many patients (22.5%). (Table 2 and 3)

**Table 1. Age group of patients with hair loss.**

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 to 30 years</td>
<td>48</td>
</tr>
<tr>
<td>31 to 40 years</td>
<td>22</td>
</tr>
<tr>
<td>41 to 50 years</td>
<td>7</td>
</tr>
<tr>
<td>51 to 60 years</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table 2. Haemoglobin, serum ferritin and serum biotin.**

<table>
<thead>
<tr>
<th></th>
<th>Normal (number of patients)</th>
<th>Low (number of patients)</th>
<th>Percentage showing low value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemoglobin (12 – 16 g %)</td>
<td>65</td>
<td>35</td>
<td>43.8%</td>
</tr>
<tr>
<td>Serum ferritin (10-125 ng/ml)</td>
<td>79</td>
<td>5</td>
<td>6.25%</td>
</tr>
<tr>
<td>Serum biotin (7.8 – 500 pg/ml)</td>
<td>80</td>
<td>Nil</td>
<td>Nil</td>
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</tbody>
</table>

**Table 3. Thyroid profile.**

<table>
<thead>
<tr>
<th></th>
<th>Normal (number of patients)</th>
<th>Low (number of patients)</th>
<th>Percentage showing low value</th>
</tr>
</thead>
<tbody>
<tr>
<td>T&lt;sub&gt;3&lt;/sub&gt;</td>
<td>80</td>
<td>0</td>
<td>Nil</td>
</tr>
<tr>
<td>T&lt;sub&gt;4&lt;/sub&gt;</td>
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<td>4</td>
<td>5%</td>
</tr>
<tr>
<td>TSH</td>
<td>76</td>
<td>4</td>
<td>5%</td>
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</tbody>
</table>
Discussion

Hair loss is a common complaint in women and affects over 25% of women in developed countries. Female pattern hair loss (FPHL) and chronic diffuse telogen effluvium (TE) account for majority of cases. Increased shedding of telogen hair results either from synchronous transition of hair follicles from the growing (anagen) to the resting stage of the hair cycle, or from progressive shortening of duration of anagen. The former mechanism underlines TE, the later FPHL. In TE, the telogen rate is elevated in all regions of scalp, including the occipital area; in FPHL, the telogen rate is elevated in the frontal and centroparietal scalp region and spares the occipital scalp.

Anagen effluvium, radiotherapy, drugs, malnutrition, iron deficiency, hypothyroidism, hyperthyroidism, diffuse alopecia areata, telogen gravidarum are some of the other causes of diffuse hair loss.

Iron deficiency is the world’s most common nutritional deficiency. In premenopausal women, the most common cause of iron deficiency anemia are menstrual blood loss, and pregnancy. In postmenopausal women, the most common cause of iron deficiency anaemia are gastrointestinal blood loss, and malabsorption. Haemoglobin concentration can be used to detect for iron deficiency, whereas serum ferritin concentration can be used to confirm iron deficiency.

Ferritin is a highly conserved protein complex that plays an important role in iron storage and is recognized as the main iron-binding protein in nonerythroid cells. Generally serum ferritin is directly related to intracellular ferritin and thus total body iron stores. Only iron deficiency causes very low serum ferritin concentrations; therefore a low serum ferritin concentration is very specific for iron deficiency. Hence serum ferritin investigation is considered to be the most powerful screening tool for iron deficiency.

A study by Rushton et al. has shown reduced haemoglobin in 6% of patients and reduced serum ferritin in 72% of patients. A study by Moltz showed a reduced serum ferritin in 42% of patients. Moeinmaziri et al have also reported reduced serum ferritin in females with diffuse hair loss. This is in contrast to our study where 6.25% of patients have shown reduced serum ferritin. This could be because of the difference in the lower limit of serum ferritin considered in our study. The lower limit of serum ferritin considered in our study was 20ng/ml compared to 40 ng/ml in the above studies. Studies by Bregy A et al, Sinclair and Chamberlain AJ et al also have shown no association of serum ferritin with hair loss in women.

Biotin is a water soluble B-complex vitamin, available in various dietary sources and is also synthesized by intestinal bacteria. Biotin deficiency has been associated with diffuse hair loss and is often used in the management of such cases. However there is no concrete evidence for its association. None of the patients in our study showed reduced serum biotin. After extensive literature search no studies were found which evaluated the role of serum biotin in diffuse hair loss in women.

Diffuse telogen hair loss may occur in association with thyroid abnormalities. Diffuse scalp alopecia occurs in about a third of hypothyroid patients. Hyperthyroidism, when severe, is said to cause a diffuse alopecia in up to 50% of cases. Hypothyroidism inhibits cell division both in epidermis and in skin appendages. In a proportion of patients, this inhibition of mitosis induces catagen and delays re-entry of telogen hair into anagen. The mechanism of hair loss in hyperthyroidism is unknown. With thyroxine replacement, the hair rapidly re-enter anagen and the telogen count falls. Replacement therapy generally leads to re-growth of hair within a few months. An exception to this occurs when the hypothyroidism has been present for many years and the hair follicles have atrophied. Hair loss in the hyperthyroid patient usually stops within 3 months of becoming euthyroid.

A study by Moltz has shown abnormal thyroid function tests in 20% of patients. In our study 10% of patients showed features of hypothyroidism.

Conclusion

Biotin and iron supplements are commonly used in the treatment of hair loss. From the findings of our study, association of serum ferritin with hair loss is not conclusive and also the role of biotin in hair loss has to be evaluated with further larger studies.
References

3. Bergy A. Trueb R. No association between serum ferritin levels> 10 mg/mL and hair loss activity in women: Dermatology. 2008;217:1-6
DERMATOLOGICAL DISEASES AMONG OCTOGENARIANS IN A TERTIARY CENTER

Low DW¹, Adawiyah J¹, Norazirah MN¹, Leelavathi M²

Abstract

Introduction: Our country is fast becoming a developed country with improved life expectancy. The healthcare system should be prepared to manage medical conditions which are prevalent in the older age group. Skin diseases are commonly observed in the geriatric population. We seek to characterize the dermatological conditions affecting patients at the extremes of age.

Methods: To determine the types of dermatological diseases affecting patients over 80 years of age, and to determine their clinical characteristics and comorbidities.

Objectives: Subjects with photodamage were older, and had lower education and employment rates compared to subjects without photodamage. There was no significant difference in knowledge on the harmful effects of sun exposure and on sun protection or in sun avoidance behaviour (other than use of protective sunglasses) between the two groups, though more patients with photodamage felt that they take adequate sun protection measures. Of note, only a low percentage of subjects in both groups (24.5% of subjects with photodamage and 23.1% of subjects without photodamage) practise regular use of sunscreen.

Methods: This was a retrospective study conducted at the Dermatology Unit, University Kebangsaan Malaysia Medical Center (UKMMC). All patients aged ≥80 years who attended the Dermatology Clinic UKMMC in 2015 were identified from the clinic database. Their clinical notes were reviewed. Demography, clinical characteristics and dermatological diagnosis were recorded and analyzed using SPSS Version 22.

Results: One hundred and three octogenarians were included in the study. Fifty one (49.5%) were females, and 52 (50.5%) were males. The age ranged from 80 to 89 years. The majority were Chinese, 76 (73.8%), 16 (15.5%) were Malays, 6 (5.8%) were Indians and remaining 5 (4.9%) were of other ethnicities. The most commonly seen diseases were endogenous eczema 46 (44.7%), cutaneous malignancy 10 (9.7%), psoriasis 8 (7.8%), bullous pemphigoid 7 (6.8%) and fungal infection 6 (5.8%). More than half of patients [25 (24.3%)] with endogenous eczema had unclassified eczema. Other conditions were seborrheic keratosis 5 (4.9%), adverse drug eruption 5 (4.9%), viral infections 4 (3.9%) and lichen amyloidosis 3 (2.9%). Comorbidities of the patients were 48 (46.6%) hypertension, 29 (28.2%) diabetes, 25 (24.3%) atherosclerosis related disease, 22 (21.4%) dyslipidemia, 9 (8.7%) chronic lung disease and 9 (8.7%) non-skin malignancy.

Conclusions: Eczema is very common in elderly patients. In the majority of patients the clinical features of eczema are often not typical of endogenous eczema subtypes. We propose the term senectus eczema as a diagnosis, however its clinical characteristics has yet to be clearly delineated. Skin cancers, psoriasis, bullous pemphigoid, fungal infections, drug eruption and viral infection are other conditions which should not be missed in assessing these patients.
Introduction
Skin disease affects 45-83% of the geriatric population\textsuperscript{1,4}. Aging changes the structure and physiology of skin. Lipid content in the stratum corneum is decreased, trans-epidermal water loss increases, there is epidermal and dermal atrophy, loss of collagen and elastin, reduced vascularity and reduced cytokines and numbers of melanocytes and Langerhan cells\textsuperscript{5-7}. These results in impaired barrier function reduced chemical clearance capacity, reduced immune responsiveness and wound healing, impaired sensory perception and thermoregulation\textsuperscript{8,9}. Inevitable changes such as dryness, roughness, fragility, wrinkling and laxity are observed in elderly population. Consequently, xerosis, eczema, and infections are common in the geriatric population.

Our country is fast becoming a developed country with improved life expectancy. In 2016, about 1.9 million of Malaysia’s 31.7 million population are \( \geq 65 \) years old\textsuperscript{8}. It is estimated that there would be 5.6 million senior citizens by the year 2035\textsuperscript{8}. Healthcare services should be prepared to provide quality care for patients in this age group. We aimed to characterize the dermatological conditions that affect patients at the extremes of age in order to better manage diseases which are prevalent in this population.

Methods
This was a retrospective study conducted at the Dermatology Unit, University Kebangsaan Malaysia Medical Center (UKMMC). The primary objective was to determine the types of dermatological diseases affecting patients over 80 years of age. Secondary objectives were to determine their clinical characteristics and comorbidities. All patients aged \( \geq 80 \) years who attended the Dermatology Clinic UKMMC in 2015 were identified from the clinic database. Their clinical notes were retrieved and reviewed. The dermatological diagnoses captured were according to the patients’ presenting complaint. Data on demography, dermatological diagnosis, clinical characteristics and comorbidities were recorded and analyzed using SPSS Version\textsuperscript{22}.

Results
A total of 103 octogeriatric patients were seen at the Dermatology outpatient clinic in 2015. The median age of the study population was 84.6 years old. The age range was from 80 to 89 years. Seventy six (73.8%) were Chinese, 16 (15.5%) were Malay, 6 (5.8%) were Indian and the remaining 5 (4.9%) patients were of other ethnicities. There were 51 (49.5%) were females, and 52 (50.5%) males. Forty eight (46.6%) had hypertension, 29 (28.2%) had diabetes, 25 (24.3%) had atherosclerosis related disease, 22 (21.4%) had dyslipidemia while 9 (8.7%) had chronic lung disease and another 9 (8.7%) had non-skin malignancy (Table 1).

The most common diseases were eczema, 49 (47.6%); cutaneous malignancy 10 (9.7%), psoriasis 8 (7.8%), bullous pemphigoid 7 (6.8%) and fungal infection 6 (5.8%). Other diseases were seborrheic keratosis 5 (4.9%), adverse drug eruption 5 (4.9%), viral infections 4 (3.9%) and lichen amyloidosis 3 (2.9%).

Eczema was the most frequently diagnosed disorder. The majority of patients had endogenous eczema [46 (44.7%)], 3 (2.9%) patients had exogenous eczema. Out of 46 patients with endogenous eczema, more than half were diagnosed with unclassified eczema [25 (24.3%)]. This was followed by stasis eczema [12 (11.7%)], seborrheic eczema [6 (5.8%)] and hand and feet eczema [3 (2.9%)].

In patients with cutaneous malignancy, the commonest was basal cell carcinoma [5 (4.9%)], followed by squamous cell carcinoma [4 (3.8%)] and Bowen’s disease [1 (1%)]. We did not find any association between dermatological diagnoses and comorbidities. Table 2 summarizes the dermatological diagnoses of our study population.

Table 3 shows the distribution of cutaneous disease in octogenerians according to gender. Drug eruption was more common in male patients. Psoriasis, bullous pemphigoid and lichen amyloidosis were more common in females. However, statistically significant difference was observed only in psoriasis.

Discussions
Dermatological diseases affecting the elderly have been described in a few studies. Liao et al reviewed 16,924 geriatric patients who attended their dermatology outpatient clinic\textsuperscript{4}. More than half had dermatitis and about a quarter was diagnosed with fungal infection. Bilgili et al\textsuperscript{10} and Jindal et al\textsuperscript{11} reported similar findings. Another study in Turkey found malignant skin tumours as the second most common condition following eczematous dermatitis\textsuperscript{12}. Table 4 summarizes the results of these studies in comparison to this current study.
Table 1. Characteristics of the study population.

<table>
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<th>Characteristics</th>
<th>Mean or n (%)</th>
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<tr>
<td>Age</td>
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</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
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<tr>
<td>Male</td>
<td>52 (50.5)</td>
</tr>
<tr>
<td>Female</td>
<td>51 (49.5)</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
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<tr>
<td>Malay</td>
<td>16 (15.5)</td>
</tr>
<tr>
<td>Chinese</td>
<td>76 (73.8)</td>
</tr>
<tr>
<td>Indian</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>Others</td>
<td>5 (4.9)</td>
</tr>
<tr>
<td><strong>Co morbidities</strong></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>48 (46.6)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>29 (28.2)</td>
</tr>
<tr>
<td>Atherosclerosis disease</td>
<td>25 (24.3)</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>22 (21.4)</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>9 (8.7)</td>
</tr>
<tr>
<td>Non-skin malignancy</td>
<td>9 (8.7)</td>
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</table>

Table 2. Dermatological diseases in the study population.

<table>
<thead>
<tr>
<th>Dermatological disease</th>
<th>n (% )</th>
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<tbody>
<tr>
<td>Endogenous eczema</td>
<td>46 (44.7)</td>
</tr>
<tr>
<td>Unclassified eczema</td>
<td>25 (24.3)</td>
</tr>
<tr>
<td>Statis eczema</td>
<td>12 (11.7)</td>
</tr>
<tr>
<td>Seborrheic eczema</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>Hand and feet eczema</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Exogenous eczema</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Cutaneous malignancy</td>
<td>10 (9.7)</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>5 (4.9)</td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>Bowen’s disease</td>
<td>1 (1.0)</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>8 (7.8)</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>7 (6.8)</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>6 (5.8)</td>
</tr>
<tr>
<td>Drug eruption</td>
<td>5 (4.9)</td>
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<tr>
<td>Seborrheic keratosis</td>
<td>5 (4.9)</td>
</tr>
<tr>
<td>Viral infection</td>
<td>4 (3.9)</td>
</tr>
<tr>
<td>Lichen amyloidosis</td>
<td>3 (2.9)</td>
</tr>
<tr>
<td>Others</td>
<td>6 (5.8)</td>
</tr>
</tbody>
</table>
Table 3. Distribution of skin diseases according to gender.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Male, n (%)</th>
<th>Female, n (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endogenous eczema</td>
<td>26 (25.2)</td>
<td>20 (19.4)</td>
<td>0.43</td>
</tr>
<tr>
<td>Unclassified eczema</td>
<td>13 (12.6)</td>
<td>12 (11.7)</td>
<td></td>
</tr>
<tr>
<td>Statis eczema</td>
<td>7 (6.8)</td>
<td>5 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Seborrheic eczema</td>
<td>4 (3.9)</td>
<td>2 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Hand and feet eczema</td>
<td>2 (1.9)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Exogenous eczema</td>
<td>1 (1)</td>
<td>2 (1.9)</td>
<td>0.61</td>
</tr>
<tr>
<td>Cutaneous malignancy</td>
<td>5 (4.8)</td>
<td>5 (4.8)</td>
<td>1</td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>2 (1.9)</td>
<td>3 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>2 (1.9)</td>
<td>2 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Bowen’s disease</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Psoriasis</td>
<td>1 (1)</td>
<td>7 (6.8)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>2 (1.9)</td>
<td>5 (4.9)</td>
<td>0.26</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>3 (2.9)</td>
<td>3 (2.9)</td>
<td></td>
</tr>
<tr>
<td>Drug eruption</td>
<td>4 (3.9)</td>
<td>1 (1)</td>
<td>0.36</td>
</tr>
<tr>
<td>Seborrheic keratosis</td>
<td>3 (2.9)</td>
<td>2 (1.9)</td>
<td>1</td>
</tr>
<tr>
<td>Viral infection</td>
<td>3 (2.9)</td>
<td>1 (1)</td>
<td>0.62</td>
</tr>
<tr>
<td>Lichen amyloidosis</td>
<td>0 (0)</td>
<td>3 (2.9)</td>
<td>0.11</td>
</tr>
<tr>
<td>Others</td>
<td>4 (3.9)</td>
<td>2 (1.9)</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 4. Skin diseases among geriatric population in various countries.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>No. (n)</td>
<td>16924</td>
<td>128</td>
<td>2217</td>
<td>1380</td>
<td>103</td>
</tr>
<tr>
<td>Population/age</td>
<td>Taiwan ≥ 65 years</td>
<td>Turkey ≥ 85 years</td>
<td>Turkey ≥ 75 years</td>
<td>India ≥ 60 years</td>
<td>Malaysia ≥ 80 years</td>
</tr>
<tr>
<td>Eczema</td>
<td>58.7 %</td>
<td>14.1%</td>
<td>33.2%</td>
<td>15.3%</td>
<td>47.6%</td>
</tr>
<tr>
<td>Malignant skin tumor</td>
<td>2.1%</td>
<td>12.5%</td>
<td>0.8%</td>
<td>0.8%</td>
<td>8.7%</td>
</tr>
<tr>
<td>Psoriasis</td>
<td>3.9%</td>
<td>-</td>
<td>2.1%</td>
<td>5.4%</td>
<td>7.8%</td>
</tr>
<tr>
<td>Bullous pemphigoid</td>
<td>0.8%</td>
<td>2.3%</td>
<td>1.8%</td>
<td>-</td>
<td>6.8%</td>
</tr>
<tr>
<td>Fungal infection</td>
<td>38%</td>
<td>6.3%</td>
<td>8.4%</td>
<td>18%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>
Endogenous eczema was the most prevalent disorder in our study population. Eczema affected up to 58% of geriatric patients that presented to dermatology services. Seborrheic, astuteotic and stasis eczema, and lichen simplex chronicus were the common subtypes described. Other eczematous skin disorders in the elderly has been described as non-specific dermatitis, dermatitis not otherwise specified, and endogenous eczema (grouped separately from other subtypes of endogenous eczema). Liao et al diagnosed non-specific dermatitis in up to 75% of patients with dermatitis. However, the definitions of these terms were not clearly explained. We used the term unclassified eczema as a diagnosis in patients whose rash morphology fitted classical clinical features of eczema, but the distribution did not fall into any of the endogenous eczema subtypes. This diagnosis was made after allergic/irritant contact dermatitis and drug induced eczematous reaction were excluded following a thorough history and examination. Patch test was not routinely performed if there is no clinical suspicion of allergic contact dermatitis from the history. History taking in the elderly is challenging as most patients are unable to recall the chronology of the rash and use of possible allergens or irritants. Collateral history from care givers is unreliable most of the time.

Unclassified eczema is common in our patients. Assuming the terms non-specific dermatitis and dermatitis not otherwise specified are equivalent to our unclassified eczema, then this type of eczema is very common in the elderly. A proper name is needed for this condition and its clinical characteristics have to be defined. We propose the name senectus eczema as its pathophysiology is most likely due to the natural aging process of the skin causing altered barrier function and reduced hydration. In Latin, senectus means old age. Unfortunately we are not able to produce a list of clinical characteristics due to the retrospective nature of our study.

Cutaneous malignancy was the second most common condition diagnosed in our study population. Increased cumulative effect of sun exposure and carcinogens with age and impaired capacity of DNA repair may be responsible for the higher incidence skin cancers in the older age group. This was illustrated by Yalcin et al and our current study, the geriatric population aged 80 and above had higher percentage of cutaneous malignancy compared to those in their 60s and 70s (Table 4). Skin cancer was more common among the Chinese in our study population. This is most likely due to their skin type. In general, Malaysian Chinese has skin type III while the Malays and Indians have skin type IV or V. In Turkey there seemed to be a higher prevalence of skin cancer in 1999-2003 compared to 2007-2010 (Table 4). The authors explained that this finding was because most patients with skin tumors were referred to Plastic surgery while their study population was patients from Dermatology.

Psoriasis, bullous pemphigoid, fungal infections, drug eruption, viral infection and lichen amyloidosis were diagnosed in less than 8% of our study population. These conditions should be considered in evaluating elderly patients with skin lesions.

Conclusion
Ecema is very common and should be considered first in the geriatric population. The clinical features of eczema in these patients are often not typical of endogenous eczema subtypes. We propose the term senectus eczema as a diagnosis, however its clinical characteristics has to be clearly delineated. Other conditions like psoriasis, bullous pemphigoid, fungal infections, drug eruption and viral infection should not be missed in assessing these patients. Malignant skin tumor is more common among the Chinese compared to other ethnicities.

References
CORRELATION BETWEEN CUMULATIVE DOSE OF METHOTREXATE AND METHOTREXATE INDUCED HEPATOTOXICITY IN PSORIASIS PATIENTS UNDERGOING LIVER BIOPSY - A 15 YEARS RETROSPECTIVE STUDY

Asha G1, Tang J J1, Chan LC2

Abstract

Introduction: The use of methotrexate in treating moderate to severe psoriasis has been associated with risk of hepatotoxicity. Emerging data suggest that methotrexate may be less hepatotoxic and thus controversy lies in the role of routine liver biopsy based on cumulative dose to detect hepatotoxicity during treatment.

Objective: The primary objective was to assess the correlation between cumulative dose of methotrexate with hepatotoxicity in terms of liver biopsy grading and serum liver enzymes. Our secondary objective was to establish the possible risk factors for methotrexate induced fibrosis/cirrhosis.

Method: A retrospective study was conducted on psoriasis patients who had undergone liver biopsies after certain cumulative dose of methotrexate from year 2000 to 2014 in Department of Dermatology, Hospital Raja Permaisuri Bainun. Correlation was assessed between total cumulative dose of methotrexate with liver biopsy grading (Roenigk classification) and serum liver enzymes. Risk factors for liver fibrosis/cirrhosis (Grade III and IV) including age, gender, ethnicity, diabetes mellitus, hypertension, dyslipidemia and ethanol consumption were also assessed. Statistical analysis was done by using SPSS version 22.

Results: Skin areas treated with AEBritening Complex-01 showed significant degree of lightening effect (+1). There were 52 patients with a mean age of 49.5 ± 12.9 years. Fifty eight liver biopsies were done with 6 having second biopsies. For the first liver biopsies, 5 had normal finding [mean cumulative dose (MCD) = 1629mg]; 29 Grade I (MCD=1701mg); 10 Grade II (MCD=2046 mg); 1 with Grade IIIa (MCD=1560mg); 1 Grade IIIb (MCD=1682mg); 2 Grade IV (MCD= 1628 mg). In terms of liver enzymes, 6 patients had raised ALT (>41) (MCD= 1333 mg) whereas 46 patients had normal ALT (<41) (MCD= 1795 mg). 10 patients had raised AST (>40) (MCD= 1641 mg) compared to 42 patients with normal AST (<40) (MCD=1766 mg). There were no significant correlation between total cumulative dose with liver biopsy grading and serum liver enzymes. Age, gender, ethnicity, diabetes mellitus, hypertension, dyslipidemia and ethanol consumption were also not significant risk factors for liver fibrosis/cirrhosis (Grade III and IV). Out of 6 patients who underwent second biopsy, 3 had progression whereas 3 showed no change of liver biopsy grading.

Conclusion: There was no association between total cumulative dose of methotrexate with liver biopsy grading and serum liver enzymes. Liver biopsy should be performed according to clinical indication instead of purely based on cumulative dose of methotrexate.

Keywords: psoriasis, methotrexate, hepatotoxicity, liver biopsy, cirrhosis, fibrosis
Introduction
Methotrexate (MTX) is indicated in about 20% of all patients with psoriasis and continues to be used despite the emergence of newer therapies because of the length of experience with its use and its undoubted efficacy. Hepatotoxicity associated with MTX in psoriatic patients is well recognized, and in some patients can lead to hepatic fibrosis and even cirrhosis. In the past, the prevalence of MTX induced liver fibrosis and cirrhosis have been reported to be as high as 50% and 26% respectively in the west. Traditionally, serial liver biopsy guided by total cumulative dose of MTX has been a common practice to detect hepatotoxicity. However emerging data suggests that MTX may be less hepatotoxic than expected and thus controversy lies in the role of routine liver biopsy based on cumulative dose to detect hepatotoxicity during treatment. The main aim of our study was to assess the correlation between cumulative dose of MTX with hepatotoxicity in terms of liver biopsy grading and serum liver enzymes. Our secondary objective was to establish the possible risk factors for MTX induced fibrosis/cirrhosis.

Materials and Methods
A retrospective study was conducted on psoriasis patients who had undergone liver biopsies after certain cumulative dose of MTX from year 2000 to 2014 in Department of Dermatology, Hospital Raja Permaisuri Bainun. The case notes of these patients were traced and the following information was extracted: age, gender, ethnicity, presence of potential risk factors (diabetes, dyslipidemia, hypertension, ethanol consumption), standard liver function tests (aspartate transaminase, alanine transaminase, alkaline phosphatase, albumin, bilirubin, hepatitis B and C serology, where available), concomitant use of hepatotoxic drugs, cumulative MTX dose at the time of liver biopsy and liver biopsy findings. Histological changes of liver biopsy were graded according to Roenigk Classification (Table 1).

Table 1. Roenigk classification of liver damage.

<table>
<thead>
<tr>
<th>Grade</th>
<th>Fibrosis</th>
<th>Fatty infiltration</th>
<th>Nuclear variability</th>
<th>Portal inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>None</td>
<td>Mild</td>
<td>Mild</td>
<td>Mild</td>
</tr>
<tr>
<td>II</td>
<td>None</td>
<td>Moderate to severe</td>
<td>Moderate to severe</td>
<td>Portal expansion, lobular necrosis</td>
</tr>
<tr>
<td>IIIa</td>
<td>Mild (septa extending into lobules)</td>
<td>Moderate to severe</td>
<td>Moderate to severe</td>
<td>Portal expansion, lobular necrosis</td>
</tr>
<tr>
<td>IIIb</td>
<td>Moderate to severe</td>
<td>Moderate to severe</td>
<td>Moderate to severe</td>
<td>Portal expansion, lobular necrosis</td>
</tr>
<tr>
<td>IV</td>
<td>Cirrhosis</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Relationship between cumulative dose with liver biopsy grading and liver enzymes**

From the first series of liver biopsies, 5 showed normal findings at mean cumulative dose (MCD) of 1629mg; 29 Grade I (MCD=1701mg); 10 Grade II (MCD=2046 mg); 1 with Grade IIIa (MCD=1560mg); 1 Grade IIIb (MCD=1682mg); 2 Grade IV (MCD=1628mg). There was a total of 4 patients (8.3%) with liver fibrosis/cirrhosis (grade III or IV). Among those who had a second liver biopsy done, 3 had Grade I finding (MCD=2576mg); 2 Grade II (MCD=3885mg); and 1 Grade III a (MCD=3635mg). In terms of liver enzymes, 6 patients had raised ALT (>41) (MCD=1333mg) whereas 46 patients had normal ALT (<41) (MCD=1795mg). 10 patients had raised AST (>40) (MCD=1641mg) compared to 42 patients with normal AST (<40) (MCD=1766mg). Spearman’s rank correlation showed no significant correlation between total cumulative dose with liver biopsy grading and serum liver enzymes (P=0.362 and 0.330 respectively). Out of 6 patients who underwent a second biopsy, 3 had progression whereas 3 showed no change of liver biopsy grading.

**Risk factor analysis**

We used multiple logistic regression to assess the significance of risk factors on the grading of liver biopsy. It was found that age, gender, ethnicity, cumulative dose, diabetes, hypertension and dyslipidemia all had no significance on the grading of liver biopsy on multivariate analysis. On univariate analyses with Fisher’s exact test, gender, ethnicity, and the presence of diabetes, hypertension and dyslipidemia were also found to be of no significance with MTX associated liver fibrosis/cirrhosis. However, diabetes shows the highest association with MTX associated liver fibrosis/cirrhosis (p=0.055) but it was still statistically not significant.

<table>
<thead>
<tr>
<th>Histology grade</th>
<th>No.</th>
<th>Mean cumulative dose of MTX (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>5</td>
<td>1629</td>
</tr>
<tr>
<td>I</td>
<td>29</td>
<td>1701</td>
</tr>
<tr>
<td>II</td>
<td>10</td>
<td>2046</td>
</tr>
<tr>
<td>III a</td>
<td>1</td>
<td>1560</td>
</tr>
<tr>
<td>III b</td>
<td>1</td>
<td>1682</td>
</tr>
<tr>
<td>IV</td>
<td>2</td>
<td>1628</td>
</tr>
</tbody>
</table>

Table 2. Distribution of the grades of liver histology and the mean cumulative dose at first liver biopsy.

<table>
<thead>
<tr>
<th>Histology grade</th>
<th>No.</th>
<th>Mean cumulative dose of MTX (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>I</td>
<td>3</td>
<td>2576</td>
</tr>
<tr>
<td>II</td>
<td>2</td>
<td>3885</td>
</tr>
<tr>
<td>III a</td>
<td>1</td>
<td>3655</td>
</tr>
<tr>
<td>III b</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>IV</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

Table 3. Distribution of the grades of liver histology and the mean cumulative dose at second liver biopsy.
Recent studies have reported that MTX cumulative dose was not correlated with liver toxicity. Our present study also showed no such correlation. In fact, looking at transaminases, our patients with normal ALT had higher MCD (1795mg) compared to those with raised ALT (MCD = 1333mg). Those with normal AST had higher MCD (1766mg) whereas patients with elevated AST had a lower MCD (1641mg).

Alcohol consumption, diabetes, obesity, dyslipidemia, viral hepatitis, and the use of medications such as arsenic and vitamin A are well recognized risk factors reported to cause and accelerate the fibrotic progression in patients treated with MTX. Surprisingly in our study, it was found that age, gender, ethnicity, cumulative dose, diabetes, hypertension and dyslipidemia all had no significance on the grading of liver biopsy. Although statistically not significant, diabetes shows the highest association with MTX associated liver fibrosis/cirrhosis (p=0.055). This is because fatty liver is a well-known complication of diabetes mellitus which in turn can accelerate MTX induced hepatotoxicity.

In our study, we found that majority of the patients who had undergone liver biopsy were Chinese which is most probably a reflection of the population in our study area. Besides that, more Malays were found to have liver fibrosis (16.7%), however this finding was not statistically significant, hence the cause for this is yet to be determined and more research is needed to ascertain the correlation between ethnicity and liver fibrosis.

### Table 4. Risk factors analysis for MTX associated liver fibrosis (Univariate comparison made with Fisher’s Exact Test).

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Proportion of patients with liver fibrosis/cirrhosis (Grade III/IV)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>2/27 (7.4%)</td>
<td>0.594</td>
</tr>
<tr>
<td>Female</td>
<td>2/21 (9.5%)</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>2/12 (16.7%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Chinese</td>
<td>1/27 (3.7%)</td>
<td></td>
</tr>
<tr>
<td>Indian</td>
<td>1/9 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3/13 (23.1%)</td>
<td>0.055</td>
</tr>
<tr>
<td>No</td>
<td>1/35 (2.9%)</td>
<td></td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1/4 (25%)</td>
<td>0.302</td>
</tr>
<tr>
<td>No</td>
<td>3/44 (6.8%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1/10 (10%)</td>
<td>1.0</td>
</tr>
<tr>
<td>No</td>
<td>3/38 (7.9%)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 1.** Correlation between cumulative methotrexate dose and grades of liver biopsy (Scatter Plot).

**Discussion**

Data on MTX in psoriatic patients is well reported in the western population, however data remains scarce among Asians. Very few studies have been conducted among Asian patients treated with MTX. A study on Korean patients with rheumatoid arthritis found that MTX was safe based on fibroscan. Another retrospective study on psoriatic patients treated with MTX in Malaysia showed that hepatotoxicity was uncommon based on serum transaminases. One study in Singapore among psoriatic patients on MTX showed that the prevalence of liver fibrosis was comparable to the west and cumulative dose was not significantly associated with liver fibrosis. In our study, there were only 4 patients (8.3%) with liver fibrosis/cirrhosis (grade III or IV). In general, our findings are consistent with those of recent studies. Therefore, our findings also suggest that MTX induced hepatotoxicity may be less common than previously reported.

Alcohol consumption, diabetes, obesity, dyslipidemia, viral hepatitis, and the use of medications such as arsenic and vitamin A are well recognized risk factors reported to cause and accelerate the fibrotic progression in patients treated with MTX. Surprisingly in our study, it was found that age, gender, ethnicity, cumulative dose, diabetes, hypertension and dyslipidemia all had no significance on the grading of liver biopsy. Although statistically not significant, diabetes shows the highest association with MTX associated liver fibrosis/cirrhosis (p=0.055). This is because fatty liver is a well-known complication of diabetes mellitus which in turn can accelerate MTX induced hepatotoxicity.

In our study, we found that majority of the patients who had undergone liver biopsy were Chinese which is most probably a reflection of the population in our study area. Besides that, more Malays were found to have liver fibrosis (16.7%), however this finding was not statistically significant, hence the cause for this is yet to be determined and more research is needed to ascertain the correlation between ethnicity and liver fibrosis.
Currently, it remains uncertain whether the use of non-invasive tests can replace liver biopsy. Based on latest available evidence, use of non-invasive tests such as fibroscan, fibrotest and procollagen III N-terminal propeptide (P III N P) are not sensitive enough to predict the severity of fibrosis. At present, in our setting, we do not recommend non-invasive tests as an alternative to liver biopsy as data on Asian psoriatic patients treated with MTX is lacking.

We acknowledge that our study has some limitations. Firstly, the sample size was small and probably accounted for the non-significant findings. Besides that, due to the retrospective nature of this study, there were missing or incomplete data. In our case, lack of data on patients’ BMI made it not possible to assess the impact of obesity. Also, information on alcohol consumption was not available for most of the patients in our study. The main strength of our study is the use of liver biopsy which remains the gold standard compared to other non-invasive tests which have limitations in terms of sensitivity and specificity.

Conclusion
Hence, we conclude that there was no association between total cumulative dose of MTX with liver biopsy grading and serum liver enzymes. On the basis of the findings in this study, we suggest that liver biopsy should be performed according to clinical indication instead of purely based on cumulative dose of MTX.

Acknowledgement
We are grateful to all the doctors in Department of Dermatology, Hospital Raja Permaisuri Bainun Ipoh, both past and present, who have been responsible for the care of these patients during the past 15 years. The authors would like to thank Ms. Lim Wei Yin from CRC Perak for her contribution in statistical analysis of this study.

References
PEMPHIGUS: A SINGAPORE PERSPECTIVE

Valencia L¹, Tay YK², Teo R³

Abstract

Background: Pemphigus is a group of immunobullous diseases that are diagnosed by histology and direct immunofluorescence (DIF). Two variants are pemphigus vulgaris (PV) and pemphigus foliaceus (PF). It is mediated by autoantibodies directed against desmogleins, namely anti-desmoglein 1 in PF and anti-desmoglein 3 in PV.

Aims: To review the epidemiology of patients with pemphigus in Singapore.

Methods: This was a retrospective study of pemphigus: comparative analysis was done for patient demographics, treatment, induction of remission and relapse. Complete and partial remissions were defined according to the definitions proposed by the International Pemphigus Committee.

Results: All our PV patients had mucocutaneous disease. Oral/lip involvement was the most frequent (100%) followed by genitalia lesions (40%). Only 22.2% of PF patients had mainly cutaneous disease with mild mucosal involvement. In both variants, the cutaneous lesions were typically blisters and erosions. Our centre treats PV more aggressively than PF upon initial diagnosis. Higher initial doses of prednisolone were given with the use of adjuvants (86.7% in PV vs. 33.3% in PF). PV patients in our centre exhibited a shorter average time to disease control (1 month vs. 3 months in PF). 53.3% of PV patients went on to achieve complete remission as compared to 33.3% of PF patients.

Limitations: This study is limited by its retrospective design and small sample size.

Conclusion: Our study shows that more aggressive initial treatment of pemphigus could lead to a shorter duration to disease control. PF may run a chronic course similar to PV and cause significant morbidity.

Introduction

Pemphigus is an autoimmune bullous disease characterized by auto- antibodies directed against desmoglein (DG) 1 and desmoglein (DG) 3. Two main subtypes exist - pemphigus vulgaris (PV) and pemphigus foliaceus (PF). Histologically, there is suprabasal blister formation and acantholysis. Suprabasal cleavage is seen in pemphigus vulgaris/vegetans whereas superficial intra-epidermal bullae are found in PF. On direct immunofluorescence, (DIF), IgG and/or C3 is deposited in the intercellular spaces of the epidermis on the surface of keratinocytes in and around the lesions.

Clinically, PV is characterized by both mucosal and cutaneous blistering and erosions (Fig.1) while PF tends to manifest as solely cutaneous blistering. (Fig.2) The mortality rate ranges from 5-10%1 and the mainstay of treatment is systemic corticosteroids. Other immunosuppressants may be added for their steroid-sparing effects.

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Although PV is generally regarded as a more severe form of disease than PF, studies\(^2\) have suggested that patients with PV and mucosal involvement may have a higher likelihood of attaining CR off therapy. However, this has not been assessed in the Asian population.

The aim of this study was to review the clinical features and evaluate prognostic factors of adult patients diagnosed with pemphigus at Changi General Hospital, Singapore from 2006 to 2012.

**Materials and Methods**

**Retrieval of data**
This was an ethics-approved retrospective study. Patients aged 18 and above with a diagnosis of PV or PF diagnosed between January 2006 to December 2012 were included. The diagnosis of pemphigus was made based on clinical, histology and DIF features.

**Data collection**
Patient demographics, clinical presentations, laboratory investigations, treatment and eventual outcomes were extracted from the patients’ medical records.

**Definitions used**
A consensus statement\(^3\) has been proposed to provide definitions for stages of disease activity as well as to determine therapeutic end points for pemphigus. These definitions are listed in Table 4.

**Statistical analysis**
Fisher’s exact test was used to assess the relationships between categorical variables. The Mann-Whitney U test was used for the continuous variables. Logistic regression analyses were performed with the software STATA VERSION 10.1. P values less than 0.05 were regarded to be statistically significant.

**Results**
The data of twenty-four patients were retrieved. Table 1 shows the patient demographics of patients. Table 2 shows the clinical features of PV and PF. Table 3 shows the various treatment modalities. Table 4 shows the treatment outcomes.

**Table 2. Clinical diagnosis.**

<table>
<thead>
<tr>
<th>Clinical subtype</th>
<th>PV (%)</th>
<th>PF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 15 (62.5)</td>
<td>n = 9 (37.5)</td>
<td></td>
</tr>
</tbody>
</table>

**Table 1. Patient demographics.**

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>PV (%)</th>
<th>PF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n = 15 (62.5)</td>
<td>n = 9 (37.5)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6 (40.0)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Female</td>
<td>9 (60.0)</td>
<td>7 (77.8)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>16-63</td>
<td>45-82</td>
</tr>
<tr>
<td>Mean</td>
<td>45.5</td>
<td>60</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chinese</td>
<td>8 (53.3)</td>
<td>8 (88.9)</td>
</tr>
<tr>
<td>Indian</td>
<td>1 (6.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Malay</td>
<td>5 (33.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Others</td>
<td>1 (6.7)</td>
<td>1 (11.1)</td>
</tr>
</tbody>
</table>
Table 3. Treatment modalities.

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>PV (%)</th>
<th>PF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone monotherapy</td>
<td>2 (13.3)</td>
<td>6 (66.7)</td>
</tr>
<tr>
<td>Prednisolone and adjuvant</td>
<td>13 (86.7)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Dapsone</td>
<td>2 (13.3)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>13 (86.7)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Mycophenolate mofetil</td>
<td>3 (20)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Intravenous immunoglobulin</td>
<td>1 (6.7)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>Rituximab</td>
<td>1 (6.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>1 (6.7)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Patients treated with topical steroids alone</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Average initial dose of prednisolone to achieve disease control* (mg/day)</td>
<td>54.6</td>
<td>28.75</td>
</tr>
<tr>
<td>Average time to disease control (months)</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Average follow up (months)</td>
<td>48</td>
<td>23</td>
</tr>
</tbody>
</table>

*disease control defined as the time interval from baseline to the time at which new lesions cease to form and established lesions begin to heal.

Table 4. Treatment outcomes.

<table>
<thead>
<tr>
<th>Patients under complete remission</th>
<th>PV (%)</th>
<th>PF (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR1</td>
<td>8 (53.3)</td>
<td>3 (33.3)</td>
</tr>
<tr>
<td>CR off therapy2</td>
<td>4 (26.7)</td>
<td>1 (11.1)</td>
</tr>
<tr>
<td>CR on therapy3</td>
<td>4 (26.7)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Average time to complete 1st remission (months)</td>
<td>4.75</td>
<td>5.7</td>
</tr>
<tr>
<td>Average number of relapses3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Patients under partial remission</td>
<td>PV (%)</td>
<td>PF (%)</td>
</tr>
<tr>
<td>PR4</td>
<td>4 (26.7)</td>
<td>4 (44.4)</td>
</tr>
<tr>
<td>PR off therapy5</td>
<td>1 (6.7)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>PR on therapy6</td>
<td>4 (20)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Average time to complete 1st remission (months)</td>
<td>21.25</td>
<td>8.75</td>
</tr>
<tr>
<td>Average time required to attain partial remission from previous relapse (months)</td>
<td>1.5</td>
<td>3</td>
</tr>
<tr>
<td>Average number of relapses</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total no of patients with complete/partial remission</td>
<td>12 (80)</td>
<td>7 (77.8)</td>
</tr>
<tr>
<td>Patients with active disease (as of 2013)</td>
<td>3 (20)</td>
<td>2 (22.2)</td>
</tr>
<tr>
<td>Patients lost to follow up</td>
<td>0</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Patients who died of other causes</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Relapses (averaged for CR and PR)</td>
<td>1.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Average PR and PV maintenance6 dose of prednisolone (mg OD)</td>
<td>6.1</td>
<td>4.6</td>
</tr>
<tr>
<td>Average PR and PV control9 dose of prednisolone (mg OD)</td>
<td>54</td>
<td>25.6</td>
</tr>
</tbody>
</table>

1 CR: Complete Remission – includes both complete remission on and off therapy
2 CR off therapy: defined as the absence of new and/or established lesions while the patient is off all systemic therapy for at least two months
3 CR on therapy: defined as the absence of new or established lesions while the patient is receiving minimal therapy
4 PR: Partial remission – includes both partial remission on and off therapy
5 PR off therapy: defined as the presence of transient new lesions that heal within one week without treatment and while the patient is off all systemic therapy for at least two months
6 PR on therapy: defined as the presence of transient new lesions that heal within one week while the patient is receiving minimal therapy, including topical steroids.
7 Relapse: defined as appearance of 3 or more new lesions a month that do not heal spontaneously within 1 week, or by the extension of established lesions, in a patient who has achieved disease control
8 Maintenance dose: defined as the lowest possible dose that prevents new lesions from appearing
9 Control dose: defined as the dose at which at which new lesions cease to form and established lesions begin to heal.
Clinical features of Pemphigus Vulgaris
In our study, 7 (46.7%) with PV manifested first with oral and/or lip lesions followed by cutaneous lesions (Fig.1). Three (20%) patients manifested with both simultaneously and five (33.3%) of patients manifested with cutaneous lesions first. The mean duration for the onset of cutaneous lesions after oral lesions was 1.25 months.

Oral lesions
In our study, all had mouth and/or lip lesions. Thirteen patients (86.7%) had mouth lesions of which buccal ulcers, erosions comprised the majority. Eleven patients (73.3%) had lip lesions comprising of erosions, crusting and ulcers. Nine (60%) had both mouth and lip lesions.

Genital lesions
The second most common presentation is genital erosions (40%) These involved the labia majora in 100% of the cases for the women and shaft of penis for the men.

Ocular and ENT lesions
Ocular and ENT involvement was seen in 2 (13%) patients. The patients with ocular involvement presented with discharge and crusting around eyes and they were evaluated by ophthalmologists. Two developed odynophagia and hoarseness of voice. The presence of erosions, consistent with PV were confirmed by an ENT surgeon.

Clinical features of Pemphigus Foliaceus
Amongst the PF patients, 1 had oral mucosal lesions and another patient had conjunctival mucosal involvement. All 9 patients presented with cutaneous blisters/erosions (Fig.2).

Significant investigations
Herpes Simplex Virus (HSV) Polymerase Chain Reaction (PCR)/culture HSV PCR/ culture was done in 8 (53.3%) cases. Three (37.5%) were positive for HSV 1. For those positive for HSV 1, two achieved CR on therapy and 1 achieved PR on therapy. All 3 were treated with acyclovir. Where there is a possibility of HSV co-infection in PV, true association between disease severity and prognostic factors for exacerbation of PV is unclear.

Some studies have suggested that when patients present PV lesions which are refractory to corticosteroid therapy, herpetic infection should be considered. In our centre, repeated tests for HSV 1 after initial diagnosis of PV were not routinely performed unless the diagnosis of herpetic infection was suspected.

One patient with PF had a positive HSV PCR and culture. At the time of study, she had active disease.

Figure 1. A patient with pemphigus vulgaris presenting as erosions and crusting on the back.

Figure 2. A patient with pemphigus foliaceus showing superficial scales and crusts.
Treatment regimens

Systemic corticosteroids were the mainstay of treatment for both PV and PF. All 15 PV patients received prednisolone. Thirteen (86.7%) of them had adjuvant therapy. In contrast, 6 (66.7%) PF patients received prednisolone monotherapy. Only 2 (22.2%) had adjuvant therapy. One PF patient achieved complete remission with only topical corticosteroids.

The average initial dose of prednisolone required for PV patients to reach disease control was 54 mg/day compared to PF patients requiring 25.6 mg/day.

Azathioprine was the most commonly used adjuvant drug for both PV and PF patients. Other drugs used for treatment of PV included mycophenolate mofetil (MMF) (n=3), dapsone (n = 2), methotrexate (MTX) (n=1). Recalcitrant cases were treated with rituximab (n =1) and intravenous immunoglobulin (IVIG) (n=1). Amongst the PF patients, only 1 patient required IVIG administration. None of the PF patients required MMF, dapsone, MTX or rituximab.

Treatment outcomes

Treatment outcomes were classified at the recommendation of the consensus study. In particular, we were interested in patients who attained complete remission off therapy.

Of the PV patients, 4(26.7%) attained complete remission (CR) off therapy and 1 (6.7%) attained partial remission (PR) off therapy. Of the PF patients, 1 (11.1%) attained CR off therapy and 2 (22.2%) attained PR off therapy. CR (off and on therapy) was induced in 7 (46.6%) of PV patients 5 years after diagnosis, compared to 3 (33.3%) of PF patients for the same time period. PV patients achieved a higher rate of CR compared to PF patients.

The mean time taken to attain the first clinical remission for PV patients was 4.3 months as compared to 6 months for PF patients.

The mean duration of follow up for was 48.8 months for PV patients and 23.3 months for PF patients.

Discussion

In our study, PV seems to affect mainly two groups of individuals, mostly of ages within the 4th to 6th decade. Adolescents and young adults in the 1.5th to 3rd decade of life formed the second most common group. In contrast, PF seems to affect the middle aged- older age group mostly of ages from 6th to 8th decade followed by 4th to 5th decade. This correlates well with existing literature.

In patients with PV, oral manifestations are most common (100%, p <0.01). More than half presented first with oral lesions followed by cutaneous blisters. Oral and/or lip lesions may precede cutaneous lesions and this was also observed in our study. Intra-oral lesions were slightly more common than lip lesions, This correlates well with a 2001 study. Our study shows that pain is the most common symptom (80%).

Our study shows involvement of lining mucosa (66.7%) is more common than masticatory mucosa (26.7%). Buccal involvement is most common and gingival lesions are least common. This suggests that the type of mucosal involvement in PV is related to physiological traumatic mechanisms in polystratified squamous epithelial structures. A 2012 study by Fernandez et al reports that indeed the most common symptom is pain, and buccal mucosal is most common oral mucosal lesion (90%). Compared with other studies, our study shows that lip involvement was the most common (73.3%). Genital lesions were the second most common clinical manifestations (p= 0.05). This correlates with existing literature suggesting that involvement of the female genital tract in PV may not be infrequent. In our study, the genitals are the 2nd most common mucosal site of PV. A thorough genital examination is needed to avoid missing lesions.

Endoscopic ENT evaluation was not routinely performed in our pemphigus patients. Only patients who were symptomatic were referred to the ENT surgeon. A 2011 study by Kavala et al assessed ENT involvement in pemphigus patients found that up to 13% of patients with PV may have ENT involvement but may be asymptomatic.

For our PF patients, mucosal involvement was noted in 2 of our patients - 1 with oral lesions and 1 with conjunctival involvement. Here, the “desmoglein compensation theory” as an explanation for the localization of blisters in patients with pemphigus is challenged. Recent studies have suggested that this theory may not be perfect. It may be possible for PF patients to present with mucosal lesions as found in our study.
Our study reports a lower rate of complete remission off therapy than previous studies. This could be attributed to the mindset of our patients or dermatologists treating pemphigus. The goal of treatment is taper off immunosuppression once patient has achieved remission. A significant proportion of our patients chose to stay on prednisolone at low doses such as 2.5mg/day even when they have been considered ‘cleared’ of lesions by physicians. Our study shows that 46.6% of patients achieved complete remission within 5 years, comparable to the results of Western studies of around 50% for the same period. In a 2003 study, only 37% of physicians stated that their goal was to eliminate corticosteroids entirely, implying that most would rather keep patients on a small dose of steroids to maintain the complete remission.

This study is limited by its retrospective design and small sample size. Two of our PF patients were lost to follow up and their remission status was therefore regarded as status during the last hospital visit. The recently published ABSIS (Autoimmune Bullous Skin Disorder Intensity Score) and PDAI (Pemphigus Disease Area Index) severity scoring systems could not be used in this retrospective study since most of the patients were assessed before the release of the scoring systems.

**Conclusion**

In conclusion, we present 24 Asian patients with pemphigus seen at a general hospital in Singapore over 6 years. In PV patients, oral mucosal lesions were most common followed by genital lesions. Our study also suggests that PF may not run as benign a course as previously thought, and that initial mucosal involvement may be an important good prognostic factor for eventual attainment of complete remission off therapy for PV.
References

Case Report

METHOTREXATE TOXICITY

Long V1, Huang JX2, Huma J3, Aw CW Derrick3, Nisha SC3

Introduction
Methotrexate (MTX) is used as systemic therapy for many rheumatological and dermatological disorders. Acute toxicity presents with varied cutaneous manifestations. We review three morphologically varied cases in our centre to highlight the importance of early recognition.

Case Report
Case report 1: A 60-year old Chinese man with chronic plaque psoriasis of affected body surface area (BSA) greater than 50% was started on oral MTX 7.5mg weekly. Three days after initiation, he was admitted for severe odynophagia. There were extensive ulcers over his lips, with painful, scattered erosions over existing psoriatic plaques. Investigations revealed pancytopenia. A skin biopsy showed vacuolar interface dermatitis with apoptotic keratinocytes and epidermal disorganisation. MTX was discontinued and leucovorin was started as rescue treatment. In addition, subcutaneous GCSF was given at 300mcg daily for 5 days with eventual improvement of mucositis and blood counts.

Case report 2: A 51-year old Malay woman with chronic RA was treated with long term oral MTX 22.5mg weekly, leflunamide and prednisolone. Her MTX dose was increased to 25mg weekly in order to control her persistent joint swelling. Three months after the dose increment, she developed tender, hemorrhagic plaques over the lower limbs (Figure 1) and mouth ulcers. A skin biopsy showed epidermal atrophy with disorganisation, focal vacuolar interface change, rare eosinophils and superficial perivascular inflammation (Figure 2). MTX was stopped with symptom improvement.

Figure 1. Extensive hemorrhagic plaques over the lower limbs.

Figure 2. H&E stain showing epidermal atrophy with disorganisation, focal vacuolar interface change, rare eosinophils and superficial perivascular inflammation.

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Case report 3: A 60-year old Chinese woman with autoimmune myositis was given prednisolone and oral MTX 15mg weekly. She mistakenly took 15mg of methotrexate for ten days in a row. A week after, she presented with erythematous oedematous facial plaques with oral mucositis associated with atypical targets over her trunk (Figure 3a) and thighs with genital erosions (Figure 3b). Investigations showed bicytopenia and transaminitis. Skin biopsy also showed vacuolar interface dermatitis, apoptotic keratinocytes and epidermal changes consistent with MTX toxicity. Despite the withdrawal of MTX, initiation of leucovorin and empiric antibiotic treatment, she deteriorated rapidly and passed away.

Discussion
All patients in our series showed prominent oral mucosal involvement, but had very different cutaneous features. The oral mucosa undergoes rapid proliferation/turnover and hence is particularly affected by the cytotoxic effects of MTX. All our patients had normal MTX levels at the onset and serially. A study by Kivity et al showed that MTX levels, which are undetectable within 24 hours after administration, do not correlate with clinical toxicity. In addition, most cases of MTX toxicity have been reported in patients on low-dose MTX like our patients (7.5-25mg per week). Risk factors for low-dose MTX toxicity include clinically significant hypoalbuminemia, renal failure and the use of omeprazole particularly in patients receiving MTX. Previous reports also suggest additional risk factors such as pre-existing folate deficiency, old age >75 years old and poly-pharmacy. Prolonged low-dose MTX toxicity might be chiefly mediated by intracellular polyglutamate derivatives, which are unmeasurable by standard assays.

Of note, 1 patient presented with ulceration of existing psoriatic plaques as a subtle toxicity sign. While often mistaken as a psoriatic exacerbation leading to erroneous dose increment, it is an important herald for impending pancytopenia. This has been attributed to hyperproliferative psoriatic plaques being more susceptible to folate antagonism. This case reminds us that ulceration of psoriatic plaques even in the presence of an initially normal laboratory profile should not simply be dismissed as a flare.

Early recognition of clinical MTX toxicity facilitates prompt drug discontinuation and leucovorin administration. Treatment is supportive and we show in 2 patients that cutaneous lesions can heal rapidly with complete re-epithelization within days of MTX discontinuation. Educating the patient on the side effects of MTX and the need for prompt clinical consult upon development of symptoms is vital to avoid the tragedy of these 3 cases which can invite litigation.
Conclusion
Acute methotrexate toxicity may present as a variety of skin eruptions, gastrointestinal symptoms and mucositis. While cutaneous features may be highly variable, mucositis with cytopenias should alert physicians to possible acute toxicity. As there is currently no specific investigation that can confirm the diagnosis, we would like to stress the importance of recognizing the highly variable clinical patterns of toxicity.

References
Case Report

A CASE REPORT OF DISSEMINATED POROKERATOSIS WITH SECONDARY AMYLOID DEPOSITION

Yong AMY, Yang SSY, Tan KB, Sobti AM

Introduction
The porokeratoses are a group of disorders of abnormal epidermal keratinization. This results in the characteristic histologic feature of the cornoid lamella. A variety of subtypes of this disease have been recognised: porokeratosis of Mibelli, disseminated superficial porokeratosis (DSP), disseminated superficial actinic porokeratosis (DSAP), linear porokeratosis, punctuate porokeratosis and porokeratosis palmaris et plantaris. Rarely, DSP has been described to be in association with dermal amyloidosis in a few case reports worldwide. We present a case of disseminated porokeratosis with distinct histological manifestations associated with dermal amyloid deposits in an Asian man.

Case Report
A 66-year-old Chinese man presented to the dermatology clinic with itchy annular lesions over his arms, lower limbs and back. These lesions ranged from approximately 0.5 to 2cm in size, and had been present for 3-4 months. There was no sensory deficit or other lesions on the body. The patient was otherwise well, with primary aldosteronism, hypertension and dyslipidemia being his only medical problems. His medications included eplerenone and simvastatin. He denied a history of skin cancer, radiation, or heavy sun exposure or family history of a similar rash. There were no changes in the lesions with sun exposure.

On examination, there were multiple annular brown plaques scattered over his back, as well as upper and lower extremities (Fig. 1 and 2). The lesions were associated with a raised border without features of scaling or telangiectasia. An initial suspicion of disseminated superficial actinic porokeratosis (DSAP) was suspected, and the patient was empirically treated with topical moisturisers and advised on sun avoidance. However in view of the clinical suspicion of an underlying superficial basal cell carcinoma, a punch biopsy was performed over his right lower limb. Histology testing revealed a column of parakeratosis in the epidermis (cornoid lamella) with subjacent amyloid deposits and mild lymphocytic infiltrate. (Fig. 3) The patient was treated with one session of cryotherapy to his leg lesions. However, he was not keen for further treatment and defaulted follow up subsequently.

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action of fibroblasts and dermal macrophages. These authors state that a mutant clone from keratinocytes, responsible for induction of porokeratotic lesions, is presumed to produce dermal amyloid. This supports the fibrillar theory of amyloidosis in which abnormal protein aggregation is precipitated from defective keratinocytes.

In a retrospective histopathologic study of 30 patients on localised cutaneous amyloidosis secondary to porokeratosis, Ramirez-Santos et al found that advanced age of the patients and the chronic nature of the lesions may have been predisposing factors for amyloid deposition. Furthermore, amyloid deposits were observed in mainly skin biopsy samples from female patients and there was suggestion that racial or genetic influences may be involved. In contrast, our patient was of male gender, the lesions were only present for 3 to 4 months and he was 66 years of age.

In conclusion, the coexistence of porokeratosis and amyloidosis is a rare occurrence but may be underdiagnosed. The exact mechanisms for its coexistence remain unclear, and this spurs further efforts for an optimal therapeutic option in terms of targeting the parakeratotic cells at the cornoid lamella as well as rectifying keratinization and inhibiting cell proliferation.

Discussion

In 1893, Vittorio Mibelli first described porokeratosis and its characteristic histology of cornoid lamellae. Classically, clinical features include one or more annular plaques with a surrounding, raised, horny border. Amyloidosis, on the other hand, refers to a group of sporadic, familial, degenerative, and infectious disease processes, linked by abnormal protein folding and deposition of amyloid. In our patient, there was a classical presentation of disseminated brown annular plaques with raised borders suggestive of DSP. However, histology revealed presence of amyloid deposits in the dermis in addition to characteristic cornoid lamellae. In primary, localized cutaneous amyloidosis, this includes macular, lichen, and nodular types. Amyloid deposits are limited to the dermis without systemic involvement. Interestingly, the material in lichen and macular amyloidosis is derived from epidermal keratinocytes [keratinocyte-derived amyloid (AKJ)], whereas that in nodular amyloidosis is derived from immunoglobulin light-chains amyloid (AL).

Amanita et al have suggested a causal link between porokeratosis and amyloidosis, with both conditions caused by alterations in the keratinization process. It has been suggested that necrotic keratinocytes (colloid bodies) might transform into amyloid by the

![Figure 3. Photomicrograph of the skin biopsy showing presence of an obliquely-oriented column of parakeratosis (cornoid lamella) (arrow) and clumps of amyloid deposits in the papillary dermis (arrowheads). (Haematoxylin and Eosin, original magnification x 100).](image-url)
References

Case Report

THE WRATH OF THE RENGAS: A REPORT OF SEVERE CONTACT DERMATITIS AND IMPLICATIONS FOR PUBLIC HEALTH IN RURAL AREAS

Xavier G¹, Yong KY², Pubalan M³

Introduction
The tropical rainforest consists of a multitude of floral species providing benefits and equally causing detriment to visitors from food to poison. Some tree species within the family Anacardiaceae (genera Gluta and Mellanorrhoea), collectively named Rengas; can cause severe allergic dermatitis to those who come in contact with this plant¹.

Sap from the Rengas tree can cause severe irritation to the skin. The sap contains urushiol, a biochemical allergenic component which affects the skin via a type 4 hypersensitivity reaction²,³. It is highly potent as contact with contaminated surroundings including water can also cause an allergic response. Nevertheless the wood is not popularly made into furniture due to its effects¹. This tree is similar to the common mango tree (Mangiferaindica) albeit larger and taller with characteristic black blotches on its leaves and black sap staining on the trunk⁴,⁵. Here, we present a case of a traveler with allergic contact dermatitis to Rengas.

Case Report
We present a case of a 24 year old German who came with a chief complaint of left forearm rash. It was associated with itchiness, burning sensation, pain and swelling and redness over one week duration. Patient was afebrile.

He had a similar reaction one month prior to this episode on his legs that was worse on the right foot and was treated as cellulitis. This recovered after a week. Similar to the previous reaction the current presentation also occurred around 2 to 3 days after returning from the jungle, indicating a type 4 hypersensitivity reaction.

For the present episode he was again treated as cellulitis and was prescribed antibiotics notably penicillin. The rash began to worsen and began to involve the abdomen. The dose of penicillin was increased to its maximum dose. The lesions on the abdomen were initially macular and over the next 5 days it began to coalesce involving almost the entire trunk. The rashes were very itchy. The lesions on the left arm however was beginning to improve. The diagnosis of a possible Rengas allergy was highlighted to us by the local population although this seemed to be extremely severe. On further history the patient did note that there was a tree with black spots and he did have contact with it. Some of the sap did stain his skin however rinsing it did not readily remove it. Unaware of what it was the patient continued his work.

On day 5, the presentation included blisters with serous discharge that was not foul smelling or associated with fever (Figure 1, 2). Burning sensation, itch and pain worsened, and disturbed his sleep. The antibiotic was stopped and he was commenced on steroids and antihistamines. IV steroid was first administered three times daily for 3 days and followed by oral steroids. Tablet prolase was given to reduce the swelling. Small macular rashes began to appear at distal right forearm.

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True improvement was seen after one week of steroids which was completed after a 10 days course. There was no scarring.

**Discussion**

The potency of rengas is well documented in an article on occupational contact dermatitis to the rengas wood. It describes a group of carpenters with one in particular who worked with Rengas dead wood presenting with subacute dermatitis on his forearms, antecubital fossae, abdomen and ankles of 2 weeks duration. This is a similar presentation to our patient who apparently had the signs and symptoms for the same duration.
His dermatitis cleared with topical steroids and avoidance of exposure to the wood. As it has caused several contacts to have symptoms despite not all seeking treatment, it still does demonstrate that it can be a public health concern in particular areas of risk such as in a wood factory and in the jungle.

The potency as described by locals mentioning that by even walking under the tree, coming into contact with contaminated water and rain drops and also smoke from the burning wood\(^4\) is well documented in a case report of a patient developing allergic contact dermatitis whilst working on dead rengas wood\(^6\).

Due to this wrath effects, Rengas was promulgated in the Malaysian Camping Online Info with advice to stay away from these trees and not to camp nearby\(^6\). It describes the physical appearance of the tree, as well as immediate preventive measures of washing with soap and water, removal of contaminated clothing and seeking treatment as soon as possible. These measures were explained to the national park authorities in order to create awareness among its guides, tourist and researchers.

The Wood Database has also stated that Rengas sap causes blisters, ulcers, fever and constitutional symptoms such as malaise. It mentions of the urushiol group of allergens, isolated from poison ivy and poison oak plants, which is the common cause of this severe contact dermatitis\(^6\). The characteristics of uroshiol, an immunogenic hapten triggers T cells, monocytes and macrophages leading to a type 4 hypersensitivity reaction\(^1,8\). Our patient had been previously sensitized to uroshiol with the current presentation within 48 hours after exposure.

The mainstay of treatment includes steroids and antihistamines with avoidance of the plant and its components.

The rural health clinic in Mulu is equipped with basic antibiotics as well as emergency drugs including steroids. The presence of a doctor reduces the need for referrals to tertiary centres due to the improved services provided. Allergic reactions are common presentations to the clinic and this case constitute a very severe allergic reaction to Rengas. In conclusion, early diagnosis, treatment and prevention is important in avoiding serious health consequences of Rengas allergy. Hence, the awareness is crucial especially among rural healthcare staff and nature guides and visitors to tropical rainforest.

Acknowledgement

We wish to thank the people of Mulu for their input regarding the effects of Rengas and its characteristics, and the staff of Mulu Health Clinic who managed to provide good care to this patient. We also acknowledge Mulu National Park on the measures taken to keep the tourist from harm’s way allowing their visit to be comfortable and healthy. Finally, we thank the Director General at Ministry of Health for approving the publication of this paper.

References

Case Report

MAXILLARY ORAL CUTANEOUS FISTULA IN DIABETES MELLITUS PATIENT: A CASE REPORT

Tan ST, Gunawan L, Reginata G

Introduction
Chronic infection of the teeth and its adjacent tissue may result in a tunnel-like pathologic structure called oral cutaneous fistula, which connects dental infection focus with skin of the face or neck. This condition is preceded by chronic abscess of periapical area, impacted teeth, or radix. Oral cutaneous fistula is the most common causes of fixed nodulocyst papules and chronic suppurative nodules of the face and neck which usually is formed in the submandibular and submental region. The incidence is higher in over 40 years old age group, dominated by male. Data about oral cutaneous fistula in Indonesia is yet to be published.

Oral cutaneous fistula has several differential diagnosis such as local skin infection, pyogenic granuloma, osteomyelitis, congenital fistula, salivary gland fistula, infected cyst, and deep mycotic infection. Nevertheless, facial lesion caused by oral cutaneous fistula is often an overlooked diagnosis that treatment or surgical intervention not deemed necessary.

Case Report
A sixty-two years old male came to dermatovenerology clinic with pain at perioral area since two months ago. Pain alleviated when a blister-like lesion appeared on the right cheek, which then engorged and burst out three weeks ago. A week before the patient came, the wound broadened to the lips and made them looked swollen. The patient had seen several general practitioners beforehand and had been prescribed antibiotic and analgesic. The pain did improve, but the wound did not. The patient was diagnosed with diabetes mellitus 8 years ago, but never saw his doctor routinely. The patient was then admitted for inpatient care and referred to oral and maxillofacial surgeon and internist.

Physical examination revealed good general appearance, blood pressure 130/80 mmHg, heart rate 88 x/minute, breathing 18 x/minute, temperature 37.1°C, and body weight 65 kg. Erythematous plaque with blackish-brown crust, necrotic tissue, edema, and pus were found at facial region. Gangrenous tissue was present at teeth 15, 16, 24, 25, 26, 27, 28, 38, 43, and 44. Blood test revealed hemoglobin 12.5 g/dL, leukocytes 16.000 µL, eosinophils 4.8, lymphocytes 7.1, segmented neutrophils 72.2, monocytes 9.6, and random blood glucose 280 mg/dL. Tissue specimen was taken for pathology anatomy and culture examination. On the first day of treatment, drugs administered were intravenous ceftriaxone 1 gram b.i.d., subcutaneous novorapid 8 IU t.d.s., subcutaneous glargine 8 IU o.n., tablet paracetamol 500 mg t.d.s., also prescribed betadine mouthwash, got the wound compressed, and followed diet with 2000 kcal intake. Extraction and debridement of teeth was done on the third day.

Discussion
Oral cutaneous fistula is a sinus canal connecting dental infection focus to facial or neck skin which is responsible for extra oral infection spreading. Chronic inflammation of the teeth slowly destruct alveolar bones and spread to soft tissue to finally breach to the skin surface. Initial clinical presentation includes pain at the infected teeth. Pain would reduce after chronic abscesses or oral cutaneous fistula has formed. In this case, patient complained persistent pain since two months before coming to our clinic, which seemed alleviated when a furuncle-like lesion appeared on the right cheek.
Figure 1. Extraoral presentation of odontocutaneous sinus canal at maxillary region of the face, consisted of erythematous plaque with brown crust, erythema, necrotic tissue, edema, and pus pretreatment.

Figure 2. Hyperpigmented plaque with brown crust, edema, and pus on Day 3.

Figure 3. Minimal hyperpigmented plaque and crust, erosion on Day 7.

Figure 4. Wound had closed, a few crusts were still visible 2 weeks post teeth extraction.

Figure 5. Wound healed completely. Scar seen on the right cheek 3 weeks post teeth extraction and debridement.
Systemic diseases like malignancy, diabetes, and AIDS would aggravate the condition, as was seen in this patient who was first diagnosed with diabetes 8 years ago. Severe gum inflammation and periodontal abscess often occurred in diabetes patient who has poor oral hygiene. Uncontrolled diabetes mellitus might deteriorate immune system. Susceptibility to infection would increase as neutrophil function in chemotaxis and phagocytosis were impaired, leading to enhanced intracellular bacterial activity in causing periodontal destruction.

Diagnosis is based on anamnesis, physical examination, blood test, and pathology anatomy examination. In this patient, we found a painful wound of 3.5 cm in diameter covered by thick crust on the right cheek, edema, erythema, and pus. There were multiple gangrenous dental abscesses. Blood test revealed infection and increased blood sugar. Pathology anatomy showed polymorphonuclear cells domination, while culture did not reveal any specific bacteria with Streptococcus being the most dominant finding.

Surgical endodontic treatment or teeth extraction is treatment of choice for oral cutaneous fistula, before which stabilizing general condition and blood glucose is imperative in order to limit infection spread and ensure maximum antibiotic penetration. Oral cutaneous fistula is a local infection in which systemic antibiotic is only necessary in immunocompromised setting. In this case, patient was given intravenous ceftriaxone (a broad spectrum antibiotic) 1 gram b.i.d., subcutaneous novorapid (a rapid-acting insulin) 8 IU t.d.s., and subcutaneous glargine (a basal insulin) 8 IU o.n., paracetamol 500 mg t.d.s., betadine mouthwash, wound compression, and 2000 kcal intake.

Three days after teeth extraction-debridement, the hyperpigmented plaque, brown crust, edema, and pus had all improved. Seven days after extraction, the lesion dried up; the crust was minimal; an erosion was seen at the lesion site. Patient was sent home with tablet metronidazole 500 mg b.i.d. to eliminate anaerobic bacteria, tablet natrium diclofenac 50 mg b.i.d. for pain, subcutaneous novorapid 8 IU t.d.s., subcutaneous gargline 8 IU o.n., and betadine mouthwash to improve oral hygiene. A week after extraction, patient came for the first follow-up, crust was very minimum and lesion had gotten much better. Oral therapy was continued. A week after first follow-up, all lesion had cleared up and there was scar tissue in place of where the lesion was.

Early diagnosis and treatment would significantly lower complication risk such as sepsis, osteomyelitis, and aesthetic problem. This patient’s prognosis was quod ad vitam, quo ad sanam, quo ad cosmeticum ad bonam. Routine control and treatment helped the patient to get better.

References
LEPROSY REACTION IN MYCOBACTERIUM lepraE AND MYCOBACTERIUM TUBERCULOSIS CO INFECTION: A CASE REPORT AND LITERATURE REVIEW

Jamil A, Nik Adeeb NN, Muthupalaniappen L, Md Nor N

Introduction
Co infection by the two oldest diseases known to mankind, leprosy and tuberculosis is uncommon. A systematic review by Rajagopala et al. in 2012 identified 156 cases in the literature. In India, it is estimated that 0.019 cases of concomitant infection would be detected per 100,000 population. The pathogenesis of simultaneous Mycobacterium leprae and Mycobacterium tuberculosis infection is unclear. Tuberculosis exposure may be protective against leprosy, as the Bacillus Calmette-Guerin (BCG) vaccination has been demonstrated to confer protection against leprosy.

Leprosy reaction occurs in about 25% of paucibacillary and 40% of multibacillary leprosy patients. Presence of M leprae antigens or DNA in the skin or nerves, higher expression of mycobacterial accA3 and hsp18 genes and toll-like receptor (TLR) gene polymorphism contribute to development of reactions. Risk factors for type 1 reaction (T1R) are older age, extensive disease, positive slit skin smear, household contacts, concurrent infection and disability at presentation. Risk factors for type 2 reaction (T2R) are bacteriological index (BI) > 4 and lepromatous leprosy.

Case report
A 69 year old man with type II diabetes mellitus and hypertension presented with numbness of the upper and lower limbs with intermittent swelling of 2 years duration. Physical examination revealed peripheral neuropathy, thickened ulnar nerves and multiple neuropathic ulcers. He was diagnosed as lepromatous leprosy with recurrent type 1 leprosy reaction and was treated with Dapsone, Clofazimine and Rifampicin.

One month after MDT, he complaint of loss of appetite and 10kg weight loss over 3 months. There was no cough, fever or night sweats. On examination, there were bronchial breath sounds at the right upper zone of the chest and cervical lymphadenopathy. Chest radiograph showed consolidation, fibrosis and cavitations (Figure 1). Cavitations with ground glass and tree in buds appearance were seen on computed tomography. Broncho alveolar lavage culture grew M tuberculosis that was sensitive to all first line anti tuberculosis drugs. Polymerase chain reaction (PCR) isolated M tuberculosis complex. Ethambutol, isoniazid and pyrazinamide were added for treatment of tuberculosis. Dapsone and clofazimine were continued while Rifampicin was changed to daily dose.
The patient developed another similar episode of T1R a month after anti TB treatment. He was treated with prednisolone 30mg daily (0.5mg/kg) for a month and the dose was tapered off within 2 months. He remained asymptomatic and well 3 months after discontinuation of prednisolone.

Discussion

Tuberculosis and leprosy co infection is more common in middle age men with the first infection being leprosy, in particular lepromatous leprosy. Systemic steroid treatment for leprosy reactions was thought to be a predisposing factor to M tuberculosis infection. However, the TRIPOD studies that investigated the effect of 16 weeks prednisolone therapy for nerve impairment did not report the occurrence of tuberculosis in their patients. Rajagopalan et al identified malnutrition in more than 80% of co infected patients, about 4% were on steroid or immunosuppressive therapy. Only 1 out of 106 patients had diabetes mellitus. Our patient had diabetes, was well nourished and was not on corticosteroid.

Leprosy reaction is common in co infected patients, we reviewed the literature to identify the clinical characteristics and risk factors for leprosy reaction in these patients. The findings are summarized in Table 1. Most patients were middle aged men. Leprosy, mainly the lepromatous type was the first infection diagnosed in 8 patients, tuberculosis was the first diagnosis in 5 patients. Four patients with leprosy were on prednisolone prior to developing tuberculosis. Pulmonary tuberculosis was commonest, other sites reported were the central nervous system, skin and peritoneum. There were more T2R compared to T1R. The time leprosy reaction occurred in relation to diagnosis of tuberculosis or duration of anti TB was variable and unpredictable. We were not able to determine the effect of mycobacterium load and treatment on the occurrence of reactions as data from the reviewed articles were limited. In most patients with TB as the first infection, leprosy reaction occurred at the presentation of leprosy. However, this maybe an inaccurate conclusion as the exact time each infection is acquired cannot be confirmed. Interestingly, drug resistance was not observed except in one patient with multi drug resistant tuberculosis including rifampicin.

In the presence of suggestive symptoms, acid fast bacilli isolated from a leprosy or tuberculosis patient should be confirmed M leprosy or M tuberculosis. Leprosy reactions may complicate the diagnosis and treatment of both conditions. It is unlikely that acquiring tuberculosis infection or tuberculosis treatment predisposes to leprosy reactions, however this requires further investigation.
Table 1. Summary of cases with leprosy and tuberculosis co infection with leprosy reaction.

<table>
<thead>
<tr>
<th>Parameter / Authors</th>
<th>Age, gender</th>
<th>Disease diagnosed first</th>
<th>Duration to diagnosis of second disease</th>
<th>Type of leprosy</th>
<th>Site of TB</th>
<th>Type of lepra reaction</th>
<th>Time lepra reaction occurred</th>
<th>Immuno-suppression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argawal et al. 2000</td>
<td>40, M</td>
<td>TB</td>
<td>weeks</td>
<td>LL</td>
<td>Pulm</td>
<td>II</td>
<td>2 months on MDT+anti TB</td>
<td>Azathioprine + Prednisolone (for renal transplant)</td>
</tr>
<tr>
<td>Lee et al. 2003</td>
<td>63, M</td>
<td>TB</td>
<td>4 months</td>
<td>BL</td>
<td>Pulm</td>
<td>I</td>
<td>4 months on anti TB, at diagnosis of leprosy</td>
<td>-</td>
</tr>
<tr>
<td>Argawal et al. 2007</td>
<td>34, F</td>
<td>TB</td>
<td>weeks</td>
<td>BL</td>
<td>Pulm</td>
<td>I</td>
<td>20 days on anti TB, at diagnosis of leprosy</td>
<td>Leflunomide (for rheumatoid arthritis)</td>
</tr>
<tr>
<td>Sreerama-reddy et al. 2007</td>
<td>65, M</td>
<td>Leprosy</td>
<td>NA</td>
<td>BL</td>
<td>Pulm</td>
<td>Neuritis</td>
<td>Before diagnosis of TB</td>
<td>Prednisolone (for neuritis)</td>
</tr>
<tr>
<td>McIver et al. 2011</td>
<td>10, M</td>
<td>Leprosy</td>
<td>1 year</td>
<td>-</td>
<td>Pulm</td>
<td>II</td>
<td>Recurrent before diagnosis of TB</td>
<td>-</td>
</tr>
<tr>
<td>Prasad et al. 2010</td>
<td>31, M</td>
<td>Leprosy</td>
<td>7 months</td>
<td>BL</td>
<td>Pulm</td>
<td>II</td>
<td>At diagnosis of TB, 6 months on MDT</td>
<td>-</td>
</tr>
<tr>
<td>Trindade et al. 2013</td>
<td>31, M</td>
<td>TB</td>
<td>3 months</td>
<td>BB-BT</td>
<td>Pleura</td>
<td>I</td>
<td>3 months on anti TB, at diagnosis of leprosy</td>
<td>-</td>
</tr>
<tr>
<td>Parise-Fortes et al. 2014</td>
<td>59, M</td>
<td>Both</td>
<td>NA</td>
<td>LL</td>
<td>Perianal</td>
<td>II</td>
<td>At presentation, and recurrent before treatment of both diseases</td>
<td>Prednisolone (for presumed drug reaction)</td>
</tr>
<tr>
<td>Rawson et al. 2014</td>
<td>18, M</td>
<td>Leprosy</td>
<td>9 months</td>
<td>LL</td>
<td>Pulm</td>
<td>Neuritis</td>
<td>NA</td>
<td>-</td>
</tr>
<tr>
<td>Quyum et al. 2015</td>
<td>-</td>
<td>TB</td>
<td>6 months</td>
<td>LL</td>
<td>Skin</td>
<td>II</td>
<td>At diagnosis of leprosy &amp; before treatment of both diseases</td>
<td>-</td>
</tr>
<tr>
<td>Sendrasoa et al. 2015</td>
<td>49, M</td>
<td>Leprosy</td>
<td>13 months</td>
<td>LL</td>
<td>Pulm</td>
<td>II</td>
<td>1 month after completed MDT, before TB diagnosed</td>
<td>Prednisolone (for T2R)</td>
</tr>
</tbody>
</table>

– not available, T2R – type II leprosy reaction, Pulm-pulmonary
References

Case Report

YOUNG LADY WITH RECURRENT ABDOMINAL PAIN, IS IT ONLY GASTRITIS?

Neoh KK¹, Tang ASN¹, Kiing JW¹, Adam Malik I²

Introduction
Henoch Schonlein Purpura is a systemic vasculitis disease which is associated with lower limb maculopapular rash, abdominal pain, arthritis and occasional renal involvement. It is one of the commonest vasculitis in pediatric groups but incidence in adult is much rarer. We herein describe a case of Henoch Schonlein Purpura in a 24 years old lady with gastrointestinal involvement.

Case history
A 24 year old Chinese lady had recurrent visit to different hospitals, over a 2 years duration, with the complaint of abdominal pain. The pain was colicky in nature, over epigastric region, pain score up to 8-9/10, lasted for hours, intermittent and may spanned over 2-3 weeks duration. The symptoms were associated with vomiting with no bilious or food particles. There was no change of bowel habits. She was frequently labelled as acute gastritis and discharged with syrup Magnesium Trisilicate Mixture in casualties. She had history of admission to different hospitals for 4 times, and discharged with diagnosis of non specific abdominal pain.

In view of her recurrent unexplained symptoms, she was investigated extensively and had undergone a series of invasive investigation and imaging. Abdominal ultrasound, gynecological scan and oesophagastroduodenoscopy were normal. CECT abdomen showed multiple mesenteric lymph nodes up to 0.8cm, with mesenteric fat streakiness, multiple para-aortic lymph nodes and mild ascites. Tumor marker including beta human chorionic gonadotrophin (hCG), Ca19.9, Ca 125, alpha feto protein, and carcinoembryonic antigen (CEA) were normal. A further detailed history by medical team in her fourth admission only revealed that she had on and off bilateral palpable maculopapular rash over bilateral lower limbs, sparing foot and buttock, for past 2 years. The rash would spontaneously resolved after a few days, and occasional associated with abdominal pain. There was no fever, respiratory, cardiovascular, central nervous system and joint symptoms. There was no rash in that admission.

Blood parameter showed normal full blood count, renal and liver profile, urinalysis, coagulation profile, connective tissue screening and infective screening.

She presented again with recurring maculopapular rash over bilateral lower limbs 3 weeks after the discharge (Figure 1), and skin biopsy was performed and reported as leucocytoclastic vasculitis, with dermis layer showing neutrophilic small vessels vasculitis, leukocytoclasis and extravasation of red blood cells (Figure 2).

After two years of frequent hospital visits and a series of invasive investigations, we are only able to revise her diagnosis to adult onset Henoch Schonlein Purpura (HSP) with gastrointestinal involvement. Her symptoms resolved spontaneously and did not require treatment.

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Figure 1. Non thrombocytaenic purpura of lateral aspect of right thigh, which appeared not at same time with gastrointestinal symptoms.

Figure 2. Perivascular neutrophilic infiltrations and small vessels destruction with leukocytoclasis and extravasation of red blood cells in the upper dermis suggesting leukocytoclastic vasculitis (H&E, magnification X100).

Figure 3. Small vessels destruction with leukocytoclasia and red blood cells extravasation (H&E, magnification X 400).
Discussion

HSP is a systemic small vessel vasculitis characterized by deposition of IgA complexes in various tissue. It is frequently self-limiting.

The annual incidence of HSP in children less than 17 years old is around 6.2 to 70.3 per 100,000, and is around 3.4 to 14.3 per million population in adult. Etiology of HSP is unclear, and is postulated linked to bacteria or virus infections, connective tissue disease, vaccination, drugs and autoimmune mechanisms that lead to antigen-antibody immune complexes (IgA) formation and deposit in various tissues.

HSP is described as a tetrad of clinical manifestations of non-thrombocytopenia palpable purpura, arthritis, abdominal pain and renal disease. In adulthood, HSP may present in a more severe clinical syndrome, with higher frequency of renal involvement. However the final outcome of HSP is equally good in patients of adulthood or childhood.

The diagnosis criteria of HSP was reviewed by European League Against Rheumatism (EULAR) and Paediatric Rheumatology European Society (PRES) in 2006 as follows:

Palpable purpura (mandatory criterion) in the presence of at least one of the following features:

- Abdominal pain (usually diffuse, with acute-onset)
- Arthritis or arthralgia (acute-onset)
- Renal involvement (proteinuria, hematuria)
- Histopathological findings of leukocytoclasis vasculitis or proliferative glomerulonephritis, with predominant immunoglobulin A (IgA) deposition

Our patient had palpable purpura, abdominal pain, and leucocytoclastic vasculitis, with all of these happened at a different onset. Some case reports showed that gastrointestinal complaints precede the rash in between 15-30 percent of cases, but gastrointestinal symptoms without the appearance of skin lesion was also described in isolated case reports. The different onset of abdominal pain and cutaneous purpura had cause diagnosis dilemma and delay in reaching final diagnosis.

HSP is confirmed by the presence of IgA by immunofluorescence in purpuric skin lesions. It was not done in our case study due to resource limitation. A retrospective studies reviewed by Poterucha T.J, et al in 2013 on 68 adults with HSP revealed that those with a positive skin biopsy of leucocytoclastic vasculitis or IgA deposition were more likely to have renal involvement (3 fold risk).

Majority of HSP patients recover spontaneously and do not require specific treatment. Care of HSP patient will be towards pain relief with acetaminophen, nonsteroidal anti-inflammatory drugs or weak opioid.

Use of steroid in HSP patient is not standardized. Studies showed that prednisolone 1mg/kg/day for 2 weeks, with weaning over subsequent 2 weeks is effective in reducing abdominal pain. Optimal management of HSP associated gastrointestinal and renal involvement has not been determined. Some uncontrolled studies still favor a short course of oral steroid for abdominal symptoms relieving. Imunosuppressive medications are not indicated unless severe kidney, pulmonary or central nervous system involvement.

Prognosis of HSP in childhood is good, with two thirds of patient have no recurrent episodes, and the remaining one third may have recurrence. The prognosis of adult onset HSP was not well studied, but Lu S. et al suggested that the risk of chronic renal disease is increased in adult patient with HSP, requiring for long term follow up for kidney function.

The diagnosis of Henoch Schonlein Purpura is not uncommon in Malaysia, and we could be able to diagnose her earlier if we had taken a detailed history in early days, and avoid subjecting this lady to multiple invasive test and imaging, and hospital admissions.

This case highlights the importance comprehensive clinical history as it help us in reaching the diagnosis for this young lady, even though the patient presented with “simple gastritis.”
References


Case Report

A RARE CASE OF MULTIPLE CONGENITAL NEVOMELANOCYTIC NEVI

Lestary D, Lestari S, Yenny SW

Introduction

Congenital nevomelanocytic nevus (CNN) are benign proliferations of cutaneous melanocytes clinically apparent at birth or within the first postnatal weeks. The prevalence of CNN appears to be slightly higher in non-whites with no sexual predilections\textsuperscript{1,2}. The estimated incidence is 1 in 100 for small CNN (< 1.5 cm); 1 in 1000 for medium-sized CNN (1.5-19.9 cm) and 1 in 20,000 for large CNN (> 20 cm) and 1 in 500,000 for giant CNN\textsuperscript{3,4}. Giant has been variously defined as a lesion as large as the patient’s palm if it occurs on the head and neck (and twice that area for other anatomical sites), 30% of the body surface, or 900 cm\textsuperscript{2} in adults (or smaller if it involves a major anatomic area)\textsuperscript{1,5}.

Herein, we report a rare case of multiple congenital nevomelanocytic nevus.

Case history

A girl 6 year old was referred from Payakumbuh Hospital to us with non-pruritic hairy pigmented patches on the right forehead, right scalp, right cheek, left temple, arms, chest, abdomen, back, buttock and legs since birth. At birth, blackish coin shaped patch was seen only on the right forehead with gradual enlargement and involvement of other anatomical sites. The patches did not easily bleed and she did not experience headache, seizures nor vomiting.

Dermatological examination revealed hyperpigmentation hairy plaques with varying size (0.5 to 17 cm in diameter) on the right forehead, right scalp, right cheek, left temple, arms, chest, abdomen, back, buttock, legs (Figure 1). There were hair follicles, perifollicular hypopigmentation and homogenous areas on dermoscopy (Figure 2). Skin biopsy showed epidermal atrophy, hyperkeratosis, adnexal atrophy and proliferation of nevus cells on the dermis pars reticulare and periadnexally (Figure 3).

Figure 1. Multiple congenital nevomelanocytic nevus in various parts of the body with varying sizes.

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to UV light. The risk factors for malignant transformation in our patient are continuous trauma of the scalp lesion due to combing and hair binding.

Giant congenital melanocytic nevus on the scalp and neck may be associated with leptomeningeal melanocytosis and neurologic disorders like neurofibromatosis, epilepsy or focal neurologic abnormalities, whereas lesions over the vertebral column may be associated with spina bifida or meningomyelocele. This associated disorders were not present in the current case.

Discussion
The diagnosis was made based on the clinical presentation and histopathological findings. There are three types of congenital melanocytic nevus: (a) Giant congenital nevi are more than 20 cm in diameter (adult’s size), (b) small congenital nevi are less than 1.5 cm in diameter, and (c) intermediate nevi are in between 1.5 and 19.9 cm. The risk of malignant transformation to malignant melanoma is 8.2%, a 52% higher risk than the general population. The risk factors for malignant melanoma include genetic factor, continuous trauma and long exposure to UV light. The risk factors for malignant transformation in our patient are continuous trauma of the scalp lesion due to combing and hair binding.

Figure 2. Perifollicular hyperpigmentation with homogenous areas seen with dermoscopy.

Figure 3a. Epidermal atrophy, hyperkeratosis, adnexal atrophy and proliferation of nevus cells (H & E, magnification X 100).

Figure 3b. Proliferation of nevus cells in the dermis pars reticulare and around the adnexae suggesting congenital nevomelanocytic nevus (H & E, magnification X 400).
The partial removal of GCMN by procedures such as dermabrasion, skin curettage, tangential excision, chemical peels and laser treatment is mostly employed for cosmesis since only the most superficial cells of the lesion are removed. The size of the lesions makes their removal difficult. Serial surgical interventions, use of tissue expanders, skin flaps, grafts or a combination of surgical techniques are frequently required. Postoperative complications include contractures, seromas especially when tissue expanders are used, hematomas, infection, ischemic skin flaps, suture dehiscence and formation of keloids.

In conclusion, multiple congenital nevomelanocytic nevi are rare and poses problem in management. Regular follow ups are important as the risk of malignant transformation is high.

References

Case Report

LINEAR BASAL CELL CARCINOMA - A DIAGNOSIS ACHIEVED BY THE USE OF CONFOCAL MICROSCOPY

Long V, Chen Q, Chuah SY, Thng TGS

Introduction
Linear basal cell carcinoma (BCC) was first described by Lewis in 1985. It is a rare and distinct morphology variant. Since 1985, only 37 cases have been reported. The periocular region was the most affected, especially the lower eyelid and malar region. This report describes a lesion that has few clinical and dermoscopic features of basal cell carcinoma and was histopathologically diagnosed as an erosion. Only with confocal microscopy was the correct diagnosis clinched – showing typical features of basaloid islands with peripheral palisading and retraction clefting. This report emphasizes the importance of selecting the right site for biopsy in a case of linear basal cell carcinoma and demonstrates the usefulness of in-vivo confocal in such difficult cases when biopsy was not helpful.

Case history
An 86-year-old Chinese female presented with a 4-year history of a lesion over the left lower eyelid which was noticed coincidentally after a cataract operation. It was mostly asymptomatic with occasional pain but no bleeding. On clinical examination, she had a 2cm curvilinear hyperpigmented plaque over left lower eyelid with pearly edges with a centrally crusted erosion (Figure 1). Dermoscopic features of the lesion include a small central erosion with scant maple leaf structures scattered along the lesion. There were no arborizing vessels nor globules seen in dermoscopy. A punch biopsy of the plaque was performed near the site of the erosion.

Figure 1. Linear nodule under the left lower eyelid with central ulceration.

Figure 2. Histological image shows that the epidermis is eroded and covered with an inflamed serous crust which contains aggregates of bacteria cocci. Tiny fragments of the epidermis are seen at the base of the ulcer and there is no overt keratinocyte atypia.

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Histological examination revealed an eroded epidermis covered with an inflamed serous crust which contained aggregates of bacteria cocci. Tiny fragments of the epidermis were seen at the base of the ulcer and there was no overt keratinocyte atypia. There was a dense upper dermal infiltrate of plasma cells and lymphocytes in association with pigment incontinence (Figure 2). There were no features suggestive of basal cell carcinoma despite clinical suggestion of its diagnosis.

As the lesion was clinically suspicious of a basal cell carcinoma and histological features may not be representative, an in-vivo confocal examination was performed. Confocal microscopy revealed typical basaloid tumor islands with peripheral palisading and retraction clefting consistent with BCC (Figure 3). Hence, the diagnosis of linear basal cell carcinoma was made. This patient subsequently underwent Moh’s micrographic surgery for complete clearance and resection of the basal cell carcinoma.

**Discussion**

Linear BCC is a rare morphological variant first described by Lewis1 in 1985; since then, 37 cases have been reported. Most of these cases reported were aligned along relaxed skin tension lines. Pierard2 et al. suggested that in the reticular dermis, skin tension lines have an anatomical counterpart consisting of a preferential parallel orientation and a straightening of thin collagen bundles and elastic fibres1. These parallel bundles lie perpendicular to the direction of contraction of the underlying muscles2. Hence, the linearity of the tumour may therefore be due in part to the stromal interactions with relaxed skin tension lines, coupled with muscle contraction constraining growth in one direction3. There is also thought that linear BCCs arise along embryonic cleavage planes; Chopra4 et al. suggested that the linearity can be explained by lateral limitations to lesional spread resulting from reactive dermal fibrosis. Though rare, linear BCC should be considered differential for linear skin lesions.

Dermatoscopically, our case had only 1 feature suggestive of BCC – the presence of maple-leaf like areas without other characteristic features of arborizing vessels, globules, telangiectasias or nests. As the lesion was clinically suspicious of a basal cell carcinoma, a biopsy was performed to confirm the diagnosis; unfortunately, the histopathological features were not helpful as biopsy was performed on a site that did not have the tumor nests. The diagnosis was made when an in-vivo confocal was used to scan the length of the lesion. Our case reinforces the important learning point that biopsy may be negative in a case of linear basal cell carcinoma as the tumor nests may not extend throughout the linear lesion. Clinical suspicion for basal cell carcinoma must be high, even in the
absence of every single typical feature including arborizing vessels, tumor nests or globules. In this case, there were subtle hints of maple-leaf like areas and focal ulceration/erosion seen on histological examination. Though not fully conclusive, a high index of suspicion must exist. In cases like these, an in-vivo focal microscopy would be useful as one can scan through the whole lesion to look for the tumor nests. In areas where in-vivo confocal is not available, a repeat biopsy would be needed.

References

Case Report

COMBINATION THERAPY OF ORAL DOXYCYCLINE WITH 0.05% TRETINOIN, 3% CLINDAMYCIN, AND 0.05% DEXAMETHASONE CREAM IN SEVERE ACNE VULGARIS: THREE CASE SERIES

Sukmawati TT, Gabriela R, Joice GP, Listyani G

Introduction
Acne vulgaris (AV) is a chronic inflammatory disease affecting pilosebaceous unit marked by the presences of comedones, papules, pustules, and nodules. This is commonly found among teenagers aged from 12-15 years old and peaks in age of 17-21 years old. Despite being a self-limiting disease, AV causes scarring leading to severe aesthetical and physiological disturbances.

There are many factors causing acne eg. races, genetics, hormones, diet, psychologic stressors, cosmetics use, climates, drugs, pregnancy, and smoking behavior. Four major pathogenesis of AV are increase of sebum production, pilosebaceous follicular hyperploriferation, colonization of P. acnes, and inflammatory process.

The goal of therapy is to accelerate recovery, inhibit new lesions, and prevent scarring. Treatment of nodulocystic and conglobata acne remains challenging. We present three cases of severe AV treated with a combination of oral doxycycline and combo cream containing tretinoin 0.05%, clindamycin 3%, and dexamethasone 0.05%.

Case 1
A 20 year old man had severe nodulocystic acne for 2 years which failed to respond to antibiotics and over the counter topical anti-acne. Examination showed multiple comedones, papules, nodulocysts and scars on the face. He was given oral doxycycline 100 mg twice daily for 10 days and cream containing 0.05% tretinoin, 3% clindamycin, and 0.05% dexamethasone at night. At one month follow up, there was marked reduction in inflammatory lesions. He was commenced on combination of 0.05% tretinoin and 3% clindamycin for another 3 months.

Case 2
A 25 year old man presented with severe nodulocystic acne for 3 months. He has acne since the age of 17 and was intermittently taking oral and topical anti-acne without much improvement. Examination showed erythematous papules, pustules, nodulocysts, comedones and scars on face. He was given oral doxycyclin 100 mg twice daily for 10 days and cream containing 0.05% tretinoin, 3% clindamycin, and 0.05% dexamethasone at night. At two weeks follow up, most inflammatory lesions had improved. Once the inflammation settled, he was commenced on combination of 0.05% tretinoin and 3% clindamycin for another 3 months.

Case 3
A 19 year old woman presented with severe nodulocystic acne on the face and neck for 1 year. She depended heavily on topical herbal products for her AV. On examination, there were multiple comedones, papules and pustules distributed on her face and neck. She was given oral doxycyclin 100 mg twice daily for 10 days and cream containing 0.05% tretinoin, 3% clindamycin, and 0.05% dexamethasone at night. At one month, her lesions improved tremendously. She was changed to a combination cream of 0.05% tretinoin and 3% clindamycin for another 3 months.

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Figure 1a. Erythematous papules, pustules, nodulocysts and scars on face.

Figure 1b. After 1 month of therapy, there was marked reduction of inflammatory lesions.

Figure 2a. Papules, pustules and nodulocysts on the face.

Figure 2b. After 2 weeks of therapy, there was reduction in inflammatory lesions.

Figure 3a. There were multiple comedones, papules, pustules on the face and neck.

Figure 3b. After 1 month of therapy, there was reduction in inflammatory lesions.
Discussions

AV is one of dermatological disease that is commonly found among teenagers and adults. Despite not being a life-threatening condition, its sequelae undermined patient’s confidence and self esteem1,2. Nowadays, self medication of AV take centrestage. The three patients reported had tried multiple over the counter products to no avail. This has become challenging for dermatologist, especially in dealing with severe scarring acne.

In the three cases presented before, all patients suffered severe acne vulgaris based on clinical assessment. All our patients satisfied the Lehman et al classification of severe acne (>5 cysts, >100 comedones, >50 inflammatory lesions, >125 total lesions)7.

Effective therapy in AV significant improves the quality of life in AV sufferers. The understanding of four mechanism of AV pathophysiology formed the foundation of treatment: refinement of follicular proliferation, suppression of sebaceous gland activity, reduction of P. acnes population, and inhibition of local inflammation7. For mild AV, topical retinoid or topical antibiotic suffice but moderate to severe AV require systemic antibiotics and topical retinoid13. The three patients were treated using oral doxycyclin 100 mg twice daily for 10 days and cream containing 0.05% tretinoin, 3% clindamycin, and 0.05% dexamethasone at night. Continuing use of oral or topical broad spectrum antibiotics increases the risk of P. acnes resistance8, and this circumstance could cause AV treatment failure.

Tetracycline had been used widely in the past to treat inflammatory lesions9. It is able to reduce free fatty acid concentration and supress P. acnes growth2. Due to the high resistance rate, doxycycline, a derivative of tetracyclines, has been recommened2,9.

Topical medications given to the our patients were a combination of tretinoin, clindamycin, and dexamethasone. The topical retinoids has comedolytic activity, preventing formation of microcomedones by normalizing follicular epithelial desquamation. In addition to targeting abnormal proliferation and differentiation of keratocytes, retinoids also possesses anti-inflammatory effects10. The main topical retinoids are tretinoin, tazarotene, and adapalene11,12. These properties make topical retinoids highly favoured among dermatologists. It is also safer than the oral isotretinoin treatment13.

Topical antibiotic is also commonly utilized in inflammatory acne14. Clindamycin is a semisynthetic molecule derived from lyncomycin. It lowers free lipid acid concentration and P. acnes population in the pilosebaceous units15. It also possesses anti-inflammatory property by suppressing leukocytes chemotaxis15,16. It is much favoured compared to the oral due to its superior side effect profile.

Corticosteroid has anti-inflammatory, immunosupresive, anti-proliferative, and vasoconstrictive properties. As anti-inflammatory agent, corticosteroid inhibits A2 phospolipase release, an enzyme responsible for synthesis of prostaglandin, leukotriene, and other arachidonic acid derivates that could damage dermal collagenous tissue and leads to formation of permanent scars12. Therefore steroid administration is important especially for severe cases such as nodulocystic acne and acne conglobata for scar prevention2. The most preferred topical corticosteroid is dexamethasone. Dexamethasone has not widely used as topical therapy for skin because it is poorly absorbed. Nevertheless, in severe acne, the highly inflamed skin allows better absorption17. Thus, topical dexamethasone works well in severe inflammatory acne. This phenomenon is called “focal specific effect”, which not only minimize general adverse effects of corticosteroids, but also heal the inflamed skin area and prevent the occurrence of post-inflammation hyperpigmentation18. However topical corticosteroid has double-edged sword, where long time use could induce comedogenesis, leading to increased concentration of free fatty acids in skin surface lipids and increased numbers of bacteria in the pilosebaceous duct19.

Our three patients responded excellently with the combination of oral doxycycline and the combo cream. Steroid use was stopped after inflammatory lesions disappeared. For maintenance, the three patients treated by combination cream 0.05% tretinoin and 3% clindamycin for 3 months.

In conclusion, severe AV therapy using short course oral doxycycline with combination cream of tretinoin, clindamycin and dexamethasone is promising in the treatment of severe AV.
References

Case Report

A CASE OF VERRUCOUS PSORIASIS IN AN ERYTHRODERMIC PATIENT

Bhullar A¹, Lee BR², Norashikin S¹

Introduction
Verrucous psoriasis is an uncommon variant of psoriasis characterized by the presence of hypertrophic verrucous papules or plaques. The warty appearance of the lesions is more suggestive of dermatoses such as verruca vulgaris. These cases are usually seen in patients with longstanding plaque psoriasis. It may be difficult to diagnose, therefore a skin biopsy with histopathology correlation is warranted.

We report a case of verrucous psoriasis seen on lower extremities in a patient with pre-existing plaque psoriasis and a review of the relevant literature.

Case Report
A 51 year old Malay male presented to our center with a history of extensive chronic plaque psoriasis spanning 10 years. He was initially treated with acitretin and NBUVB but due to poor clinical response was switched to methotrexate. He has had several episodes of erythroderma precipitated by poor compliance to systemic medications. His condition has also been complicated with psoriatic arthropathy with involvement of the small joint of the hands for the last 3 years. Throughout our clinical assessments, he had been persistently erythrodermic with flexion deformities of his distal interphalangeal joints bilaterally.

Two years ago he presented with symmetrical, moderately thick warty brownish hyperkeratotic plaques occurring on pre-existing psoriatic plaques on the dorsum of both feet which did not respond to methotrexate (Figure 1). These lesions were asymptomatic but were progressively growing. Methotrexate was given for a duration of 2 months at the dose of 10mg/week.

A 6 mm punch biopsy was taken from these plaques to confirm the diagnosis of verrucous plaque psoriasis. As his condition was severe, we planned for biologic therapy to control both his cutaneous and joint disease.

Histopathology examination of the skin specimen showed a grossly acanthotic epidermis. Psoriasiform hyperplasia with elongation of the rete ridges was seen. Dilated capillary loops in the papillary dermis was also present (Figure 2). There were neutrophilic exudates with microabscesses collections within the epidermis and parakeratosis with corresponding hypogranulosis (Figure 3). Patchy superficial lymphocytic perivascular exudates were also seen. PAS staining was negative for fungal bodies. These changes were consistent with verrucous plaque psoriasis.

In the meantime methotrexate was discontinued as he had developed acute hepatitis and he was just maintained on topical corticosteroids. As his condition was severe, we planned for biologic therapy to control both his cutaneous and joint disease. He was commenced on ustekinumab shortly afterwards, which resulted in flattening of his verrucous plaques as well as improvement in his psoriasis after 2 doses. This was the drug of choice in our patient as we had limited resources to finance other biologics at that time (TNF – alpha inhibitors). He completed 4 doses of ustekinumab. We stopped this drug as the overall PASI score has increased after 4 doses. The PASI score before the initiation of ustekinumab was 30, rising to 39 after 4 doses. Our next choice of treatment was adalimumab, for which we were able to secure funding. Our patient has been on this medication for 1 year, with good clinical response seen overall (Figure 4).
Figure 1. Brownish warty hyperkeratotic plaques symmetrically distributed on the lower legs extending to the dorsum of the feet and soles.

Figure 2. The epidermis showed psoriasiform hyperplasia with elongation of the rete ridges and prominent hypogranulosis. Dilated capillary loops were noted at the papillary dermis.

Figure 3. Neutrophils collection forming microabcesses within the stratum corneum and papillary dermis.
Discussions

Psoriasis is a T-cell mediated immune disease which affects 2-3% of the general population. The common subtypes of psoriasis are defined as plaque, guttate, flexural or inverse, pustular and erythrodermic psoriasis. Verrucous psoriasis was initially considered to be a more severe form of psoriasis rather than a separate entity. Over time, it has been discussed in the literature and is accepted as a clinical variant. It has not shown to have any particular site predilection and can occur by itself as well as in patients with psoriasis vulgaris. Clinically the lesions appear thickened and hypertrophic mimicking the appearance of other dermatosis like verruca vulgaris. In our patient the verrucous appearance of the feet also resembled mossy foot, a term usually used in conditions with chronic lymphatic obstruction such as elephantiasis where the lesions are grossly papillomatous.

So far there have been 20 cases reported in the literature. The first clinical case description was documented by Nakamura et al in 1994 in a 60 year old male of Japanese origin with chronic plaque psoriasis. The largest and only case series of 12 patients was reported by Khalil et al in the western population, mostly of Caucasian patients. The overall distribution of cases seems to be more common in men, affecting 13 of the patients with 7 female patients. The common sites involved are the trunk and the extremities. Some of these lesions have arisen on a background of pre-existing chronic plaque psoriasis. One case had concomitant non melanoma skin cancer. We also came across a case treated as multiple verrucous carcinoma, which was possibly VP based on the distribution and morphology, biopsy and response to acitrenin. These lesions were hyperkeratotic plaques on dorsal of feet, ankles and thigh.

The cause of verruca psoriasis is unknown. It has been postulated to occur from obstruction in the lymphatic drainage leading to the development of extensive cutaneous papillomatosis which gives the clinical warty appearance. No studies have been done to confirm this.

The occurrence of the verrucous lesions in psoriasis patients is uncommon. Some of the possible causes include poor hygiene and poor compliance to treatment. A similar case of verrucous skin eruptions in a patient with hepatitis C during interferon treatment suggests that ongoing immunosuppressive therapy may promote and lead to the development of verrucous psoriasis.
As our patient was suffering from refractory chronic plaque psoriasis with extensive body surface involvement, we decided on biologic therapy using ustekinumab, a monoclonal antibody which targets interleukin 12 and 23. Other novel treatment modalities that have been successful in other patients are radiation treatment and adalimumab4,6. A retrospective study by Pescitelli et al had shown ustekinumab to be effective in the management of erythrodermic psoriasis with very rapid and quick resolution of cutaneous disease12. Thus far, biologics have only been approved for the plaque variant of psoriasis and the current use to biologics in erythrodermic patients is limited.

This case report presents a rare and atypical manifestation of psoriasis in a patient with chronic plaque psoriasis despite being on oral immunosuppressive therapy. Verrucous lesions often reflect poor control of the underlying psoriasis and helps to guide clinical decision making with respect to therapeutic management options.

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ANGIOLYMPHOID HYPERPLASIA WITH EOSINOPHILIA OF THE EYELID: A CASE REPORT

Abirami S, MBBS¹, Gunavathy N², Ho SF³, Mazita I¹, Adil H¹

Introduction
Angiolymphoid hyperplasia with eosinophilia (ALHE) is an uncommon benign vascular disorder described by Wells and Whimster in 1969¹,³,⁴. It is characterized by marked vascular proliferation and inflammation primarily involving the head and neck region⁵,⁷,⁹,¹¹. It has a predilection towards women mainly in the third and fifth decade of life⁶,⁸,¹¹. Although involvement of the ocular adnexa involving orbit has been reported in the literature previously, it remains a rare site of occurrence⁵,⁹,¹⁰,¹². We report a case of orbital involvement of ALHE.

Case Report
A 39 year old Malay gentleman who was an ex-illicit drug user (non-injecting type) presented with painless, progressive left upper lid swelling for 3 weeks following an insect bite (Figure 1). There were no history of fever, eye discharge, skin rashes, trauma or blurring of vision. On examination, there was a non tender, diffuse, non fluctuant and erythematous swelling of the left upper lid leading to total mechanical ptosis. Bilateral ocular findings were normal. An initial diagnosis of left preseptal cellulitis secondary to insect bite was made. He was empirically started on oral Augmentin for one week. On follow up at one week, the swelling remained the same and he was admitted for intravenous ceftriaxone. Blood investigations including full blood count were normal. Plain and contrasted computed tomography of the orbit showed thickening of the left preseptal region extending to the subcutaneous region at the left temporal region which enhances after omnipaque infusion (Figure 2). As these findings correlated with the initial diagnosis, he was continued on intravenous ceftriaxone for 3 days. However, there was no improvement.

Subsequently, a biopsy with debulking of the left upper eyelid lesion was performed. Intraoperatively, yellowish hard materials were removed and sent for histopathological examination. Histopathology results showed fragments of fibromuscular tissue displaying scattered blood vessels surrounded by mature lymphocytes and eosinophils forming a nodular pattern (Figure 3). The stroma and muscular layer is infiltrated by dense eosinophils. There were no areas of necrosis or neoplastic lymphoid cells seen. Peripheral eosinophil cunt was 3.36 X 10⁸, which was within normal range. These features were suggestive of Angiolymphoid hyperplasia with eosinophilia and the diagnosis was revised.

Post-operatively, he was started on intravenous dexamethasone for 3 days followed by topical steroids. He responded well with gradual improvement of the upper lid swelling over the course of 3 months.

Discussion
ALHE arising from orbital region is a rare presentation. The presenting features are usually vague and nonspecific especially when it involves the ocular adnexa or orbit³. This leads to a delay in diagnosis in most cases²,¹⁰. In the case of orbital involvement, the common clinical features are lid swelling, ptosis, proptosis, periorbital swelling, diplopia, watering, pruritis around the eyes and blurring of peripheral vision⁵,⁹,¹⁰. In our case, the classical presenting features of proptosis and diplopia were missing. This is because there were no extraconal lesion or recti muscle displacement. The usual sites of periorbital ALHE involvement are lacrimal glands, eyelids, conjunctiva, medial and lateral canthal region, intra- and extracanal orbital spaces⁶.
ALHE has been called the western cousin of Kimura’s disease (KD) for the similarities they share in clinical presentation. They were previously considered as the same disease in different stages. Currently, they are distinguishable as separate entities. In contrast to ALHE, Kimura disease has a predilection to Asian men and commonly presents with painless subcutaneous masses in the head and neck, lymphadenopathy, peripheral blood and tissue eosinophilia. Histologically, the salient features of KD are, florid lymphoid follicles with germinal center formation, eosinophilic microabscesses, eosinophilic infiltrates and eosinophilic folliculolysis. It does not have epitheliod cells characteristic of ALHE.

Although the exact pathogenesis of ALHE remains obscure, various theories have been proposed in previous studies. The hypotheses include a neoplastic process, reactive process and infectious mechanism. There has been data suggesting ALHE may have lymphoproliferative changes as evidenced by presence of T-cell gene rearrangements. Presence of blood and tissue eosinophilia and raised serum IgE concentration instead suggests reactive etiology. It has also been postulated that ALHE can develop following injury, insect bites, infections or administration of tetanus toxoid vaccines. Arteriovenous shunts are also believed to be associated with development of ALHE. Another postulation is that renin, via the angiotensin II, may prompt proliferation of vessels thus being associated with the etiology of ALHE.

Figure 1. showing initial presentation of left upperlid swelling with complete mechanical ptosis.

Figure 2. Transverse Orbital CT scan showing thickened preseptal region of the left eye prior to excision biopsy.

Figure 3. Blood vessels (black arrow) surrounded by eosinophils (red arrow) and lymphocytes (Hematoxylin & Eosin stain, x10 magnification).
Another condition with close similarities to orbital ALHE is idiopathic orbital inflammatory disease (IOID) which has similar clinical presentation with proptosis, pain, ptosis, lacrimal gland swelling, and thickened extraocular muscles. However they can be distinguished histopathologically where a classic case of IOID has cellular infiltrate consisting mainly of mature lymphocytes, with plasma cells, macrophages, histiocytes, eosinophils, and infrequently neutrophils.

As much as it is a challenge to diagnose, so is the treatment of ALHE. Many literatures have proposed surgical excision or debulking of the lesion as the preferred choice of treatment. However, there is a high recurrence rate following surgical intervention as high as 33%. Incomplete surgical margins has been said to contribute to the recurrence. Other treatment modalities for ALHE include intralesional corticosteroids, cryotherapy, photodynamic therapy, application of tacrolimus/imiquimod, systemic corticosteroid treatment, irradiation, interferon alpha-2a, cytotoxic agents and laser treatment with pulsed dye or carbon dioxide. In our patient, we preferred the choice of debulking as it was done simultaneously with the biopsy to aid in diagnosis. An alternative approach is to observe the patient for 3 to 6 months for possibility of spontaenous involution.

Conclusion

In conclusion, a high index of suspicion is needed to diagnose ALHE particularly in an atypical presentation. Histopathologic studies are essential for diagnosing ALHE given the unspecific clinical presentation and for subsequent management.

References

Case Report

KISSING NAEVUS OF EYELIDS - A REPORT OF TWO CASES

Gupta M

Introduction
Kissing naevus or divided naevus is a rare form of congenital naevus which appears over two adjacent sites which are fused together in-utero in the early stages of development but get separated later on like the two eyelids. The naevus is present on two adjacent sites in such a manner as when the two are apposed together, the naevus appears as a single large naevus\(^2\). Kissing naevus have mostly been reported over the eyelid but kissing naevi of the penis and fingers have also been reported.

Kissing naevus of the eyelid was first reported by Von Micheal in 1908, and the name was first used by Fuchs in 1919. Most of the cases appear in childhood but may rarely appear in adulthood. The lesions usually present a cosmetic concern but larger lesions may lead to impaired vision due to mechanical ptosis or obstruction of visual axis\(^1\). Herein we report two cases of kissing naevus of eyelids who presented with the complaints of cosmesis and visual disturbance.

Case History
Case 1
The patient, a 22 years old male, presented with a hyperpigmented melanocytic naevus on right eyelids since birth. The naevus was gradually becoming more pigmented and thickened but had remained asymptomatic throughout the course. On examination, a hyperpigmented velvety plaque of size 3.5cm X 2cm was present on the lateral aspect of the right upper eyelid while a similar lesion of size 2cm X 1.5cm was present on the lateral aspect of lower eyelid (Figure 1). On closure of the eyelids, the lesions resembled a single naevus. The conjunctiva and the cornea were not involved and the vision was normal. There was no systemic complaint and no family history was present either.

The patient had approached us for cosmetic concern. The patient was advised a biopsy of the lesion which he refused. He was counselled about the nature of the lesion and was advised regular follow-up for monitoring the lesion. After one year of follow-up, there was only mild increase in pigmentation of the lesion and the patient is still under regular follow-up without any significant change in the lesion.

Case 2
The second case, a 35 year old female, also presented with a kissing naevus over the right eyelid since birth which was a hyperpigmented, velvety plaque to begin with but had later on became nodular with increasing pigmentation and hair growth over time. As the lesion was not in the line of the visual axis in childhood, the vision was normal but gradually with the increase in size and nodularity of the naevus, the visual axis was being obstructed, causing lateral visual field obstruction. On examination, the patient had two well developed hyperpigmented nodular lesions over the lateral aspect of right eyelids. The upper eyelid lesion was larger measuring about 4cm X 2cm while the lower lid lesion was about 1.5cm X 1cm. The lesions showed irregular nodular surface with increased terminal hair and follicular dilatation (Figure 2). On ophthalmological examination, the visual acuity was normal but the field of vision was reduced laterally due to mechanical obstruction by the naevus.

The patient was advised a biopsy and surgical excision of the naevus but, unfortunately, the patient was lost in follow-up.

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The smaller naevi that do not cause any significant morbidity can be left untreated under observation but the larger naevi or those causing significant cosmetic concern or visual complaints will require a surgical procedure. In view the development of deprivation amblyopia and the malignant potential, early surgical treatment is recommended for all medium and large congenital melanocytic naevi of the eyelid. The most appropriate type of reconstructive procedure should be selected according to the size and anatomical units / segmental distribution of naevus. A lesion that is smaller than 1/4 of the upper and lower eyelids can be excised with adjacent flap advancement for reconstruction. A lesion that is large can be reconstructed with a full-thickness graft using a retroauricular or contralateral eyelid flap. A large lesion on the forehead and the isthmus area can be reconstructed via local flap surgery using a tissue expander4,5.

Discussion

Kissing naevus or divided naevus is a rare form of congenital naevus which usually appears during infancy but may rarely appear during adulthood. Usually they are seen on the medial aspect of the eyelids but may rarely be seen laterally or in the canthal region. The symmetrical borders and the contiguous pattern of the kissing naevus are related to the embryological mechanism of its development. The kissing naevi are believed to arise at the time when the eyelids are fused in-utero. The eyelids appear as ectodermal protrusions at the age of six weeks. Gradually they grow towards each other and begin to fuse and are completely fused by the age of nine weeks. They remain fused till 24 weeks after which they gradually separated. Hence the kissing naevus appears somewhere during 9-24 weeks of gestation wherein the melanoblasts accumulate at the fused eyelid, which on separation leads to formation of two distinct naevi, one each on both upper and lower lids3.

References

Case Report

PHENYTOIN INDUCED PELLAGRA – A CASE REPORT

Gupta M

Introduction

Pellagra is a nutritional deficiency disorder of niacin or its precursor tryptophan, characterized by classical 3Ds (dermatitis, diarrhea and dementia)\(^1\). This classic clinical presentation is rarely seen nowadays and most of the cases are borderline or less typical. It usually occurs in malnourished persons or with alcohol abuse. Apart from nutritional deficiency, certain conditions like malabsorption syndrome, metabolic disorders like Hartnup disease, carcinoid syndrome, and drugs like isoniazid, 6-mercaptopurine, 5-fluourouracil, pyrazinamide, phenytoin, chloramphenicol, azathioprine, phenobarbitone, ethionamide are also known to cause pellagra\(^1,2\). We report a case of pellagra in 23-year old female, taking phenytoin for generalized tonic clonic seizures for the last 16 years, who showed complete clearance of skin lesions with nicotinamide therapy.

Case Report

A 23-year old female presented with itchy skin lesions over the dorsa of hands and feet for the past two weeks. Lesions were gradually progressive and she also complained of mild to moderate burning and itching over lesions while going out in sun. The patient had a history of generalized tonic clonic seizures for the last 16 years and had been taking phenytoin for the same and was presently taking 200 mg/day phenytoin. There was no history of any other drug intake or any exposure to chemical agents and contact allergens. There was no history of memory loss or diarrhea or decreased appetite or any similar lesions in the past. On examination, well demarcated, hyperpigmented, reddish brown, scaly plaques were present over the dorsa of both hands and feet [Figure 1]. There were no lesions on the V area of neck, glossitis or cheilitis. Rest of the patient’s systemic examination including her neurological examination was within normal limits. The routine hematological and biochemical investigations were within normal limits. Due to unavailability, estimation of serum niacin or its urinary metabolites could not be performed.

Based on history, presence of skin lesions with burnt out appearance, and investigations, a diagnosis of drug-induced pellagra like dermatitis was established. Patient was started on nicotinamide (300 mg/day) in three divided doses with multivitamin B complex while continuing phenytoin therapy. There was complete resolution of the symptoms within four weeks of the therapy after which she was given a maintenance daily dose of 50 mg of nicotinamide. The patient remained symptom free and there was no recurrence of symptoms over a six month follow up period.

Discussion

Long recognized as a disease due to dietary deficiency of nicotinic acid or its precursor tryptophan, pellagra is now known to be of multifactorial origin, with concomitant deficiency of pyridoxine, riboflavin, thiamine, and proteins. Generally, pellagra is a disease of a maize-eating population with an insufficient intake of animal protein, fruits, and vegetables and has also been reported in some jowar (Sorghum vulgare) eating populations\(^1\).

Cutaneous lesions resembling sunburn with a burnt-out appearance are the hallmark of pellagra. Dermatitis seen in pellagra begins as symmetric erythema that later becomes hyperpigmented associated with desquamation and rarely crusting may occur. It is predominantly located on the face, dorsal surfaces of the hands and arms known as Gauntlet of Pellagra and around the neck known as Casal’s necklace. Cheilosis (dry fissured lips), angular stomatitis, and oral and perirectal sores are seen. In late stages, the entire tongue and oral mucosa, including the gingival mucosa, become inflamed, swollen, and ulcerated, and assume a bright scarlet color (scarlet glossitis and stomatitis). Poor appetite, epigastric discomfort, gastritis, nausea, vomiting and diarrhea are the common granular cell...
Figure 1. Symmetric, hyperpigmented, well-defined plaques with desquamation surrounded by dusky discoloration over dorsa of hands and feet.

layer loss, and architectural disarray with dysmaturaiton. Sebaceous glands and hair follicles are often atrophic.

Various drugs have been implicated in manifesting niacin deficiency which include antitubercular drugs (isoniazid, ethionamide, pyrazinamide), 5-fluorouracil, mercaptopurine and anticonvulsants (phenobarbital, carbamazepine, phenytoin). The exact mechanism of drug induced pellagra is not known, although there have been various hypotheses. Antitubercular drugs, isoniazid, pyrazinamide, and ethionamide, are structurally similar to NAD, therefore, they competitively replace NAD from the metabolic pathways leading to pellagra. 5-flourouracil inhibits conversion of tryptophan to niacin, whereas, 6-mercaptopurine causes inhibition of NAD phosphorylase thereby leading to deficiency of niacin. Phenytoin, chloramphenicol, azathioprine and phenobarbital interfere in the tryptophan-niacin pathway causing pellagroid dermatitis4.

Nicotinamide is the preferred drug over niacin in the management of pellagra as it does not cause vasomotor disturbances. World Health Organization (WHO) recommends a dose of nicotinamide 300 mg orally in divided doses or 100 mg parentally in divided doses for 3-4 weeks with vitamin B complex supplementation and high protein diet. Usually, neurological symptoms are the earliest to resolve and improve within 24 to 48 hours, but skin lesions may take 3 to 4 weeks to resolve. A maintenance dose with nicotinamide 50 to 100 mg/day is recommended3,5.

We present this case to highlight this under reported, easily treatable adverse effect which may occur with prolonged anticonvulsant use.

References
Case Report

LINEAR LICHEN PLANUS PIGMENTOSUS, A CASE REPORT AND LITERATURE REVIEW

Anisha B, Norashikin S

Introduction
Lichen planus pigmentosus (LPP) is a pigmented disorder first reported in 1974 in India in dark skinned individuals by Bhutani et al. Since then, it has also been reported in other racial and ethnic groups worldwide. It mainly affects women, and commonly presents on sun exposed areas with a morphological appearance of brownish hyperpigmented macules. These lesions are asymptomatic. Histologic features of LPP are vacuolar basal cell layer degeneration with band-like lichenoid infiltration of inflammatory cells seen hugging the dermo-epidermal junction and prominent melanin incontinence. Unlike classical lichen planus, involvement of the scalp, nail or mucosal area is rare. The linear form of LPP has features of LPP and linear lichen planus, exhibiting a linear pattern of distribution along the lines of Blaschko. There have been only a few reports in the dermatologic literature on linear LPP, mostly in Orientals. Herein we report a case of linear LPP on the face along the review the relevant literature.

Case Report
A 48 year old healthy Indian female presented with several months history of hyper pigmented macules on the right side of the chin. The macules had coalesced and seemed to spread backwards in a linear pattern along the right mandible. There was no history of trauma or new medication. There was also no preceding history of erythema on the affected area. Our patient denied the use of aromatic oils, perfumes or herbal medication and new cosmetics.

Clinical examination revealed reticulated dark brown linear patches along the right mandible measuring 2 cm at the widest diameter and 10.5 cm in length (Figure 1 and Figure 2). There was visible surface atrophy without mucosal, hair and nail involvement or other skin lesions. Our differential diagnoses included LPP, zosteriform or linear lichen planus, lichen striatus and post-inflammatory hyperpigmentation.

A skin biopsy showed atrophic epidermis with a band-like lymphocytic infiltrates at the dermo-epidermal junction and basal cell vacuolation (Figure 3). There was prominent pigmentary incontinence and presence of melanophages with perivascular lymphocytic infiltrates (Figure 4). These features are consistent with a lichenoid interface dermatitis reaction such as lichen planus pigmentosus. This patient was initiated on super potent topical steroids but despite being on treatment for months, the lesions did not regress.

Discussion
Lichen planus pigmentosus, a variant of lichen planus is a pigmented disorder with unknown etiology mostly affecting adults and sometimes children. These patients are usually darker skinned individuals and the first case was reported in the Indian literature. Subsequently we found similar cases being reported in the Japanese and Koreans as well. In a large study by Kanwar et al of 124 patients, it showed a slight female preponderance. This condition has been commonly described as hyperpigmented brownish macules and patches but occasionally slate grey or brownish black in colour, typically distributed on sun-exposed areas. There have been varying patterns of presentations including flexural, zosteriform, segmental and linear patterns. It is mostly diffuse but can also be reticulate, blotchy and perifollicular. There have also been reports of classical LP coexisting with LPP. The linear pattern of LPP is unique with only a few reports thus far in the current literature, mainly in Oriental patients.
**Figure 1.** Reticulated dark brown linear patches along the right mandible measuring 2 cm at the widest diameter and 10.5 cm in length.

**Figure 2.** Linearly distributed brownish macules and patches extending along the right mandible.

**Figure 3.** Atrophic epidermis with a band-like lymphocytic infiltrates at the dermo-epidermal junction and basal cell vacoulation.

**Figure 4.** Heavy pigmentary incontinence and presence of melanophages with perivascular lymphocytic infiltrates.

**Table 1.** Clinical characteristics of linear LPP seen in case reports.

<table>
<thead>
<tr>
<th>Case Report</th>
<th>No. of Cases</th>
<th>Age of Onset</th>
<th>Gender</th>
<th>Ethnicity</th>
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<td>61 years</td>
<td>male</td>
<td>Korean</td>
<td>Forehead</td>
</tr>
<tr>
<td>Zhang et al 2012⁸</td>
<td>1</td>
<td>25 years</td>
<td>female</td>
<td>Chinese</td>
<td>Right mandibular region</td>
</tr>
<tr>
<td>I Hassan et al 2012⁹</td>
<td>1</td>
<td>30 years</td>
<td>male</td>
<td>Indian</td>
<td>Left forehead and face</td>
</tr>
<tr>
<td>Monteaquado B et al 2014¹⁰</td>
<td>1</td>
<td>39 years</td>
<td>female</td>
<td>Spanish</td>
<td>Right axilla, Intramammary sulcus</td>
</tr>
</tbody>
</table>
Linear LPP predominantly involves the head and neck region and the extremities. Linear LPP occurs by itself and its association with underlying illness has not been established. In our review we identified 11 case reports of linear LPP patients of more than 16 years of age. There were 7 cases of women and 4 cases of men with majority of the patients in early adulthood. One patient with underlying hepatitis C infection presented with bilateral lesions and another had facial nerve palsy but there was no established link between these conditions and LPP11. Most of the cases reported so far are in the Asian population with a single case found in the Spanish population. Table 1 summarizes all cases of linear LPP reported in the literature.

The upper limbs was the major site of presentation at 44.5%, followed by the head and neck region (36.4%) and the lower limbs (18.1%). Histopathology examination of all 11 cases demonstrated basal cell vacuolar degeneration, lymphocyte infiltrates, pigmentary incontinence and dermal melanophages. In our patient, we had considered zosteriform/linear lichen planus (LP), lichen striatus and post inflammatory hyperpigmentation as differential diagnoses. Erythema dyschromicum perstans (EDP) is another important differential diagnosis to be considered. Due to the rarity of this disease, a careful history was essential to determine the initial presentation. Of these diseases, the linearity of lichen striatus bears a similar morphological appearance to linear LPP. The onset of asymptomatic hyperpigmented lesions without a preceding history of erythema does not support the diagnosis of lichen striatus. The histology of lichen striatus demonstrates lichenoid interface changes, but lacks the pigmentary incontinence. In zosteriform LP the lesions are flat topped, polygonal, purplish papules arranged in a dermatomal pattern with pruritus, unlike LPP where the lesions are completely asymptomatic. Histologically also zosteriform LP would show characteristic LP histology which were not seen in our case. The histology findings in post inflammatory hyperpigmentation on the other hand, lack features of interface dermatitis and mainly show pigmentary incontinence. EDP clinically presents as ash coloured asymptomatic macules with a raised erythematous border initially. Over time, the border disappears leaving behind a grayish lesion. Histopathologically EDP has mild basal vacuolar degeneration with perivascular mononuclear infiltrates, pigment incontinence. The melanin is deposited in the deeper dermis in EDP unlike LPP where it is in the superficial dermis instead11. Together with the clinical features and histopathology results we were able to clinch the diagnosis of LPP.

Topical steroids, topical calcineurin inhibitors and ND YAG laser have been used as treatment options but with little improvement seen. We report this unusual presentation of LPP as it is not commonly encountered.

References

Leprosy, also known as Hansen’s disease, is a disease that has been known to man since time immemorial. It is amongst the world’s oldest and most dreaded diseases and also one of the most important dermatologic diseases from the sociologic viewpoint. This disease probably originated in Egypt and other Middle Eastern countries as early as 2400 BC. It played a unique role in the history of mankind due to many centuries of rejection and segregation of individuals and whole communities afflicted with this condition.

Famous as a cause of the leonine facies, it is clinically characterised by one or more of the three cardinal features: hypopigmented or erythematous plaques with loss of sensation, thickened peripheral nerves and acid-fast bacilli detected on skin smears or biopsy. Lack of knowledge about the disease and its treatment facilitated its spread throughout the world. Those who were unfortunate enough to contract it were isolated, stigmatised and excluded from society. Mycobacterium leprae, the causative agent of leprosy was finally discovered by G.H. Armauer Hansen in 1873, making it the first bacterium to be identified as causing disease in humans.

**Book of Leviticus**

Chapters 13-14 of the Book of Leviticus, the third book of the Old Testament of the Christian Bible, describes skin afflictions. The Hebrew term tzaraat, originally used in chapter 13 of Leviticus, is the root word. It referred to a collective group of skin diseases, including biblical leprosy, which referred to a person who was unclean. The decision to diagnose someone as a leper was made by a priest. He, or she, was then physically segregated from the community - this was more to prevent moral contamination, rather than physical contamination.

**Leprosy - Biblical vs Modern interpretation**

It is interesting that the priests were given the power to diagnose these conditions, as this very same “power” is what we, as dermatologists and physicians, strive so hard to obtain and be good at. In the modern day clinician’s assessment of this entity, five categories of leprosy using clinical, histopathological and immunological criteria can be identified. These include, from the least to the most severe (i.e. greatest to least immune response): tuberculoid polar leprosy, borderline tuberculoid, midborderline, borderline lepromatous and lepromatous polar leprosy. Essentially, this method of classification correlates with the immune response to M. leprae infection.

We now know that patients with borderline forms of the disease can experience either upgrading (i.e. improvement) or downgrading (i.e. worsening) of their conditions. Upgrading is often experienced during treatment, and downgrading can occur during during systemic illness, chemotherapy, pregnancy and emotional stress. In biblical times, if the leprosy sufferer had an “upgrading” of the clinical picture with clinical resolution, he or she could return to society. Otherwise, the quarantine would continue indefinitely.

Medical knowledge during that era was limited and there is a growing consensus that the term leprosy used in the Bible referred to a diverse group of skin diseases that bears no resemblance to Hansen’s disease as we know it today. These include psoriasis, fungal infections, seborrheic dermatitis, atopic dermatitis, pityriasis rosea, syphilis, scabies, lupus erythematosus and sarcoidosis.

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White leprosy

“White leprosy” as described in the bible was characterised by bright white hypopigmented patches of the skin associated with white hair. There was a possibility this was mistaken for other conditions with a combination of hypopigmented lesions and loss of melanin in the hair (i.e. poliosis). This includes vitiligo which can manifest with leukotrichia. Piebaldism, a rare autosomal dominant disorder of melanocyte development, is characterised by symmetrical hypopigmented white forehead and hypopigmented patch of the central portion of the forehead. It is one of the defining features of Waardenburg syndrome (together with heterochromia iridis) and Ziprkowski-Margolis syndrome. It is also observed in tuberous sclerosis, Yaws and Vogt Koyanagi Harada Disease.

Indeed, the “pallor” of white leprosy was likened to the skin tone of the dead, a terrifying thought especially to those with darker skin at the time. It is through this similarity to the dead that the horror derived from benign forms of leprosy traces its religious roots. The Bible discloses a close and important relationship in the biblical times was that between sin and sickness, the ultimate consequence of sin being death. In 1 Corinthians 11:27-32: “Whoever, therefore, eats the bread or drinks the cup of the Lord in an unworthy manner will be guilty concerning the body and blood of the Lord. Let a person examine himself, then, and so eat of the bread and drink of the cup. For anyone who eats and drinks without discerning the body eats and drinks judgment on himself. That is why many of you are weak and ill, and some have died.” Physical Illness, many of which has manifestations in the skin, is described as the sequel to sin and the prologue to death.

Southeast Asia

Since the introduction of multi-drug therapy (MDT) in the early 1980s, the global burden has significantly reduced and many countries have achieved World Health Organisation’s (WHO) goal of reducing prevalence to less than 1:10’000 of the population. Despite so, South-east Asia (SEA) remains a hotbed for leprosy. In 2012, the SEA region accounted for 71% of new cases detected worldwide with 166 445 cases reported. Of these, more than 7% presented with visible deformities. The highest prevalence was noted in Indonesia, India, Bangladesh, Myanmar.

Conclusion

Today, this disease still affects large populations around the world. This epidemiological picture highlights continued transmission of infection and delayed detection of the disease. The main challenges in the control of leprosy is the delay in detection of new cases and stigma surrounding this ancient disease. The WHO Global Leprosy Srategy 2016-2020 was launched as a result, calling for stronger commitments and accelerated efforts to eradicate the disease. The main goals of this global strategy is to, by 2020, reduce the number of children diagnosed with leprosy and related physical deformities to zero; reduce the rate of newly-diagnosed leprosy patients with visible deformities to less than one per million; and ensure that all legislation that allows for discrimination on the basis of leprosy is overturned. Leprosy is very much still a public health concern, as it was thousands of years ago.

References

Quiz

ASYMPTOMATIC SKIN COLORED PAPULES ON THE LIMBS OF AN ADULT FEMALE

Long V, Huang JX

History
A 60-year-old woman with a history of Graves’ disease and thyroid eye disease presents with a 6-month history of asymptomatic skin colored papules on her shins, amongst few scattered erythematous macules (Figure 1).

Examination
On examination, she had eight flesh colored discrete papules localized to the anterior shin, some coalescing to form a plaque. There were also a few erythematous macules. The papules were non tender nor pruritic. She had evidence of mild active thyroid eye disease with periorbital swelling, but otherwise without chemiosis, nor limitation in extraocular movements. She did not have any finger clubbing. She was clinically euthyroid.

Question 1: What is the diagnosis?
A. Cutaneous mucinosis
B. Pretibial myxedema
C. Scleromyxedema
D. Fibrosing dermopathy
E. Elephantiasis

Question 2: What is the treatment of choice?
A. Topical steroids
B. Oral steroids
C. Plasmapheresis
D. Surgical excision
E. Intravenous immunoglobulin

Discussion
Laboratory investigations showed raised thyroxine levels 17.7 pmol/L, low thyroid stimulating hormone levels <0.02 mIU/L. A skin biopsy of the skin colored papules revealed dermal mucinosis with vacuolar interface and superficial perivascular dermatitis suggestive of localized myxedema (Figure 2a).

There was also presence of superficial perivascular dermatitis with extravasated red blood cells and vacuolar interface change (Figure 2b) suggestive of concomitant pigmented purpuric dermatosis (PPD).
limbs – this can be best explained by mechanical factors as low level dermopathy is likely a systemic process and dermopathy can also occur in upper body if traumatized. Treatment of the underlying hyperthyroidism does not necessarily eradicate the skin lesions of pretibial myxedema, which may occasionally become more pronounced after the treatment of the thyrotoxicosis, particularly with radioactive ablation therapy. First line treatment usually involves topical or intralesional corticosteroids with compression bandages giving additional benefit. Pentoxyfylline has also been shown to be effective. This patient’s dermopathy improved with use of topical clobetasol ointment.

That this patient has concomitant PPD is interesting, although an association between pretibial myxedema and PPD is unknown.

**Diagnosis:**

Pretibial myxedema with concomitant pigmented purpuric dermatosis.

Pretibial myxedema is a rare and late dermopathy of Graves’ disease, usually developing after the onset of ophthalmopathy and affecting women more commonly than men (3.5:1). Both nodular and plaque forms are recognized, whilst polypoid and elephantiasic variants are rarer. Important differentials to consider for pretibial myxedema are chronic edema with secondary skin changes may mimic non pitting pretibial myxedema. Mucinosis associated with obesity, or as a result of underlying chronic venous insufficiency, hypertrophic lichen planus should also be considered in the appropriate setting. Interestingly, pretibial myxedema tends to affect dependent areas and less commonly the upper limbs – this can be best explained by mechanical factors as low level dermopathy is likely a systemic process and dermopathy can also occur in upper body if traumatized. Treatment of the underlying hyperthyroidism does not necessarily eradicate the skin lesions of pretibial myxedema, which may occasionally become more pronounced after the treatment of the thyrotoxicosis, particularly with radioactive ablation therapy. First line treatment usually involves topical or intralesional corticosteroids with compression bandages giving additional benefit. Pentoxyfylline has also been shown to be effective. This patient’s dermopathy improved with use of topical clobetasol ointment. That this patient has concomitant PPD is interesting, although an association between pretibial myxedema and PPD is unknown.

**References**


**Answers**

*Question 1*: B. Pretibial myxedema

*Question 2*: A. Topical steroids