Highlights

1 Cosmesis for infantile haemangiomas

2 Methotrexate in Psoriasis - local patients’ response

3 Managing persistent ENL with high dose chlofazimine

4 Fusarium infection in Acute Lymphoblastic Leukaemia

5 Test your diagnostic skill
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Refer to patients by number or letters; names or initials should not be used.

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*No abstract required
Contents

DERMATOLOGY THERAPEUTICS

**Original Article**
Local Experience on the use of methotrexate in the treatment of psoriasis in Hospital Sultanah Aminah, Johor Bahru
*Chong YT, MRCP, Tey KE, MRCP, Choon SE, FRCP*

**Case Reports**
Treatment of erythema nodosum leprosum with high-dosed clofazimine in patients with lepromatous leprosy
*Ong ML, MRCP, Rohna R, MRCP*

Fusarium cutaneous infection in a neutropenic girl with acute lymphoblastic leukaemia
*Pan JY, Ker KJ, Audrey T*

GENERAL DERMATOLOGY

**Case Reports**
Churg Strauss Syndrome in a 40 year old woman
*Tan SS, Chan LC, Tan WC*

Childhood disabling pansclerotic morphea complicated by leg ulcers, contractures and gangrene
*Pan JY, FAMS, Ker KJ, MBBS, Tang MBY, FAMS*

Wegener’s granulomatosis: a case report and literature review
*Tang JJ, Tang MM, Lee BR*

**Self Assessment**
3rd Diagnostic clinical skill test for primary care providers
*RR*

DERMATOSURGERY

**Original Article**
Treatment of infantile haemangiomas with 585 nm pulse dye laser
*Sabeera B, MMED (Paeds), Mardziah A, MMED(Paeds), Gangaram HB, FRCP*

PAEDIATRIC DERMATOLOGY

**Original Article**
A study of the cause and prognosis of chronic urticaria in Malaysian children
*Sabeera B, MMED(Paeds), Asmah J MMED, Mardziah A MMED (Paeds)*

**Case Reports**
Netherton Syndrome presenting with erythroderma in newborn
*Raoul RS, MBBS, Muzhirah AH, MRCPCH, Suhaila O, MRCPCH, Rohna R, MRCP*

Netherton Syndrome presenting with erythroderma in newborn
*Raoul RS, MBBS, Muzhirah AH, MRCPCH, Suhaila O, MRCPCH, Rohna R, MRCP*
Local experience on the use of Methotrexate in the treatment of Psoriasis in Hospital Sultanah Aminah, Johor Bahru

Chong YT¹, MRCP, Tey KE², MRCP, Choon SE³, FRCP

Abstract

Introduction: The efficacy of methotrexate in the treatment of psoriasis is well established. However, high-quality data concerning its efficacy and side effects are sparse. The initial administration dose differs among various centres. In Hospital Sultanah Aminah, Johor Bahru, methotrexate is initiated at a starting dose of 0.3mg/kg body weight weekly and is continued until significant clinical response before being tapered to the lowest maintenance dose.

The aim of this study is to determine the profile of our local psoriasis patients treated with methotrexate, their response to treatment, their tolerability and the side-effects experienced.

Methods: This is a retrospective study of all patients who were on methotrexate from January 2005 to December 2008 at the Department of Dermatology, Hospital Sultanah Aminah, Johor Bahru.

Results: Out of a total of 128 patients, 111 were started on an initial dose of methotrexate of between 15mg/week to 25mg/week. The mean age was 43 years old. 56.8% (63) were males and 43.2% (48) females. The mean body weight was 66 kg, ranging from 39 kg to 103 kg. Methotrexate was indicated for moderate to severe psoriasis in 77.5% (86), psoriatic arthropathy in 7.2% (8) and 15.3% (17) for both indications. Methotrexate was started as a first line in 57.7% (64) of patients, whereas, 19.8% (22) had received phototherapy, 14.4% (16) acitretin and 7.2% (8) cyclosporine in the past prior to being given methotrexate. Good response was noted in 79.3%, (88) of patients, 17.7% (19) moderate and 2.7% (3) had a poor response. Side-effects were noted in 19.8% (22) of patients within the first 6 months, 12.6% (14) due to raised liver enzymes, 3.6% (4) to bone marrow suppression, 2.7% (3) to gastro-intestinal symptoms and 0.9% (1) to central nervous system symptoms. Methotrexate was stopped due to adverse events in 15.3% (17) of patients.

Conclusion: Methotrexate is effective in the treatment of psoriasis but is limited by side effects, especially raised liver enzymes. However, most of the side effects are mild and reversible on stopping the drug.

Keywords: Methotrexate, psoriasis, side effects

Introduction

Methotrexate has been used for the treatment of psoriasis for the past 50 years. Its use predates the age of randomized clinical trials. Recommended starting dose used to be between 0.2-0.4 mg/kg body weight²². However, high-quality data concerning its efficacy and side effects are sparse²⁰. Most guidelines have recommended starting methotrexate at doses of 5.0 to 7.5 mg/week, after a test dose of 2.5-5.0 mg 8,11. Nevertheless, differences were reported among dermatologists in their prescribing and monitoring practices²⁰.
particular the dosing regimen, as well as a broad range of maximum weekly doses from 5 to 70mg weekly. In Hospital Sultanah Aminah, Johor Bharu, methotrexate is initiated at a starting dose of 0.3mg/kg body weight weekly. It is continued until significant clinical response before being tapered to the lowest maintenance dose.

The aim of this study was to determine the demographic profile of psoriasis patients, their response to methotrexate treatment, tolerability and the side-effects experienced.

Materials and methods
This is a retrospective study of records from patients who were on methotrexate from January 2005 to December 2008 at the Department of Dermatology, Hospital Sultanah Aminah, Johor Bahru. The diagnosis of psoriasis was made clinically by the attending doctors. Inclusion criteria included patients who were started on methotrexate for a minimum duration of at least 4 weeks. Pretreatment assessment of all patients included a full blood count, renal profile, liver enzymes, and serology screening for virus hepatitis B and C. Blood counts and liver enzymes were monitored regularly during follow up, initially every week and then every two to six weeks. Methotrexate was initiated in a single weekly intramuscular or oral dose of 0.3 mg per kg body weight, or a maximum dose of 25 mg. It was continued until there was clinical improvement of the skin lesions and then tapered to the lowest possible maintenance dose. All the patients had failed to respond to topical treatment before initiation of methotrexate and during the treatment, the topical medications were continued. In addition, folic acid 5 mg once daily was prescribed to reduce the possible side effects of methotrexate. Patients who were started on an initial lower dose of methotrexate or follow up duration of less than four weeks were excluded from the analysis.

Short-term response to treatment (within 6 months) was assessed using the following criteria:

**Good:** Defined as significant clinical response with continuation of treatment to the lowest maintenance dose within the first six months.

**Moderate:** Defined as initial clinical response with tapering to maintenance dose, but had a flare-up requiring increased dose within the first six months, or inability to taper to a lower dose from the initial dose.

**Poor:** Defined as discontinuation of treatment within 6 months due to poor clinical response.

Side effects of methotrexate, in particular any abnormality of the blood counts and liver enzymes were noted. The severity of the adverse events were graded as mild, if the side effect was tolerable without stopping the drug; moderate, if the drug was stopped and the side effect recovered fully; and severe, if the drug was stopped as well as needing hospitalization or permanent disability.

The data were analyzed using SPSS® Version 12.0.

Results
A total of 128 case records of patients on methotrexate was retrieved, out of which, 111 patients were started on an initial dose of methotrexate of between 15mg/week to 25mg/week. Seventeen patients were excluded from the analysis as 2 were started on an initial lower dose of methotrexate (7.5 mg/week) and 15 had defaulted after being on methotrexate for less than four weeks.

63 (56.8%) were males and 48 (43.2%) females. The mean age was 43 years old with a range of 16 to 76 years old. The mean body weight was 66 kg, with a range of 39 to 103 kg. The duration of disease varied from less than a year to 44 years. Ten patients (9%) had a family history of psoriasis. Majority (92%) had plaque psoriasis while 32% had arthritis. Concomitant diseases were present in 40 (36%) patients. See Table 1.

63 (56.8%) were males and 48 (43.2%) females. The mean age was 43 years old with a range of 16 to 76 years old. The mean body weight was 66 kg, with a range of 39 to 103 kg. The duration of disease varied from less than a year to 44 years. Ten patients (9%) had a family history of psoriasis. Majority (92%) had plaque psoriasis while 32% had arthritis. Concomitant diseases were present in 40 (36%) patients. See Table 1.

The most common indications for methotrexate were for moderate to severe psoriasis (more than 10% body surface involvement) in 86 patients (77.5%), followed by psoriatic arthropathy in 8 patients (7.2%) and for both in 17 patients (15.3%). Methotrexate was started as first line in 64 patients (57.7%), whereas, 22 (19.8%) had received phototherapy, 16 (14.4%) acitretin, 15 (13.5%) methotrexate, 8 (7.2%) cyclosporine and 4 (3.6%) sulphasalazine in the past before being given methotrexate. The initial starting dose ranged from 15 mg/week to 25 mg/week and the majority of patients (62.1%) were able to taper to a maintenance dose of 10 mg/week or less. See Table 2.
Table 1  Patient demographics and baseline clinical characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=111</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>01 - 20</td>
<td>Mean = 43.8 + 13.2, range (16 - 73)</td>
</tr>
<tr>
<td>21 – 39</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>40 – 59</td>
<td>37 (33%)</td>
</tr>
<tr>
<td>60 - 79</td>
<td>61 (55%)</td>
</tr>
<tr>
<td>11 (10%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>63 (57%)</td>
</tr>
<tr>
<td>Female</td>
<td>48 (43%)</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
</tr>
<tr>
<td>Malay</td>
<td>49 (44%)</td>
</tr>
<tr>
<td>Chinese</td>
<td>42 (38%)</td>
</tr>
<tr>
<td>Indian</td>
<td>20 (18%)</td>
</tr>
<tr>
<td>Age of onset</td>
<td>Mean = 34 + 13, range (7 - 71)</td>
</tr>
<tr>
<td>Duration of disease</td>
<td>Mean = 9.8 + 8.5, range (1 - 44)</td>
</tr>
<tr>
<td>Family History</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10 (9%)</td>
</tr>
<tr>
<td>No</td>
<td>101 (91%)</td>
</tr>
<tr>
<td>Type of psoriasis</td>
<td></td>
</tr>
<tr>
<td>Plaque</td>
<td>102 (91.9%)</td>
</tr>
<tr>
<td>Pustular</td>
<td>4 (3.6%)</td>
</tr>
<tr>
<td>Erythroderma</td>
<td>5 (4.5%)</td>
</tr>
<tr>
<td>Arthritis</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>35 (32%)</td>
</tr>
<tr>
<td>No</td>
<td>76 (68%)</td>
</tr>
<tr>
<td>Concomitant disease</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>12 (10.8%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>27 (24.3%)</td>
</tr>
<tr>
<td>Ischaemic heart disease</td>
<td>5 (4.5%)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>5 (4.5%)</td>
</tr>
</tbody>
</table>

Table 2  Patients’ treatment profile

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=111</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior treatment</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>64 (57.7%)</td>
</tr>
<tr>
<td>Phototherapy</td>
<td>22 (19.8%)</td>
</tr>
<tr>
<td>Retinoids</td>
<td>16 (14.4%)</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>15 (13.5%)</td>
</tr>
<tr>
<td>Sulphasalazine</td>
<td>4 (3.6%)</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>8 (7.2%)</td>
</tr>
<tr>
<td>Indication for methotrexate</td>
<td></td>
</tr>
<tr>
<td>Moderate to severe psoriasis</td>
<td>6 (77.5%)</td>
</tr>
<tr>
<td>Psoriatic arthropathy</td>
<td>8 (7.2%)</td>
</tr>
<tr>
<td>Both</td>
<td>17 (15.3%)</td>
</tr>
<tr>
<td>Body weight</td>
<td>Mean 66 kg, range (39-103 kg)</td>
</tr>
<tr>
<td>Initial dose</td>
<td></td>
</tr>
<tr>
<td>25 mg/week</td>
<td>7 (6.3%)</td>
</tr>
<tr>
<td>20 mg/week</td>
<td>62 (55.9%)</td>
</tr>
<tr>
<td>15 mg/week</td>
<td>42 (37.8%)</td>
</tr>
<tr>
<td>Maintenance dose</td>
<td></td>
</tr>
<tr>
<td>20 mg/week</td>
<td>5 (4.5%)</td>
</tr>
<tr>
<td>15 mg/week</td>
<td>17 (15.3%)</td>
</tr>
<tr>
<td>12.5 mg/week</td>
<td>20 (18.0%)</td>
</tr>
<tr>
<td>10 mg/week</td>
<td>23 (20.7%)</td>
</tr>
<tr>
<td>7.5 mg/week</td>
<td>30 (27.0%)</td>
</tr>
<tr>
<td>5 mg/week</td>
<td>16 (14.4%)</td>
</tr>
</tbody>
</table>

Figure 1  Clinical response
A total of 88 (79.3%) patients were estimated to have a good response, while 19 (17.7%) had moderate and 3 (2.7%) a poor response. See Figure 1. Adverse events, were seen in 22 (19.8%) patients within the first 6 months, of which, 14 (12.6%) were due to raised liver enzymes, 4 (3.6%) to bone marrow suppression, 3 (2.7%) to gastrointestinal symptoms and 1 (0.9%) to central nervous system symptoms. No serious event was reported. In 17 (15.3%) patients, methotrexate treatment was terminated due to adverse events, 15 before 6 months and 2 after. As of 31st May 2009, 45 (40.5%) patients were still on methotrexate treatment while 66 (50.5%) had stopped treatment due to various reasons. See Table 3.

Table 3 Adverse events

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>N=111</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event within 6 months</td>
<td>89 (80.2%)</td>
</tr>
<tr>
<td>None</td>
<td>4 (3.6%)</td>
</tr>
<tr>
<td>Bone marrow suppression</td>
<td>14 (12.6%)</td>
</tr>
<tr>
<td>Raised liver enzymes</td>
<td>3 (2.7%)</td>
</tr>
<tr>
<td>Gastro-intestinal symptoms</td>
<td>1 (0.9%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Severity</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>15 (13.5%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Severe</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason for stopping</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse event</td>
<td>17 (15.3%)</td>
</tr>
<tr>
<td>No response</td>
<td>10 (9%)</td>
</tr>
<tr>
<td>Remission</td>
<td>12 (10.8%)</td>
</tr>
<tr>
<td>Exceeded recommended cumulative dose</td>
<td>2 (1.8%)</td>
</tr>
<tr>
<td>Default</td>
<td>20 (18%)</td>
</tr>
<tr>
<td>Patient’s wish</td>
<td>4 (3.6%)</td>
</tr>
<tr>
<td>Planned pregnancy</td>
<td>1 (0.9%)</td>
</tr>
<tr>
<td>Still on</td>
<td>45 (40.5%)</td>
</tr>
</tbody>
</table>

Discussion and conclusion

For more than 50 years, ever since the discovery of the beneficial effects of folic acid antagonist aminopterin by Gubner in 1951 and the introduction of methotrexate treatment by Edmundson and Guy in 1958, the use of methotrexate in psoriasis has undergone few changes with regards to its regimens and dosing.

The initial schedule reported by Rees and co-workers used methotrexate in small daily dose for about seven days before restarting another course. Van Scott and co-workers recommended the use of a large parenteral dose of methotrexate at an average of 25 to 50 mg intramuscularly once weekly, while Roenigk et al administered methotrexate orally in slightly lower doses of 12.5 to 20 mg weekly. In 1971, Weinstein and Frost introduced a new schedule of administering methotrexate orally in small doses of 2.5 to 7.5 mg at 12-hour intervals for a total of three doses at weekly intervals. It has the advantages of lower total dose per week and better tolerable toxicity.

The first guidelines on methotrexate therapy for psoriasis were introduced in 1972 and have since been revised several times. Despite this, variation in the schedules have been reported. Previously, the starting dose of methotrexate was in the higher range (15mg to 25mg per week). Kumar et al reported a protocol of initiating methotrexate at a full therapeutic dose, and tapering when the disease was controlled. Methotrexate was given in a single weekly oral dose ranging from 0.3 to 0.5 mg/kg, subject to a maximum of 30 mg and then reduced by 2.5-5mg every fortnight once clearance of 90% or more had been achieved.

The American Academy of Dermatology and the British Association of Dermatology have recommended a starting dose of 2.5 to 5.0 mg per week with gradual increment up to clinical response or maximum dose of 30 mg per week.

Similarly, guidelines published by the Dermatological Society of Malaysia also recommend the starting dose of 2.5 to 5.0 mg per week with gradual increment of dose to maximum 25 mg per week.

In Hospital Sultanah Aminah, Johor Bahru, it has been a standard practice that methotrexate treatment is initiated at a starting dose of 0.3 mg/body weight (maximum 25 mg) and gradually tapered to a maintenance dose according to clinical response.

Despite the efficacy of methotrexate, good quality design studies are sparse. In a systemic review of five systemic treatments for severe psoriasis, none of the studies on methotrexate could be included mainly because of the ‘obsolete dosages and outdated dosing schemes used’ which was considered too high. In addition, many of the
published data were case series with inadequate documentation. In their sub-analysis of four studies that partially satisfied the inclusion criteria, there were a total of 99 patients treated, out of which, the percentages of patients with clearance and good, moderate and poor responses were, respectively, 51%, 65%, 23% and 12%.

A number of randomized controlled studies involving methotrexate published in the recent years used different starting, maintenance and maximum dosages in their protocols. This reflects non-standardized practices among the dermatologists worldwide despite the various guidelines. Thus, the efficacy in achieving PASI 75 (75% improvement in Psoriasis Area Scoring Index) at 16 weeks ranged from 35% when the starting dose was low (7.5mg/week), to 60% when the starting dose was higher (15mg/week).

It is of particular note that Saurat et al reported the first double-blind, placebo-controlled study of methotrexate versus adalimumab (a biologic). They used a starting dose of 7.5 mg/week for the first 2 weeks, 10 mg/week for the next 2, 15 mg/week for the next 4, and thereafter slowly increased depending on the response and toxicity. After 16 weeks, the mean methotrexate dose was 19 mg. However, their primary end point of PASI 75 achievement at 16 weeks was only 35.5% for methotrexate, as compared to placebo (18.9%) and adalimumab (79.6%).

On the other hand, Heyndael et al compared methotrexate to cyclosporine without a placebo arm. There were 44 patients in methotrexate arm. Methotrexate was initiated at a dose of 15 mg/kg and after 4 weeks, only 4 patients had the dose further increased up to 22.5 mg/week. At 16 weeks, 26 patients (60%) achieved PASI 75.

Kumar et al in their short term methotrexate therapy in psoriasis using higher starting dose and a tapering down regime reported an impressive 88% of patients achieving 75% improvement in 8.5+5.1 weeks. Similar findings were documented in two other studies from India, although the number of patients was small.

We were not able to document the efficacy of methotrexate objectively in our patients as this was a retrospective study and measuring of PASI score was not done routinely. We estimated that if the initial dose of methotrexate was tapered to a lower maintenance dose, then the patients probably had good response. This was noted in the majority of the patients (79%). Moderate response was taken as the inability of methotrexate dose to be lowered or if the initial dose was lowered, but patients had developed flare within the first six months requiring the need of increasing the maintenance dose. Only few patients (3%) needed to stop methotrexate treatment within six months due to failed response.

In terms of adverse events, our study revealed raised liver enzymes as the most common followed by abnormal blood counts, gastrointestinal and neurological symptoms. This is in contrast to previous studies where gastrointestinal symptoms were the most common side effects. This could probably be due to the fact that the gastrointestinal symptoms were mild and were not properly documented. Fourteen patients (12.6%) had raised liver enzyme with a mean ALT (alanine amino transferase) level of 79 IU/L and the highest ALT was 155 IU/L. Four patients did not stopped treatment as their ALT level were less than 60 IU/L. Four patients had abnormal blood counts, 2 were due to anaemia (haemoglobin of 8.2-9.3 gm/dl) and 2 to leucopenia (white cell counts of 3.5-3.9 x 109). All the blood abnormalities resolved on stopping methotrexate. A 38-year-old man, with psoriasis of 13 years duration, had taken methotrexate for 56 weeks, with an accumulated dose of 445 mg. The response was good. However, the treatment was stopped due to nose bleed and was later diagnosed to have nasopharyngeal carcinoma.

Thirty patients (24%) dropped out of the treatment programme within the first 6 months with 15 patients because of adverse events. In the 15 patients who were excluded from analysis as they had taken methotrexate for less than 4 weeks, none had any abnormality of the blood counts or liver enzymes after the initiation of methotrexate. Heyndael et al reported a drop out rate of 29%, all due to raised liver enzymes. It should be noted that folic acid supplementation was not given. However, in the Indian series, most of the patients tolerated the regime well with only a small drop out rate. In contrast, two other studies which started with a low dose, had a low drop out rate. See Table 4.

The limitations of the current report are the retrospective nature of the study as well as the
inadequacy of an objective clinical assessment (e.g. PASI 75) and documented side effects. Future studies should adopt a well-designed protocol to look into the different regimes of starting methotrexate in respect to its efficacy and tolerability, using standardized assessment outcomes, for example Psoriasis Area and Severity Index (PASI) and quality of life scores.

Conclusion
Methotrexate is effective in the treatment of psoriasis but has side effects, especially raised liver enzymes. However, most of the side effects are mild and reversible on stopping the drug. Proper patient selection and appropriate monitoring is crucial in order to minimize the toxic effects of methotrexate.

References
Treatment of Erythema Nodosum Leprosum with high-dose Clofazimine in patients with Lepromatous Leprosy

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**Keywords** erythema nodosum leprosum; multibacillary leprosy; clofazimine; steroid-dependent

**Introduction**
ENL is a type II leprosy reaction and occurs in people with borderline lepromatous and lepromatous leprosy, usually as a complication following treatment. The treatment of choice for ENL is prednisolone in view of its ready availability and affordability. However, glucocorticoid therapy, even in low doses, can produce substantial toxicity. The risk is clearly greater as the dose increases. However, in cases where there are steroid-induced complications, high-dosed clofazimine may be used to reduce or withdraw corticosteroids in steroid-dependant cases. We described 2 steroid-dependent ENL patients with steroid-induced complications who are successfully managed with the addition of high-dosed clofazimine and the resultant weaning down of systemic glucocorticoids.

**Case report**
**Case 1**
A 54 years old Chinese lady presented with multiple tender red nodules involving the extremities, gluteus and lower back of 4 months duration.

Biopsy taken on the left arm revealed macrophage granuloma with occasional acid fast bacilli. Grenz zone was absent. Slit skin smear done showed a bacteriological index (Bl) of 3.3 and morphological index (MI) of 2.1. Hence, she was diagnosed to have lepromatous leprosy with ENL.

She was commenced on intensive multidrug therapy (MDT) regime comprising of rifampicin 600mg daily, dapsone 100mg daily and clofazimine 100mg daily. After a month of intensive therapy, her morphological index was noted to be 0. Thus she was commenced on maintenance therapy using Sungei Buloh regime (modified World Health Organization regime) consisting of rifampicin 500mg and chlofazimine 300mg monthly, dapsone 100mg daily and clofazimine 50mg daily.

Her ENL was treated with oral prednisolone 25mg per day. Her fever resolved and the ENL was less tender and reduced in number and pain. However, the nodules were persistent so the prednisolone dose was increased gradually over 2 weeks until 60 mg per day and was continued on this dose for 1 month to no avail. During this time, she developed steroid-induced diabetes (fasting blood glucose was 11.1mmol/l) requiring diamicron 40mg twice a day for control.

When the clofazimine dose was increased to 100mg twice daily, ENL was controlled within 8 weeks and her prednisolone was able to be tapered down to 22.5 mg per day over 12 weeks. After 12 weeks, the clofazimine dose was reduced to 150mg per day and her prednisolone was able to be weaned down to 17.5mg per day over 4 weeks with no recurrence of ENL reaction. Her repeated fasting blood glucose was within the normal range without oral hypoglycaemic agent. She is currently on a monthly follow-up with a plan to withdraw her prednisolone completely in 3 months time.

**Case 2**
A 67 years old Chinese gentleman was diagnosed with multibacillary leprosy when he presented with hypoaesthetic erythematous plaques with thickened ulnar nerves. Slit skin smear revealed a bacteriological index (Bl) of 4.2 and a morphological index (MI) of 4.8. He was started on intensive MDT comprising of rifampicin 600mg daily, dapsone 100mg daily and clofazimine 100mg daily. Maintenance therapy on modified WHO regime was commenced 1 month later when his morphological index became 0.
He developed ENL, 6 months into his treatment and which resolve within a week with prednisolone at 30mg daily. It was not possible to tail down the prednisolone below 15mg daily because of the frequent reactivation of the erythema nodosum leprosum. Therefore, he was restarted back on prednisolone 30mg daily and remained on 3 cycles of increasing and tapering dose of prednisolone over 1 year. He developed steroid-induced psychosis, diabetes and hypertension, purpura, weight-gain.

18 months following intensive MDT therapy, his clofazimine was increased to 150mg daily. ENL went into remission within 8 weeks and his prednisolone was finally able to be tapered down to 5mg alternate with 2.5mg daily within 12 weeks.

**Discussion**

ENL is an inflammatory cutaneous and systemic complication of multibacillary leprosy, usually as a complication of the treatment but sometimes, even before treatment. It has been reported to occur in 24 percent and 31 percent of multibacillary lepromatous patients on MDT regime in India and Brazil respectively.

ENL is characterized by crops of painful and tender, erythematous or deep purple subcutaneous nodules, which are variably distributed on the body but which mostly occur on the legs, arms and face. During the episode, the patients may suffer additional symptoms, including fever, arthritis, dactylitis, myositis, lymphadenitis, iridocyclitis, orchitis and neuritis. The skin signs are obligatory criteria whereas the general signs are optional.

There are several treatments for ENL, but the mainstays of initial treatment are systemic corticosteroids and thalidomide. But for the reason of well-known teratogenic side effects, WHO does not support use of thalidomide for the management of ENL in leprosy. On the other hand, systemic glucocorticoids also have adverse effects that ranges from just purpura and Cushingoid appearance to osteoporosis and cataract and life-threatening complications like serious infections.

According to the World Health Organization (WHO) and International Federation of Anti-Leprosy Association (ILEP) guidelines for management of erythema nodosum leprosum, clofazimine may be extremely useful for reducing or withdrawing corticosteroids in steroid-dependant cases. Clofazimine is a riminophenazine dye used in combination with rifampicin and dapsone as MDT for the treatment of leprosy as well as its reaction, ENL. It has been used in combination with other anti-mycobacterial drugs to treat Mycobacterium avium infections in acquired immune deficiency syndrome patients and multi-drug resistant tuberculosis. The availability of loose clofazimine is limited to the treatment of severe ENL reactions only. The “off-label” use of clofazimine is actively discouraged by WHO because it is a first line drug for the treatment of leprosy, and its indiscriminate use must be guarded against to prevent resistance. A systematic review of 13 randomized controlled trials found clofazimine to be superior to prednisolone and thalidomide for the treatment of ENL. However, clofazimine should never started as the sole agent for the treatment of severe ENL since it takes 4 to 6 weeks to develop its full effect.

The dose of clofazimine needed to control ENL is higher than the dose used in MDT. The guideline recommended supplementing the prednisone therapy with higher doses of clofazimine initially. The patients may be started on clofazimine 100mg thrice a day to for up to 12 weeks. This is then reduced to 100mg clofazimine twice a day for 12 weeks and then 100mg once a day for 12 to 24 weeks. The dose and duration of clofazimine may be adjusted by the physician according to individual patient's needs. The ENL reaction is usually controlled within 2 to 4 months of treatment with clofazimine, and then the prednisone can gradually be reduced and eventually withdrawn.

Disadvantages of continuous high doses of clofazimine are gastrointestinal symptoms like crampy abdominal pain and diarrhoea, particularly with doses above 100mg daily. The other signification side effect is skin pigmentation which usually develops within a few weeks after starting clofazimine treatment and may take two or more years after stopping treatment to disappear. Both our patients developed obvious skin
pigmentation which is accepted because they appreciate the efficacy of clofazimine in controlling ENL.

In conclusion, clofazimine appears to be an effective and safe treatment for managing lepromatous patients with ENL when corticosteroid is needed to be reduced to the lowest possible dose.

References

Fusarium Cutaneous infection in a Neutropenic girl with Acute Lymphoblastic Leukaemia

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Keywords  Fusarium, Acute Lymphoblastic Leukaemia

Introduction

Fusarium species are common plant pathogens present in the environment but can cause invasive infections in immunocompromised patients, especially those with haematologic malignancies and bone marrow transplant recipients. Tissue and blood cultures are especially important as they offer a high diagnostic yield in invasive fusariosis. Amphotericin B has been used as the mainstay of treatment although resistant rates are high, especially in Fusarium solani species. The treatment outcome is also closely related to rate of recovery of neutropenia.

Case report

A 10-year-old Chinese girl was diagnosed with acute lymphoblastic leukaemia in November 2003. Initial full blood count showed bicytopenia (neutropenia and anemia) with no blasts. Her first bone marrow aspirate showed 65% lymphoblasts with a flow cytometry consistent with precursor B-cell acute lymphoblastic leukaemia. Involvement of the central nervous system was confirmed on lumbar puncture. She completed a course of chemotherapy and cranial irradiation, but had a relapse two years later and underwent chemotherapy. Nine months later in October 2007, she underwent an autologous bone marrow transplant complicated by two episodes of neutropenic fever and graft-versus-host disease of the skin. Two months later, she suffered a relapse involving the central nervous system and intraventricular chemotherapy was initiated. A subsequent bone marrow aspirate and lumbar puncture showed no evidence of B lymphoblasts.

The patient had cytomegalovirus infection in March 2008 which was treated with intravenous foscarnet and changed to oral valganciclovir due to acute renal impairment. She was also treated with intravenous ganciclovir for 2 weeks in May 2008 due to cytomegalovirus reactivation. In August 2008, the patient had disseminated varicella-zoster treated with intravenous acyclovir and cloxacillin (for possible bacterial superinfection). In November 2008, she developed neutropenic fever with septic shock from Salmonella typhi and ESBL-positive Escherichia coli bacteraemia treated with intravenous meropenem and amikacin. This was followed by a second relapse of acute lymphoblastic leukaemia, and intraventricular chemotherapy was initiated.

She also had acute appendicitis and cholecystitis in February 2009 that was treated conservatively with intravenous ceftriaxone, gentamicin and metronidazole.

In March 2009, the patient presented with a day’s duration of fever and painful rash involving her limbs. The rash started as erythematous patches on the abdomen, upper and lower limbs; they subsequently developed into dusky red papules and nodules with central areas of necrosis. She was unable to move her legs due to the painful rash. There was no history of trauma or insect bites to the affected areas. Systemic review was unremarkable.

On examination, the child was febrile but other vital signs were normal. Examination of her cardiovascular, respiratory and gastrointestinal systems did not reveal any abnormalities. She had oral candidiasis of the tongue and buccal mucosa. Multiple erythematous plaques and nodules with central necrosis were seen on her

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chest, arms and legs which were tender and warm to palpation. (Figure 1 and 2) There was no discharge from the lesions or ulceration. All her nails were normal. Her hips, knees and ankles were held in flexion due to pain.

The differential diagnoses include inflammatory causes like erythema nodosum, atypical erythema multiforme, early pyoderma gangrenosum and sarcoidosis; infective causes like deep fungal infections (aspergillosis and fusariosis), erythema induratum and ethyma gangrenosum; neoplastic causes like leukaemia cutis; and medium-vessel vasculitis like polyarteritis nodosa.

Her full blood count showed bicytopenia; total white count was 0.56 x 10⁹ /L with neutropenia (Absolute neutrophil count: occasional neutrophils seen only) with thrombocytopenia (platelet count 28 x 10⁹ /L). Multiple blood and urine bacterial and fungal cultures were negative.

A skin biopsy performed was consistent with deep fungal infection. (Figure 3) Periodic acid-Schiff and Grocott's Methenamine Silver stains demonstrated hyphae and spores in the lower dermis. (Figure 4 and 5) Fungal tissue culture grew Fusarium species, subtyping was not performed. Tissue pyogenic culture was negative.

New papules appeared with persistent fever despite treatment with intravenous ceftazidime and gentamicin that was subsequently changed to intravenous piperacillin/tazobactam. Her fever lysed with the introduction of intravenous amphotericin (1mg/kg/day).

The patient was discharged with infusion pump-delivered intravenous amphotericin and completed a twenty-one day course, with gradual resolution of the lesions after therapy. Her absolute neutrophil count on discharge had recovered to 2.84 x 10⁹ /L.
Fusarium spp. are saprophytes pervasively found in soil, water or air. Only a few out of the 50 different Fusarium species are pathogenic in humans and among these, half of the reported invasive fusariosis infections in humans are due to Fusarium solani. In Fusarium infection, primary sites of entry are the skin and respiratory tract, less commonly paranasal sinuses and gastrointestinal tract. Disseminated fusariosis has also been associated with central venous catheters, continuous ambulatory peritoneal dialysis catheters, patients with extensive burns and neutropenic patients with localized skin and nail infections. In our patient, she was neutropenic and had fusariosis of the skin without evidence of fungaemia, respiratory or gastrointestinal involvement. The skin was the presumed portal of entry.

The initial presentation of invasive fusariosis in neutropenic patients is persistent fever despite broad-spectrum antibiotics. This was the case in our patient. Despite prophylactic or empiric treatment with amphotericin B or triazoles, breakthrough fusariosis infections are common due to high resistance rates to antifungals. Our patient had solely cutaneous involvement without nail or respiratory involvement. This is unusual. She also had no penetrating injury or trauma to the lower limb.

**Discussion**

**Figure 4** PAS stain (10 x 40 magnification): Hyphae and spores in the lower dermis / subcutis

![PAS stain](image)

**Figure 5** GMS stain (10 x 40 magnification): Hyphae and spores in the lower dermis / subcutis

![GMS stain](image)
Use of glucocorticoids impair anticonidial macrophage function and predispose patients to fusariosis. The mortality rate from fusariosis of haematologic cancer patients receiving glucocorticoids has been reported to be more than twice of those not on glucocorticoids. Our patient had not received glucocorticoids in the recent months preceding the onset of skin lesions.

The histopathology of Fusarium lesions is similar to that of Aspergillus species and may cause misidentification. However, differences in hyphae diameter and degree of branching have been reported.

The gold standard to differentiate between Fusarium and Aspergillus species requires appropriate tissue culture. The Fusarium colony is seen microscopically as a white patch that progresses to a pink, purple or yellow centre surrounded by a lighter periphery. Microconidia, macroconidia and chlamydospores are different types of Fusarium conidia present in cultures, with canoe-shaped macroconidia being the hallmark of the Fusarium genus.

Differences have been reported in clinical characteristics between fusariosis and invasive aspergillosis (IA). First, 50-70% of patients with disseminated fusariosis have positive blood cultures while disseminated IA is seldom isolated in cultures. Positive Fusarium blood cultures can be obtained early in disseminated infections whereas those in disseminated IA manifest late in the course of the infection. Secondly, 50-70% of invasive fusariosis cases exhibit skin lesions compared with less than 10% in disseminated aspergillosis. Most patients have concomitant myalgia. These signs and symptoms were present in our patient. She had extremely tender erythematous papules and nodules with central necrosis on her extremities which resulted in great pain, resulting in her holding her limbs in flexion.

Traditionally, Amphotericin B has been used as the mainstay of treatment against Fusarium infections, albeit with mediocre in vitro susceptibility and high resistance rates especially with Fusarium solani species. In current clinical practice, high doses of amphotericin B are prescribed as there are reports of lower mortality rates (>50%) in liposomal formulations have been useful in improving bioavailability. In our patient, 1 mg/kg/day of Amphotericin B was administered for 21 days.

New broad-spectrum triazoles like voriconazole and posaconazole show promise in the treatment of fusariosis. Voriconazole was recently approved by U.S. FDA for treatment of refractory fusariosis. It is most effective against non-solani Fusarium species. Pfaffer et al reported voriconazole to be effective in a neutropenic leukaemic patient with disseminated fusariosis where amphotericin B treatment had failed. Upon completion of voriconazole, there were no recurrences of fusariosis even after re-commencement of chemotherapy.

Prompt recovery of neutrophil counts is associated with good prognosis in patients with fusariosis. In profound, prolonged neutropenia, there is a 100% mortality rate for fusariosis compared to 30% when neutrophil counts are normal. Therapies have been initiated utilizing recombinant granulocyte colony-stimulating growth factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) or granulocyte transfusion. Our patient did not receive any granulocyte-stimulating or transfusion therapies but her skin lesions responded to intravenous amphotericin B and neutrophil counts had recovered on discharge.

Finally, in patients with hematologic malignancies, the suspected source of Fusarium infection should be removed, be it nail avulsion in Fusarium onychomycosis, surgical debridement of infected tissue or removal of infected catheters.

References
Treatment of Infantile Haemangiomas with 585nm pulsed dye laser

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Abstract

Background

Hand and/or feet eczema may be due to contact dermatitis, either irritant or allergic in nature. Difficulties often arise in distinguishing purely endogenous eczema from the possibility of contact dermatitis clinically. Patch test is carried out to detect the presence of allergic contact dermatitis. This is important for optimum patient care and to obtain a favourable outcome.

Objectives

To identify the demography, clinical characteristics and causative allergens of hand and/or feet eczema among patients from the patch test clinic.

Methods

Patients who attended the patch test clinic in the Department of Dermatology, Hospital Kuala Lumpur from 2003 to 2007 were evaluated retrospectively. All of them were having hand and/or feet eczema. Data were collected for their demography, sites affected and patch test findings.

Results

379 patients were included in the study. The age of patients ranged from 6 years to 78 years with an average of 36.7 years. Their occupations ranged from blue collar (20.3%) and white collar (38.3%) workers, housewives (9.5%), pensioners (7.1%) and students (20.3%). Clinical presentations included isolated hand eczema (34.6%), isolated feet eczema (21.9%), hand and feet eczema (19.0%), and hand and/or feet with eczema with involvement of other parts of the body (24.5%). The mean duration of eczema was 3.8 years. The rate of positive patch test was 58.0% (n = 220/379). Clinically relevant allergens were identified in 123 (32.5%) patients only. Fifty two percent of the clinically relevant allergens were identified from the European Standard Series patch test, 9.0% from the Specific Series patch test and 39.0% from the patients' own personal products that were tested. The most common source was metal items containing nickel (33.3%), followed by toiletries (14.6%) and detergents (10.6%). Other sources include fragrance, cosmetics, rubber, medicaments and hair dye. In 256 (67.5%) patients, there were no underlying causes detected, and they were managed as endogenous hand and feet eczema. There is a possibility that the causative allergen was not suspected/tested and hence not detected.

Conclusion

Hand and/or feet eczema can affect any age group and patch testing forms a very important diagnostic tool in the management.

Keywords

Clinical pattern, allergens, hand and/or feet eczema, patch test

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Churg Strauss Syndrome in a 40 year old woman
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**Keywords** Churg-Strauss syndrome, vasculitits

**Introduction**
Cutaneous vasculitis is a common manifestation of many systemic diseases. In the setting of asthma, eosinophilia and multiple disparate signs and symptoms, more serious cause of vasculitis like Churg-Strauss syndrome (CSS) should always be considered.

**Case report**
A 40 year-old Malay housewife presented with a two months history of purpuric rash and non-healing leg ulcers followed by one month history of bilateral hand numbness. She was diagnosed to have bronchial asthma about a year ago and was started on inhalers. She did not have history of fever, oral ulcer, photosensitivity rash or alopecia.

Physical examination showed varying sizes of ulcers on both ankles and anterior abdominal wall with multiple non blanching purpuric lesions over the both hands and both feet (Figure 1, 2, 5 & 6). Neurological examination revealed peripheral mixed sensory and motor neuropathy with the right side more affected then the left side. Other systemic examinations were normal.

Investigations showed white blood cell count of 19,200/mm³ with eosinophilia of 22.3%, ESR of 45 mm/hour and positive pANCA. Other investigations like ANA, serum cryoglobulin, hepatitis B, C and HIV were negative. Her chest x-ray and complements C3/C4 levels were normal. Lung function test showed obstructive lung disease picture. Histopathology of the skin biopsy from her left leg was consistent with leukocytoclastic vasculitis with infiltration of eosinophils and neutrophils within and around vessels (Figure 3). The direct immunofluorescence showed deposition of C3, C4, IgM and fibrin within the dermal vessel walls (Figure 4).

Nerve conduction study was suggestive of mononeuritis multiplex. Churg-Strauss syndrome was subsequently diagnosed. She responded to treatment with prednisolone at 1mg/kg/day (Figure 5 & 6).
Unfortunately, she developed worsening of vasculitic lesion, cyanosis of right middle and ring fingers and bilateral wrist drop after missing her medication for a week. She was then treated with intravenous (IV) methyprednisolone, followed by oral prednisolone and monthly pulses of IV cyclophosphamide. After four pulses of cyclophosphamide, all her skin lesions had resolved. However, she still had residual peripheral mixed sensory and motor neuropathy.

**Discussions**

CSS is a rare syndrome that affects small- to medium-sized arteries and veins. It was first described in 1951 by Churg and Strauss. The American College of Rheumatology (ACR) has proposed 6 criteria for the diagnosis of Churg-Strauss syndrome. The presence of 4 or more criteria yields a sensitivity of 85% and a specificity of 99.7%. The 6 criteria are as follow:

1. Asthma (wheezing, expiratory rhonchi)
2. Eosinophilia of more than 10% in peripheral blood
3. Paranasal sinusitis
4. Pulmonary infiltrates (may be transient)
5. Histological proof of vasculitis with extravascular eosinophils
6. Mononeuritis multiplex or polyneuropathy

This patient fulfilled four of the six ACR criteria for the diagnosis of CSS. These include vasculitis, adult onset asthma, peripheral neuropathy with mononeuritis multiplex and eosinophilia.
The incidence of CSS is approximately 2.4 to 3.3 per 1 million population. Symptoms usually appear between 20 and 40 years of age, with a slight predominance in men.

The cause of CSS is unknown. It is possibly an allergic or autoimmune reaction to an environmental agent or drug.

The most prominent signs and symptoms of CSS are those related to pulmonary, cardiac, dermatologic, renal, and peripheral nerve. Pulmonary involvement may be seen in 96 to 100% of patients in the form of asthma, pleural effusions, or nonfixed patchy infiltrates on chest films. The neurologic findings may be either mononeuritis multiplex or polyneuropathy in 66 to 75% of patients.

Laboratory findings include anemia, eosinophilia, elevated ESR, CRP & serum IgE level, hypergammaglobulinemia, positive rheumatoid factor and abnormal renal function test with proteinuria and hematuria if there is renal involvement. ANCA is present in approximately 40% of patients with Churg-Strauss syndrome (CSS). Most of these patients are perinuclear-ANCA (p-ANCA)-positive (antimyeloperoxidase antibodies).

Levels of eosinophil cationic protein (ECP) and soluble interleukin-2 receptor (sIL-2R) in CSS are elevated which indicate an immunoregulatory defect associated with vasculitis and eosinophilia. Besides, soluble thrombomodulin (sTM), which is a marker of endothelial cell damage, are also elevated.

Other investigations that are done only when clinically indicated include bronchoalveolar lavage, chest x-ray, computed tomography scan, ECG, echocardiogram, endoscopy, biopsy, electromyelogram & others. Pulmonary opacities can be found in 26% to 77% of cases of Churg-Strauss syndrome, and films demonstrate no abnormalities in approximately 25% of patients.

CSS is associated with high mortality especially when major organs like cardiac, pulmonary or renal are involved. The principal causes of morbidity and mortality in Churg-Strauss syndrome are myocarditis and myocardial infarction secondary to coronary arteritis. A 5-year survival rate is about 25% without treatment. However, if it is treated, the 1-year survival rate is 90% and the 5-year survival rate is 62%.

Glucocorticoids alone are usually adequate for the treatment of Churg-Strauss syndrome. High dose corticosteroids and other cytotoxic agents like cyclophosphamide, oral mephenolate or azathioprine are required if it involved major life-threatening organ. High doses of interferon can maintain remission in patients who have responded incompletely to cyclophosphamide.

Conclusion
Many systemic diseases can present with vasculitis. Early recognition and prompt treatment of those vasculitides associated with major complications like CSS is essential.

Special acknowledgement to Dr. Lee SK, Department of Pathology, Hospital Pulau Pinang for histopathology interpretation.

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GENERAL DERMATOLOGY - Case Report

Childhood disabling Pansclerotic Morphoea complicated by leg ulcers, contractures and gangrene

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Keywords morphea, ulcers, contracture, gangrene

Introduction
Disabling pansclerotic morphoea of childhood is a subset of localized scleroderma. It is a rare disease in both the adult and paediatric population. Etiological factors are unknown although autoimmune, infectious, genetic and environmental factors have been postulated. Sclerotic plaques predominantly affect the scalp, face, trunk and extensor surfaces of limbs, leaving fingertips and toes uninvolved. The absence of Raynaud’s phenomenon, dysphagia, visceral involvement and certain laboratory derangements differentiate systemic sclerosis and disabling pansclerotic morphoea of childhood. Diagnosis can be supported by histology. There are several management options including topical.

Case report
An 11-year-old Chinese boy presented with Raynaud’s phenomenon, progressive skin hardening and joint contractures at the age of four (Figure 1). There were no dysphagia or sicca symptoms. A skin biopsy showed morphea (Figure 2).

Anti-nucloear antibody, anti-double stranded dDNA and extractable nuclear antigen (ENA) antibodies were negative. As the cutaneous symptoms were severe and Over the years, the sclerosis of the skin and tendon and joint contractures became progressively more severe. He had difficulty ambulating and had to use a wheelchair for long distances. His quality of life was severely impaired. In spite of his medical condition, he was able to cope well with his studies.

The patient developed bilateral lower leg ulcers three years after the diagnosis of disabling pansclerotic morphoea. The ulcers were more severe over the left medial malleolus and there was also cellulitis at his right ankle. The family was not keen for a biopsy of the skin. He developed the complications of Staphylococcus aureus bacteraemia and septic arthritis of the left knee and was treated with intravenous cloxacillin. There were resultant contractures and flexion deformities of his knees due to disuse, and the patient became wheelchair-bound.

He was started on prednisolone, followed by azathioprine, methotrexate and cyclosporine. However, he did not show any response and his parents opted to discontinue oral therapy after three years of failed treatment. He also developed persistent transaminitis even after the discontinuation of methotrexate. Hepatitis markers and hepatic imaging were unremarkable, and the transaminitis resolved with empiric treatment with prednisolone. He was diagnosed to have probable autoimmune hepatitis.

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Investigations showed white blood cell count of 19,200/mm³ with eosinophilia of 22.3%, ESR of 45 mm/hour and positive pANCA. Other investigations Thereafter, he developed progressive painful dark discolouration of his left big toe for a week’s duration after his mother accidentally stepped on it. Other toes were not involved. On examination, he was afebrile with normal vital signs. Dry gangrene was seen involving the left big toe, extending proximally to the first metatarso-phalangeal joint. (Figure 3) There was generalized sclerosis involving the face, trunk and limbs with fixed flexion deformities of both legs. Foul smelling exudates with crusted areas were seen on dorsum of the left foot. Multiple excoriated scaly plaques and macerated ulcers were present on the extremities.

The full blood count showed a normal total white cell count (9.98 x10⁹/L) and mild anemia (hemoglobin 11.3 g/dL). Erythrocyte sedimentation rate and C-reactive protein were elevated at 65mm/min and 15.5 mg/L respectively. Blood bacterial cultures were negative. Bacterial wound culture from the left big toe grew Staphylococcus aureus and Gram-negative bacilli. A radiograph of the left foot did not suggest an abscess or osteomyelitis.

Intravenous ampicillin and cloxacillin were commenced, which were oralised after four days of therapy. His parents were not keen for surgical intervention. A decision was made for conservative treatment and auto-amputation of the affected toe.

Figure 2 Progressive skin hardening with joint contractures

Figure 3 Ulceration of the lower limbs progressing to gangrene of the left big toe
Discussion

Scleroderma is characterized by skin induration and thickening with tissue fibrosis. It is differentiated into systemic sclerosis and localized scleroderma. Peterson et al.\(^1\) further classified localized scleroderma into five major categories: plaque, generalized, bullous, linear, and deep morphea. Involvement of deep dermis, subcutaneous tissue, fascia and muscle characterizes deep morphea. Disabling pansclerotic morphea of children (DPMC) is a subtype of deep morphea that can extend to the fascia, muscle, tendons and bones.\(^2\)

Localized scleroderma (LS) is a rare disease with an incidence of 27 cases per million in the adult population in an epidemiological review done by Peterson et al., out of which about 11% are cases with deep morphea. In the paediatric population, localized scleroderma is far commoner than systemic sclerosis but the actual prevalence has not been well evaluated. A retrospective analysis by Uziel et al.\(^4\) in 30 paediatric patients with LS showed female predominance of 1.5:1; 7.9 years being the average age of onset with a range of 1 to 14 years old. Kornreich et al.\(^5\) reported a series of 35 paediatric patients, with age of 6 years being the average age of onset. Our patient presented with sclerotic plaques and joint contractures at 3 years old.

It is unknown what causes LS. Several etiologies like autoimmune, infectious, genetic and environmental factors have been postulated but never proven. Circulating autoantibodies can be found in cases of LS and may point to an autoimmune cause. LS may also be genetically linked as reported by Kuhn et al.\(^6\) where development of morphea is related to HLA-A3B7 and DR2. 

*Borrelia burgdorferi* infection has been associated with morphea. There has been conflicting reports of borrelial antibodies being detected in patients with morphea, with up to 45% of patients with morphea testing positive in a Scandinavian study and none in a Canadian study.\(^4,7\) Infection by Epstein-Barr virus has also been thought to cause LS.\(^3\) Other factors like trauma, surgery, vaccination, varicella infection, post radiotherapy in oncology patients and ischaemic injury have been associated with LS. In our patient with DPMC, no possible causative factors have been identified.

The pathogenesis of morphea can be divided into 3 pathways, namely vascular alteration, disrupted collagen metabolism and immunoregulatory defects. Endothelial cell damage and perivascular infiltration of macrophages and mast cells feature prominently in biopsies. Autologous complement also contributes to vascular damage as levels of complement regulatory proteins are decreased in morphea.\(^8\) Disruption to collagen metabolism occurs in morphea due to increased expression of pivotal cytokines like transforming growth factor (TGF-\(\beta\)) and interleukin-4. They stimulate dermal fibroblasts, causing the buildup of extracellular matrix components, in particular types 1 and 3 fibrillar collagen. Immunoregulatory defects involving cellular and humoral abnormalities have been implicated in the pathogenesis of LS. There is abnormal activation of B and T cells.

In DPMC, sclerotic plaques predominantly affect the scalp, face, trunk and extensor surfaces of limbs, leaving fingertips and toes uninvolved. Multiple joint contractures result from skin sclerosis over the joints.\(^10,11\) The absence of Raynaud’s phenomenon, dysphagia and visceral involvement differentiate systemic sclerosis and disabling pansclerotic morphea of childhood. Sclerotic plaques occurred in the typical distribution in our patient, together with fixed flexion deformities in both his knees and multiple contractures in other joints. He had Raynaud’s phenomenon but no evidence of visceral involvement, dysphagia or sicca symptoms.

Certain laboratory abnormalities are present in children with localized scleroderma. A positive anti-nuclear antibody (ANA), rheumatoid factor (RF), hypergammaglobulinaemia, eosinophilia and high erythrocyte sedimentation rate (ESR) are the more commonly detected abnormalities.\(^12,13\)

In localized scleroderma, ANA can be positive in between 23% to 73% of patients and in a study by Falanga et al.\(^14\) ANA positivity was more prevalent in patients with severe and extensive linear scleroderma. 39% of patients with localized scleroderma show RF positivity and similar to ANA, it was associated with more severe disease in those with linear scleroderma. Anti-histone antibodies and anti-single stranded DNA antibodies can also be present.\(^14\) Hypergammaglobulinaemia with raised IgG and IgM levels occur in between 13% to 50% of patients and those with joint contractures have higher IgG levels.\(^15,16\)
Raised ESR and blood and tissue eosinophilia characterize deep morphoea. An association has been shown between blood eosinophilia and clinical disease activity with eosinophilia preceding exacerbations and declining levels indicating disease remission.

Patients with localized scleroderma do not have antibodies to extractable nuclear antigens (ENA) like anti-Scl 70, which differentiates them from those with systemic sclerosis. Our patient with DPMC had raised ESR (65mm/50 minutes) and negative ANA, RF and ENA antibodies.

Histopathological findings are characterized by fibrosis and thickened homogenized collagen bands. The depth of inflammation and sclerosis is used to differentiate between the different subtypes. In the subcutis, there are lymphocytes and plasma cells with thickened collagen and hyalinization. Thickened septa and obliteration of fat lobules are present. Deep dermis hyalinization is common. Sclerosis of the entire dermis and panniculus characterize disabling pansclerotic morphoea. The fascia is fibrotic and sclerotic, with vacuolated muscle fibres separated by edematous stroma and inflammatory infiltrates. The histology of our patient corresponded to that of deep morphoea.

The majority of children with localized scleroderma do not have systemic manifestations but it has been reported by Uziel et al that up to 40% have arthritis or arthralgia. Diaz et al reported 43% of children with DPMC had pulmonary or esophageal abnormalities. Although there have been reports of morphoea progressing to systemic sclerosis, it is extremely rare. Our patient did not have any systemic manifestations.

As a result of pansclerotic involvement, painful ulcers and severe joint contractures can develop. These ulcers often have super-imposed bacterial infections, of which Pseudomonas aeruginosa, Enterobacteriaceae spp, Streptococci, Enterococci, Stenotrophomonas maltophilia and Serratia Marcescens have been reported. Systemic antibiotics are often necessary and in some patients, repeated wound debridements may be needed. Our patient developed disabling joint contractures, chronic non-healing lower limb ulcers and dry gangrene of his left big toe after minimal trauma. The bacterial culture from his ulcers grew Staphylococci and Enteric bacilli. There was no evidence of underlying osteomyelitis.

Other complications include soft tissue calcification. There have been reports of squamous cell carcinomas arising from long-standing ulcers in patients with DPMC. The annual incidence of patients with DPMC developing squamous cell carcinoma is 6.7%, far higher than patients who were cancer survivors and those with hereditary cancer prone syndromes. Visceral complications like abnormal pulmonary function tests, esophageal motility disorders and myopathic electromyographic disorders in sclerotic areas can occur.

The management of a paediatric patient with morphoea requires a holistic approach. Both medical and psychosocial needs of the patient and the family have to be addressed. Medical therapy include topical and systemic treatments, phototherapy, physical and surgical options. All treatments have to be individualized.

Topical therapies include topical or intralesional corticosteroids and calcipotriene ointment. These treatment options are the initial choices for mild, localized plaque morphoea but in our patient with generalized morphoea, the therapeutic effects would be minimal.

Systemic therapy is indicated for severe extensive disease, linear scleroderma across joints where contractures result and facial involvement like en coup de sabre. Multiple treatment regimes and options like D-penicillamine, systemic corticosteroids and antibiotics, phenytoin, retinoids, cyclosporin and plasma exchange have been reported but there has been none with universal good results.

Use of systemic corticosteroids in the therapy of LS is questionable. Joly et al reported an improvement in 76% of patients after 6 weeks of 0.5 to 1mg/kg of oral corticosteroid but relapse rate was high (35%) after discontinuation. In contrast, Rosenwasser et al reported ineffectiveness of oral corticosteroids. Methotrexate has been reported to be useful in the treatment of adults with widespread morphoea and anecdotal reports in children have shown encouraging results as well. The need for regular blood monitoring, systemic toxicity issues and drug interactions have to be considered. Our patient was initially started on oral prednisolone at
1mg/kg/day and methotrexate 7.5mg/week. The dose of methotrexate was gradually increased for a steroid-sparing effect but the patient developed transaminitis and methotrexate had to be eventually stopped.

Oral calcitriol is also an option in the treatment of LS. Humbert et al23 reported the use of oral calcitriol (1,25-dihydroxyvitamin D3) in an adult with severe LS and improvement was noted. In a study by Elst et al24 in paediatric patients with linear scleroderma, 5 of 7 patients showed good improvement, 1 had a relapse that responded to a second course of calcitriol and 1 with severe disease showed no benefit.

Ultraviolet (UV) A irradiation alone, or together with psoralens, a photosensitizing agent, has been utilized in the treatment of LS. Encouraging results have been noted with UVA (320-400nm), UVA-1 (340-400nm) and psoralens with UVA (PUVA). There has been positive results of PUVA and UVA-1 in treatment of DPMC25,26, especially for UVA-1, which has been thought to retard disease progression, including joint contractures.27 Although phototherapy is useful in the therapeutic armamentarium of LS, concerns regarding possible long-term carcinogenic risks, especially in children, may restrict its use.

Physiotherapy involving heat, splinting, casting, muscle strengthening exercises and joint mobilization are useful in patients with flexion contractures. Surgical procedures are rarely considered as impaired tissue perfusion leads to difficulties in wound healing.

Roldan et al28 reported the use of bosentan, a dual oral endothelin receptor antagonist, for 4 weeks in a paediatric patient with DPMC and chronic ulcers. An improvement was noted in the ulcers, degree of skin sclerosis and joint mobility. This could be utilized in our patient as he had chronic non-healing ulcers that did not respond well to dressings alone.

For non-healing chronic ulcers that are not infected, topical agents like chlorhexidine and betadine can be used as they have a broad antimicrobial spectrum with low tissue toxicity. Antimicrobial products containing silver, polyhexamethylene biguanide, Cadoxemer Iodine or polyacrylates can be used to treat superficial infections.29 Necrotic tissue impairs wound healing and encourages bacterial growth thus surgical debridement may be considered at times. However, in patients with DPMC, impaired tissue perfusion could also lead to difficulties in wound healing post-operatively. Dressings that facilitate autolytic debridement can be used. These include hydrogels, films and hydrocolloids. Moisture balance is essential to wound healing, and the nature of exudates in chronic ulcers in DPMC may impair this.30 Thus, the removal of exudates in chronic ulcers is necessary to promote wound healing. Dressings that serve this function include calcium alginate, foam, fibre and composite dressings. Synthetic skin grafts could also be considered to aid in tissue healing. Our patient had been on various dressings including silver dressings (mepilex silver), iodosorb, hydrogels and duoderm.

Systemic antibiotics are required to treat infected ulcers and these should be tailored according to the sensitivities of the organisms. Our patient was treated empirically with intravenous ampicillin and cloxacillin and converted to oral cloxacillin and amoxicillin when culture results of his ulcers showed Staphylococci and Enteric bacilli sensitive to the above antibiotics.

Wollina et al20 reported efficacy on use of sildenafil together with porcine small intestinal submucosal acellular matrix in the treatment of chronic ulcers associated with DPMC. A porcine acellular matrix skin substitute was applied on the ulcers and together with oral sildenafil for 2 weeks, significant improvement in granulation of the ulcers was noted. This combination therapy had a synergistic effect that was far more efficacious than either therapy alone. In addition, sildenafil has also been reported to improve digital flexibility and dexterity.31 The combination therapy could be considered in our patient as his ulcers are long-standing and has been showing poor response to conventional therapies of antibiotics and wound care.

Daily transcutaneous application of dry carbon dioxide gas can also be utilized to reduce colonization of the ulcers and aid in the granulation process.32 A 5-day course of intravenous immunoglobulin, followed by another dose a month later, has been used by Wollina et al33 with good effect. The improvement noted in the ulcers lasted for nearly a year. Intravenous pentoxyphillin had been tried with poor results.33
In conclusion, treatment of patients with disabling pansclerotic morphea of childhood is difficult and quality of life is often severely impaired. Judicious skin care and prompt treatment of complications such as joint contractures and chronic ulcers is essential.

References

Wegener’s Granulomatosis: 
A case report and literature review

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Keywords Wegener’s granulomatosis, systemic vasculitis, anti-neutrophil cytoplasmic antibody

Introduction
Wegener’s granulomatosis is a rare multisystem necrotizing granulomatous vasculitis affecting small - and medium-sized vessels. Its clinical manifestations can be nonspecific during the initial stages and indistinguishable from a variety of neoplastic, infectious, and inflammatory diseases. The disease may run a course from indolence to one of rapid progression leading to life-threatening multiorgan failure. We report a rare case of rapidly progressing Wegener’s granulomatosis.

Case report
A 39 year old Malay housewife with no co-morbidity, presented to us with a 2-month history of multiple painful non healing ulcerated nodules and plaques involving the left face, right thigh and both shins. The lesions were initially papular and progressively enlarged to form nodules which ruptured with pus discharge and eventually formed ulcers. Apart from that, she also had non productive cough, symptoms of rhinitis, anorexia and loss of weight for the past 1 month. This was associated with bilateral reduced hearing but without ear discharge or pain. There was no fever, epistaxis, haemoptysis, dypsnoea or urinary symptoms.

Clinically, she was afebrile and normotensive. She had an ulcerated plaque on left cheek (Figure 1), 3 ulcerated plaques on both shins (Figure 2 and 3) and an ulcerated plaque on right thigh. All these ulcers were extremely tender with deep punched-out margins and covered with a haemorrhagic crust. The diameter of these ulcers ranged from 1 to 2cm.

Figure 1
Single ulcerative plaque with haemorrhagic crust on left cheek

Figure 2
Multiple ulcerative plaque on both shins

Figure 3
Close view of a ulcerative plaque with haemorrhagic crust on right shin

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There was also a tender nodule with normal overlying skin on the right cheek measuring 1x1 cm. Examination of the respiratory, cardiovascular and neurologic systems were essentially normal. There was no organomegaly on abdominal examination. An ear, nose and throat assessment revealed the nasal septum to be ulcerated and crusted with bilateral moderate to profound mixed hearing loss, otitis media and chronic sinusitis. At this point of time, our differential diagnosis included Wegener’s granulomatosis, polyarteritis nodosa, pyoderma gangrenosum, a deep fungal infection, cutaneous tuberculosis or non tuberculous mycobacterium infection.

Investigations revealed that she had normochromic normocytic anaemia (Hb 10.8). Her erythrocyte sedimentation rate and c-reactive protein were both raised at 108 mm/hour and 35.75 mg/dl respectively. Tumour markers for CA125, CA19-9, alfa-fetoprotein and carcinoembryonic Antigen were all normal. There was no haematuria or proteinuria. Her chest x-ray, renal profile and liver function tests were normal. Serology for human immunodeficiency virus, hepatitis B and hepatitis C were negative. A swab from the ulcer grew Staphylococcus aureus. However, a swab from the ears did not grow any organism. CT scan of brain and neck showed pansinusitis, bilateral mastoiditis with otitis media and small subcutaneous abscess collection at the angle of the mandible.

**Figure 4**
Biopsy of the ulcerated skin showed granulation tissue with marked neutrophils infiltration. Evidences of vasculitis were absent. However, a few vague granulomas were present. (Haemotoxylin and Eosin x400)

**Figure 4**
Biopsy from the nasal mucosa showed granulomas as well as multinucleated giant cells admixed lympho-plasmacytic cells surrounding the blood vessel. (Haemotoxylin & Eosin x 400)

**Figure 5**
Biopsy from nasal mucosa: Fibrinoid necrosis of the small arterioles and neutrophilic infiltration of the blood vessels were clearly seen at tissue distance from the ulcerated mucosa. (Haemotoxylin and Eosin x 400)
A skin biopsy of the ulcer on her left shin showed a cluster of granuloma with multinucleated giant cells and abundant surrounding neutrophils and plasma cells (Figure 4). There were no features to suggest vasculitis from the skin biopsy. Special stains for PAS, GMS and Ziehl Neelsen were all negative. Tissue culture for mycobacterium, fungus and bacteria were negative. However, her nasal biopsy showed a chronic necrotizing granulomatous inflammation with small vessel vasculitis (Figure 5, 6). Serology using indirect immunofluorescence for anti-neutrophil cytoplasmic antibody (ANCA) was positive for cytoplasmic pattern antineutrophil cytoplasmic antibodies (c-ANCA) but negative for perinuclear pattern antineutrophil cytoplasmic antibodies (p-ANCA). These features confirmed the diagnosis of Wegener’s granulomatosis. The patient however, insisted on being discharged against medical advice to seek for traditional treatment before any treatment specific treatment could be initiated. She did not improve with alternative therapy and presented to another hospital 1 month later with acute renal failure. Unfortunately, she succumbed to severe pulmonary haemorrhage eventually.

**Discussion**

Wegener’s granulomatosis (WG) is a multisystem disease characterized by necrotizing granulomatous inflammation of the upper, lower respiratory tracts and kidneys with necrotizing vasculitis affecting small- and medium-sized vessels. It is an autoimmune inflammatory process with antineutrophil cytoplasmic antibodies (c-ANCA) directed at neutrophil proteinase 3 (PR3). It is uncommon with a prevalence of approximately 3 per 100,000 in USA. It affects males and females equally. The age group as reported in the literature, is between 40 to 55 years as in our patient. There is increasing evidence that Staphylococcus aureus plays a role in the pathogenesis of WG but the mechanism is still unclear.

The clinical course of WG is characterized by an initial localized or limited phase followed by a generalized or systemic phase. In the initial limited phase, symptoms arise from granulomatous inflammation of the upper and/or lower respiratory tract whereas generalized WG is characterized by clinical signs of systemic vasculitis. Limited WG accounts for 25% of cases and it usually spares the kidney. In generalized WG, patients present with life threatening pulmonary-renal syndrome as a result of necrotizing alveolar vasculitis and rapidly progressive necrotizing glomerulonephritis.

In general, over 90% of patient with WG initially seek medical attention for upper and/or lower airway symptoms. The most frequently affected sites of granulomatous inflammation are the nose and paranasal sinuses (60-80%). Patients may complain of nasal congestion, epistaxis, pain of the sinuses cavities, persistent rhinorrhea, perforation of the nasal septum, hyposmia and saddle nose deformity. Ear disease occurs in 25 to 40% of WG and most commonly manifest as otitis media with effusion due to eustachian tube obstruction as a result of luminal granuloma or nasopharyngeal inflammation. Hearing loss is also common and it may be sensorineural, conductive or mixed. Oral cavity and oropharynx involvement are uncommon. The most common oral lesion is strawberry gingivitis which presents as an exophytic gingival growth with petechiae. This may be the first sign and is nearly pathognomonic of WG. Lung involvement is almost universal in patients with WG and it can affect pulmonary parenchyma, bronchi and pleura. Typically the patient presents with cough, haemoptysis, dyspnea and pleuritic pain. Chest radiograph may show pulmonary nodules, cavitating lesions, or diffuse alveolar haemorrhage. Our patient had evidence to suggest upper airway involvement of WG which included persistent rhinitis, chronic sinusitis and otitis media with hearing loss. However, there was no radiological evidence to suggest lung involvement on her initial presentation even though she succumbed to pulmonary haemorrhage eventually.

Cutaneous manifestations of WG encompass a diverse spectrum and occur in 40-50% of cases. The most common skin lesion is palpable purpura due to leucocytoclastic vasculitis. Other presentations include nodules, papules, vesicular lesions, ulcerative pyoderma gangrenosum-like lesions and deep erythema nodosum-like subcutaneous nodules. These lesions commonly occur on the distal arms and legs. Our patient presented with multiple ulcerative plaques mimicking pyoderma gangrenosum or cutaneous infections. In fact, skin lesions were the main problem that brought her to our hospital. However, it can be very challenging to determine the underlying cause at the initial stage as histopathology of skin biopsy can be non specific as shown in our patient.
Renal involvement is the most serious manifestation of WG and presents in about 20% of patients at diagnosis but develops in 80% of patients during the course of their disease. The patient can develop rapidly progressive renal failure as a result of necrotizing glomerulonephritis. Renal biopsy is not a routine as findings are usually nonspecific and it most often shows a focal and segmenting necrotizing proliferative glomerulonephritis. Our patient did not have any renal involvement initially. Unfortunately her disease progressed rapidly within a month after she was discharged on her own accord. She subsequently presented with acute renal failure in another hospital. WG can also involve other organs such as the eye (causing proptosis, necrotizing keratocleritis conjunctivitis, retinal vasculitis), cardiac (causing pericarditis, myocarditis, conduction abnormalities) and neurologic system (causing mononeuritis multiplex, cerebral vasculitis). Our patient did not have any of these rare presentations.

Diagnosis of WG is generally based on a combination evidence of clinical findings, biopsy of involved tissue showing necrotizing granulomas/vasculitis and laboratory evidence of cANCA. The American College of Rheumatology has proposed that the diagnosis of WG can be made if two of the following criteria are included: 1) ulcerative lesions in oral mucosa or nasal bleeding or inflammation, 2) nodules, fixed infiltrates or cavities in chest radiograph, 3) abnormal urinary sediment (red cell cast or 5 red blood cell per high power field), and 4) granulomatous inflammation on biopsy. Our patient had evidence to suggest WG based on clinical presentation, histopathology from nasal biopsy and a positive cytoplasmic pattern antineutrophil cytoplasmic antibodies (c-ANCA).

Three major histopathologic findings of Wegener’s granulomatosis include parenchymal necrosis, vasculitis, and granulomatous inflammation. The site of biopsy affects the diagnostic yield with paranasal sinus biopsy offering the highest yield. Cytoplasmic pattern ANCA (cANCA) positivity is found in more than 90% of generalized WG but only 50% in limited WG. Levels of c-ANCA also correlates with disease activity in WG. The titers of these antibodies decline during treatment but may rise again before relapse. As was the case in this patient, an increase in erythrocyte sedimentation rate and C-reactive protein is common in WG.

WG is highly fatal if not treated early with more than 90% mortality in the first two years and renal failure is the most common cause of death. Delay in the diagnosis of WG is mainly due to the nonspecific symptoms or signs that are experienced by the patient during the initial phase of the disease. Hence, early diagnosis and treatment is important as the presence of advanced disease at diagnosis limits the potential benefit of therapy. Treatment of WG requires induction of remission followed by maintenance. Current remission induction treatment protocols in systemic WG consist of cyclophosphamide and corticosteroids supported by plasma exchange in case of severe renal vasculitis or pulmonary hemorrhage. Cyclophosphamide may be given as continuous low dose oral treatment or by intravenous pulses initially at 2-3 week interval. This treatment is continued for 3 to 6 months until patient has achieved remission. During maintenance therapy, cyclophosphamide should be withdrawn and substituted with either azathioprine or methotrexate to avoid the side-effects of cyclophosphamide. Patients should continue maintenance therapy for at least 24 months following successful disease remission. Optimization of treatment protocols has led to remission rates of 70-90% in the first year and 5-year survival rate is now reported to be over 75%. However, relapse rate is high ranging from 10% in the first year to 66% during long-term follow-up. Long term treatment with low dose of trimethoprim/sulfamethoxazole has shown satisfactory response to control bacterial infection. This treatment is based on the hypothesis that infection exposes neutrophil proteases to autoantibodies and justifies the attempt to control the infection. In this patient, we were not able to initiate appropriate treatment as she insisted on discharge against medical advice upon confirmation of her diagnosis.

Conclusion
This report has described one case of rapidly progressing Wegener’s granulomatosis based on clinical, histopathology, and laboratory evidence of cANCA. Our patient presented initially with an upper airway and skin manifestation but her disease progressed rapidly with subsequent renal and pulmonary involvement 1 month after she was discharged. Diagnosis of this condition may be very
at the initial stage and requires a high index of suspicion due to non specific presentation. Treatment need to be initiated as early as possible to improve the outcome of this condition as it carries a high mortality rate.

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GENERAL DERMATOLOGY - Self Assessment

Clinical diagnostic skill test

Tick at the provided space [✔] against answers that correlate to the slide. Check your answer on page . Refer to the given criteria in page to discover your clinical diagnostic skill status.

Slide A

A
- bacterial Infection
- fungal infection
- allergy
- viral exanthem
- drug exanthem
- skin scalding syndrome
- atopic dermatitis
- candidiasis
- impetigo
- seborrhoeic dermatitis

Slide B

B
- allergy
- ADR
- dermatitis
- bacterial infection
- viral infection
- angioedema
- photodermatitis
- hypereosinophilic sensitivity syndrome (HESS/DRESS)
- psoriasis
- contact dermatitis

Slide C

C
- allergy
- skin infection
- dermatitis
- impetigo
- acne
- deep fungal infection
- chickenpox
- viral wart
- molluscum contagiosum
- eczema herpeticum
D
- deep fungal infection
- cutaneous tuberculosis
- atypical mycobacterium infection
- tumour
- lymphadenitis
- abscess
- squamous cell carcinoma
- sporothricosis
- fish tank granuloma

E
- allergy
- non infective inflammation
- dermatitis
- insect bite reaction
- autoimmune disease
- contact dermatitis
- bullous impetigo
- pemphigoid
- pemphigus
- eczema herpeticum

F
- ADR
- hormonal disorders
- fungal infection
- viral infection
- appendageal disorders
- candidiasis
- varicella zoster
- milia crystalina
- herpes viral infection
- molluscum contagiosum
A study of the cause and prognosis of chronic Urticaria in Malaysian children

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prednisolone post renal transplant might play a role in escalating her tumour progression as she experienced the first relapse of thymoma a year after the renal transplant. Studies have shown that organ-transplant recipients have an increased incidence of cancer as compared with an age-matched healthy population or with patients undergoing dialysis. London NJ et al found that after 20 years of immunosuppressive therapy, 40 percent of recipients had cancer\textsuperscript{7}. Sasaki et al reported immune suppression may have been a contributing factor in the induction of thymoma\textsuperscript{8}. In our patient, the dose of cyclosporine was reduced and the MMF was taken off successfully without compromising the renal graft function. However the thymoma progressed for the next 4 years since the diagnosis of pemphigus folicaceous and she succumbed to her malignancy with metastases. The aggressive nature of her malignant thymoma was the main contributing factor to the mortality. Her skin lesions were well controlled few months before she passed away, probably because she received a cycle of palliative chemotherapy consisting of Doxorubicin, Carboplatin and Cyclophosphamide and also dexamethasone in her palliative care period.

In conclusion, we reported 2 cases of pemphigus foliaceous associated with thymic neoplasms which could be the manifestations of immune system instability. Based on our experience managing these 2 patients, it is pertinent for us to seriously consider the possibility of thymoma if there is abnormal mediastinal widening or mass in the chest radiograph of patients presenting with pemphigus foliaceous. Further studies are needed to analyze the pathogenesis of the natural course of pemphigus foliaceous co-existing with, or after discovery of thymoma and also the role of thymectomy in relation to the natural course of the cutaneous manifestations.

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Netherton Syndrome presenting as Erythroderma in newborn

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Keywords Netherton syndrome, erythroderma

Introduction
Erythroderma in newborn is rarely seen by paediatrician in neonatal intensive care unit. If not for the characteristic features of ichthyosis linearis circumflexa and the trichorrhexis invaginata, Netherton Syndrome (NS) would have been missed and the associated metabolic disorders would have not been anticipated. Netherton syndrome (NS) is a rare autosomal recessive hereditary ichthyosiform disease. The classical triad of clinical features includes ichthyosis, hair shaft abnormalities, and atopic diathesis. In 1958, Netherton described a patient with erythroderma and hair shaft abnormality. In addition, a variant mode of impaired cellular immunity, aminoaciduria, recurrent infections, delayed growth and development, as well as mental retardation have also been described. This genodermatose is potentially fatal and requires close monitoring, family counselling and good family support.

Case report
A boy was born borderline premature via emergency C-section. He did not have family history of atopy or skin disease. Patient was born with paper thin erythematosus dry scaly skin with erythema prominently seen on the scalp, face, neck, ears, perigenital and gluteal regions. The nails and mucous membranes were spared. Staphylococcus coagulase negative was isolated from blood culture during this time and patient was treated with intravenous antibiotics accordingly. However, the whole skin gradually appeared more erythrodermic with extensive scaling. He later developed severe hypernatremic dehydration which required aggressive fluid resuscitation. This was attributed to extreme insensible fluid loss.

Due to the worsening skin condition a skin biopsy was done which revealed features suggestive of Congenital Ichthyosis. Histopathology of skin revealed mild hyperkeratosis, parakeratosis with acanthosis and mild spongiosis. The upper dermis showed mild lymphocytic infiltrate in the

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superficial perivascular region. Patient was reviewed by a visiting Paediatric Dermatologist and a diagnosis of Netherton Syndrome was made when scalp hair showed trichorrhexis invaginata. Immunodeficiency work up was also carried out revealing generalized hypogammaglobulinemia. The patient was treated with emollients and mild topical steroids. He was discharged well after achieving his birth weight at Day 10 of life.

He was closely monitored for infections and weight gain during his clinic follow up. His skin condition showed encouraging improvement with topical application. After the first few months of life, the erythroderma slowly disappeared and plaques typical of ichthyosis became evident. Despite being able to tolerate well, he had chronic diarrhoea with severe failure to thrive and hence he was admitted at 6 months of age for observation of feeding pattern and optimization of his calorie intake. He developed multiple complications during this admission including difficulty in setting the intravenous line, hypoglycaemia and severe osmotic diarrhoea. He was discharge against medical advice and was brought in very ill few days later to Casualty where he succumbed to death despite active resuscitation.

Discussion
The early diagnosis of the NS is usually difficult due to erythroderma in the first few months of life, which later slowly disappears, and lesions typical for ichthyosis linearis circumflexa become evident as in this patient. During the first months of life erythroderma predominates with hypernatremic dehydration and failure to thrive. Erythroderma can be caused by multiple factors: immunodeficiency, metabolic disease like acrodermatitis enteropathica, ichthyosis, atopic dermatitis, psoriasis and seborrhoeic dermatitis. Sometimes the origin remains unknown. The specificity of clinical and histopathological features is low in neonates so it usually takes a long period before the final diagnosis is established.

Ultrastructural analyses of skin in patients with NS, congenital ichthyosiform erythroderma, and erythrodemic psoriasis can be of great value in establishing a correct diagnosis. Ultrastructural analyses of skin in patients with NS show replacement of stratum corneum with parakeratotic cells. Distinctive features as premature secretion of lamellar bodies and foci of electron dense material in the intercellular spaces of stratum corneum, which are not observed in other erythrodermic disorders, appear to be frequent and relatively specific markers for NS. Ultrastructural analyses of the skin of patient with NS may facilitate the early diagnosis of NS.

Erythrodermic neonates are at risk to get sepsis, hypernatremic dehydration, malnutrition, failure to thrive, and are at risk to die from life threatening condition. In some patients with NS an intermittent aminoaciduria has been observed. It has been proposed that increased caloric demands consequent to increased epidermal metabolism and hyper proliferation are the basis for failure to thrive in this condition. However, it is unclear that the caloric and nutrient drain of a hypermetabolic epidermis alone can account for the extra caloric requirements for adequate weight gain in children with this condition.

Specific nutritional deficiencies arising from skin exfoliation or gastrointestinal malabsorption may also be a problem. Nutritional deficiencies could exacerbate the barrier defect in these patients. For example, essential fatty acids may be lost through excessive desquamation, and gastrointestinal malabsorption, if present, could further amplify this deficiency. Linoleic acid is a critical constituent of the stratum corneum lamellar membranes. Essential fatty acid deficiency results in an epidermal phenotype characterized by erythroderma, hyperplasia, and transepidermal water loss (TEWL), a phenotype similar to that seen in patients with erythrodermic ichthyosis. Thus, a potentially vicious cycle could arise in the patient with ichthyosis who also has essential fatty acid deficiency.

Gastrointestinal malabsorption from a primary or secondary enteropathy may also contribute to growth failure in these patients. Two studies have demonstrated jejunal villous atrophy in some infants and children with Netherton syndrome. Our patient suffered from gastrointestinal involvement which could be the reason for a dystrophy and a poor weight gain during his infancy period.

In the second year of life in patients with NS erythroderma slowly disappears and migratory gyrate lesions with double-edged scaling become evident. Hair shaft abnormalities on patient's scalp
manifested as trichorrhexis invaginata, pili torti and/or trichorrhexis nodosa. In our patient ultra structural analysis of the hair disclosed trichorrhexis invaginata. Some patients can remain severely affected with erythrodermic flares or have erythroderma with pustules. In patients with NS atopy is usually manifested as angioedema, allergic rhinitis, asthma, urticaria and elevated IgE. Our patient was not tested for IgE. Patients with NS usually have normal values of serum immunoglobulin levels but selective antibody deficiency to bacterial polysaccharide antigens can be found, so it is important to evaluate the functional antibody response to both protein and bacterial polysaccharide. In our patient the IgG, IgA and IgM were low.

The therapy with topical steroids, tars, emollients, PUVA, and oral vitamin A derivatives is not satisfactory, and offers temporary effects. A long-term treatment with topical tacalcitol was tried in few cases with good results and without severe side effects, but its effect should be additionally proved on a larger group of patients. Children with ichthyosis and growth failure may have uncompensated caloric needs because of an impaired skin barrier (unpublished data). Gastrointestinal dysfunction and nutritional deficiencies are uncommon and do not appear to be primary causes of the growth failure in these children. Because growth failure is of early onset in these children, we suggest that nutritional evaluation and caloric supplementation should be instituted early to maximize growth potential. Close monitoring of patient’s nutritional status as well as prompt recognition and treatment of infections are fundamental in ensuring patient’s survival to adulthood. In our patient, even the strict hypoallergenic diet does not improve skin condition and dystrophy characterized by a poor weight gain.

Conclusion

Netherton Syndrome should be excluded in newborn with erythroderma. Besides the close monitoring and management, recurrent family education and support is essential for patient compliance. Lesson learn here is to sent parents for counselling on how to cope with a child with chronic diseases and not to give up when survival rate is possible with continuous intensive therapy.

References

3. Caputo R, Vanutti P, Bertani E. Intermittent aminoaciduria have been observed in some patients. Arch Dermatol 1984; 120: 220-2
Answers to Clinical Diagnostict Skill Test

Slide A

1. bacterial Infection
2. fungal infection
0. allergy
0. viral exanthem
0. drug exanthem
2. skin scalding syndrome
-1. atopic dermatitis
-1. candidiasis
-1. impetigo
-1. seborrhoeic dermatitis

This condition because of the risk of toxaemia. Misdiagnosis can result in fatality if therapy is delayed.

Slide B

1. allergy
1. ADR
2. dermatitis
2. bacterial infection
2. viral infection
2. angioedema
2. photodermatitis
2. hypereosinophilic sensitivity syndrome (HESS/DRESS)
2. psoriasis
2. contact dermatitis

When patient presents with angioedema with dermatitis or vasculitis, think of hypereosinophilic sensitivity syndrome especially if patient has been on medication before development of skin lesions. This condition may be associated with fever, eosinophilia and raised liver enzymes. If the drug is not stopped, it can result in prolonged morbidity.

Slide C

-3. allergy
1. skin infection
-3. dermatitis
-3. impetigo
-2. acne
2. deep fungal infection
1. chickenpox
-2. viral wart
1. molluscum contagiosum
1. eczema herpeticum

Suspect cutaneous deep fungal infection when patient with human immunodeficiency virus presents with persistent crops of papular lesions with central umbilication or scab on the face. Fungal spores can be detected by bedside Tzanck test within one day if the facility is available. Thus urgent antifungal therapy can be institutes as this sign is an AIDS defining disease.

Slide D

1. granuloma
1. deep fungal infection
1. cutaneous tuberculosis
1. atypical mycobacterium infection
1. tumour
1. lymphadenitis
1. abscess
0. Squamous cell carcinoma
1. sporothricosis
1. fish tank granuloma

Suspect cutaneous deep fungal infection or atypical mycobacterial infection if there is a persistent ulcer with multiple nodules arranging in a linear fashion (lesion with sporothricoid or lymphatic spread).
This patient has skin scalding syndrome as evidence by the golden crust radiating from the corners of the corners of the mouth & eyes. It is important to recognise suspect autoimmune bullous disease if an adult present with flaccid blisters that ends in crust. It can be induced by certain drug ingestion. Misdiagnosis may result in delayed commencement of immunosuppressant resulting in prolonged morbidity and can be fatal if untreated.

Firm pearly papules with central umbilication in children prompt the diagnosis of molluscum contagiosum.

<table>
<thead>
<tr>
<th>SCORE</th>
<th>TOTAL NUMBER COLLECTED</th>
<th>IMPLICATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>-3</td>
<td></td>
<td>Delayed diagnosis may result in irreversible outcome / deformity</td>
</tr>
<tr>
<td>-2</td>
<td></td>
<td>Delayed diagnosis may result in prolonged morbidity</td>
</tr>
<tr>
<td>-1</td>
<td></td>
<td>Therapy for wrong diagnosis may worsen the primary skin lesion</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>No effect on outcome of primary skin lesion but cost wastage of medication, investigation kit and money</td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>Therapy for this diagnosis can have good outcome</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>Correct diagnosis enables appropriate investigations, therapy and even long term follow-up</td>
</tr>
</tbody>
</table>

How did you performed? You should aim for correct diagnosis and minimize delayed diagnosis.