

AUTOIMMUNE DISORDERS - Case Report

Mucous membrane pemphigoidLee CK¹, MRCP, Zuraiza MZ², MDSc, ROKIAH I¹, FRCP**Keywords** *Pemphigoid, mucous membrane***Introduction**

Mucous membrane pemphigoid is a group of putative autoimmune, chronic inflammatory, subepithelial blistering diseases predominantly affecting mucous membranes, characterised by linear deposition of IgG, IgA, or C3 along the epithelial basement membrane¹. This variant of pemphigoid is rare and encompasses a heterogeneous group manifesting a varying constellation of oral, ocular, skin, genital, nasopharyngeal, oesophageal and laryngeal lesions. In severe cases, it may lead to blindness due to ocular involvement and may even be life threatening due to airway obstruction. We report a case of mucous membrane pemphigoid with oral and genital involvement.

Case report

A 66-years old Chinese gentleman presented with recurring blisters and erosions over the oral cavity and genitalia for the past 6 months. The lesions started as an intact blister that breaks off leaving painful erosion with clear discharges. It had started on the glans and shaft of his penis before involving the oral cavity. There were no eye, skin, respiratory and airway complaints. He also denied joint, gastrointestinal and neurological involvement. There was no recurring high fever associated with the flare up of the blistering condition.

He was on glibenclamide, metformin, chlorothiazide, aspirin and lovastatin for his

diabetes, hypertension, hypercholesterolemia and ischemic heart disease, all of which had been consumed for at least more than 3 years. There was no history of ingestion of any traditional medication.

On examination, there were numerous well defined erosions involving his palate (Figure 1) and buccal mucosa. His glans penis was erythematous with well defined erosions discharging serous fluid (Figure 2). There were no skin or ocular lesions. The joints were normal.

A gingival biopsy showed subepithelial blister with subepithelial chronic inflammatory cells mainly consisting of lymphocytes and some plasma cells (Figure 3a). Few colloid bodies are seen in the epithelium. There was no basal cell degeneration. Direct immunofluorescence staining was positive with linear deposition of IgG, fibrinogen and C3 at the basement membrane (Figure 3b). It was stained negative with IgA and IgM.

The diagnosis of mucous membrane pemphigoid was made based on the clinical presentation, histopathological findings as well as the direct immunofluorescence staining.

We adopted a multidisciplinary approach in the management of this patient with the involvement of the dermatology, dental and ophthalmology units. The lesions showed a 50% response to topical betamethasone dipropionate served in a customised oral tray as well as topical hydrocortisone acetate 1% to his genital erosions. He was started on dapsone initially but unfortunately, he developed drug hypersensitivity syndrome manifesting as maculopapular rash 3 days after starting the drug. He was then started on prednisolone 10mg BD as well as doxycycline 100mg OD with improvement of his lesions. Besides the topical and systemic treatment, he was also referred to the ophthalmology team who excluded ocular involvement and will follow-up this patient due to the risk of ocular involvement in the disease.

Correspondence

Dr Lee CK, MRCP

¹Dermatology Unit, Department of Medicine
Faculty of Medicine, Universiti Malaya, Kuala Lumpur²Department of Oral Pathology
Oral Medicine and Periodontology
Faculty of Dentistry, Universiti Malaya, Kuala Lumpur



Figure 1 Erosions over the hard palate



Figure 2 Erosions over the glans penis

Discussion

Mucous membrane pemphigoid is a rare idiopathic and progressing autoimmune blistering disorder that may produce severe sequelae if not detected accurately to enable prompt and adequate treatment. It may affect any or all mucous membranes, with or without skin involvement, in decreasing frequency: oral cavity (90%), eye (65%), nose, nasopharynx, anogenital region, skin (20-30%), larynx (8-9%), and oesophagus².

Autoantibodies involved in this condition are directed to the basement membrane components. Many antigens had been identified as the target to this process, including bullous pemphigoid antigen 1 (BPAg1, 230kD), bullous pemphigoid antigen 2 (BPAg2, 180kD), laminin 5, laminin 6, α_6 -integrin subunit, β_4 -integrin subunit, collagen VII and other proteins of unknown identity and function^{1,3}. Several studies had reported an increased occurrence of HLA-DQB1*0301 allele with this condition¹. Cellular immunity and cytokines are believed to be involved in the pathogenesis of this condition and some studies have indicated that chronic inflammation may be responsible for precipitating mucous membrane pemphigoid by an epitope spreading phenomenon¹.

The exact incidence and prevalence of mucous membrane pemphigoid is unknown. It predominantly affects elderly women with the mean age of onset between 51 to 62 years of age⁴. Females are affected more than males (2:1). For the diagnosis of mucous membrane pemphigoid, clinical and direct immunopathology criteria are essential and must be demonstrated before a diagnosis of mucous membrane pemphigoid is assigned¹.

It is important to recognise this entity, as mucous membrane pemphigoid can often lead to scarring and may be potentially sight threatening if there is ocular involvement. Rarely, it may be life threatening when airway or oesophagus is involved. When the disease occurs in only the oral mucosal or oral mucosa and skin, the patients are categorised as a “low-risk patient”¹. Some of these patient with localised disease may remain stable for years, whilst others may develop rapidly progressive ocular involvement despite immunosuppression⁵. *Higgins et al* reported an incidence rate of 0.03 per person per year over 5 years for development of ocular disease in patients with established oral mucous membrane pemphigoid⁵. Due to this significant risk of developing ocular disease and that many patients may be asymptomatic in the

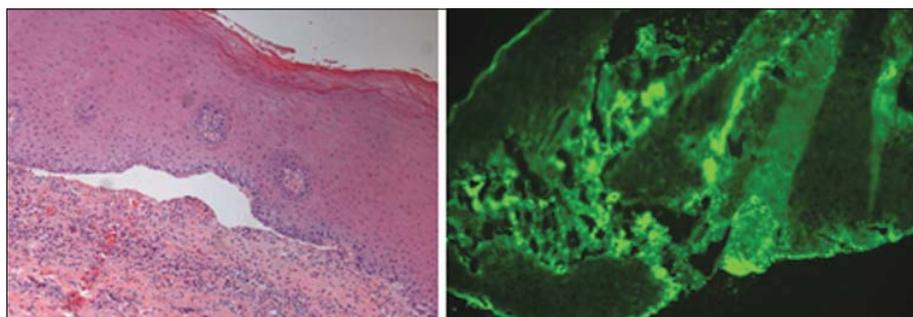


Figure 3
 (a) Subepidermal bullae demonstrated in gingival biopsy stained with hematoxylin-eosin stain.
 (b) Direct immunofluorescence microscopy studies demonstrating linear bands of IgG deposited at the oral mucous membrane basement membrane

initial phase of ocular involvement, regular ophthalmic review is indicated to detect this serious complication.

There are no large-scale, well-controlled studies on the management of mucous membrane pemphigoid. The First International Consensus on Mucous Membrane Pemphigoid recommended dividing patients into “low-risk” and “high-risk” groups¹. “Low-risk” patients are those who have disease occurring in only oral mucosa or oral mucosa and skin. For this group of patients, a more conservative approach was recommended by using either topical corticosteroid of moderate to high potency or systemic therapy like tetracycline, nicotinamide, dapsona or low dose prednisolone with or without low doses of azathioprine¹. Topical steroids can be delivered orally via a custom tray, as was used by this patient. Successful treatment of mucous membrane pemphigoid with topical tacrolimus has also been reported⁴.

Patients with ocular, genital, nasopharyngeal, oesophageal and laryngeal mucosal involvement are defined as “high-risk” patients¹. Treatment modalities for this group of patients include

dapsone, prednisolone, cyclophosphamide and azathioprine¹. Methotrexate, mycophenolate mofetil and intravenous immunoglobulins are also advocated to treat this condition³. Biologics such as etanercept and infliximab had been reported to be successful in the treatment of recalcitrant mucous membrane pemphigoid³.

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ANNOUNCEMENT - Continuous Professional Development

Satellite Meeting 2009

- Organizers** LADS/ AADV and the Vietnam Dermatological Society
with the support of the National Institute for Dermatology and
Venereology, Vietnam
- Theme** Psoriasis and Eczema-a double-edged challenge
- Venue** Hilton Hotel, Hanoi
- Date** 6 - 9 November 2009
- Program** website: www.asianderm.org
- Inauguration of the Asian Academy of Dermatology and Venereology
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- The LADS/AADV will be accepting nominations to the Roll of
Foundation Members and Charter
- Members of the AADV in recognition for their contribution and
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- Gala Dinner "A Nite @ the Opera" at the Hanoi Opera House on
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E-mail: secretariat@asianderm.org | webmaster@asianderm.org

GRANULOMATOUS DISEASES - Original Article

Risk factors for type 1 leprosy reaction in a tertiary skin clinic in Sarawak

Yap FBB, MRCP, Pubalan M, MRCP

Abstract

Introduction Identifying risk factors for leprosy reactions can preempt clinicians to initiate prompt treatment to prevent associated morbidities. Thus, a retrospective study was done to elucidate the risk factors among 44 newly diagnosed leprosy patients in Sarawak General Hospital from 1993 to 2007.

Materials and methods Case folders were searched for demographic data, clinical characteristics, slit skin smear results, and the presence of type 1 leprosy reactions, its treatment and outcome. Analysis was done to determine the relative risks for development of this reaction. Student t test was used for comparison of means. The level of significance was set at 0.05.

Results Type 1 reaction was seen in 25% (n=11) of patients. It occurred in 44.4% (n=4) of borderline lepromatous (BL), 33.3% (n=1) of mid borderline (BB), 37.5% (n=3) of borderline tuberculoid (BT) and 30% (n=3) of tuberculoid (TT) patients. Borderline spectrum of disease gave a relative risk of 2 (95% CI 0.3-0.9) and age of 40 gave a relative risk of 1.8 (95% CI 0.3-0.9) for the development of type 1 reaction. Older mean age (mean 53.7 years cf. 37.0 years, $p = 0.01$) and earlier presentation to health care workers (mean 5.8 months cf. 11.9 months, $p = 0.02$) was also significant risk factors. Extent of disease and gender were not identified as risk factors.

Conclusion Risk factors for type 1 leprosy reaction were borderline leprosy, older patients and shorter duration of illness on presentation.

Keywords leprosy, type 1 reaction, risk factors

Introduction

Type 1 reaction or reversal reaction is caused by spontaneous increases in T-cell reactivity to mycobacterial antigens¹. This reaction typically occurs in patients with borderline leprosy encompassing mid borderline (BB), borderline tuberculoid (BT), and borderline lepromatous (BL) leprosy². These borderline patients are considered immunologically unstable, thus allowing alteration of the dynamic immunologic mechanism leading to modifications of the cytokine profiles in the skin lesions and nerves causing inflammation³. The incidence rate is reported to be 8.7/100 person years

at risk⁴. It mainly occurs during treatment. Clinically, it presents with inflammation of the existing skin lesions causing erythema, oedema, pain and sometimes ulceration. Accompanying acute neuritis is also common. Untreated this will lead to deformities and disabilities due to permanent nerve damage. Thus, it is important to determine the risk factors predicting this reaction to help clinicians anticipate them and start treatment early to prevent the associated morbidities. Here, a retrospective study was undertaken to determine the risk factors for type 1 leprosy reaction among all the newly diagnosed patients with leprosy seen in the skin clinic, Sarawak General Hospital between 1993 and 2007.

Correspondence

Dr Felix Boon Bin, Yap
Department of Dermatology, Sarawak General Hospital
Jalan Hospital, 93586 Kuching, Sarawak, Malaysia
Email : woodzlamp@yahoo.com
Conflict of interest : Nil

Materials and methods

A retrospective review of all the newly diagnosed patients with leprosy in the skin clinic, Sarawak General Hospital between 1993 and 2007 was undertaken. Data regarding the baseline

demographics, clinical characteristics and slit skin smear results on initial presentation, and the presence of type 1 leprosy reactions, its treatment and outcome were retrieved from the case folders in the skin clinic.

Clinical characteristics on initial presentation retrieved from the case folders included number of skin lesions, number of thickened nerves, and duration of skin lesions prior to presentation, earlobe thickening and loss of lateral third of the eyebrows. The skin lesions consist of hypopigmented macules and patches; and erythematous macules, papules, patches, plaques and nodules with or without loss of sensation. Thickened nerves included all the superficial peripheral nerves namely ulnar, median, radial cutaneous, greater auricular, lateral popliteal and posterior tibial nerves.

All the slit skin smears utilized 6 sites, 1 on each earlobe and 4 on the skin lesions on the body. Bacteriologic index (BI) is a logarithmic scale from 1+ to 6+ quantifying the density of *Mycobacterium leprae* in the smear. The BI presented in this study is the average BI from these 6 sites. Morphological index (MI) is the percentage of regularly stained bacilli signifying the percentage of live bacilli in the smear.

All the patients in this study were classified based on the Ridley-Jopling classification⁵ of indeterminate leprosy (IND), tuberculoid leprosy (TT), borderline tuberculoid leprosy (BT), mid borderline leprosy (BB), borderline lepromatous leprosy (BL) and lepromatous leprosy (LL). They were also classified according to the WHO classification⁶ into multibacillary (MBL) and paucibacillary (PBL) leprosy. Patient is considered to have borderline leprosy if they have BT, BB or BL leprosy. Those with PBL were considered to have IND, TT and BT whereas MBL consisted of BB, BL and LL.

Type 1 Leprosy Reaction in Sarawak General Hospital (n=44)

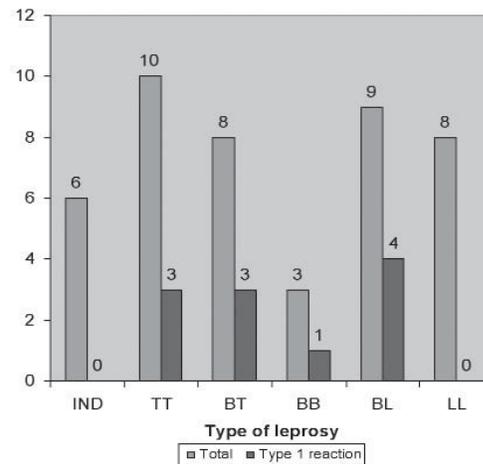


Table 1 Relative risks for type 1 leprosy reaction based on demographics and clinical characteristics in Sarawak General Hospital

Risk Factors	With reaction (n=11)	Without reaction (n=33)	RR	95% CI
Male Sex	8 (72.7%)	25 (75.8%)	0.9	0.7-1.6
Age>40	8 (72.7%)	13 (39.4%)	1.8	0.3-0.9
Borderline leprosy	8 (72.7%)	12 (36.3%)	2.0	0.3-0.9
Loss of eyebrow	2 (18.2%)	6 (18.2%)	1.0	0.7-1.4
Earlobe thickening	2 (18.2%)	9 (27.3%)	0.7	0.4-6.3
Nerve thickening	7 (63.6%)	15 (45.5%)	1.4	0.4-1.3
Skin lesions>5	5 (45.5%)	15 (45.5%)	1.0	0.5-1.9
MI>3	5 (45.5%)	11 (33.3%)	1.4	0.3-1.7
BI>3	3 (27.3%)	9 (27.3%)	1.0	0.3-3.2

RR - relative risk, 95% CI - 95% confidence interval

Patients were deemed to have type 1 leprosy reactions or reversal reactions if their original skin lesions became inflamed, swollen, painful and tender.

Statistical analysis using SPSS version 15 was done to determine the relative risks for development of type 1 reaction. Student t test was utilized for comparison of means in those with or without type 1 reaction. The level of significance was set at 0.05.

Results

Demographics and clinical course

There were 44 newly diagnosed patients with leprosy in the skin clinic, Sarawak General Hospital from 1993 to 2007. Six (13.6%) had indeterminate leprosy (IND), 10 (22.7%) had tuberculoid leprosy (TT), 8 (18.2%) had borderline tuberculoid leprosy (BT), 3 (6.8%) had midborderline leprosy (BB), 9 (20.5) had borderline lepromatous leprosy (BL) and 8 (18.2%) had lepromatous leprosy (LL). Male constituted 75% (n=33) of the patients. The mean age was 41.2 ± 20.0 years, ranging from 8 to 94 years old. Twenty five percent (n=11) of patients developed type 1 reaction. Type 1 reaction occurred in 44.4% (n=4) of BL, 33.3% (n=1) of BB, 37.5% (n=3) of BT and 30% (n=3) of TT patients (Figure 1). None with IND or LL leprosy developed this reaction.

Of the 11 patients with type 1 leprosy reaction, 8 were males and 3 were females. Five (45.5%) patients had their reactions prior to treatment. The remaining 6 had the reaction between 7 and 160 days after treatment. The duration of the reactions lasted between 1 to 17 months. The mean period was 7 months. All the patients except 2 had oral corticosteroids to treat their reactions. These 2 patients had only non steroidal anti inflammatory drugs (NSAID). Neuritis was noted in 5 (45.5%) patients. However, there were only 2 patients with permanent deformity. One had foot drop and another had claw hand. No death was reported.

Risk factors

Table 1 shows the relative risks of developing type 1 leprosy reaction in Sarawak General Hospital. It was noted that borderline spectrum of disease and age more than 40 years old gave an increased risks of developing type 1 leprosy reaction. Borderline spectrum of disease gave a relative risk of 2 (95% CI 0.3-0.9) while age more than 40 years old gave a

relative risk of 1.8 (95% CI 0.3-0.9). Other variables including gender, MI, BI, presence of nerve thickening, number of skin lesions, loss of lateral third of the eyebrows and earlobe thickening were not identified as risk factors for development of type 1 leprosy reaction.

Analysis of means using student t test revealed that those with the reaction was significantly older (mean 53.7 years cf. 37.0 years, $p = 0.01$) and presented earlier to the health care workers (mean 5.8 months cf. 11.9 months, $p = 0.02$). However, there were no differences in the mean skin lesion count (7.1 cf. 8.2, $p = 0.75$), mean thickened nerve count (1.3 cf. 0.9, $p = 0.48$), mean MI (5.8 cf. 4.9, $p = 0.76$) and mean BI (1.7 cf. 1.7, $p = 0.97$) on initial presentation.

Discussion

Type 1 leprosy reaction is reported to occur in 8% to 32% of patients with leprosy^{7,8,9}. In Penang,

27.4% of the 95 patients with leprosy seen in the Penang General Hospital developed type 1 reaction, whereas in Hospital Sultanah Aminah, Johor Bahru, the rate was 21.1%^{10,11}. Here, 25% of our leprosy patients developed this reaction, similar to regional and international figures. Type 1 reaction is seen in borderline spectrum of disease. In a tertiary hospital in Delhi, the reaction was most commonly seen in those with BB followed by BL, BT and LL⁷. In Thailand, there were a statistically significant increasing proportion of patients with severe reversal reaction starting from tuberculoid and going toward borderline lepromatous¹². In Hyderabad, the reaction was seen mostly in those with BL and BT⁹. In Penang, it is seen mostly in BT followed by LL, BB, BL and TT¹⁰. Here, the pattern was BL, BT, TT and BB. None of the patients with LL developed the reaction. The pattern seen here and in Penang corresponded to finding by others in that borderline leprosy comprising BB, BL and BT are risk factors for type 1 reaction.

Among patients developing type 1 reaction, up to 60% developed the reaction at the time of presentation^{7,13}. In Thailand, among patients with PBL developing this reaction, 82% had it during the initial visit while among MBL patients, 35% had it before treatment¹². In Penang, only 15.4% of the 26 patients developed the reaction prior to treatment¹⁰. Most of their patients developed the reaction during

the first 3 months of therapy¹⁰. Here, 45.5% had the reaction prior to treatment, 66.7% among patients with PBL and 20% among those with MBL. Our rate is much higher than that observed by Tan et al in Penang but similar to those reported in India and Thailand.

Scollard et al noted that type 1 reactions occurred with significantly greater frequency in women, and did not appear to be influenced by age of onset of leprosy⁸. Similarly, female gender was also seen as a risk factor for reversal reaction in Northern India¹³. Widespread disease and multibacillary disease were also identified as risk factors. In West Nepal, extensive clinical disease and borderline leprosy was identified as a risk factor for type 1 leprosy reaction during the first year of treatment⁴. In Brazil, among patients with MBL, segmentary skin lesions and BI < 3 was significantly associated with reversal reactions¹⁴. Higher level of serum tumour necrosis factor alpha and interleukin 1 were also identified as a prognostic marker for reversal reactions¹⁵.

Here, it was noted that patients with borderline spectrum of disease, age more than 40 years old and had shorter duration of illness possessed higher risk for reversal reactions. Extent of disease, measured by number of lesions on presentation, MI and BI was not identified as a risk factor. The reason for the shorter duration of illness before presentation was because most of the patients presented with type 1 reaction rather than the disease per se. It is postulated that older patients had higher risk for reversal reaction because there are more likely to have past infection or exposure to mycobacterium tuberculosis, a possible trigger for this reaction¹⁶. Tuberculosis is a major public health problem in Sarawak.

This study is limited by the number of patients and the retrospective nature. Limitation in number of patients affected the statistical power. The retrospective nature limited the type of data collected. Some of the data are also missing, limiting the scope of the study.

In conclusion, risk factors for type 1 leprosy reaction were borderline leprosy, older patients and shorter duration of illness on presentation. Finding these clinical characteristics in patients with leprosy can forewarn the treating clinician to the possibility

of reactions in the near future. This will thus facilitate earlier treatment to prevent deformities and disabilities.

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GRANULOMATOUS DISEASES - Short Communication

A lady with complicated erythema nodosum leprosum

Yap FBB, MRCP, Pubalan M, MRCP

Dear Editor,

We have encountered a 28 year old Penang lady presented with hyperpigmentation and tight skin in July 2004. She was initially diagnosed as scleroderma. However, 2 months after diagnosis, she developed multiple painful nodules on the body. Examination showed multiple erythematous tender nodules on the body associated with multiple hypopigmented anaesthetic lesions and thickened earlobes (Figure 1). Slit skin smear showed presence of *Mycobacterium leprae* with a morphological index (MI) of 12 and bacteriologic index (BI) of 5.6. A diagnosis of MBL with ENL was made. She was commenced on the WHO multiple drug therapy (MDT) for a year. She was also given oral prednisolone for her ENL. On completing of the MDT, her MI was 0 and BI fell to 3.8. Two years after diagnosis, her ENL worsened requiring addition of azathioprine. Her prednisolone was titrated to the maximum of 2 mg/kg/day. Due to this severe immunosuppression, she was admitted twice to the hospital because of severe septicaemia. Fortunately, she managed to survive these episodes. In order to reduce her dependence on steroids, oral thalidomide at 400 mg daily was added after discussion of the benefits and the risks, especially teratogenicity, with the patient. This helped her for a few months. In January 2008, her ENL was again out of control requiring up titration of her steroid. Her BI in April 2008 went up to 4.0. Skin biopsy for mycobacterium culture and sensitivity was sent.

Second line treatment of daily rifampicin 600 mg, minocycline 100 mg, ofloxacin 400 mg was commenced. This did not improve her ENL. However, her BI fell to 2.6 in August 2008. As her ENL was not improving, pentoxifylline was added

in September 2008. Her azathioprine was changed to cyclosporine. This alteration in therapy helped the ENL.

In October 2008, her BI fell further to 2.3. Nevertheless, in December 2008, with an upper respiratory tract infection, her ENL worsened. Her prednisolone had to be increased from 0.5 mg/kg/day to 1 mg/kg/day to control the reaction. Up to February 2009, she still has crops of skin lesions despite on oral prednisolone 0.5 mg/kg/day, thalidomide 400 mg daily, cyclosporine 4 mg/kg/day and pentoxifylline 400 mg twice daily (Figure 2). Complications of prolonged corticosteroid treatment were apparent.



Figure 1 Presence of multiple erythematous papulonodules on the neck with thickened earlobes



Figure 2 Presence of multiple papulonodules on the upper limbs

Correspondence

Dr Felix Boon Bin, Yap
Department of Dermatology, Sarawak General Hospital
Jalan Hospital, 93586 Kuching, Sarawak, Malaysia
Email : woodzlamp@yahoo.com

Discussion

Treatment of ENL with immunosuppressive medications is usually successful. In Nepal 48% of their patients with ENL are successfully treated within a year³. However, in 13% of cases, ENL can persist for more than 5 years³.

Complicated ENL usually requires the use of more potent immunosuppression. Miller et al had successfully treated difficult ENL with cyclosporine A⁴. In our case, the use of cyclosporine and azathioprine had limited success.

Thalidomide and pentoxifylline are used in the treatment of leprosy because of their anti tumour necrosis alpha (TNF α) property. TNF α is found to play a key role in the symptomatology of ENL⁵. By blocking this inflammatory mediator, it is postulated that the propagation and progression of ENL will cease. Thalidomide is proven to be more superior to corticosteroid and pentoxifylline^{6,7}. Thalidomide is drug of first choice in man with severe ENL. However, the use of this highly teratogenic drug in women of reproductive age group is difficult⁸. The risks and benefits have to be weighed and proper discussion between the patients and the treating physician is essential to get the optimal outcome. The use of thalidomide usually controls the ENL within 48 hours. However, in our patient the use of thalidomide at a recommended dosage of 400 mg daily only managed to control the reaction for the first few months. Addition of another TNF α blocker, pentoxifylline also failed to effectively control her ENL.

In this complicated case of ENL, the use of monoclonal antibody against TNF α e.g. infliximab and etanercept might be useful. However, due to the high cost of this medication and lack of clinical data on its effectiveness and adverse effects in leprosy patients, it was not tried.

This case illustrates the difficulty in treating complicated ENL. Fortunately, complicated ENL occurs in the minority of cases.

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GRANULOMATOUS DISEASES - Short Communication

Post vaccination lupus vulgaris

Masliza H, MD, Ong CL, MRCP, Zamri, MD, Nor A, MD

Dear Editor,

We have encountered a 25 year old Malay lady, single, presented with hyperpigmented raised scaly plaque over the left shoulder for 13 years. She claimed that the lesion originated from BCG scar. It was increasing in size and new lesions were noted on her back and right thigh. No history of contact with tuberculosis and leprosy patient. There is no history of weight loss, decrease appetite, malignancy nor symptoms of connective tissue disease.

On examination there were well demarcated scaly plaque with area of atrophy and poikiloderma over the left shoulder (10 x 20cm), back (6 x 5cm) and left thigh (5 x 3cm). Investigation results revealed lymphocytosis. Mantoux test was 20mm. CXR was normal. Skin biopsy showed granulomatous inflammation.

A diagnosis of post vaccination lupus vulgaris was made based on the history, skin biopsy and strongly positive mantoux test. Patient was put on anti-tuberculosis for 6 month (daily doses for 2 months, IM Streptomycin 1gm, Isoniazide 250mg,

Rifampicin 450mg and Pyrazinamide 1250mg followed by biweekly doses for 4 months of Rifampicin 450mg and Isoniazide 750mg (Table 1). The skin lesion resolved completely after 6 months of therapy.

Discussion

Tuberculosis of the skin is caused by Mycobacterium Tuberculosis, Mycobacterium Bovis and under certain condition BCG (an attenuated strain of M. Bovis used in vaccination). Fragmented Tuberculosis of the skin has a worldwide distribution. The 2 most frequent form of skin tuberculosis are lupus vulgaris and scrofuloderma^{1,2,3,4}.

Lupus vulgaris is rare whereas scrofuloderma and verrucous lesion predominate⁴. Lupus vulgaris occurs more than twice in woman whereas TB verrucosa cutis is more often found in men. Generalized milliary TB is seen in infant and adult with severe immunosuppression or AIDS^{5,6} as is primary inoculation tuberculosis. Scrofuloderma usually occurs in adolescents and the elderly whereas lupus vulgaris may affect all age groups.



Figure A & B shows well demarcated scaly, hyperkeratotic erythematous plaque with area of poikiloderma



Figure C & D After completed treatment

Correspondence

Dr Masliza Hanuni
Department of Dermatology
Hospital Sultanah Nur Zahirah, Pahang

Lupus vulgaris is an extremely chronic, progressive form of cutaneous tuberculosis occurring in individuals with moderate immunity and high degree tuberculin sensitivity. It is a post primary paucibacillary form of tuberculosis - **fragmented** result from direct extension of underlying tuberculous foci of lymphatic or hematogenous spread, after primary inoculation, BCG vaccination, or in scars of old scrofuloderma. Complete healing rarely occurs without therapy.

Lesions are usually solitary and more than 90% involve the head and neck. Started with small, sharply margined, red-brown papules of gelatinous consistency (apple-jelly nodules) slowly evolve by peripheral extension and central atrophy into large plaques. However, many clinicians in Asian countries who see large numbers of this entity have avoided using the descriptive term "apple jelly nodules" since this is seldom seen in pigmented patients.

Reappearance of new nodules within previously atrophic or scarred lesions is characteristic. The cartilage (nose, ears) within the affected area is progressively destroyed (lupus vorax); bone however is usually spared. Buccal, nasal, and conjunctival mucosae may be involved primarily or by extension.

Clinical variants are numerous and are seen in the following forms:

Plaque forms:

Disease extension occurs with little central atrophy. Scaling can occur, especially on the lower legs where it may resemble psoriasis. Irregular scarring is common and the active edge may be thickened and hyperkeratotic.

Ulcerating form:

Scarring and ulceration predominate. Crusts form over areas of necrosis. Deep tissues and cartilage are invaded by scar tissue that cause contractures and deformity.

Vegetative form:

Necrosis, ulceration and papillomatous granulation tissue are seen.

Nodular form:

Absence of ulceration and scarring. Large soft tumors occur, especially on ear lobes.

Histologically⁷, the most prominent feature is a typical granulomatous tubercle with epithelioid cells, Langhans giant cells and a mononuclear infiltrate. Caseation necrosis is minimal and detection of acid-fast bacilli is rare. Tissue histology varies with secondary changes of abscess.

Table 1 Guidelines For Mycobacterium Tuberculosis Infection Therapy

	OPTION 1		OPTION 2			OPTION 3
	Initial 8/52	Then 16/52	Initial 2/52	Then 6/52	Then 16/52	9/12
RIFAMPICIN 10mg/kg	DAILY	2-3 X / WEEK	DAILY	DAILY	DAILY	3X / WEEK
ISONIAZIDE 5mg/kg	DAILY	2-3 / WEEK	DAILY	DAILY	DAILY	3X / WEEK
PYRAZINAMIDE 30mg/kg	DAILY		DAILY	DAILY		3X / WEEK
ETHAMBUTOL 15mg/kg	DAILY		DAILY	2X / WEEK		3X / WEEK
OR						
STREPTOMYCIN 15mg/kg	DAILY		DAILY	2X / WEEK		3X / WEEK

Total duration of treatment 6 months except in patient with HIV infection, in whom treatment duration is at least 9 months.

Diagnosis can be made based on :

- Typical LV plaque recognized by the softness of the lesions, brownish red color and slow evolution.
- The apple jelly nodule revealed by diascopy is highly characteristic.
- Strongly positive tuberculin test
- Bacteria culture is usually negative
- Positive PCR for MTB can support the diagnosis in some cases⁸.
- LV is a chronic disorder. Without therapy it progresses causing functional impairment and disfiguration.

Long standing LV may lead to the development of carcinoma especially squamous cell carcinoma⁹. The risk of metastases is high. 40% associated with tuberculous lymphadenitis. 10 - 20% associated with active pulmonary tuberculosis or tuberculosis of bones and joints¹⁰. Pulmonary tuberculosis is 4 - 10 times more frequent in patient with LV than in general population¹⁰.

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An outbreak of Rove Beetle dermatitis in Penang Hospital: A report of 37 cases

Tan WC, MRCP, Chan LC, MMed

Abstract

Background Rove beetle dermatitis is a peculiar form of acute irritant dermatitis following the contact with body fluid of an insect which is belonging to genus *Paederus*. This retrospective study is to evaluate the epidemiology and clinical manifestations of rove beetle dermatitis during the outbreak of rove beetle dermatitis in Penang (March 2009 - April 2009).

Methods We describe 37 patients with clinical diagnosis of rove beetle dermatitis presented to our department. Only those patients with a definite history of contact with the insect were included in the study. Demographic characteristics, reason for referral and details of skin lesions were documented and analysed.

Results Male patients outnumbered female patients - 21 males (56.8%); 16 females (43.2%). The mean age of patients was 28.3 years. Of the 37 patients, 18 patients (48.6%) were Malay, 14 Chinese (37.8%), 4 Indians (10.8%) and 1 foreigner (2.8%). The mean duration of lesions before presentation to our clinic was 3.4 days. The mean duration of lesions before presented to our clinic was 3.4 days. Symptom of burning sensation (25, 67.7%) was more pronounced than itching (6, 16.2%). Fourteen of our patients (37.8%) reported a positive family history. Clinically, the most common presentation consisted of linear, geographic, erythematous plaques with a "burnt" appearance. In 59.5% of patients, more than one lesion was present. Pustules and vesicles were seen in 12 (32.4%) and in 10 (27.1%) of the patients respectively. "Kissing lesions" were seen in 5 (13.5%) patients. The neck and arms were the most common sites of involvement. Periorbital involvement occurred in 16.2% of patients. Only 8 patients (21.6%) were diagnosed to have "insect related dermatitis" at initial presentation. No one was referred as "rove beetle dermatitis".

Conclusion Rove beetle dermatitis is a common condition. Awareness of these condition and its clinical features will prevent misdiagnosis and unnecessary worry.

Keywords Rove beetle dermatitis, *Paederus dermatitis*, *Dermatitis linearis*

Introduction

Rove beetle dermatitis (also known as *night burn*, *paederus dermatitis*, *dermatitis linearis*, *blister beetle dermatitis*, *whiplash dermatitis*) is a specific form of acute irritant contact dermatitis caused by contact with the vesicant chemical pederin contained in the body fluids of insects of the genus *Paederus*¹. The condition is characterized by bullous lesion (vesicles & pustules) on an

erythematous base with sudden onset of stinging or burning sensation on exposed areas of the body².

Paederus beetles have been associated with outbreak of dermatitis in various countries including Australia³, Malaysia⁴, India⁵, Sri Lanka⁶, Iran⁷ and others⁸. From literature search, there were only 2 outbreak of rove beetle dermatitis recorded in Malaysia. In 1993, Mokhtar N et al reported *paederus dermatitis* among medical students in USM, Kelantan, Malaysia. In September 2002, an epidemic of *dermatitis linearis* caused by rove beetles affected thousands of high rise flat dwellers and dormitory students in Penang, Malaysia. In March 2009, the second outbreak of rove beetle dermatitis in Penang state, Malaysia. This study is

Correspondence

Dr Tan Wooi Chiang
Department of Dermatology
Penang Hospital, Jalan Residensi, 10990 Penang
Email : tanwooichiang@yahoo.com

to evaluate the epidemiology and clinical manifestations of rove beetle dermatitis during this outbreak.

Materials and methods

This is a retrospective review of 37 patients with clinical diagnosis of rove beetle dermatitis who presented to dermatology department, Penang Hospital during the second outbreak of Rove Beetle dermatitis in Penang (March 2009 - April 2009).

The diagnosis was made clinically and no histopathologic examination was performed. Only those patients with a definite history of contact with the insect were included in the study. Patients with a doubtful history of contact with the beetle or other plausible causes of contact dermatitis were not included in the study. Patients with a previous history of chronic skin disease or allergy were also excluded.



Figure 1
Typical Rove Beetle



Figure 2 Typical "burnt like" lesion secondary to Rove Beetle dermatitis



Figure 3 Typical linear pustular lesion



Figure 4 Pustular lesions on the intense inflamed area



Figure 5 Nairobi eye



Figure 6 Kissing lesion

Demographic characteristics including family history of similar skin lesions were recorded and analysed. Reason for referral, presenting symptoms, number of skin lesions, site of involvement, morphology of the lesions, patterns of distribution were also documented and analysed. Species identification of the Rove Beetles was not done.

All the cases of Rove Beetle dermatitis were notified to state health department for further action.

Results

A total of 37 patients were included in our study. Male patients outnumbered female patients - 21 males (56.8%); 16 females (43.2%). Their ages ranged from 5 years to 69 years (mean age, 28.3 ± 16.6 years, median age 26 years). Of the 37 patients, 18 patients (48.6%) were Malay, 14 Chinese patients (37.8%), 4 Indian patients (10.8%) and 1 patient (2.8%) was foreigner. No significant difference was observed in the clinical features in relation to gender and ethnics.

The cutaneous lesions were present from 1 to 10 days before presentation (mean 3.4 ± 1.7 days, median 3 days). The burning sensation was more pronounced compared to itching. Twenty five patients (67.6%) complained of tingling / burning sensation over the lesions and 6 (16.2%) had itching at the site of lesions. There were 6 (16.2%) patients who were asymptomatic and presented with skin lesions only. Fifteen patients (40.5%) presented with a single lesion. The remaining 22 (59.5%) cases, 12 (32.4%) had two lesions, 6 (16.2%) had 3 lesions and 4 (10.8%) had more than 3 lesions. Fourteen of our patients (37.8%) reported a positive family history of similar problem.

There were various morphological (Table 1) and distribution pattern of the skin lesions observed (Table 2). Twelve patients (32.4%) presented with erythematous geographic patches with a “burnt” appearance at the time of initial presentation. Twenty two patients (59.5%), had typical linear lesions and 5 patients (13.5%) had demonstrated striking feature of “kissing lesions.” The most common sites of involvement in descending order of frequency were the head and neck (24, 64.9%), upper extremities (7, 18.9%), trunk (4, 10.8%) and lower extremities (2, 5.4%).

Table 1 Morphological pattern of the skin lesions of rove beetle dermatitis observed in our cohort

Morphology of the skin lesion	No. of cases (%)
Maculopapular	2 (5.4%)
“Burnt like”	12 (32.4%)
Pustular	12 (32.4%)
Vesico-bullous	10 (27.1%)
Wheal like	1 (2.7%)

Table 2 Pattern of distribution of the skin lesions of rove beetle dermatitis observed in our cohort

Morphology of the skin lesion	No. of cases (%)
Linear	22 (59.5%)
Herpetiformis	9 (24.3%)
Bizarre	2 (5.4%)
Annular	4 (10.8%)

Looking at the reasons for referral to Dermatology Clinic, only 8 patients (21.6%) were referred for insect related dermatitis. Fifteen patients (40.5%) were referred to rule out herpes zoster infection, 6 patients (16.2%) to rule out contact dermatitis, 4 patients (10.8%) to rule out herpes simplex infection and other diagnosis in 4 patients (10.8%). No one was referred as "rove beetle dermatitis".

There were limitations of this study; species identification of the rove beetles was not done. In addition, skin biopsy of the lesions with histopathological examination was not done.

Discussion

Rove beetle dermatitis is the result of mucocutaneous contact with the haemolymph of members of the genus *Paederus* that contain *pederin*⁹. The genus *Paederus* belongs to family *Staphyllinidae*, order *Coleoptae*, class *Insecta*. The genus *Paederus* consists of more than 600 species, which are widely distributed worldwide⁷. The major species found in Penang is *Paederus fuscipes*. Local Malay name of *Paederus fuscipes* is "*Semut Semai*", "*Semut Kayap*" or "*Charlie*".

The rove beetle (Fig 1) is less than 1cm long. The body is dark orange and the tip of the abdomen, the upper abdomen and the head are black. The upper middle iridescent greenish region of the abdomen is the hard wings (elytra). A pair of transparent wings are neatly folded and hidden under the hard wings. During the daytime, the beetle will be seen crawling around swiftly with hidden wings resembling ants. When disturbed it raises the abdomen in a threatening gesture like a scorpion and can fly away.

The beetle has been observed in the paddy fields (since 1919), school fields - within the grass etc. It is carnivorous and eats smaller insects. Thus it plays an important role as a biological control of 'paddy pests'. During heavy rains / floods, the beetle may migrate to drier areas. They become active after the rains⁶.

The haemolymph in the beetle's entire body (except the wings) contains the most poisonous animal contact toxin in the world called '*pederin*' (C₂₄ H₄₃ O₉ N) named in 1952⁷. It is 12 times more poisonous than cobra venom. Dried and stored rove beetle for 8 years still retains its toxicity.

Paederus beetles can fly, but they prefer to run. They neither bite nor sting, but when crushed against the skin or the eye, they release a toxin called *pederin* which will cause irritation and blistering¹. Acute irritant contact dermatitis which characterized by "burn-like" lesions occur within 12-36 hours after exposure⁹ (Fig 2). The rashes then develop into vesicles, bullae or pustules¹⁰ (Fig 3 & 4) which dry out to become crusted and scaly within a week. The lesions correspond in shape and dimensions to the area affected by *pederin*¹. These beetles are highly attracted to artificial light sources especially fluorescent lighting at home⁷. Our cohort is somewhat different from others. Our patients are mostly from urban area, away from the paddy fields. Most of the patients in our cohort sleep with the light on. This may explain why they have rove beetle dermatitis.

Rove beetle dermatitis occurs predominantly on exposed parts of the body. Face and neck were found to be the most commonly involved sites in an Iranian⁷ and Pakistani study¹¹. Our study also observed a similar finding. The majority of the lesions were on the neck and face.

Ocular involvement in the form of periorbital dermatitis and keratoconjunctivitis is not uncommon. A periorbital predilection was present in 6 patients (25%) of the head and neck lesions in our study (Fig 5). It is usually secondary to the transfer of the toxic chemical from elsewhere on the skin by the fingers. This is similar to reports of periorbital dermatitis and keratoconjunctivitis caused by blister beetle exposure from Tanzania, which has been named "Nairobi eye."¹²

"Kissing lesions" can occur from the spread of *pederin* to adjacent skin surfaces, usually on flexural surfaces¹³ (Fig 6). However Zargari et al reported that 5 percents had kissing lesions, whereas 5 (13.5%) of our patients had kissing lesions. The lesions usually heal completely in 10 to 12 days with transient post-inflammatory hyperpigmentation¹⁴.

An atypical variant of rove beetle dermatitis has been reported, which is characterized by diffuse erythematous and desquamative lesions predominantly on the upper body¹⁵. Zargari et al described diffuse desquamation and epidermal necrosis in 15 percent of cases, which were not

found in any of our patients. The severity of the reaction probably is attributable to a more potent toxin produced by the species of *Paederus sabaesus* Erichson compared with the Malaysian species, *Paederus fuscipes*.

The clinical differential diagnoses of rove beetle dermatitis include acute allergic or irritant contact dermatitis⁹, herpes zoster⁹, herpes simplex⁷, thermal burn¹, bullous impetigo and phytophotodermatitis⁹. In the case of rove beetle dermatitis, the uncommon association of acute dermatitis with minimal or no complaints facilitates diagnosis², which is corroborated by the characteristic linear appearance of the lesion, their predilection for exposed area, the presence of kissing lesions, Nairobi's eye and epidemiological feature (occurrence of similar cases in a given area, the seasonal incidence and identification of insect)¹⁶. An interesting point to take note, those who sleep with light on may give an additional clue to the diagnosis of rove beetle dermatitis.

The treatment of rove beetle dermatitis should be the same as irritant contact dermatitis. Removal of irritant, washing with soap and water and application of cold wet compression followed by topical steroid are the mainstay of management. If secondarily infected, topical antibiotic or systemic antibiotic will be needed¹⁷. Prevention is always better than treatment. Preventing human-beetle contact is the primary method of preventing pederin based trauma.

Malaysia as an agricultural and tropical country makes rove beetle more prevalent. However the report on this condition is scarce. The incidence of rove beetle dermatitis is probably under-reported. The possible explanation to this being lack of awareness among the public and healthcare workers. High index of suspicion among the medical practitioners will aid in early diagnosis and prompt treatment¹⁷.

Conclusion

Rove beetle dermatitis is a common condition. An outbreak of rove beetle dermatitis can occur in any part of Malaysia and any time especially after rainy season. Awareness of this condition and its clinical features will prevent misdiagnosis and prevent unnecessary worry. Simple preventive measures can

be undertaken based on the behavioural pattern of this nocturnal beetle.

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GENERAL DERMATOLOGY - Short Communication

Twin psoriasis

Zaigham Mahmood

Dear Editor,

We have encountered identical Chinese twin brothers of 17 years of age presented with erythematous scaly plaques on the left side of the occipital scalp region since 6 months, almost at the same site in both brothers. Patient denied any history of psoriasis in the family. On examination there were three erythematous mildly scaly plaques, over the occipital scalp region with no hair loss. No nail changes were appreciated. Blood investigations were within normal limits, especially ANF and a fungal culture.

Punch biopsies from both twins showed similar histopathologic findings of acanthosis and parakeratosis with elongation and widening of rete pegs and an oedematous suprapapillary dermis and a perivascular lymphoplasmacytic cell infiltrate in the dermis consistent with a diagnosis of psoriasis.

Discussion

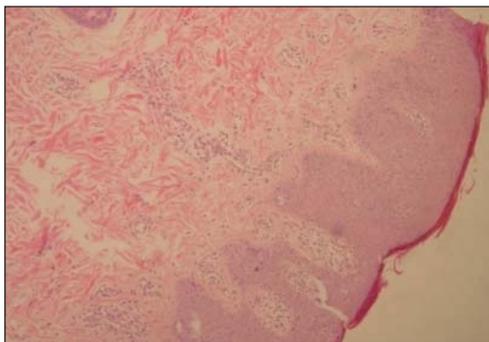
The unique aspect of this case report is identical

twins developing scalp psoriasis simultaneously, at the same site and time. A literature search revealed only a few cases with a similar presentation¹.

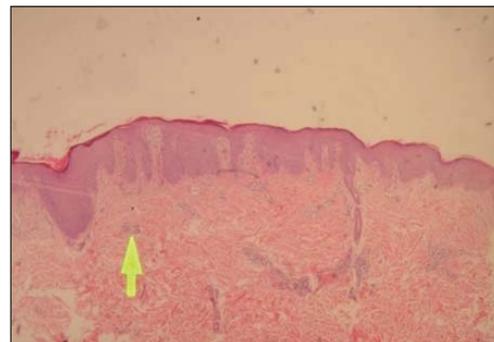
Psoriasis has been found to be genetically determined for single-gene autosomal dominant inheritance with reduced penetrance. Twin studies confirm a role for inheritance in psoriasis. A study of 61 pairs in whom at least one member of each pair had psoriasis revealed that 73% of monozygotic pairs, compared with only 20% of dizygotic pairs had concordant disease. A Danish Twin Register, which included analysis of concordance among monozygotic twins does, however, indicate that environmental factors contribute to the aetiology. The role of the HLA system in psoriasis is now well recognized and HLA-CW6 has been shown to be strongly associated with psoriasis².

The patients responded well to a combination regime of calcipotriol and betamethasone 17-valerate ointment and coal tar shampoo.

FIRST TWIN HPE



SECOND TWIN HPE



Both twin serial sections show skin with acanthosis and parakeratosis. There is elongation and widening of rete pegs with oedematous suprapapillary dermis. There is moderate perivascular lymphoplasmacytic cell infiltrate seen within dermis."

Correspondence

Dr Zaigham Mahmood
Department of Dermatology
Hospital Queen Elizabeth, Karung Berkunci No.2029
88586 Kota Kinabalu, Sabah, Malaysia

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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 68**. Refer to the given criteria in **page 69** to discover your clinical diagnostic skill status.

Slide A



A

- bacterial infection
- viral infection
- fungal infection
- dermatitis
- non-infectious disease
- impetigo
- tinea capitis
- contact allergy
- psoriasis
- seborrhoeic capitis

Slide B



B

- bacterial infection
- viral infection
- fungal infection
- dermatitis
- non-infectious disease
- pustules
- tinea capitis
- eczema herpeticum
- psoriasis
- seborrhoeic capitis

Slide C



C

- bacterial infection
- viral infection
- fungal infection
- dermatitis
- autoimmune disease
- skin scalding syndrome
- chickenpox
- SLE
- dermatomyositis
- seborrhoeic dermatitis

Slide D



D

- bacterial infection
- viral infection
- fungal infection
- dermatitis
- autoimmune disease
- skin scalding syndrome
- chickenpox
- SLE
- dermatomyositis
- seborrheic dermatitis

Slide E



E

- non-infective inflammation
- ADR
- fungal infection
- viral infection
- contact dermatitis
- dengue
- viral exanthem
- tinea corporis
- candidiasis
- erythroderma

Slide F



F

- non-infective inflammation
- ADR
- fungal infection
- viral infection
- contact dermatitis
- skin atrophy
- ecchymoses
- tinea corporis
- candidiasis
- erythroderma

Slide G



G

- non-infective inflammation
- ADR
- fungal infection
- viral infection
- contact dermatitis
- skin atrophy
- ecchymoses
- tinea corporis
- candidiasis
- erythroderma

DERMATOSURGERY - Surgical Tips

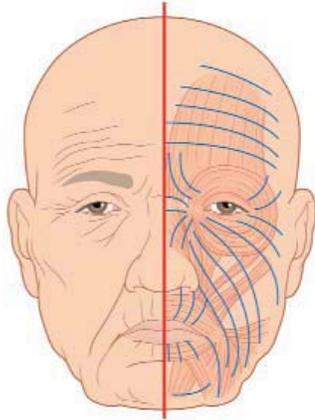
Know your lines - Skin tension lines of the face (STLs)

Gangaram H

Key points

- Skin tension lines are the distinctive furrowed or wrinkled lines on the face.
- Dynamic & relaxed STLs lie perpendicular to the action of underlying muscle fibers.
- Lines become more visible & deeper with age & sun damage.
- Knowledge of the skin tension lines is required for successful cutaneous surgery & proper use of cosmetic injectables.

Skin tension lines



For good cosmesis (a hidden, fine-lined scar) & proper use of cosmetic injectables, surgical planning must include a thorough knowledge of the STLs. The reconstruction of surgical defects should be designed to minimize perceptible scarring. One such way is to align the long axis of a repair within or parallel to the STLs. This places the scar under the least amount of tension, allowing the scar to fall within a natural wrinkle. Wounds close more easily in this orientation, as the skin is approximately three times more distensible perpendicular to the STLs than parallel.

Tension, created by the intermittent contraction of the muscles of facial expression, is transmitted by fibrous bands from the SMAS (superficial musculoaponeurotic system) to the skin. The elasticity of the skin with youth opposes this tension and maintains a smooth appearance. With

age, the elastic fibers decrease in their ability to resist tension, and collagen fibers elongate, decrease in size, and become cross-linked. With damaged collagen and elastin, linear wrinkles form along the attachments of the SMAS to the skin.

Generally these wrinkles, termed skin tension lines (STLs), run perpendicular to the underlying muscle fibers. For example, the STLs of the forehead are horizontal because the frontalis muscle contracts vertically. The skin tension lines of the lateral periocular skin (crow's feet) radiate away from the lateral canthus, as the fibers of the *ocularis oculi* circumferentially wrap from the superior to inferior eyelid. The horizontal wrinkles of the upper eyelid, which at first seem to contradict this principle, lie perpendicular to the axis of the underlying *levator palpebrae superioris*.

In elderly patients with severe damage, the relaxed STLs will be obvious to any observer. However, certain techniques may be utilized to accentuate these lines where the static wrinkles may not be so noticeable. Furrows can be accentuated by asking patients to perform exaggerated facial expressions, such as smiling, frowning, puckering lips, or whistling. Active manipulation of the skin by a gentle pinch or massage may also reproduce the natural folds and tension lines.

STLs may be softened or eliminated by cosmetic injectable treatments. Injectable botulinum toxin targets the dynamic STLs and moderately fine relaxed STLs by blunting the actions of the underlying musculature. However, deeper relaxed STLs, accentuated by the gravitational pull of sun-damaged skin, are better treated by injectable fillers, which replace volume loss.

Correspondence

Dr. Gangaram Hemandas
Prince Court Medical Centre
39, Jalan Kia Peng, 50450 Kuala Lumpur

THERAPEUTICS - Original Article

Efficacy and safety of tacrolimus ointment in patients with moderate to severe atopic dermatitis - Malaysian experience

Ng TG¹, Mardziah A², Roshidah BB³, Heng YH⁴, Najeeb A⁵, Lo Kang SC⁶, Pubalan M⁷, Loh LC⁸, Suraiya HH¹

Abstract

Objectives To evaluate the efficacy and safety of tacrolimus ointment 0.1% in adult and 0.03% in pediatric patients with moderate to severe atopic dermatitis in Malaysia.

Methods This is an open-labeled and single arm multi-center study. 36 adult and 37 pediatric patients were enrolled. Tacrolimus ointment is applied twice daily for four weeks. The primary efficacy outcome is based on the Physician's Global Evaluation of Clinical Response (PG) at Week 4. The secondary efficacy outcomes are Eczema Area and Severity Index (EASI) score, changes from baseline in individual scores of signs and symptoms and body surface area affected and Patients Assessment of Treatment Effects.

Results Overall success rate were 97.1% and 91.2% in the adult and pediatric groups respectively. The decline in EASI, percentage of total BSA affected and patient's assessment of pruritus were significant ($P < 0.001$). Of adults and pediatric patients, 97.2% and 75.7% respectively reported adverse effect. The most common adverse effect reported was skin burning sensation in 91.7% adult patients and pruritus in 67.6% pediatric patients.

Conclusion Tacrolimus ointment 0.1% in adult and 0.03% in pediatric patients is effective for the treatment of moderate to severe atopic dermatitis in Malaysia.

Keywords tacrolimus, atopic dermatitis

Introduction

Atopic dermatitis (AD) is a chronic relapsing, intensely pruritic, inflammatory and immunologically-based skin disease with a genetic predisposition where symptoms are often triggered

by various environmental and psychological factors¹. Tacrolimus ointment is a topical immunomodulator which gives a new therapeutic option for atopic dermatitis patients.

Its mode of action suppresses the activation and proliferation of antigen-specific T-cells. This is an open-labeled, single arm, multi-center study conducted in seven centers in Malaysia. Patients who met entry criteria were given tacrolimus ointment to be applied twice daily on affected areas for four weeks. Pediatric patients (2-15 years old) were given 0.03% tacrolimus ointment and adult patients (> 16 years old) were given 0.1% tacrolimus ointment.

Objectives of study

Primary objective

To evaluate the safety and efficacy of tacrolimus ointment 0.1% in adult and 0.03% in paediatric patients with moderate to severe atopic dermatitis.

Correspondence

Dr Felix Boon Bin, Yap
Department of Dermatology, Kuala Lumpur Hospital
Jalan Pahang, Kuala Lumpur Malaysia
Email : @hottinguanng mail.com
Conflict of interest : Janssen Cilag supported this study

¹Kuala Lumpur Hospital

²Pediatric Institute, Kuala Lumpur Hospital

³Melaka General Hospital

⁴Ipoh General Hospital

⁵Seremban General Hospital

⁶Penang General Hospital

⁷Sarawak General Hospital

⁸University Malaya Medical Center

Secondary objectives

1. To assess improvement in Eczema Area and Severity Index (EASI)
2. To assess patient's assessment of overall response
3. To determine patient's assessment of itch
4. To determine the effect of treatment on quality of life of patients with atopic dermatitis

Patient Selection:

Inclusion criteria

- Patients diagnosed with atopic dermatitis using Hanifin and Rajka criteria and is rated as moderate to severe based on Rajka and Langland criteria
- Body surface area must be at least 10%
- Patient is at least 2 years of age

Exclusion criteria

- Patients having a skin disorder other than atopic dermatitis in the areas to be treated and pigmentation or extensive scarring in the areas to be treated
- Clinically infected atopic dermatitis at baseline

Non-steroidal immunosuppressants (e.g. cyclosporine, methotrexate), light treatments (UVA, UVB) or sun exposure, systemic corticosteroids and other investigational drugs were not allowed for 4 weeks prior to start of study and restricted throughout the study period. Intranasal and/or inhaled corticosteroids, if > 2mg prednisone equivalent /day required were discontinued for at least 2 weeks prior to tacrolimus therapy. Terfenadine and other non-sedating systemic antihistamines were not to be taken 1 week prior to the study. Topical corticosteroids, topical antihistamines and other medicated topical agents were also stopped 1 week prior to the study.

Treatment Plan and Outcome measures:

Patients were evaluated weekly for four weeks.

Primary study endpoint:

- Physician's Global Evaluation of Clinical Response at week 4.
 - Investigators were instructed to use 'cleared' to indicate improvement of 100%, 'excellent' for improvement of 90-99%, 'marked' for 75-89%, 'moderate' for 50-74%, 'slight' for 30-49%, 'no appreciable improvement' for 0-29% and 'worse' for worsening of the condition.

Secondary endpoints

- EASI score
 - EASI is a composite score comprising severity rating of erythema, edema / induration / papulation, excoriations and lichenification weighted according to the estimated percentage of affected body surface (BSA) of each body region. For each body region (head / neck, upper limbs, trunk and lower limbs), an affected area score of 0-6 was assigned for the percentage of affected BSA (0-100%).
- Assessment of Itch
 - Assessment of itch was done by using visual analogue score of scale from 0 to 10.
- Quality of Life assessment
 - Patients were assessed on the quality of life before and at week 4 of study using Finlay Dermatology Life Quality Index. It assessed the physical and psychosocial aspects of the disease state that may affect the patient's functioning. The responses to each survey item ranges from 0 reflecting 'not at all affected' to 3, reflecting 'very much affected'. Category scores are calculated by summing the score of each question corresponding to its category.

Statistical Analysis:

All statistical tests were two-sided with significance level of $\alpha = 0.05$. For efficacy endpoints based on Physician's Global Evaluation of Clinical Response, EASI score, changes from baseline in individual scores of signs and symptoms and the BSA affected and the Patient's Own Assessment of Treatment Effects, the paired t test was used to evaluate. The Wilcoxon signed-rank test was used for nonparametric analyses.

Results

Demographic and Baseline Characteristics:

A total of 73 patients were enrolled from seven separate centers in Malaysia. There were 36 (49.3%) adult patients and 37 (50.7%) pediatric patients. Demographics and baseline characteristics were tabulated. (Table 1)

Treatment efficacy

Primary endpoint

At Week-4, Physician's Global Evaluation of Clinical Response showed that treatment was effective in 34/35 (97.1%) adult patients and 31/34 (91.2%) pediatric patients (Table 2).

Table 1 Demographic and Baseline characteristics

Demographic	Adult (N = 36)	Pediatric (N =37)
Male	19 (52.8%)	21 (56.8%)
Female	17 (47.2%)	16 (45.2%)
Malay	12 (33.3%)	22 (59.5%)
Chinese	22 (61.1%)	12 (32.4%)
Indian	2 (5.6%)	3 (8.1%)
Disease Severity		
Moderate	23 (63.9%)	9 (24.3%)
Severe	13 (36.1%)	28 (75.7%)
Total %BSA affected	32.8 +17.3 (12.5 - 76.0)	52.5 +21.0 (16.4 - 93.1)

Table 2 Physician's Global evaluation of Clinical Response, (p<0.001)

Scores and Rating	Adult (N = 35)	Pediatric (N = 34)
1 = Cleared (100%)	3 (8.6%)	0 (0.0%)
2 = Excellent Improvement (90 - 99%)	13 (37.1%)	8 (23.5%)
3 = Marked Improvement (75 - 89%)	10 (28.6%)	20(58.8%)
4 = Moderate Improvement (50 - 74%)	8 (22.9%)	3 (8.8%)
5 = Slight Improvement (30 - 49%)	1 (2.9%)	3 (8.8%)
6 = No Appreciable Improvement (0 - 29%)	0 (0.0%)	0 (0.0%)

**Response is defined as a rating of better than moderate (50%) improvement*

Secondary endpoints

There was significant improvement in the secondary endpoints. These include EASI score, percentage of body surface area, itch score and patient's assessment of overall response. (Fig 1-3 and Table 3)

Figure 1 Changes in EASI mean score, $p < 0.001$

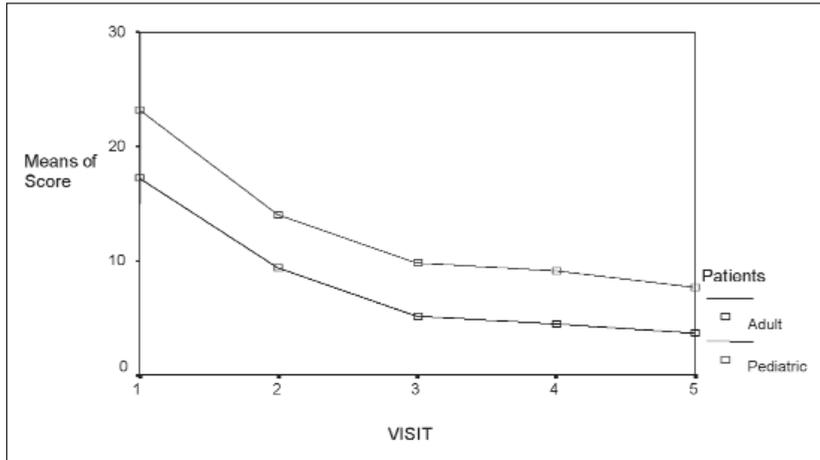


Figure 2 Changes in percentage of body surface area, $p < 0.001$

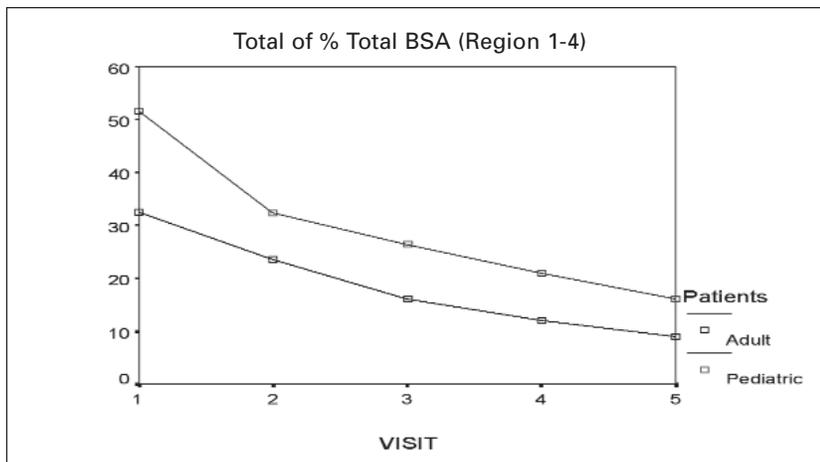


Figure 3 Changes in patient's Itch score, $p < 0.001$

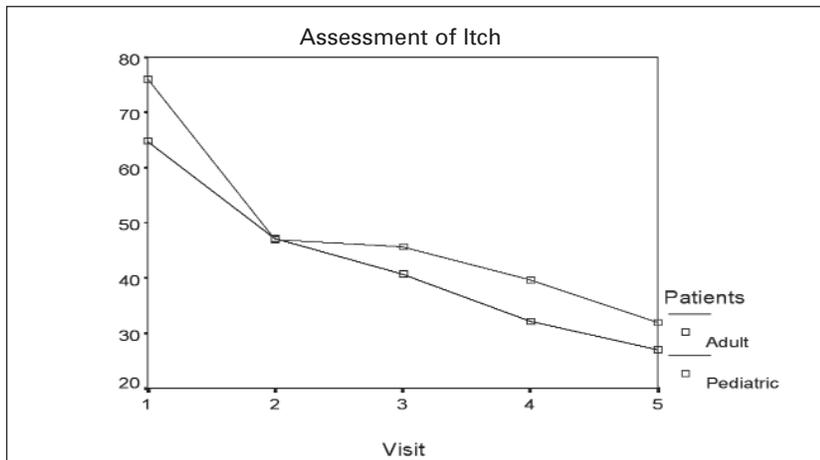


Table 3 Patient's assessment of overall response (p<0.001)

Response	Adult (N = 35)	Pediatric (N = 34)
Much better	20(57.1%)	14(41.2%)
Better	12 (34.3%)	14(41.2%)
Slightly better	2 (5.7%)	5(14.7%)
Same	0(0.0%)	1(2.9%)
Slightly worse	0 (0.0%)	0 (0.0%)
Worse	1 (2.9%)	0 (0.0%)
Much worse	0 (0.0%)	0 (0.0%)

Adverse events

All 73 patients were included in the safety evaluation based on the reported adverse events. In both treatment groups, most of the adverse events were mild in severity. 35 (97.2%) of adult patients and 28 (75.7%) of pediatric patients reported adverse events. Skin burning sensation in 33 (91.7%) of adult patients was the most common adverse events reported. However, these are mild and transient and usually decreasing after 2 to 3 days of application.

Quality of life assessment

All 73 patients in the study reported an improvement in the quality of life after the Week-4 treatment. To illustrate the QoL burden of atopic dermatitis, Figure 5 and 6 show the percentage of patients in adult and pediatric age group respectively at baseline and End of Week 4. They were either very much affected/a lot affected/ a little affected, or not at all affected by their skin disease for each of the survey items.

Table 4 Adverse Events

Event	Adult (N = 35)	Pediatric (N = 34)
All adverse events	35 (97.2%)	28 (75.7%)
Skin burning/Stinging	33 (91.7%)	18 (48.6%)
Pruritus	28 (77.8%)	25 (67.6%)
Skin Erythema	10 (27.8%)	4 (10.8%)
Skin Infection:		
Bacterial	4 (11.0%)	7 (18.9%)
Viral	(0.0%)	1 (2.7%)
Acne	11 (30.6%)	2 (5.4%)
Rash	1 (2.8%)	0 (0.0%)
Others	9 (25.0%)	5 (13.5%)

Figure 5 Adult Quality of life assessment

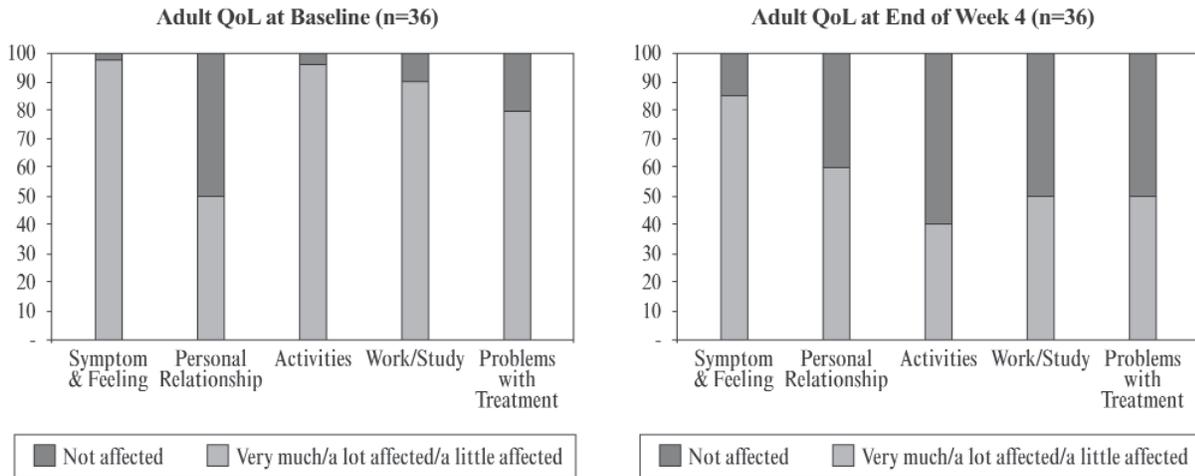
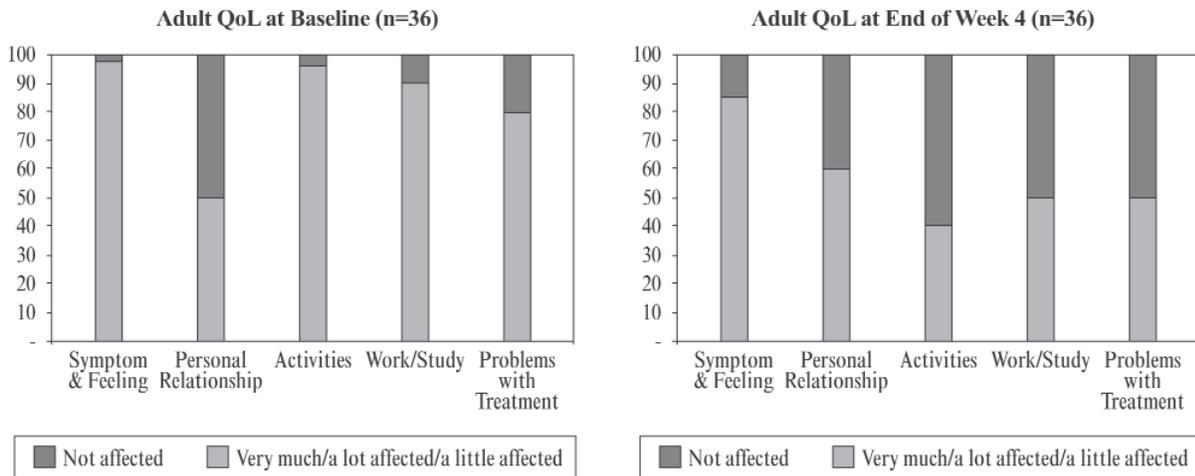


Figure 6 Children Quality of life assessment



Discussion

This report presents the first clinical experience with topical tacrolimus for Atopic Dermatitis (AD) treatment in Malaysia. Our results show that tacrolimus is effective and safe for the treatment of moderate to severe AD in both pediatric and adult patients.

At Week-4, Physician’s Global Evaluation of Clinical Response showed that treatment was successful in 34/35 (97.1%) adult patients and 31/34 (91.2%) pediatric patients. Our pediatric patients had more severe atopic dermatitis with higher mean percentage of body surface area involvement, pediatric (52.5%) and adult (32.8%) and mean EASI score, pediatric (15.6) and adult (11.6). There were significant reductions in

percentage of body surface area involvement and mean EASI score, p value <0.001.

Subjectively, AD patients also appreciated the significant improvement in itch score in both adult and pediatric patients using visual analog scale. The mean itch score had reduced by about 50% after one week of treatment in both groups of patients. Transient mild to moderate skin burning at the site of ointment application occurred more significantly in adult than pediatric patients. The sensation of skin burning usually lasts for about 10 to 20 minutes in the first 2 to 3 days of application. Previous studies have reported the sensation of skin burning last around 10 minutes. For the majority of patients in this study, this discomfort was not sufficient to warrant discontinuation of treatment.

Figure 7 An 18 year adult patient with erythematous, scaly and excoriated patches over his posterior neck and back of knee had marked improvement after 4 weeks of topical tacrolimus



Figure 8 A 2 year old girl with severe erythrodermic atopic dermatitis with excellent improvement after 4 weeks of treatment



Figure 8 A 2 year old girl with severe erythrodermic atopic dermatitis with excellent improvement after 4 weeks of treatment



The heightened local irritation at start of treatment can probably be attributed to the severity of the baseline disease in the patients, and improved later as the lesions healed.

Infections are particular interest with topical treatments containing immunomodulators because of possibility of local immunosuppression. Pediatric patients reported higher incidence of bacterial infections. Only one case of viral infection was reported in pediatric patients. A recent analysis of the data set for 1554 patients with AD treated with tacrolimus ointment in five clinical trials found that there was no increase in the risk of cutaneous bacterial, viral or fungal infections, even with long term treatment.

The Food and Drug Administration (FDA) had included a 'black box warning'. This warning, with associated medication guide, implies that tacrolimus ointment pose a significant risk to our patients over the long term. The black box warnings state that "although a causal relationship has not been established, rare cases of malignancy (e.g. skin and lymphoma), have been reported in patients treated with topical calcineurin inhibitors".

The aim of any treatment is to improve the health and quality of life of the patient. The considerable improvement in the disease symptoms experienced by the tacrolimus treated patients in this study means a substantial improvement in their quality of life. A study conducted in the USA reported significantly better health related quality of life benefits in adult and children with AD who were treated with 0.03% and 0.1% tacrolimus ointment for a period of 12 weeks. Although our study was only done in 4 weeks, it had already showed improvement in patient's QoL benefits in adult and pediatric patients with AD. The QoL benefits were observed across all QoL categories measured, including symptoms, feeling, daily activities, sleep and treatment impact. Patients treated with tacrolimus had attended their school, work and involved in social activities and sports more often. Parents of children with atopic dermatitis treated with tacrolimus ointment had observed their

children's sleep was less affected. Our study showed that tacrolimus ointment 0.03% and 0.1% are effective for the treatment of both pediatric and adult patients respectively. This result are comparable to those previously reported in Europe³, USA^{2,5,6}, Japan⁴ and Taiwan⁷.

Conclusion

This study demonstrated that tacrolimus ointment 0.03% and 0.1% are effective for the treatment of both pediatric and adult patients respectively and associated with significant QoL benefits. The 4 week treatment was tolerable to both adult and pediatric patients. Long term study is needed to establish its long term safety profile. In addition, tacrolimus ointment is available in different concentrations (0.03% and 0.1%). Further study should develop guidelines on how to use this modality in long term for AD.

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THERAPEUTICS - Original Article

A 5-year retrospective study on the outcome of patients with acne vulgaris treated with oral isotretinoin in Ipoh Hospital

Tang JJ, MRCP, Chan LC, MMed, Heng A, MRCP

Abstract

Objective The purpose of this study is to determine the outcome of patients with acne vulgaris treated with oral isotretinoin from January 2003 till January 2008.

Methodology This is a 5-year retrospective study of patients with acne vulgaris who were started on oral isotretinoin from January 2003 to January 2008. Only patients who have completed at least 4 months of treatment were included. Case notes were retrieved and analyzed with regards to demographic data, total cumulative dose of oral isotretinoin, duration of treatment, average daily dose of isotretinoin, response, relapse and subsequent treatment. Patients who defaulted follow-up were contacted via phone to ascertain if they had any relapse. Laboratory data that were analyzed included serial liver enzymes, total cholesterol, triglyceride and LDL levels.

Results A total of 110 case notes were reviewed but only 83 patients fulfilled the inclusion and exclusion criteria. Average daily dose of isotretinoin was 0.24 mg /kg/day and mean duration of treatment was 9.56 months. Mean total accumulated dose of isotretinoin was 61.96 ± 34.15 mg/kg (range from 11.18 mg/kg to 151.79mg/kg). There were only 6 (7.2%) patients who achieved total accumulated dose of more than 120mg/kg/day. All of our patients responded to treatment with 24 (28.9%) of them were in complete clearance. However, a high percentage (71.2%) of patients developed mucocutaneous side-effects out of which 27.7% required dose reduction. Relapse rate among those who completed treatment and follow up or contactable for at least 6 months post treatment was 24.2% (8 out of 33 patients). There were only 3 (3.6%) patients who developed raised transaminases during treatment but all were less than twice the upper normal limit. Mean total cholesterol, triglyceride and LDL level were significantly raised at 4 months of treatment when compared to the baseline ($p < 0.05$).

Conclusion Low dose Isotretinoin (< 0.5 mg/kg) is an effective treatment for moderate to severe acne vulgaris in our population. All of our patients showed good response to isotretinoin even though some of them relapsed subsequently. Intolerability as a result of mucocutaneous side-effects seems to be a challenging issue when starting isotretinoin in our population.

Keywords Acne vulgaris, Isotretinoin, Response rate, Relapse rate, Side-effect, Tolerability, Dosage

Introduction

Acne vulgaris is a chronic, inflammatory disease with a multifactorial aetiology affecting the pilosebaceous units of the skin. It is extremely common with a prevalence of 80-85% among

adolescents which leads to significant physical and psychological impact¹. It has been reported that 44% of patients had clinically significant anxiety whereas 18% had depression as a result of acne vulgaris². Systemic isotretinoin revolutionized the treatment of acne when it was introduced in 1982. It is the most effective sebosuppressive agent that strongly affects all four major pathogenetic factors of acne. The response rate of isotretinoin varies from one centre to another but generally between 85% to 96.7%^{3,4,5,6,7}. Relapse occur in 10-25% of

Correspondence

Dr Agnes Heng, MRCP
Department of Dermatology, Ipoh Hospital
Jalan Pahang, Kuala Lumpur Malaysia
Email: @hot tingguannng mail.com

patients after one isotretinoin cycle, but often shows a mild severity grade and can be controlled with topical therapy alone or combined with oral antibiotics¹. Isotretinoin has always been associated with reports of adverse events ranging from the serious side effect such as teratogenicity to the common mucocutaneous side effect. These side effects generally increase at higher daily dose⁴ and thus tolerability can be a problem when higher dose of isotretinoin is given to patients. Our main objective of this study is to determine the response and relapse rates of our patients with acne vulgaris treated with oral isotretinoin. Secondly we would like to ascertain the side-effects and tolerability of oral isotretinoin in our local population.

Methodology

This is a retrospective study involving patients with acne vulgaris started on oral isotretinoin from January 2003 to January 2008 who had completed at least 4 months of treatment. Case notes were retrieved and analyzed with regards to the following data: age, gender, race, previous treatment, site of acne, indication of isotretinoin, average daily dose of isotretinoin, total cumulative dose of isotretinoin, duration of treatment, response, relapse and time to relapse, subsequent treatment for relapse, side effects, tolerability, liver enzymes and lipid profile. We classified the indication of isotretinoin into 5 groups according to the "Roaccutane treatment guidelines: results of an international survey" by Cunliffe et al^{8,9} as follows: 1) severe/ nodulocystic acne vulgaris 2) acne unresponsive to conventional oral and topical therapies 3) acne patients with marked scarring 4) acne patients with psychological problems such as severe depression or dysmorphophobia 5) unusual acne variants including Gram-negative folliculitis, inflammatory rosacea and rosacea fulminans. All patients were counselled about the side effects of oral Isotretinoin especially regarding teratogenicity and informed consent was obtained prior to treatment. For female with childbearing potential, pre-therapy pregnancy test was done and they must use 2 method of effective contraception during therapy. Response of treatment is classified into 3 categories: 1) complete clearance: total or near total resolution of lesion; 2) partial clearance: significant degree of improvement/clearance; 3) non-responder: insignificant improvement or deterioration of lesion. However, there is difficulty in categorizing them accurately due to the retrospective nature of this study. Relapse is defined as deterioration in acne sufficient to merit systemic therapy (antibiotic or oral isotretinoin). Patients who had stopped treatment and followed-up for at

least 6 months post-treatment will be included for analysis of relapse rate. Patients who defaulted follow-up were contacted via phone or mail to ascertain if they had any relapse i.e. if they had been prescribed systemic therapy for further flares of acne. A patient is considered as non-relapser if acne remained stable for at least 6 months after stopping treatment. Intolerability is defined as inability to tolerate isotretinoin as a result of side-effects which required dose reduction. Analyses of laboratory abnormalities were performed only in patients who had serial alanine aminotransferase (ALT), aspartate aminotransferase, total cholesterol, LDL and triglyceride recordings. These data were analyzed using Student's *t*-test.

Results

A total of 110 patients were started on isotretinoin from January 2003 to January 2008 but only 83 patients completed at least 4 months of treatment. Patient characteristics and clinical data are shown in Table 1. Majority of our patients were Malay (41%) followed by Chinese (37.3%) and Indian (16.9%). Most of the patients were male (68.7%) and the mean age was 19.5 years old (range from 12 to 43 years old). Oral isotretinoin was mainly given as second-line treatment for moderate-severe acne unresponsive to conventional treatment (57.8%). Majority of our patients had acne lesions on the face and trunk (53%) and most of them had been started on at least 1 type of oral antibiotic before isotretinoin (68.2%). Average daily dose of isotretinoin was 0.24 mg/kg/day (Range 0.09 to 0.53) and mean duration of treatment was 9.56 months. Mean total accumulated dose of isotretinoin was 61.96 ± 34.15 mg/kg (range from 11.18 mg/kg to 151.79mg/kg). There were only 6 (7.2%) patients who achieved total accumulated dose of more than 120mg/kg/day. All of our patients (100%) responded to treatment at the end of treatment and 24 (28.9%) of them had complete clearance. The partial clearance group was found to have higher average daily dose (0.24 mg/kg/day) and total accumulated dose (62.25 mg/kg) of oral Isotretinoin as compared to complete clearance group with average daily dose of 0.22 mg/kg/day and total accumulated dose of 61.24mg/kg. Side effect profile was purely analysed based on the records in patient's notes. There was a high percentage (71.2%) of patients who had developed mucocutaneous side-effect and out of this, about 27.7% of them were unable to tolerate the side-effect which required dose reduction despite appropriate preventive measures. The commencement dose among the patients who had intolerability due to mucocutaneous side effect

Table 1 Demographic data

Race	Malay	41.0%
	Chinese	37.3%
	Indian	16.9%
	Others	4.8%
Gender	Male	68.7%
	Female	31.3%
Age	Mean : 19.5 y/o	Range: 12 to 43 y/o
Site of acne	Face	45.8%
	Face+ trunk	53.0%
	Trunk	1.2%
Previous treatment	Antibiotic	68.2%
	Isotretinoin	5.9%
	Nil	25.9%
Indication of isotretinoin	Severe /nodulocystic acne vulgaris	30.1%
	Acne vulgaris unresponsive to conventional treatment	57.8%
	Acne vulgaris with scarring	12.1%
	Acne with psychological distress	0%
	Unusual acne variants	0%

Table 2 Data relating to treatment with isotretinoin

Duration of treatment (month)	Mean : 9.56 ± 4.74	Range: 4 to 27
Average daily dose (mg/kg/day)	Mean : 0.24 ± 0.09	Range: 0.09 to 0.53
Total Accumulated dose (mg/kg)	Mean : 61.96 ± 34.15	Range: 11.18 to 151.79
Response rate	Complete clearance	28.9%
	Partial clearance	71.1%
	Nonresponder	0
Relapse rate	Overall	8 (24.2%)
Time of relapse (months)	Mean : 7.75	Range: 3 to 17
Treatment of Relapse	Antibiotic + Isotretinoin	4 (50%)
	Isotretinoin	4 (50%)

Table 3 Side effect profile

Mucocutaneous side-effects			
1. Cheilitis		65.5%	
2. Dry skin		4.6%	
3. Bleeding nose		1.1%	
4. Nil		28.7%	
Lipid Profile	Mean Pre Rx	Mean Post Rx	p value (student t test)
Total cholesterol	4.23	4.57	p<0.05
Triglyceride	0.92	1.28	p<0.05
LDL	2.71	2.93	p<0.05

ranged from 0.25 to 0.48 mg/kg. The mean daily dose of oral Isotretinoin among patients who developed mucocutaneous side effect was 0.24 mg/kg/day whereas it was 0.22 mg/kg/day among patients without mucocutaneous side effect ($p < 0.05$). Eighteen patients defaulted follow-up and were not contactable after completing 4 months of treatment. Thirty-two patients were still taking isotretinoin at the time this study was conducted. These 2 groups of patients were excluded from analysis of relapse rate. As for the remaining 33 patients who completed treatment and followed-up or contactable for at least 6 months post treatment, 8 (24.2%) of them developed a relapse after isotretinoin was stopped. We were unable to ascertain the correlation between total accumulated dose and relapse rate as the sample size was too small. The mean time to relapse from the time of cessation of isotretinoin was about 7.75 months (range from 3 months to 17 months). Treatment option for relapse was decided by the treating dermatologist based on severity of lesion. 4 of them were given systemic antibiotic initially but unfortunately they failed to respond and were put back on oral Isotretinoin. The remaining 4 were put on a second course of isotretinoin from beginning of relapse. There were only 3 (3.6%) patients who developed raised transaminases during treatment but all were less than twice the upper normal limit. On the other hand, the mean total cholesterol, triglyceride and LDL level were significantly raised at 4 months of treatment when compared to the baseline ($p < 0.05$). There were 35 (42.2%) patients with raised total cholesterol, 34 (40.9%) with raised triglyceride and 32 (38.5%) with raised LDL level of various range following treatment with oral Isotretinoin.

Discussion

Oral isotretinoin is currently the most effective acne treatment available, with reported long-term remission rates as high as 70-89%⁶. It has been traditionally used as a first line treatment for severe (nodulocystic, conglobata) acne vulgaris. Over the recent years, dermatologists have increasingly used oral isotretinoin to treat acne not responding to combination topical therapy and systemic antibiotics. In 2003, European Directive was launched to harmonize the treatment of acne vulgaris with isotretinoin in European countries. The new recommendations suggest isotretinoin should only be used as second-line treatment for severe (nodular, conglobate) acne and acne not responding to an appropriate combination treatment by a systemic antibiotic and topical therapy¹⁰. The inference of this being that it should now not be used at all as first-line therapy. The recommended

commencement dose of isotretinoin therapy is 0.5mg/kg with titration up to 1 mg/kg depending on individual response and side-effects. A single 4 to 6 months treatment course is adequate and it should ideally reach a cumulative dose between 120 and 150 mg/kg to reduce relapse rates¹. This recommended dosage is relatively high and was chosen to reduce the time of treatment in view of the isotretinoin associated teratogenicity⁴. It has been recommended that lower doses less than 0.5 mg/kg are also clinically effective but resolution may take longer¹.

In our study, the mean daily dose of isotretinoin was only 0.24 mg/kg/day which was much lower than the recommended dose. However our mean duration of treatment (9.56 months) was longer than the recommended regime. There was a wide variation in average daily dose (range 0.09 to 0.53mg/kg/day) in our study due to lack of standardization with dose regime of Isotretinoin in our centre. Despite using a lower dosage with longer duration, our overall response rate was 100% which is comparable with 96.6% reported by Ng *et al* (mean daily dose of 0.64 mg/kg/day) from Singapore³. Our response rate was also higher than the meta-analysis by Wessels *F et al* which reviewed 84.22% to 86.71%⁷. In view of retrospective in nature, there was interobserver variation in the method of treatment response assessment. However to our surprise, the partial clearance group was found to have higher average daily dose and total accumulated dose of oral Isotretinoin as compared to complete clearance group. This may be because the partial clearance group had more severe acne lesion as compared to complete clearance group and thus required higher dose to control the lesions.

Low-dose protocols (<0.5 mg/kg/day) and intermittent protocols have been used by many authors in recent years especially for moderate or mild acne with promising response rate ranging from 69% to 94.8%^{11,12,13,14}. The main reason for using these low dose regime was to reduce side-effects and improve tolerability of isotretinoin while still inducing sebum suppression^{11,12,13,14}. Low dose regime can be associated with a higher relapse rate if the cumulative dose of 120 to 150 mg/kg is not reached¹. Other factors linked with relapse are younger age (less than 25 years at the beginning of therapy), female sex, truncal acne and acne with less than nodular lesions¹. Our mean total accumulated dose was only 61.96 mg/kg which is much lower than the recommended cumulative dose and in fact there were only 7.2% patients who achieved total accumulated dose of more than 120mg/kg. Despite not achieving the target

cumulative dose, our relapse rate (24.2%) is lower than 47.4% by Ng *et al* (Singapore)³ and 39% by Layton AM *et al* (UK)⁶ who had achieved higher total cumulative dose than ours. On the other hand, our relapse rate was comparable with the studies using low dose and intermittent protocol which range between 9.8% to 39%^{11,12,13,14}.

The most serious side-effect is teratogenicity. All women of child-bearing potential must be coupled to a pregnancy prevention program that requires the use of 2 effective contraceptive methods and the monitoring for pregnancy before, during, and after therapy¹⁵. Mucocutaneous side-effects including dry chapped lip, dry skin and dry eyes are the most common side effect and are experienced by virtually all patients¹. Patients who experience severe mucocutaneous adverse effects should have their dose regime reduced as the majority of these side-effects are dose dependant¹⁶. There was a high percentage of patients (27.7%) who could not tolerate isotretinoin and required dose reduction due to mucocutaneous side-effects. We were unable to classify the severity of each mucocutaneous side-effect due to the retrospective nature of this study. From this result we could infer that intolerability due to mucocutaneous side-effects was rather significant among our population as compared to other studies which reported that these side-effects are generally manageable⁸. Hypertriglyceridemia, hypercholesterolemia, and elevated liver enzymes occurred in 15-25% of patients but were rarely of clinical significance or severe enough to require dose reduction or discontinuation of treatment¹⁶. Lipids rapidly dropped to pre-treatment levels after cessation of therapy¹⁶. Our study suggested that there was no significant increment of liver enzymes as a result of isotretinoin. This might be due to low dose regime used in our population. However the total cholesterol, LDL and triglyceride were significantly raised following treatment with isotretinoin. It is therefore important to monitor fasting lipid profile during the treatment with isotretinoin.

Conclusion

Low dose isotretinoin (<0.5mg/kg) is an effective treatment for moderate to severe acne vulgaris in our population. All of our patients showed good response to isotretinoin even though some of them relapsed subsequently. Intolerability as a result of mucocutaneous side-effects was a significant problem when commencing isotretinoin in our population. There are limitations to our study which included small sample size for analysis of relapse rate and the retrospective nature that made analysis of certain data difficult. We suggest a well-designed prospective study in future to further evaluate the

efficacy of low dose isotretinoin and relationship with relapse rate in treating acne vulgaris.

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THERAPEUTICS - Short Communication

Penicillin-treated plaque psoriasis: Report of 2 cases from Taiwan

Ang XX and Wong SM, MRCP

Dear Editor,

We report two cases of plaque psoriasis which were successfully treated with penicillin.

Case 1

A 63-year-old Chinese lady attended Tzu Chi Hospital, Taiwan in December 2008 with multiple itchy erythematous skin lesions over her back, chest, abdomen, buttocks, bilateral plantar of foot and limbs for 10 years. She was diagnosed to have psoriasis by a dermatologist and was prescribed with long term topical steroids with no significant improvement and frequent relapses. After the conventional treatment failed, she decided to seek another doctor's opinion and subsequently she came to Tzu Chi Hospital.

On examination, there were multiple diffuse silvery scales over her back, chest, abdomen, buttocks and extremities (Figure 1).

Figure 1 A 63-year-old lady with erythematous plaques on the sole



A skin biopsy was done and histopathology confirmed the diagnosis of psoriasis. Her condition affected her physically and emotionally. After obtaining consent, she was admitted and started on parenteral benzylpenicillin 3 million units 6 hourly.

Correspondence

S M Wong, MRCP
Dermatology unit, Department of Medicine
University Malaya Medical Center, Kuala Lumpur
E-mail : smwong@um.edu.my

Ang XX, Medical student
MBBS, University Malaya, Kuala Lumpur

She tolerated the therapy well and her skin condition improved after 2 weeks of therapy. She was subsequently discharged and followed up in skin clinic.

Case 2

A 57-year-old Chinese lady visited Tzu Chi Hospital with a background history of psoriasis for the past 7 years. Initially it affected her back and elbows, extending to the legs gradually. Over the years, her psoriasis was relatively well-controlled with topical corticosteroid treatment. However, her condition worsened over the past few months with increasing plaques which were itchy.

On examination, psoriatic plaques were noted over the whole body sparing the face, palms and soles.

Figure 2 Progression of psoriatic plaque on the forearm after penicillin therapy



Initial lesion



6 days after treatment



10 days after treatment

Figure 3 The back

(A) Before treatment



(B) 10 days after treatment



As she was keen to try on penicillin, she was admitted and started on parenteral benzylpenicillin 3 million units 4 hourly. She showed excellent improvement after 10 days of treatment and was subsequently discharged (Figure 2 and 3).

Discussion

In acute inflammatory or exanthematic psoriasis, scaling can be minimal and erythema may be the predominant clinical sign.

Chronic plaque psoriasis affects approximately 2 percent of the world's population and may result in disability similar to or exceeding that associated with other major illnesses, such as diabetes mellitus, arthritis, depression, and cancer².

There is a strong relationship between guttate psoriasis and streptococcus; either a preceding or concurrent infection³. Some authorities have claimed that chronic plaque psoriasis may worsen by infection. There is some evidence that streptococcal infection also plays a role in the pathogenesis of chronic plaque psoriasis¹. It is postulated that the streptococcus carries a protein called the M-protein, which acts as a superantigen. Superantigens are bacterial or viral products that can stimulate T cells to proliferate without prior intracellular processing by an antigen-presenting cell. This leads to polyclonal T-cell activation with release of immune cytokines such as interleukin-2, which are important in the pathogenesis of psoriasis. The hypothesis is further supported by the experiment where uninvolved skin from psoriasis patients grafted on to severe combined immune-deficient mice will develop psoriasis when injected with autologous superantigen-treated leukocytes⁴.

Often times, the use of systemic therapies are limited by their toxic effects and cost. The unmet need for safe and effective therapies, coupled with an improved understanding of the pathogenesis of psoriasis, has prompted clinicians to use other alternative treatment. The usage of penicillin in plaque psoriasis is based on the postulation that a continuing sub-clinical streptococcal infection might be responsible for chronic plaque psoriasis. Treatment with benzathine penicillin 1.2

million units intramuscularly fortnightly for 24 weeks, followed by maintenance dose of 1.2 million units monthly showed excellent improvement at two years⁵. In addition, throat carriage of *Streptococcus pyogenes* is common in patients with chronic plaque psoriasis. In our case, both patients showed good respond to the usage of penicillin.

However, a literature review by Cochrane stated that two controlled trials of antistreptococcal interventions, which involved the use of phenoxymethylpenicillin or erythromycin with or without additional rifampicin revealed no clinical improvement of psoriasis in either treatment group throughout the study⁶.

In conclusion, plaque psoriasis is a chronic problem with high morbidity and significant psychosocial impact on an individual. Although the two reported patients showed significant improvement after treatment with penicillin, further well designed, randomized controlled trials are needed to establish if there is any place for antibiotic therapy in patients with plaque psoriasis.

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Quiz

Dermatology Care Plan Quiz for nurses

State the nursing care plan required by each patient.

e.g.

Nursing problem	Nursing intervention	Expected Outcome	Comment
Weeping lesion	Wet wrap with astringent solution regularly	Dry scaly lesion	Stop using astringent when lesions are dry

Slide A Patient has angioedema following penicillin ingestion. He had contact pustular reaction following calamine lotion application



Slide B Patient has toe web candidiasis



Answer is given on page 70

NURSING - Short Communications

Nursing challenges in a teenager with pemphigus vulgaris and toxic epidermal necrolysis

Hazfaneza AH¹, Kasmahwati T², Norradiah J², Norhasmie R²

Dear Editor,

We would like to share with you the nursing challenges faced by nurses while nursing a 17-year old teenager with pemphigus vulgaris initially involving about 20% of cutaneous surface area but later progressed to TEN-like lesions on the second week of admission.

On examination, patient was in a flexed posture and her range of movements were limited due to stiffness and pain. There were large erosions on the back covered with haemorrhagic and serous crust with scattered flaccid blisters and crusted erosions on the face, periorbital, perioral, arms, abdomen, thighs and involvement of all mucosal surfaces. Her pain score was 10 on a visual pain score chart.

She was commenced on systemic steroids (prednisolone 1mg/kg/day) and oral cloxacillin for secondary impetigo. Azathioprine was added on the fourth day of admission when the lesions continued to evolve. Cloxacillin was suspected to have contributed to TEN and was withheld.

She was subsequently transferred to the burns unit and intravenous (IV) immunoglobulin (0.4mg/kg/day) was started and completed for four days. Her response was partial with persistence of 6% of scattered raw erosions. Currently, she requires high dose oral steroid (1.5g/kg per day), azathioprine (2mg/kg/day) and oral doxycycline (100mg twice a day) to induce remission.

Correspondence

Dr Hazfaneza Ab Halim

¹Department of Dermatology

Selayang Hospital, Selangor, Malaysia

Email :

²Dermatology Nurses, Selayang Hospital

Nursing management

Supportive and nursing care is an important but often underreported therapeutic intervention in pemphigus.

There were several specific issues that need to be dealt with specifically in this patient, namely: pain control, wound dressing, infection control, diet, physiotherapy as well as the psychosocial aspect.

Pain

This is a major problem while managing the patient because of the extensive area of cutaneous involvement which appears to be directly proportional to her pain score. Her pain was assessed every four hours with a visual pain score chart. Pain score during skin nursing was 9/10 despite oral paracetamol (1g four times per day) and oral tramadol (50mg thrice a day). Oral tramadol was increased to 100mg thrice a day and IV fentanyl (50mcg, 10 minutes before dressing) was added. However, the latter was withheld due to the pain associated with administration. Patient-controlled analgesia (PCA) morphine was then started with better results i.e. her pain score improved to 5/10 during wound dressing. As her skin condition recovered, her pain was adequately controlled with non-narcotic analgesia.

Besides medications, another technique to minimize the pain during wound dressing involved planning and organizing dressing and nursing care materials prior to exposing the wound so as to shorten the dressing time. Also, distractions such as story-telling, music-listening and TV watching were helpful in a young patient such as her.

Dressing

Dressing is a very important part of the management of pemphigus. The ideal dressing would be able to keep tissue moisture in while allowing enough oxygen to penetrate it and maintaining the integrity of reepithelization. Also, in view of the denuded skin, thermoregulation is

compromised. Therefore, the challenge here is finding the right dressing, using the right dressing technique as well as keeping the patient warm and comfortable during the dressing procedure.

This patient was dressed in 3 layers: Vaseline netted-gauze, sterile gauze and gamgee from the inner to the outer layer. Dressings are changed three times a day preceded by potassium permanganate 5% diluted 1:10,000 bath for the first two weeks until lesions are drier. In view of the frequency of dressings, silicon based dressings was not used due to cost factors.

During the dressing procedures, adequate analgesia was prescribed as mentioned, and care was taken to remove the dressing gently while avoiding inadvertent removal of reepithelised skin. This is possible with the use of Vaseline netted- gauze and the use of warmed distilled water to soak the gauze before removing it.

Bath and solutions used are warmed before use and room temperature was increased while dressing or bathing is performed. These procedures are also done in parts to allow only body area for dressing to be exposed while other areas are covered with warm blankets. Attention is also given to ensure doors and windows are closed during dressing. She was placed in a single room with an attached bath to facilitate her intensive dressing regime.

Other specific dressing techniques are as follows: Normal saline wash for the face three times per day. To remove the crusted lesions, Vaseline was applied to it 20 minutes before wash to soften it. The hair was washed with 2% cetrimide shampoo once daily. Frequent normal saline eyes toileting was performed following by local application of chloramphenicol ointment at periorbital areas. Genitals are washed with diluted potassium permanganate every two hours and with every urination until the erosions dried up.



Figure 1 Crusted Haemorrhagic lesion



Figure 2 TEN-like



Figure 3 Apparent fixed flexion on the neck on admission. Lower limbus seen

Infection control

Our patient was assessed regularly for signs of infection such as increased pain or tenderness, swelling, erythema, warmth or temperature for early detection and control of infection. For infection prevention, she was put in reverse isolation with strict aseptic technique during dressing or any form of contact. Contact with visitors is restricted with the same strict aseptic rules. Blisters are prophylactically aspirated not only to reduce pain, but also to preserve the roof of the blisters which acts as a barrier to infection.

Diet

Adequate diet in our patient posed a challenge as she had low intake due to pain from her oral ulcers and higher output of fluids and albumin due to significant area of erosions. To reduce pain during eating, she was given systemic analgesics as well as local analgesics such as viscous lignocaine. She was also prescribed triamcinolone in orabase to reduce oral inflammation. Concomitant oral thrush was treated with syrup nystatin (500,000 unit four times per day).

She was initially given liquid diet as it is better tolerated and supplemented with high caloric and protein liquid. Her diet was closely supervised by the attending dietician and her weight was monitored on a daily basis.

Physiotherapy

Early assistant from Physiotherapist was required in relieving patient's torticollis (neck stiffness) and joint stiffness due to prolonged immobilisation at home. Immediate care with physiotherapist had resulted in marked improvement in this patient. She was able to ambulate slowly from bed to the toilet with assistant from the nurse and family members on the first day of admission. Passive and active limb and joint movement was introduced.

Subsequently, she was able to fully flex and extend the neck on 3rd day, rotate the neck at 45 degrees and sit on the chair on the 4th day, Ambulate to the toilet independently on the day 5th day and stand, rotate in standing position on the 10th day of admission. She is able to balance herself on standing. She had been encouraged to walk around in the room. At present, she has no limited joint movement and able to move freely.

Psychosocial

The most important psychosocial issue in our patient was dealing with the psychological impact of having a disfiguring disease. She was suffering from low self-esteem and in this situation, family and friends support was imperative.

Patient and family education cannot be stressed enough especially because of the chronic nature of the disease. They were also educated on the disease, medications and their adverse effects and wound care which was communicated in simple understandable terms.

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ANNOUNCEMENT - Administrative Update

Guidelines for diagnosis of occupational skin disease and its compensation

Mohammed AAM, LFOMRCP, Zainul AMH, M SC (OM)

Social Security Organisation (SOCSO), Malaysia provides benefits to its 5 million workers under the Employee Social Security Act 1989 for loss of earning capacity. The employment injury scheme covers loss of earnings due to occupational injury and diseases including skin diseases. The invalidity scheme provides coverage for loss of earnings due to whatever reasons.

The Medical and Rehabilitation Department, SOCSO with the cooperation of occupational health and medicine experts produced the Guidelines on the Diagnosis of Occupational Diseases 2007. Chapter 14 (pages 108 -122) is on Occupational Skin Diseases. The objective is to assist medical professionals concerned with occupational skin diseases to conduct more objective occupational and medical history taking, clinical examinations and investigations (general, specific and confirmatory).

For diagnostic purposes the skin patch test is ideal. However if it cannot be performed due to certain reasons, especially among the small and medium scale industries, an acceptable alternative is to provide photos of working conditions showing evidence of significant exposure to the skin disease causing agents.

The Guidelines are essential to determine if the risk factors in the workplace caused the skin disease as well as to exclude other non-workplace factors e.g. environmental, hereditary, lifestyle or other factors. All these have been specified in the prescribed form

for application of occupational disease which has to be filled in by the Occupational Health Doctor after conducting a walk-through survey. A supporting confirmatory report from a dermatologist is also required.

The risk factors identified during the course of investigations are emphasized during the preventive programme for occupational skin disease. This Guidelines is important to the independent medical board and appellate medical board members who will finally decide on whether disease is due to occupation or not and subsequently determine the impairment rating.

Under the Occupational Safety and Health (OSH), Regulations 1996 workplaces with more than 40 workers must have a Safety & Health Committee to carry out the hazard identification, risk assessment, control and investigations. Under the OSH Regulations 1997, the Chemical Safety Data Sheet produced by the manufacturer must include 16 items including the toxicology of the chemical and if it can be absorbed through the skin, it must have the 'skin' notation. For chemicals that cause skin disease, the personal Permissible Exposure Limit (PEL) is spelled out in the OSH, 2000. These PELs are adopted from the American Congress of Government Industrial Hygienist publications. The health and skin effects of chemicals must be conducted according to Assessment of the Health Risks Arising from the Use Hazardous Chemicals in the Workplace 2000.

Correspondence

Dr Zainul Abidin Md Hussain
Medical and Rehabilitation Department
10th Floor, Menara PERKESO
281, Jalan Ampang, 50538 Kuala Lumpur, Malaysia
Email : drzainul@perkeso.gov.my

In Malaysia compensation for occupational skin disease is in accordance with The Guidelines on Impairment and Disability Assessment of Traumatic Injuries, Occupational Diseases and Invalidity, SOCSO 2006 as in Table 1

Table 1 SOCSO 2006 Criteria for Rating Permanent Impairment Due to Skin Disorders

Class 1 0% - 11% Whole Person Impairment	Class 2 12% - 29% Whole Person Impairment	Class 3 30% - 65% Whole Person Impairment	Class 4 66% - 84% Whole Person Impairment	Class 4 85% - 100% Whole Person Impairment
Skin disorder signs and symptoms present or intermittently present	Skin disorder signs and symptoms present or intermittently present	Skin disorder signs and symptoms present or intermittently present	Skin disorder signs and symptoms constantly present	Skin disorder signs and symptoms constantly present
and	and	and	and	and
Few limitations in performance of activities of daily living	Limited performance of some activities of daily living	Limited performance of many activities of daily living	Limited performance of many activities of daily living, including intermittent confinement at home or other domicile	Limited performance of most activities of occasional to constant confinement at home or other domicile
Exposure to certain chemical or physical agents may temporarily increase limitation	and may require intermittent to constant treatment	and may require intermittent to constant treatment	and may require intermittent to constant treatment	and may require intermittent to constant treatment
and				
Requires no or intermittent treatment				

Answers to Clinical Diagnostic Skill Test

Slide A	<ul style="list-style-type: none"> <input type="checkbox"/> -2 bacterial infection <input type="checkbox"/> -2 viral infection <input type="checkbox"/> -2 fungal infection <input type="checkbox"/> 1 dermatitis <input type="checkbox"/> 1 non-infectious disease <input type="checkbox"/> -2 impetigo <input type="checkbox"/> -2 tinea capitis <input type="checkbox"/> 2 contact allergy <input type="checkbox"/> 1 psoriasis <input type="checkbox"/> -2 seborrhoeic capitis 	<p>This infant has scalp psoriasis but develop contact dermatitis to hair care lotion. Topical steroid would have cleared the lesion. Failing to suspect contact dermatitis and stopping the contact allergen may result in patient having recurrent contact dermatitis.</p>
Slide B	<ul style="list-style-type: none"> <input type="checkbox"/> 1 bacterial infection <input type="checkbox"/> 2 viral infection <input type="checkbox"/> -2 fungal infection <input type="checkbox"/> -1 dermatitis <input type="checkbox"/> -2 non-infectious disease <input type="checkbox"/> 1 pustules <input type="checkbox"/> -2 tinea capitis <input type="checkbox"/> 2 eczema herpeticum <input type="checkbox"/> 0 psoriasis <input type="checkbox"/> 1 seborrhoeic capitis 	<p>This infant has seborrhoeic capitis complicated by eczema herpeticum. The latter is recognized by the numerous monomorphic small round superficial ulcers with secondary crusting. Failing to recognize this viral infection and continuing topical steroid may result in persistent and worsening of the herpes infection.</p>
Slide C	<ul style="list-style-type: none"> <input type="checkbox"/> 0 bacterial infection <input type="checkbox"/> 0 viral infection <input type="checkbox"/> 0 fungal infection <input type="checkbox"/> 2 dermatitis <input type="checkbox"/> 0 autoimmune disease <input type="checkbox"/> 0 skin scalding syndrome <input type="checkbox"/> 0 Chickenpox <input type="checkbox"/> 0 SLE <input type="checkbox"/> 0 dermatomyositis <input type="checkbox"/> 2 seborrhoeic dermatitis 	<p>This infant has seborrhoeic dermatitis on the face with accentuation of shiny, dry and erythematous skin on the periorbital, nasolabial fold and perioral areas when crying.</p>
Slide D	<ul style="list-style-type: none"> <input type="checkbox"/> 1 bacterial infection <input type="checkbox"/> -2 viral infection <input type="checkbox"/> 0 fungal infection <input type="checkbox"/> 0 dermatitis <input type="checkbox"/> 0 autoimmune disease <input type="checkbox"/> 2 skin scalding syndrome <input type="checkbox"/> -2 chickenpox <input type="checkbox"/> -1 SLE <input type="checkbox"/> -1 dermatomyositis <input type="checkbox"/> -1 seborrhoeic dermatitis 	<p>Note the sign of impetiginous skin - golden crust and scales radiating from the corner of the mouth and lateral canthus. Similar lesion is seen at the neck. The patient appears erythematous because of the underlying toxemia. This patient has skin scalding syndrome which needed prompt antibiotic therapy. Delay in diagnosis worsen morbidity and may be fatal.</p>

Slide E	<input type="checkbox"/> -2	non-infective inflammation	This gentleman has atrophied skin noted on the trunk which tears and bruise easily. He is suspected of having drug induce skin atrophy and ecchymoses. He admitted to chronic consumption of Chinese medication which is probably contain steroid taken to relieve his joint pain.
	<input type="checkbox"/> -2	ADR	
	<input type="checkbox"/> -2	fungal infection	
	<input type="checkbox"/> 1	viral infection	
	<input type="checkbox"/> 1	contact dermatitis	
	<input type="checkbox"/> -2	skin atrophy	
	<input type="checkbox"/> -2	ecchymoses	
	<input type="checkbox"/> 2	tinea corporis	
	<input type="checkbox"/> 1	candidiasis	
<input type="checkbox"/> -2	erythroderma		
Slide F	<input type="checkbox"/> 1	non-infective inflammation	Patient has erythroderma in which the cause may be the result of drug reaction, internal malignancy, uncontrolled dermatitis or psoriasis.
	<input type="checkbox"/> 1	ADR	
	<input type="checkbox"/> -2	fungal infection	
	<input type="checkbox"/> -2	viral infection	
	<input type="checkbox"/> 1	contact dermatitis	
	<input type="checkbox"/> -2	dengue	
	<input type="checkbox"/> 1	viral exanthem	
	<input type="checkbox"/> -2	tinea corporis	
	<input type="checkbox"/> -2	candidiasis	
<input type="checkbox"/> -2	erythroderma		
Slide G	<input type="checkbox"/> -2	non-infective inflammation	This patient has cushingoid features - truncal obesity, thin limbs and buffalo hump. Thus it is not surprising that she has extensive tinea corporis as shown by the annular rash with well define red scaly edge and central erythema which is non-homogenous.
	<input type="checkbox"/> -1	ADR	
	<input type="checkbox"/> 1	fungal infection	
	<input type="checkbox"/> -2	viral infection	
	<input type="checkbox"/> -1	contact dermatitis	
	<input type="checkbox"/> -2	skin atrophy	
	<input type="checkbox"/> -2	ecchymoses	
	<input type="checkbox"/> 2	tinea corporis	
	<input type="checkbox"/> 0	candidiasis	
<input type="checkbox"/> -1	erythroderma		

Sum up the number of score 2, 1, 0, -1, -2 and -3 that you have collected.

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

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

Answers to Dermatology Care Plan Quiz

Slide A

Nursing problem	Nursing intervention	Expected Outcome	Comment
Anioedema	Antihistamine Avoid urticariogenic food Advice patient on urticaria preventive measures Issue allergy card	No more periorbital swelling	On discharge, reeducate patient regarding his allergy.
Pustular lesion	Wet wrap with astringent solution regularly	Dry scaly lesion	Stop using astringent when lesions are dry and scaly. On discharge, reeducate patient regarding his allergy.
Dry scaly skin	Moisturising soap	Moist non-scaly skin	Stop moisturizing soap when skin normalise

Slide B

Nursing problem	Nursing intervention	Expected Outcome	Comment
Macerated toe web	Paint toe web with astringent solution Use toe spacer to aerate toe webs	Dry scaly toe webs	Stop astringent solution once skin dries up
Dry scaly toe webs	Apply antifungal cream	Normal skin	Stop using antifungal cream 2 weeks after skin normalised