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Highlights

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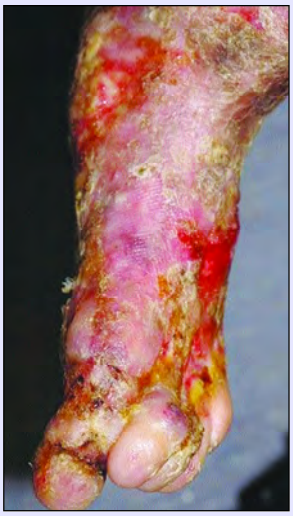

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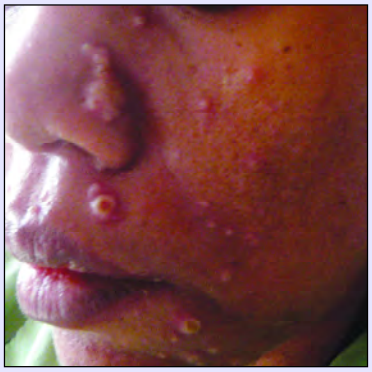

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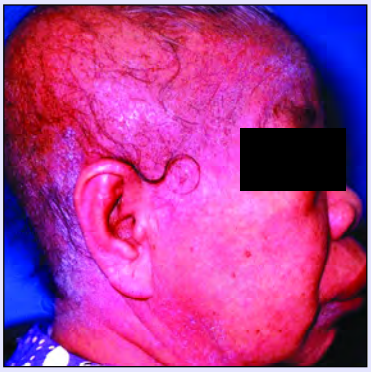

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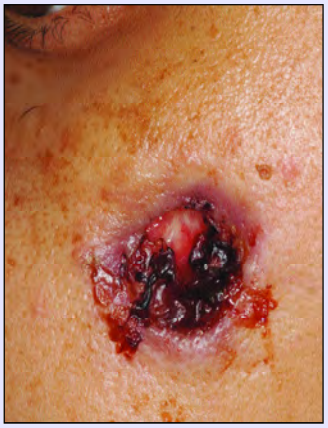

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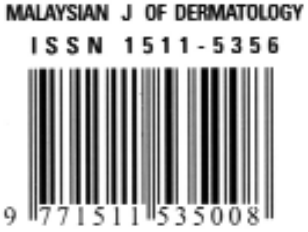

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Contributions should be written for one of the following categories:

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A report of 400-600 words, illustrated by no more than three illustrations. This category offers a means for rapid communication about a single subject.

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All measurements should be according to the metric system. If confusion could result, please include other measurement systems in parentheses.

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

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

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Abstract submission deadlines for Free papers: 31 October 2010

DERMATOLOGY THERAPEUTICS - Original Article

Local experience on the use of Methotrexate in the treatment of Psoriasis in Hospital Sultanah Aminah, Johor Bahru

Chong YT[1], *MRCP*, Tey KE[2], *MRCP*, Choon SE[2], *FRCP*

Abstract

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

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

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

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

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

Keywords *Methotrexate, psoriasis, side effects*

Introduction

Methotrexate has been used for the treatment of psoriasis for the past 50 years. Its use predates the age of randomized clinical trials. Recommended starting dose used to be between 0.2-0.4 mg/kg body weight[22]. However, high-quality data concerning its efficacy and side effects are sparse[20]. Most guidelines have recommended starting methotrexate at doses of 5.0 to 7.5 mg/week, after a test dose of 2.5-5.0 mg[8,11]. Nevertheless, differences were reported among dermatologists in their prescribing and monitoring practices[20], in particular

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the dosing regimen, as well as a broad range of maximum weekly doses from 5 to 70mg weekly. In Hospital Sultanah Aminah, Johor Bharu, methotrexate is initiated at a starting dose of 0.3mg/kg body weight weekly. It is continued until significant clinical response before being tapered to the lowest maintenance dose.

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

Materials and methods

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

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

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

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

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

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

The data were analyzed using SPSS® Version 12.0.

Results

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

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

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

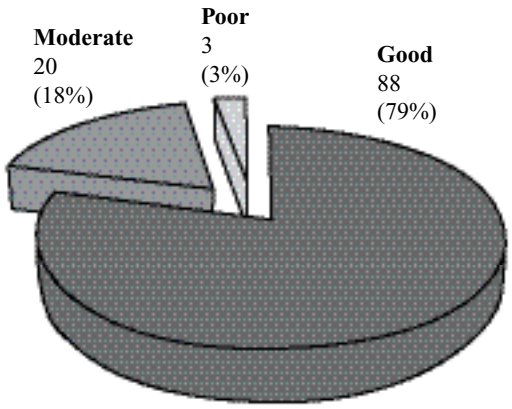
Table 1 Patient demographics and baseline clinical characteristics

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

Table 2 Patients' treatment profile

Characteristics	N=111
Prior treatment	
None	64 (57.7%)
Phototherapy	22 (19.8%)
Retinoids	16 (14.4%)
Methotrexate	15 (13.5%)
Sulphasalazine	4 (3.6%)
Cyclosporin	8 (7.2%)
Indication for methotrexate	
Moderate to severe psoriasis	86 (77.5%)
Psoriatic arthropathy	8 (7.2%)
Both	17 (15.3%)
Body weight	Mean 66 kg, range (39-103 kg)
Initial dose	
25 mg/week	7 (6.3%)
20 mg/week	62 (55.9%)
15 mg/week	42 (37.8%)
Maintenance dose	
20 mg/week	5 (4.5%)
15 mg/week	17 (15.3%)
12.5 mg/week	20 (18.0%)
10 mg/week	23 (20.7%)
7.5 mg/week	30 (27.0%)
5 mg/week	16 (14.4%)

Figure 1 Clinical response



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

Table 3 Adverse events

Characteristics	N=111
Adverse event within 6 months	
None	89 (80.2%)
Bone marrow suppression	4 (3.6%)
Raised liver enzymes	14 (12.6%)
Gastro-intestinal symptoms	3 (2.7%)
Headache	1 (0.9%)
Severity	
Mild	7 (6.3%)
Moderate	15 (13.5%)
Severe	0 (0%)
Reason for stopping	
Adverse event	17 (15.3%)
No response	10 (9%)
Remission	12 (10.8%)
Exceeded recommended cumulative dose	2 (1.8%)
Default	20 (18%)
Patient's wish	4 (3.6%)
Planned pregnancy	1 (0.9%)
Still on	45 (40.5%)

Discussion and conclusion

For more than 50 years, ever since the discovery of the beneficial effects of folic acid antagonist aminopterin by Gubner in 1951 and the introduction of methotrexate treatment by Edmundson and Guy in 1958, the use of methotrexate in psoriasis has undergone few changes with regards to its regimens and dosing[23].

The initial schedule reported by Rees and co-workers[1] used methotrexate in small daily dose for about seven days before restarting another course. Van Scott and co-workers[2] recommended the use of a large parenteral dose of methotrexate at an average of 25 to 50 mg intramuscularly once weekly, while Roenigk et al[3] administered methotrexate orally in slightly lower doses of 12.5 to 20 mg weekly. In 1971, Weinstein and Frost introduced a new schedule of administering methotrexate orally in small doses of 2.5 to 7.5 mg at 12-hour intervals for a total of three doses at weekly intervals. It has the advantages of lower total dose per week and better tolerable toxicity[4].

The first guidelines on methotrexate therapy for psoriasis were introduced in 1972[5] and have since been revised several times[6,7,8]. Despite this, variation in the schedules have been reported. Previously, the starting dose of methotrexate was in the higher range (15mg to 25mg per week)[9]. Kumar et al[10] reported a protocol of initiating methotrexate at a full therapeutic dose, and tapering when the disease was controlled. Methotrexate was given in a single weekly oral dose ranging from 0.3 to 0.5 mg/kg, subject to a maximum of 30 mg and then reduced by 2.5-5mg every fortnight once clearance of 90% or more had been achieved.

The American Academy of Dermatology[8] and the British Association of Dermatology[11] have recommended a starting dose of 2.5 to 5.0 mg per week with gradual increment up to clinical response or maximum dose of 30 mg per week.

Similarly, guidelines published by the Dermatological Society of Malaysia[12] also recommend the starting dose of 2.5 to 5.0 mg per week with gradual increment of dose to maximum 25 mg per week.

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

Despite the efficacy of methotrexate, good quality design studies are sparse. In a systemic review of five systemic treatments for severe psoariasis, none of the studies on methotrexate could be included mainly because of the 'obsolete dosages and outdated dosing schemes used' which was considered too high[13]. In addition, many of the

published data were case series with inadequate documentation. In their sub-analysis of four studies that partially satisfied the inclusion criteria, there were a total of 99 patients treated, out of which, the percentages of patients with clearance and good, moderate and poor responses were, respectively, 51%, 65%, 23% and 12%.

A number of randomized controlled studies involving methotrexate published in the recent years used different starting, maintenance and maximum dosages in their protocols[14,15,16]. This reflects non-standardized practices among the dermatologists worldwide despite the various guidelines. Thus, the efficacy in achieving PASI 75 (75% improvement in Psoriasis Area Scoring Index) at 16 weeks ranged from 35% when the starting dose was low (7.5mg/week)[15], to 60% when the starting dose was higher (15mg/week)[14].

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

On the other hand, Heydendael et al[14] compared methotrexate to cyclosporine without a placebo arm. There were 44 patients in methotrexate arm. Methotrexate was initiated at a dose of 15 mg/kg and after 4 weeks, only 4 patients had the dose further increased up to 22.5 mg/week. At 16 weeks, 26 patients (60%) achieved PASI 75.

Kumar et al[10] in their short term methotrexate therapy in psoriasis using higher starting dose and a tapering down regime reported an impressive 88% of patients achieving 75% improvement in 8.5+5.1 weeks. Similar findings were documented in two other studies from India[17,18], although the number of patients was small.

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

In terms of adverse events, our study revealed raised liver enzymes as the most common followed by abnormal blood counts, gastrointestinal and neurological symptoms. This is in contrast to previous studies[14,16] where gastrointestinal symptoms were the most common side effects. This could probably be due to the fact that the gastrointestinal symptoms were mild and were not properly documented. Fourteen patients (12.6%) had raised liver enzyme with a mean ALT (alanine amino transferase) level of 79 IU/L and the highest ALT was 155 IU/L. Four patients did not stopped treatment as their ALT level were less than 60 IU/L. Four patients had abnormal blood counts, 2 were due to anaemia (haemoglobin of 8.2-9.3 gm/dl) and 2 to leucopenia (white cell counts of 3.5-3.9 x 109). All the blood abnormalities resolved on stopping methotrexate. A 38-year-old man, with psoriasis of 13 years duration, had taken methotrexate for 56 weeks, with an accumulated dose of 445 mg. The response was good. However, the treatment was stopped due to nose bleed and was later diagnosed to have nasopharyngeal carcinoma.

Thirty patients (24%) dropped out of the treatment programme within the first 6 months with 15 patients because of adverse events. In the 15 patients who were excluded from analysis as they had taken methotrexate for less than 4 weeks, none had any abnormality of the blood counts or liver enzymes after the initiation of methotrexate. Heydendael et al[14] reported a drop out rate of 29%, all due to raised liver enzymes. It should be noted that folic acid supplementation was not given. However, in the Indian series, most of the patients tolerated the regime well with only a small drop out rate. In contrast, two other studies which started with a low dose[15,16], had a low drop out rate. See Table 4.

The limitations of the current report are the retrospective nature of the study as well as the

inadequacy of an objective clinical assessment (e.g. PASI 75) and documented side effects. Future studies should adopt a well-designed protocol to look into the different regimes of starting methotrexate in respect to its efficacy and tolerability, using standardized assessment outcomes, for example Psoriasis Area and Severity Index (PASI) and quality of life scores[19].

Conclusion

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

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DERMATOLOGY THERAPEUTICS - Case Report

Treatment of Erythema Nodosum Leprosum (ENL) with high-dose Clofazimine in patients with Lepromatous Leprosy

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

Introduction

ENL is a type ll leprosy reaction and occurs in people with borderline lepromatous and lepromatous leprosy, usually as a complication following treatment. The treatment of choice for ENL is prednisolone in view of its' ready availability and affordability[1]. However, glucocorticoid therapy, even in low doses, can produce substantial toxicity. The risk is clearly greater as the dose increases. However, in cases where there are steroid-induced complications, high-dosed clofazimine may be used to reduce or withdraw corticosteroids in steroid-dependant cases[2,3]. We described 2 steroid-dependent ENL patients with steroid-induced complications who are successfully managed with the addition of high-dosed clofazimine and the resultant weaning down of systemic glucocorticoids.

Case report

Case 1

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

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

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

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

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

Case 2

A 67 years old Chinese gentleman was diagnosed with multibacillary leprosy when he presented with hypoaesthetic erythematous plaques with thickened ulnar nerves. Slit skin smear revealed a bacteriological index (BI) of 4.2 and a morphological index (MI) of 4.8. He was started on intensive MDT comprising of rifampicin 600mg daily, dapsone 100mg daily and clofazimine 100mg daily. Maintenance therapy on modified WHO regime was commenced 1 month later when his morphological index became 0.

He developed ENL, 6 months into his treatment and which resolve within a week with prednisolone at 30mg daily. It was not possible to tail down the prednisolone below 15mg daily because of the frequent reactivation of the erythema nodosum leprosum. Therefore, he was restarted back on prednisolone 30mg daily and remained on 3 cycles of increasing and tapering dose of prednisolone over 1 year. He developed steroid-induced psychosis, diabetes and hypertension, purpura, weight-gain.

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

Discussion

ENL is an inflammatory cutaneous and systemic complication of multibacillary leprosy, usually as a complication of the treatment but sometimes, even before treatment[4]. It has been reported to occur in 24 percent[5] and 31 percent[6] of multibacillary lepromatous patients on MDT regime in India and Brazil respectively.

ENL is characterized by crops of painful and tender, erythematous or deep purple subcutaneous nodules, which are variably distributed on the body but which mostly occur on the legs, arms and face. During the episode, the patients may suffer additional symptoms, including fever, arthritis, dactylitis, myositis, lymphadenitis, iridocyclitis, orchitis and neuritis. The skin signs are obligatory criteria whereas the general signs are optional[7,8].

There are several treatments for ENL, but the mainstays of initial treatment are systemic corticosteroids and thalidomide. But for the reason of well-known teratogenic side effects, WHO does not support use of thalidomide for the management of ENL in leprosy[3]. On the other hand, systemic glucocorticoids also have adverse effects that ranges from just purpura and Cushingoid appearance to osteoporosis and cataract and life-threatening complications like serious infections.

According to the World Health Organization (WHO) and International Federation of Anti-Leprosy Association (ILEP) guidelines for management of erythema nodosum leprosum, clofazimine may be extremely useful for reducing or withdrawing corticosteroids in steroid-dependant cases. Clofazimine is a riminophenazine dye used in combination with rifampicin and dapsone as MDT for the treatment of leprosy as well as its reaction, ENL. It has been used in combination with other anti-mycobacterial drugs to treat Mycobacterium avium infections[9,10] in acquired immune deficiency syndrome patients and multi-drug resistant tuberculosis. The availability of loose clofazimine is limited to the treatment of severe ENL reactions only. The "off-label" use of clofazimine is actively discouraged by WHO because it is a first line drug for the treatment of leprosy, and its indiscriminate use must be guarded against to prevent resistance. A systematic review of 13 randomized controlled trials found clofazimine to be superior to prednisolone and thalidomide for the treatment of ENL[11]. However, clofazimine should never started as the sole agent for the treatment of severe ENL since it takes 4 to 6 weeks to develop its full effect[2].

The dose of clofazimine needed to control ENL is higher than the dose used in MDT. The guideline recommended supplementing the prednisone therapy with higher doses of clofazimine initially. The patients may be started on clofazimine 100mg thrice a day to for up to 12 weeks. This is then reduced to 100mg clofazimine twice a day for 12 weeks and then 100mg once a day for 12 to 24 weeks. The dose and duration of clofazimine may be adjusted by the physician according to individual patient's needs. The ENL reaction is usually controlled within 2 to 4 months of treatment with clofazimine, and then the prednisone can gradually be reduced and eventually withdrawn[2,3]. The dose of clofazimine was increased from 100mg per day to 200mg per day and from 100mg per day to 150mg per day in patient 1 and patient 2 respectively. These relatively small increases were sufficient to control the ENL lesions and to reduce their steroids requirement in both our patients within 8 weeks.

Disadvantages of continuous high doses of clofazimine are gastrointestinal symptoms like crampy abdominal pain and diarrhoea, particularly with doses above 100mg daily. The other signification side effect is skin pigmentation which usually develops within a few weeks after starting clofazimine treatment and may take two or more years after stopping treatment to disappear[2,12]. Both our patients developed obvious skin

pigmentation which is accepted because they appreciate the efficacy of clofazimine in controlling ENL.

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

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DERMATOLOGY THERAPEUTICS - Case Report

Fusarium Cutaneous Infection in a neutropenic girl with Acute Lymphoblastic Leukaemia

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Keywords *Fusarium, Acute Lymphoblastic Leukaemia*

An immunocompromised girl with acute lymphoblastic leukaemia and previous autologous bone marrow transplant presented with fever and a painful rash on her extremities and trunk. There were multiple tender erythematous papules and nodules with central necrosis. Neutropenia was also present. A skin biopsy revealed hyphae and spores in the lower dermis and tissue culture grew Fusarium species. The patient responded well to systemic amphotericin B therapy with resolution of skin lesions and recovering neutropenia.

Introduction

Fusarium species are common plant pathogens present in the environment but can cause invasive infections in immunocompromised patients, especially those with haematologic malignancies and bone marrow transplant recipients[1]. Tissue and blood cultures are especially important as they offer a high diagnostic yield in invasive fusariosis[2-3]. Amphotericin B has been used as the mainstay of treatment[4] although resistant rates are high, especially in *Fusarium solani* species[5]. The treatment outcome is also closely related to rate of recovery of neutropenia[6].

Case report

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

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

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

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In March 2009, the patient presented with a day's duration of fever and painful rash involving her limbs. The rash started as erythematous patches on the abdomen, upper and lower limbs; they subsequently developed into dusky red papules and nodules with central areas of necrosis. She was unable to move her legs due to the painful rash. There was no history of trauma or insect bites to the affected areas. Systemic review was unremarkable. She was clinically in remission at this time and was not on chemotherapy.

On examination, the child was febrile but other vital signs were normal. Examination of her cardiovascular, respiratory and gastrointestinal systems did not reveal any abnormalities. She had oral candidiasis of the tongue and buccal mucosa. Multiple erythematous plaques and nodules nodules with central necrosis were seen on her chest, arms and legs which were tender and warm to palpation. (Figure 1 and 2) There was no discharge from the lesions or ulceration. All her nails were normal. Her hips, knees and ankles were held in flexion due to pain.

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

Her full blood count showed bicytopenia; total white count was 0.56 x 10^9/L with neutropenia (Absolute neutrophil count: occasional neutrophils seen only) with thrombocytopenia (platelet count 28 x 10^9/L). Multiple blood and urine bacterial and fungal cultures were negative.

Figure 1 Erythematous dusky tender nodule on calf with central necrosis

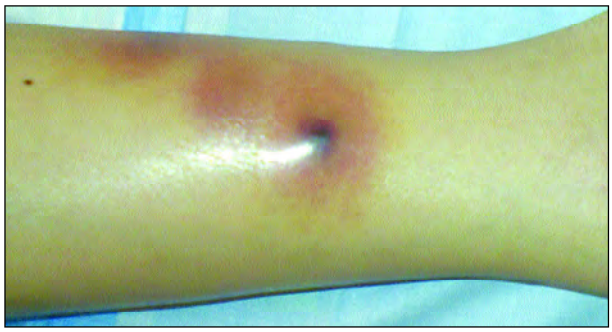


Figure 2 Dusky indurated tender lesions on the the calf with central necrosis upper thighs

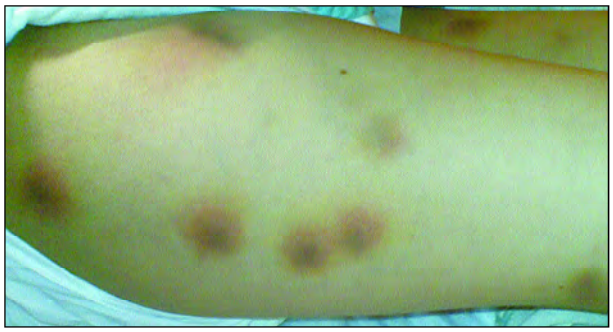


Figure 3 H&E stain (10 x 4 magnification): Superficial and deep perivascular infiltrate of lymphocytes and neutrophils with fat necrosis and an abscess seen in the lower dermis

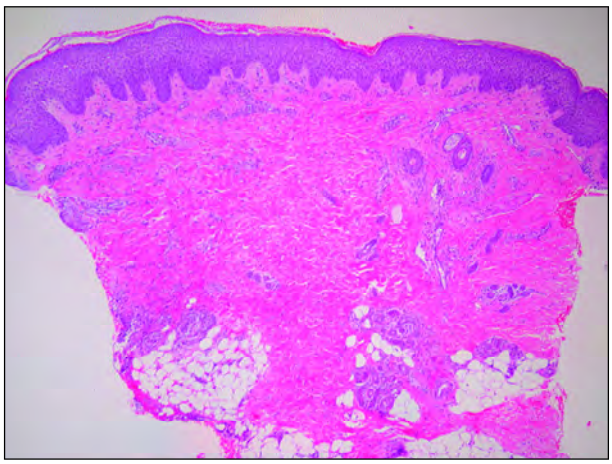


Figure 4 PAS stain (10 x 40 magnification): Hyphae and spores in the lower dermis / subcutis

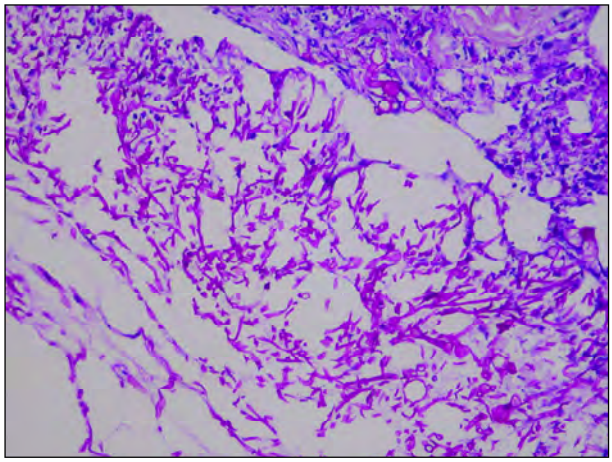
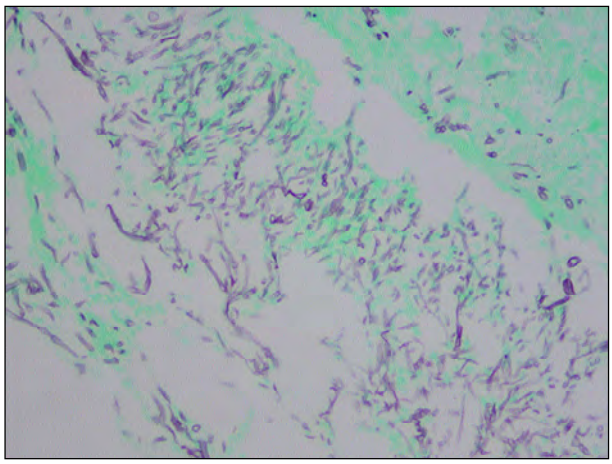


Figure 5 GMS stain (10 x 40 magnification): Hyphae and spores in the lower dermis / subcutis



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

New papules appeared with persistent fever despite treatment with intravenous ceftazidime and gentamicin that was subsequently changed to intravenous piperacillin/tazobactam. Her fever lysed with the introduction of intravenous amphotericin (1mg/kg/day). The patient was discharged with infusion pump-delivered intravenous amphotericin and completed a twenty-one day course, with gradual resolution of the lesions after therapy. Her absolute neutrophil count on discharge had recovered to 2.84 x 10^9/L.

Discussion

Fusarium spp. are saprophytes pervasively found in soil, water or air[7]. Only a few out of the 50 different Fusarium species are pathogenic in humans and among these, half of the reported invasive fusariosis infections in humans are due to *Fusarium solani*. In Fusarium infection, primary sites of entry are the

skin and respiratory tract6, less commonly paranasal sinuses and gastrointestinal tract[7]. Disseminated fusariosis has also been associated with central venous catheters, continuous ambulatory peritoneal dialysis catheters[8], patients with extensive burns and neutropenic patients with localized skin and nail infections. In our patient, she was neutropenic and had fusariosis of the skin without evidence of fungaemia, respiratory or gastrointestinal involvement. The skin was the presumed portal of entry.

The initial presentation of invasive fusariosis in neutropenic patients is persistent fever despite broad-spectrum antibiotics[7]. This was the case in our patient. Despite prophylactic or empiric treatment with amphotericin B or triazoles, breakthrough fusariosis infections are common due to high resistance rates to antifungals[7]. Our patient had solely cutaneous involvement without nail or respiratory involvement. This is unusual. She also had no penetrating injury or trauma to the lower limb.

Use of glucocorticoids impair anticonidial macrophage function and predispose patients to fusariosis[9]. The mortality rate from fusariosis of haematologic cancer patients receiving glucocorticoids has been reported to be more than twice of those not on glucocorticoids[10]. Our patient had not received glucocorticoids in the recent months preceding the onset of skin lesions.

The histopathology of Fusarium lesions is similar to that of Aspergillus species and may cause misidentification[11]. However, differences in hyphae diameter and degree of branching have been reported[12].

The gold standard to differentiate between Fusarium and Aspergillus species requires appropriate tissue culture. The Fusarium colony is seen microscopically as a white patch that progresses to a pink, purple or yellow centre surrounded by a lighter periphery[11]. Microconidia, macroconidia and chlamydospores are different types of Fusarium conidia present in cultures, with canoe-shaped macroconidia being the hallmark of the Fusarium genus[11].

Differences have been reported in clinical characteristics between fusariosis and invasive aspergillosis (IA). First, 50-70% of patients with disseminated fusariosis have positive blood cultures[7] while disseminated IA is seldom isolated in cultures[3]. Positive Fusarium blood cultures can be obtained early in disseminated infections whereas those in disseminated IA manifest late in the course of the infection[3]. Secondly, 50-70% of invasive fusariosis cases exhibit skin lesions compared with less than 10% in disseminated aspergillosis[3]. Most patients have concomitant myalgia[7]. These signs and symptoms were present in our patient. She had extremely tender erythematous papules and nodules with central necrosis on her extremities which resulted in great pain, resulting in her holding her limbs in flexion.

Traditionally, Amphotericin B has been used as the mainstay of treatment against Fusarium infections, albeit with mediocre in vitro susceptibility[13] and high resistance rates especially with *Fusarium solani* species[14]. In current clinical practice, high doses of amphotericin B are prescribed as there are reports of lower mortality rates (>50%)[15]. Liposomal formulations have been useful in improving bioavailability. In our patient, 1 mg/kg/day of Amphotericin B was administered for 21 days.

New broad-spectrum triazoles like voriconazole and posaconazole show promise in the treatment of fusariosis[16-19]. Voriconazole was recently approved by U.S. FDA for treatment of refractory fusariosis. It is most effective against non-solani Fusarium species. Pfaller et al[19] reported voriconazole to be effective in a neutropenic leukaemic patient with disseminated fusariosis where amphotericin B treatment had failed. Upon completion of voriconazole, there were no recurrences of fusariosis even after re-commencement of chemotherapy[19].

Prompt recovery of neutrophil counts is associated with good prognosis in patients with fusariosis. In profound, prolonged neutropenia, there is a 100% mortality rate for fusariosis compared to 30% when neutrophil counts are normal[20]. Therapies have been initiated utilizing recombinant granulocyte colony-stimulating growth factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF) or granulocyte transfusion[21]. Our patient did not receive any granulocyte-stimulating or transfusion therapies but her skin lesions responded to intravenous amphotericin B and neutrophil counts had recovered on discharge.

Finally, in patients with hematologic malignancies, the suspected source of Fusarium infection should be removed, be it nail avulsion in Fusarium onychomycosis, surgical debridement of infected tissue or removal of infected catheters[7].

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DERMATOSURGERY - Original Article

Treatment of Infantile Haemangiomas with 585nm pulsed dye laser

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Abstract

Haemangiomas usually develop within the first few weeks of life, most regressing spontaneously before the age of 7 to 10 years. Some may ulcerate or compromise a vital function, in which case systemic corticosteroids, surgery or radiotherapy may be helpful. All of these treatment modalities are associated with significant morbidity. Treatment with 585nm flashlamp pulsed dye laser is safe and effective in the management of ulcerated and superficial proliferating haemangiomas. We report a retrospective review of 33 children under the age 12 months, who were treated at our centre with 585nm pulsed dye laser over a period of 4 years. Forty eight percent of these children presented with rapidly proliferating haemangiomas causing functional impairment, 40% with ulcerated haemangiomas and others for re-growth after stopping oral treatment. Patients were treated with the 585nm pulsed dye laser (fluence: 5.5-7J/cm2; spot size: 7mm and duration: 0.45s). Patients received treatment until the lesion was almost clear or until lesion failed to respond. All lesions ulcerated haemangiomas healed after an average 3 treatment. Both the physician and parental perception of improvement were analysed based on three parameters, which include reduction in redness, thickness and size. All the haemangiomas showed significant reduction in size, thickness and colour. Less than 1% of patients had atrophic scaring. We conclude that the flashlamp-pulsed dye laser may successfully prevent enlargement and promote involution of superficial haemangiomas with minimal adverse effect. Therapy is most appropriate for patients with ulcerated haemangiomas and haemangiomas at sites of potential functional impairment.

Keywords *Infantile haemangiomas, 585 nm Pulse dye laser*

Introduction

Haemangiomas are common vascular neoplasms, with approximately 2.6% incidence in neonates[1]. The rapid proliferation of the endothelial cells is characteristic of haemangiomas which often leads to rapid growth in the first few months after birth, and may ulcerate or obstruct a vital organ or function. The majority will regress spontaneously after 18 months of life. The attitude of 'wait and see' policy is frequently recommended, whereas in case of complications, steroids or surgical therapy are applied[2,3]. Meanwhile, the application of the flashlamp-pumped pulsed dye laser (FPDL) has become a standard therapy for haemangiomas in many centre[4,5,6]. By selective photothermolysis, laser irradiation destroys a superficial layer of blood vessels in the haemangiomas.

This seems to prevent further proliferation in the haemangiomas which clinically may lead to a slow proliferation or may stop of the tumour growth[7]. We share the review of forty three complicated childhood haemangiomas, who underwent the FPDL therapy at our department from December 1999 to December 2003. The objective of the review is to determine the response or outcome and the side effects of FPDL.

Materials and methods

This is a retrospective review of children with complicated haemangiomas who had FPDL therapy at our department over a 4 year period, from December 1999 to December 2003. The data was collected from the laser unit and counter checked with the patients' medical records. Pre and post laser digital photographs of each patient were reviewed from the computerized photographs folders.

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Complicated haemangiomas in this study include:

(i) haemangiomas located on the head and neck region which obstruct vital organs or functions e.g. ophthalmic problems related to periorbital lesions.
(ii) haemangiomas that ulcerate and/or bleed
(iii) rapidly proliferating haemangiomas at the macular stage (head & neck region).

The indications of laser in this group of patients are shown in Figure 1.

Patients had photographs taken prior to each FPDL therapy. FPDL therapy is done as a day care procedure by the 'Laser team' consisting laser surgeon, paediatric dermatologist, anaesthetist and laser nurse at 4 to 8 weekly intervals. The procedure is done under general anaesthesia (GA). SPTL1b with the following parameters were most frequently used; fluence: 5.5-7J/cm^2 ; spot size: 7mm and duration: 0.45s. After FPDL patients are observed in the paediatric wards before discharging home.

Responses to therapy was done by analysing three parameters including: Reduction of (i) redness (ii) thickness and (iii) size of haemangiomas. First, parental views on the reduction of redness of the haemangiomas were assessed as slight, mild, moderate and marked reduction.

Second, the thickness of the haemangiomas before and after FPDL was recorded in millimetres.

The thickness was grouped into flat lesions, lesions than 3mm, and lesions >3mm. Last, the reduction in the sizes of the haemangiomas were recorded in centimetres and grouped into 0 to 5cm, 6 to 10cm and >10cm.

Treatment is continued until the haemangiomas had partial or complete response or parentral request for discontinuation of therapy.

The short and long term complications were recorded. Long term complications were obtained after a minimum of 6 months period following the last laser therapy. And the maximum period in this review was 2 years post laser therapy. Data was tabulated and analysed accordingly.

Results

There were forty three haemangiomas observed in 33 children who were either referred from private or government paediatrician or dermatologist. There were 82% female and 18% male (female to male ratio; 4.5: 1), with 42% being Chinese, 35% Malays and 23% Indians.

Fifty percent of haemangiomas were noticed at birth, and another 50% by the first 4 weeks of life. Age of presentation to us is shown on Figure 2. The mean age of presentation is at 4 months. 60% of the patients presented before the age of 6 months, during the rapid proliferative phase of haemangioma. The oldest patient in this series is 12 years old.

Figure 1 Common indications of laser therapy

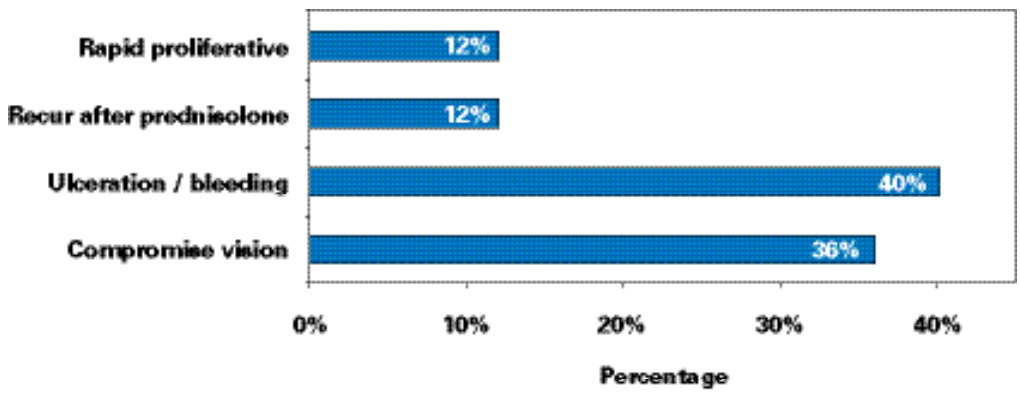


Figure 2 Age of presentation in months

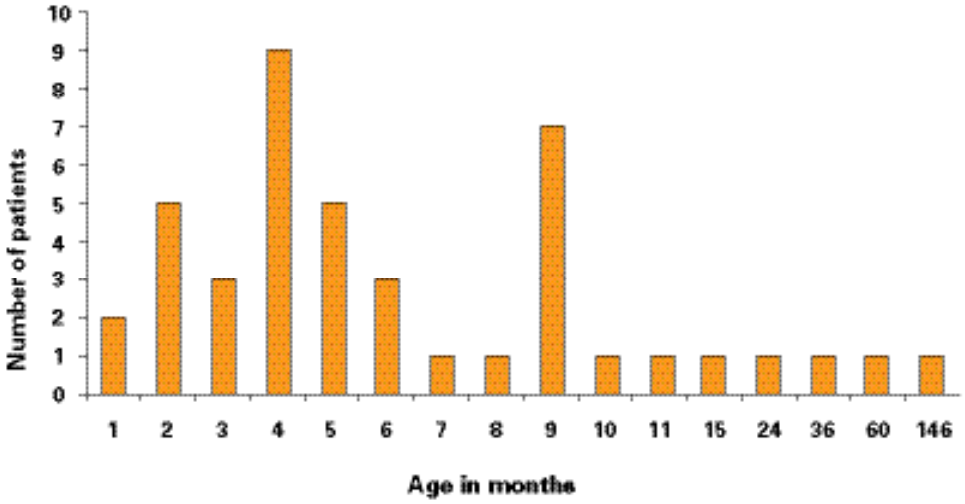
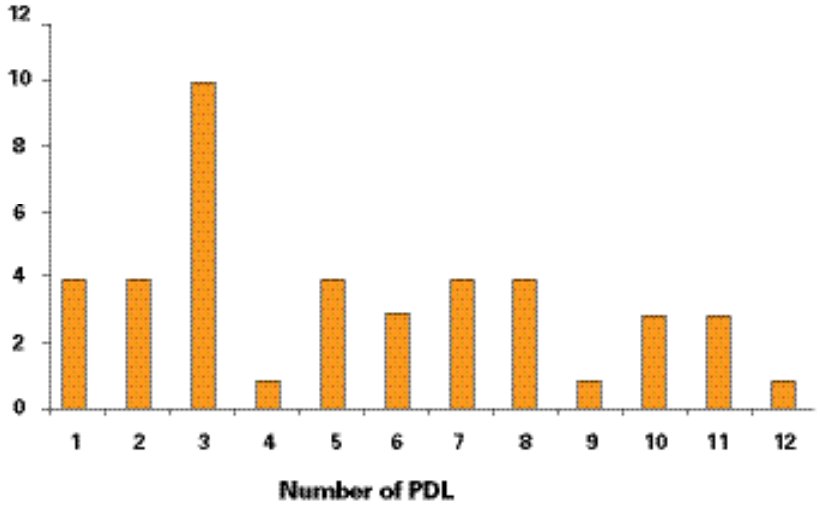


Figure 3 Number of FPDL received by patients



Sixty percent of the haemangiomas were superficial and 40% were mixed. Eight percent haemangiomas were observed on the head and neck region of which; 63% periorbital, 12% on the cheek, 10% perioral and rest forehead and scalp. Seven percent were present on the buttock, 7% on the trunk, and 6% on the extremities.

The most common complication were ulceration and bleeding (40%), followed by compromised vision (36%). 24% were noted at the rapid proliferating stage, and there was a concern of vital organ obstruction. Two patients had laser for regrowth after stopping the systemic steroid therapy. 40% of patients had systemic and 2 had received intralesional steroid prior to FPDL

The mean age of first laser treatment was at 5 months. Figure 3 shows the number of FPDLs received by patients in this series. 4 lesions responded to one laser session and there was one lesion which responded only after 12 sessions. The mean number was 3 for each patient before any desired clinical response was seen.

The response was assessed by the reduction in colour, thickness and size. Tables 1,2,3 and 4 are the summary of the response and outcome of the FPDL.

The use of general anaesthesia is not without any risks, and needs proper assessment of patient. The short term complications were pain in all patients and transient blister in 20%. The long term complications include 37% with either hypo or hyperpigmentation, (5%) atrophic scaring, (9%) with textural changes.

Figure 4 1a & b: Pictures of perioricular haemangioma pre and post 4FPDLs.
2 a & b: Haemangioma on the left cheek pre and post 5 FPDLs.

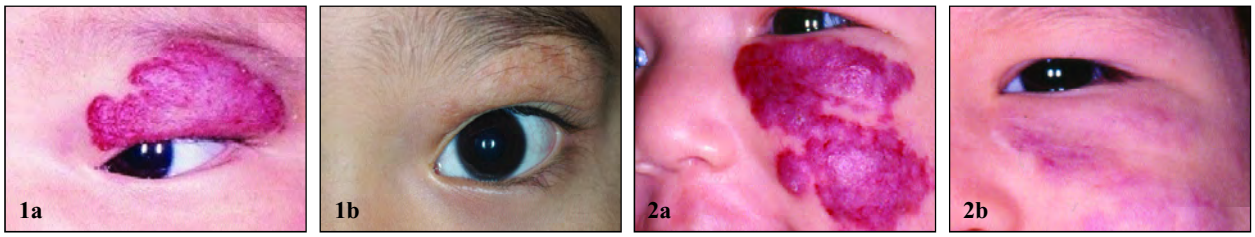


Figure 5 1 a & b: Pictures of scalp haemangioma pre and post 5 FPDLs.

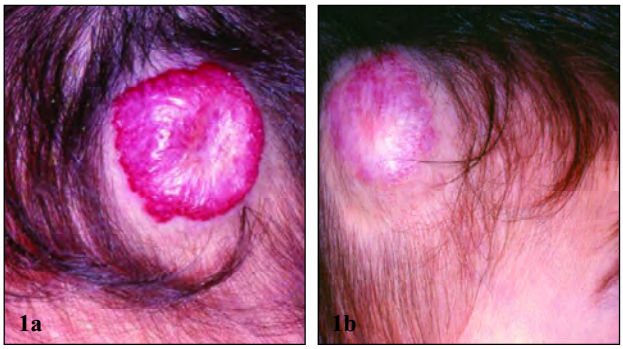


Figure 6 1 a, b, c & d: Complete resolution after 12 sessions of FPDL.

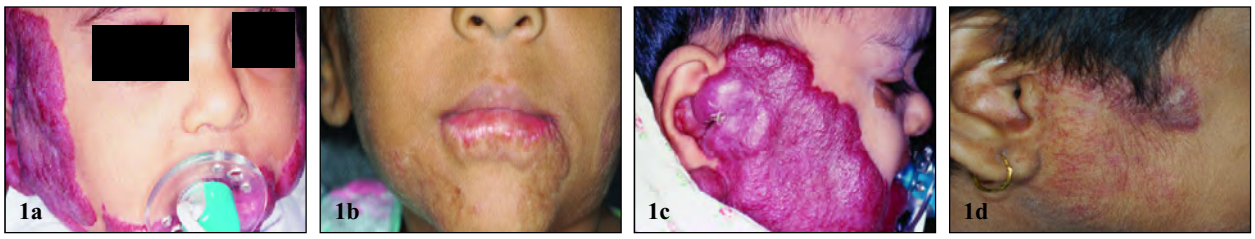
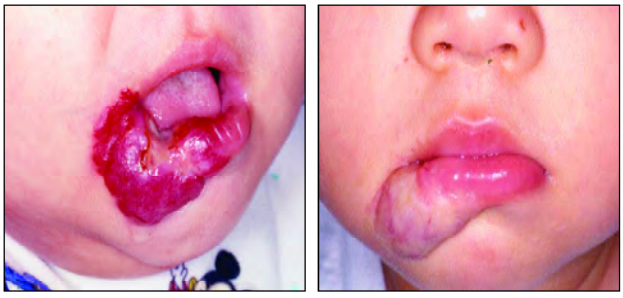


Figure 7 Complete resolution of ulcerated haemangioma after 3 sessions of FPDL.



Discussion

Haemangiomas may be complicated by medical and psychological issues that can be overwhelming to the patient's family as well as humbling to the physician. There is tremendous degree of variation in the rate, duration, and degree of growth, as well as the rate of involution. The clinical heterogeneity and 'auto-involutive' nature, makes the treatment controversial. Therefore, treatment must be highly individualized taking into account; age, anatomical site, size, rate of growth, and other factors, always weighing potential risks and benefits[8].

Since the study by Sherwood and Tan[9] of the successful treatment of a haemangioma of the finger with the FPDL, several authors have reported equally successful results[10]. FPDL has proved to be a safe and effective treatment modality for Port wine stain, in treating small vessels found in childhood Port wine stains[11].

We reviewed complicated haemangiomas in this series, which would not reflect the true demographic features of haemangiomas of infancy.

The demographic feature of this series, with respect to sex ratio and age of onset is similar to other studies[12]. More Chinese than Malays were noted as compared to the attendance at our department (public sector healthcare) where Malays represent 50%, Chinese (30%) and Indians (20%). Most Chinese patients are referred from the private sector for laser treatment.

Although all regions of the body can be affected by haemangiomas, eighty percent localised on the head, with 63% at periorbital region, giving rise to visual compromise. This figure is comparable with another study[13]. Superficial haemangiomas are more common than mixed ones[14].

Use of lasers to treat haemangiomas must be divided into three separate indications: (i) treatment of ulcerated haemangiomas, (ii) treatment of proliferative phase[3] and (iii) treatment of residual telangiectases.

Ulceration is the most frequent indication for FPDL in this series. The ophthalmic compromise during the proliferative phase is the second most common indication followed by rapid proliferation and re-growth after cessation of systemic steroid.

Seventy five percent of these haemangiomas had more than 75% reduction in redness similar to the study by Landhaler et al where 198 patients with haemangiomas were treated, and 74% of these patients had 75% or greater lightening of their lesions with no evidence of permanent scaring[13]. Flat lesions responded to FPDL completely. Nearly 90% of haemangiomas with 3mm and less in thickness responded much better to FPDL treatment and involuted more completely. The size of the haemangiomas remained the same. Our study demonstrates a better outcome in the superficial haemangiomas group. Treatment of mixed haemangiomas has been the source of some controversy in the literature[14].

Bleeding from ulcerated haemangiomas responded completely after one laser whereas ulceration healed after a mean of 3 FPDLs. This observation is similar to a study by Hans Peter et al[13].

Table 1 Characteristics of the haemangiomas

Indicator	Characteristics	N=43
Size	0-5cm	36 (83)
	6-10cm	5 (12)
	>10cm	2 (5)
Thickness	Flat	2 (5)
	<3mm	35 (81)
	> 3mm	6 (14)
Colour	Bright red	40 (93)
	Violaceous	3 (7)

Table 2 Reduction in the redness of the haemangiomas after FPDL

Indicator	Response	Number, N=40(%)
Reduction of redness (Parental perception)	Slight (<25%)	0
	Mild (26-50%)	3 (7)
	Moderate (51-75%)	7 (18)
	Marked (>75%)	30 (75)

Besides the risk of GA, the morbidity of the long term complications should be considered. The percentage of transient hypopigmentation and hyperpigmentation in our series was 10% and 8% respectively compared to 2.6% and 1% in another series. Higher percentage of both pigmentation can be explained by the type 3 or 4 skin type in our series. The hypopigmentation or hyperpigmentation is a transient phenomena and these patients need long term follow up. Atrophic scaring was noted in 4.5% compared to 0.1% in the above study[15].

Conclusion

Treatment with FPDL is safe and effective for ulcerated haemangiomas. FPDL should be offered to infants with proliferative haemangiomas on the head and neck region which may compromise vision or other vital organs or structures. This mode of therapy may further help in slowing the process of proliferation of the haemangiomas. We recommend early treatment, especially in problematic lesions (around eyes, ears, nose, genital, anal region) where early treatment can prevent disfigurement or other complications.

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