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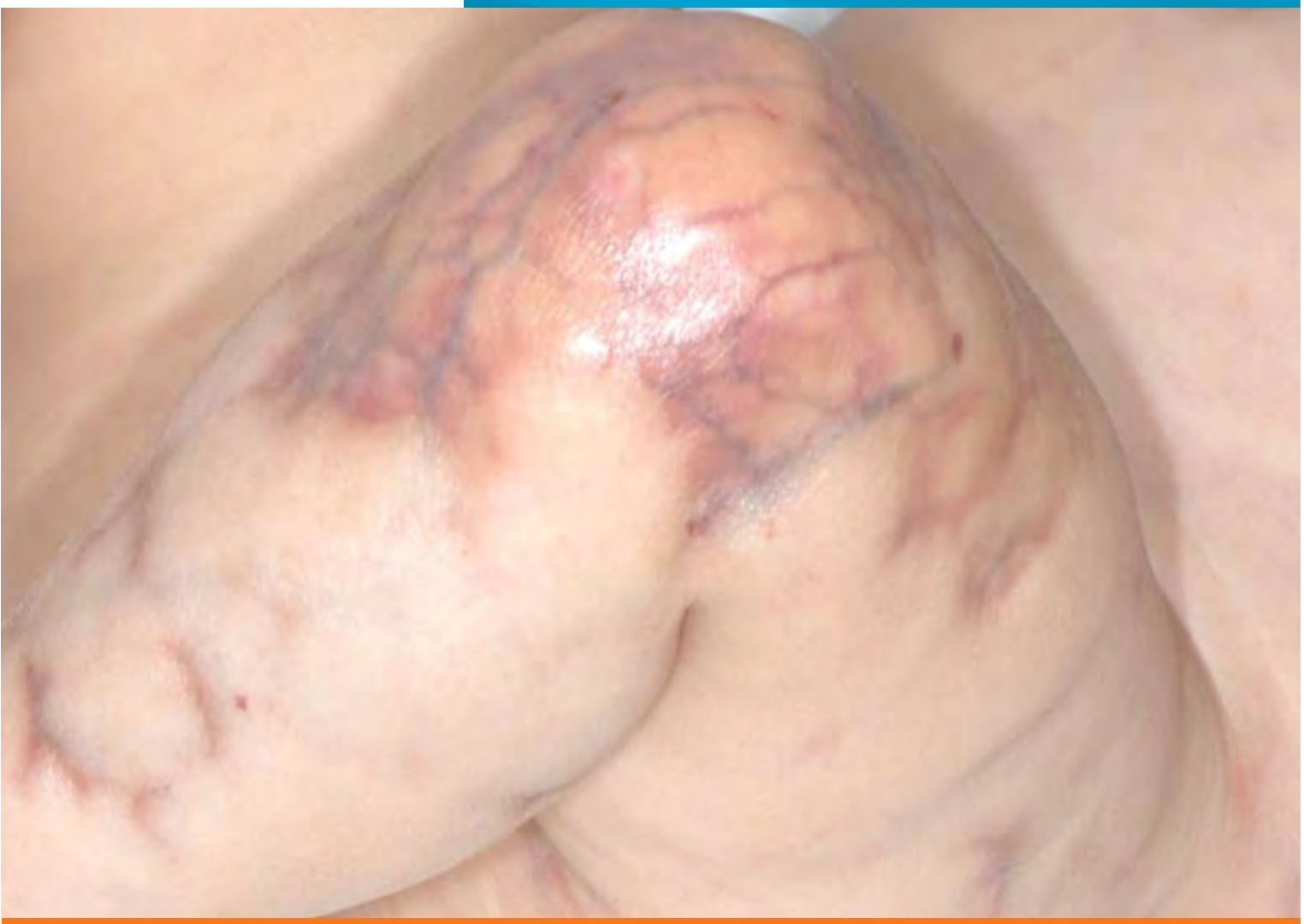

PERSATUAN DERMATOLOGI MALAYSIA | DERMATOLOGICAL SOCIETY OF MALAYSIA

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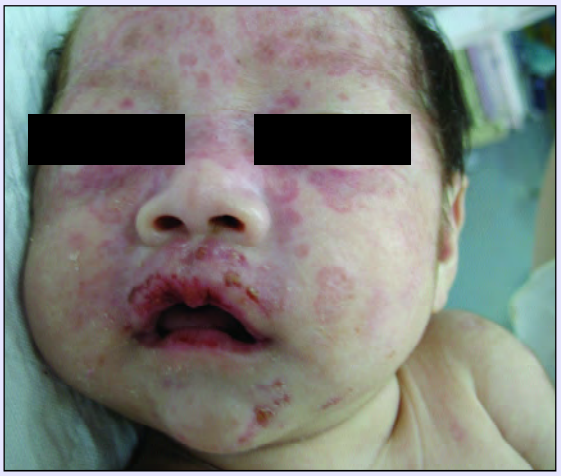
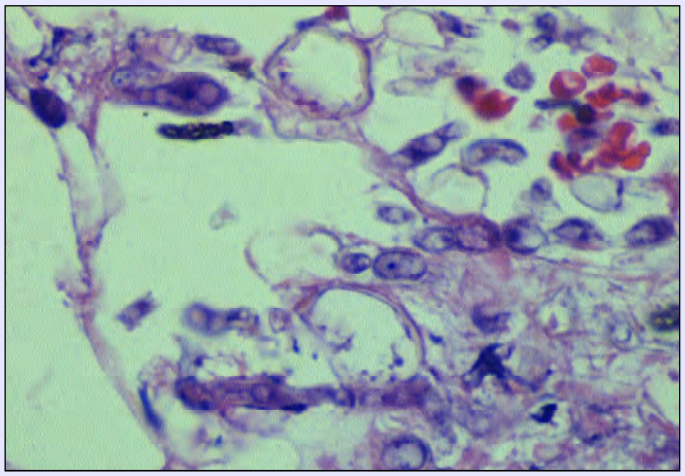
Highlights

Editorial

The decision to revert back to World Health Organisation (WHO) regime of multidrug therapy for Hansen disease was based on the outcome study done by Felix Yap together with the group of dermatologists when they compared the outcome of patients who had WHO and the Sungai Buloh augmented leprosy multi-drug therapy. Paucibacilliary leprosy will need only 6 months anti-leprosy therapy while multibacilliary leprosy a year. There is a unanimous decision to prolong the Hansen therapy to 2 years instead of 1 for patients presenting with bacteriological index more than 4.

Today's challenge is how we attract medical officers to become dermatologists. This has become the main agenda for Malaysian Dermatological Society meeting - creating more dermatologists to meet the increase in demand for this service. The attainment of Saint John's Diploma of Dermatology and in-house dermatology training was initially adequate to fulfil one to be credentialed as a dermatologist. After 1986 a pass in post-graduate course in internal Medicine locally, United Kingdom or from Australia is a prerequisite to a fellowship dermatology training. In 2004, the attainment of Masters in Advance Dermatology following an exit examination and production of a thesis is the preferred criteria for credentialing.





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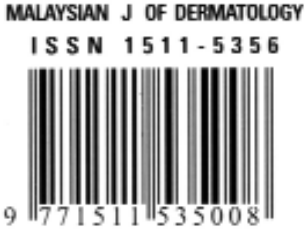

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Case Report*
A report of 400-600 words, illustrated by no more than three illustrations. This category offers a means for rapid communication about a single subject.

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An article of 700-1200 words concerning a drug evaluation. This category provides rapid publications and is meant to be a succinct presentation with a minimum of graphs and tables.

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

Clinicopathological Challenge
A photographic essay that includes both clinical and pathological photographs in color. The diagnosis and legends for the photographs should be listed after the references in the article. The article should be no more than 2-3 pages in length.

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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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GENERAL DERMATOLOGY - Original Article

Antibiotic sensitivity of propionibacterium acnes isolated from patients with acne vulgaris in Hospital Kuala Lumpur, Malaysia

Tang JJ[1], Heng A[1], Chan LC[2], Tang MM[3], Roshidah B[3]

Abstract

Background Antibiotic therapy directed against *Propionibacterium acnes (P. acnes)* has been a mainstay of treatment in acne vulgaris for more than 40 years. Prolonged antibiotic usage has been associated with emergence of antibiotic-resistant *P. acnes* and is linked to treatment failure. Little work has been done in Malaysia on drug resistance in *P. acnes* and there is no surveillance data on this aspect to guide the clinical decision.

Objective This study aims to evaluate antibiotic sensitivity of *P. acnes* isolated from patients with acne vulgaris in Kuala Lumpur Hospital, Malaysia.

Methods This is a non interventional, single centered, cross-sectional hospital-based survey of antibiotic sensitivity of *P. acnes* isolated from patients with acne vulgaris in Kuala Lumpur Hospital from January 2010 to June 2010.

Results A total of 100 patients were recruited in our study. *P. acnes* was isolated in 53% of patients and 11% had gram negative organism. Antibiotic resistant *P. acnes* was found in 15.1% of positive isolates. Clindamycin resistance was the highest (15.1%) followed by erythromycin (7.5%), doxycycline (5.7%), tetracycline (1.9%) and minocycline (0%). Isolates of antibiotic resistant *P. acnes* was significantly higher in patients treated with antibiotics within the last 6 months (29%) as compared with non antibiotic treated patients (0%) ($p<0.05$).The mean duration of prior antibiotic treatment was significantly longer in the group of antibiotic resistant *P. acnes* as compared with antibiotic sensitive *P. acnes* (17.13 weeks vs 5.74 weeks, $p<0.05$).

Conclusion Antibiotic resistant *P. acnes* is present locally with clindamycin and erythromycin accounting for the highest resistance. Longer duration of antibiotic treatment predisposes to antibiotic resistant *P. acnes* and may also induce emergence of gram negative organisms. Strategies to reduce antibiotic resistance should be emphasized when prescribing antibiotic for acne vulgaris in order to achieve optimal therapeutic results while reducing the potential for antibiotic resistance.

Keywords *Acne vulgaris, Antibiotic sensitivity, Antibiotic resistance, Propionibacterium acnes, Clindamycin, Erythromycin, Doxycycline, Tetracycline, Minocycline*

Introduction

Acne vulgaris is a disorder of the pilosebaceous follicle characterized by non-inflammatory (comedones) and inflammatory lesions (papules, pustules, nodules and cysts). Although the pathogenesis of acne vulgaris is multifactorial, a commensal skin bacteria, Propionibacterium acnes *(P. acnes)* plays a major role in the formation of inflammatory

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acne lesion and comedogenesis. Antibiotic therapy directed against *P. acnes* has been a mainstay of acne treatment for more than 40 years. However, prolonged antibiotic usage whether oral or topical has been associated with an increased risk of antibiotic-resistant *P. acnes* overgrowth. There are evidences linking the carriage of antibiotic-resistant *P. acnes* to treatment failure.[1] The first clinically relevant erythromycin resistant *P. acnes* strains was reported in 1979 from a small group of patients in the United States.[2] Subsequently, more cases of antibiotic resistant *P. acnes* were reported from various countries[3,4,5,6].

Acne vulgaris is highly prevalent and is of concern in our population. However, little work has been done in Malaysia on antibiotic resistant *P. acnes* and there is no surveillance data to guide the clinical decision. Hence, the aim of the study is to assess the antibiotic sensitivity pattern of *P. acnes* among patients with acne vulgaris. This information would be useful in the formulation of appropriate local prescription practices and increase the awareness of judicious use of antibiotics in acne vulgaris among our doctors.

Methodology

This is a non interventional, single centered, cross-sectional hospital-based survey of antibiotic sensitivity of *P. acnes* isolated from patients with acne vulgaris in Kuala Lumpur Hospital, Malaysia. Both old and new cases of acne vulgaris were consecutively sampled over a 6-month period from January 2010 till June 2010. The patients with active acne vulgaris characterised by both inflammatory (papules, pustules, nodules or cysts) and non inflammatory (closed and open comedones) lesions and more than 12 years old were recruited. Those with disease in clinical remission were excluded from the study.

The study consisted of three parts. The first part of the study involved interviewing patients with acne vulgaris by using a standard data collection sheet. Data collected included age, gender, ethnicity, family history of acne vulgaris, duration of disease, previous and current treatment taken within the last 6 months. This was followed by assessment of acne severity according to lesional count. Acne severity assessment was based on criteria defined by Lehmann et al 2002 i.e. mild : < 20 comedones, or < 15 inflammatory lesions, or total lesion count < 30; moderate: 20-100 comedones, or 15–50 inflammatory lesions, or total lesion count 30-125; severe : > 5 cysts, or total comedones count > 100, or total inflammatory lesion count > 50, or total lesion count > 125[7].

The third part of study consisted of swab sampling for *P. acnes* culture after informed consent was obtained. The entire surface of the acne affected area (face and/or trunk) was swabbed with a sterile swab stick. The swab was immediately inoculated onto sheep blood agar plate. It was then placed in an air tight anaerobic chamber and sent to microbiology laboratory, Kuala Lumpur Hospital, for culture and sensitivity. The blood agar plate was then incubated in anaerobic conditions at 37ºC for 5 days. All agar plates were opened after 5 days of incubation. *P. acnes* colony was first identified from the appearance of the colony on the blood agar which typically has small, dome-shaped colony with beige to pink colour. Gram stain, Catalase test and Indole test were done on all suspected colonies. *P. acnes* is a Gram-positive, non motile bacilli with short branching and coryneform appearance which shows positive Catalase and Indole production tests. The suspected colonies were then analyzed by an automated bacteriology system - VITEK 2 compact to confirm the species of the organism. Antibiotic sensitivity to the five common antibiotics include tetracycline, doxycycline, minocycline, erythromycin and clindamycin were then determined for all positive cultures with *P. acnes*. The Minimal inhibitory concentration (MIC) to the five antibiotics was measured by using E tests. The MICs breakpoint by European Committee on Antibiotic Susceptibility Testing (EUCAST2003) was used to define the resistance strain. Documentation and analysis of the data were carried out using the Statistical Product and Services (SPSS version 14.0) software for Windows. Mann-Whitney U test was used to analyze non-normally distributed variables and the values were expressed as median. Non-parametric tests such as Fisher‘s exact test was used to examine the relationship between 2 categorical variables (with two levels). A 2-tailed p value of <0.05 is considered as statistically significant.

Results

The general characteristics of our patients as shown in Table 1. A total of 100 patients were recruited with mean age of 22.8 ± 5.6 years old. The female to male ratio was comparable (1.04: 1). Majority of our patients were Malay (67%) followed by Chinese (15%) and Indian (14%). Up to 63% of our patients have an immediate family history of acne vulgaris. The mean duration of disease was 61.5 ± 50.3 months. Majority of our patients had moderate to severe acne vulgaris (78%). as the clinic is a tertiary referral centre.

Majority of our patients were prescribed both topical benzoyl peroxide (96%) and a topical tretinoin (95%). Topical sulphur was used in 19% of our patients. Sixty one percent of our cohort had used over-the-counter treatment from a pharmacy. However, majority of them were unsure of the content of their treatment. As topical clindamycin and topical erythromycin are not available in our centre, only 1% of our cohort were on these topical antibiotics. This figure may not reflect the real usage of topical clindamycin and topical erythromycin as these treatment are easily available over the counter in most of the pharmacies. There were 80 patients (80%) on oral antibiotic with the remaining 20 patients (20%) on topical treatment alone. Majority (68%) of our patients were given oral Doxycycline. This was followed by oral Erythromycin (21%) and Tetracycline (18%). Only 9 patients (9%) were prescribed oral Isotretinoin. All of the patients who were given oral Isotretinoin had been on oral antibiotic previously. There was only one patient on oral Bactrim and oral contraceptive pill (Diane 35) respectively. None of our patients were given oral Minocycline, Clindamycin or Spironolactone.

Table 1 Dermographic data

Characteristics		n=100 (%)
1. Age (years)	Mean	22.78 ± 5.62
	Median	23
	Range	12 to 44
2. Gender	Male	49 (49%)
	Female	51 (51%)
3. Ethnic	Malay	67 (67%)
	Chinese	15 (15%)
	Indian	14 (14%)
	Others	4 (4%)
4. Immediate family history of acne vulgaris	Yes	63 (63%)
	No	37 (37%)
5. Duration of acne vulgaris (months)	Mean	61.50 ± 50.29
	Range	2 to 252
6. Severity of acne based on lesional count (Lehmann et al 2002)	Mild	22 (22%)
	Moderate	59 (59%)
	Severe	19 (19%)

Figure 1 summarizes the type of organism cultured from swab sampling. Positive cultures for *P. acnes* was seen in 53 patients, giving an isolation rate of 53%. As for the remaining 47 swabs: 24 grew Staphylococcus species; 11 *Klebsiella species*; 10 *Corynebacterium species*; 1 *P ropionibacterium granulosum* and *Propionibacterium propionicus* respectively. It is interesting to note that 11% of swab sampling actually grew gram negative organism (*Klebsiella species*) which is not a normal commensal on the skin. Antibiotic sensitivity to the five antibiotics include tetracycline, doxycycline, minocycline, erythromycin and clindamycin were determined for all positive cultures with *P. acnes. P. acnes* strain with resistance to at least one of the five antibiotics was found in 15.1% of positive isolates (8 out of 53 positive isolates).

Figure 2 shows the sensitivity pattern of *P. acnes* according to the types of antibiotic. Clindamycin resistance was the highest (15.1%) followed by erythromycin (7.5%), doxycycline (5.7%) and tetracycline (1.9%). There was no resistance noted to minocycline. Virtually all the isolates with antibiotic-resistant *P. acnes* were resistant to clindamycin. All isolates resistant to erythromycin were also resistant to clindamycin. Isolates of antibiotic resistant *P. acnes* was significantly higher in patients treated with antibiotics within the last 6 months (29%) as compared with non antibiotic treated patients (0%) ($p<0.05$).The mean duration of antibiotic given within the last 6 months was significantly longer in the group of antibiotic resistant *P. acnes* as compared with antibiotic sensitive *P. acnes* (17.13 weeks vs 5.74 weeks, $p< 0.05$).

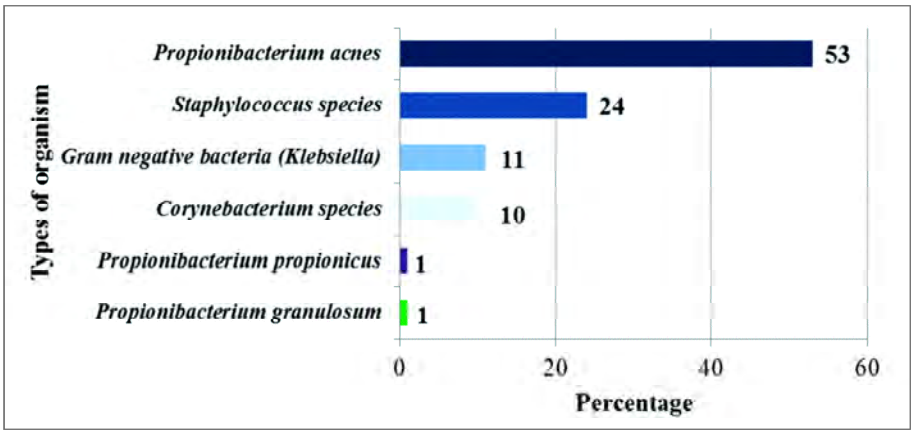

Figure 1 Types of organism from swab sampling culture

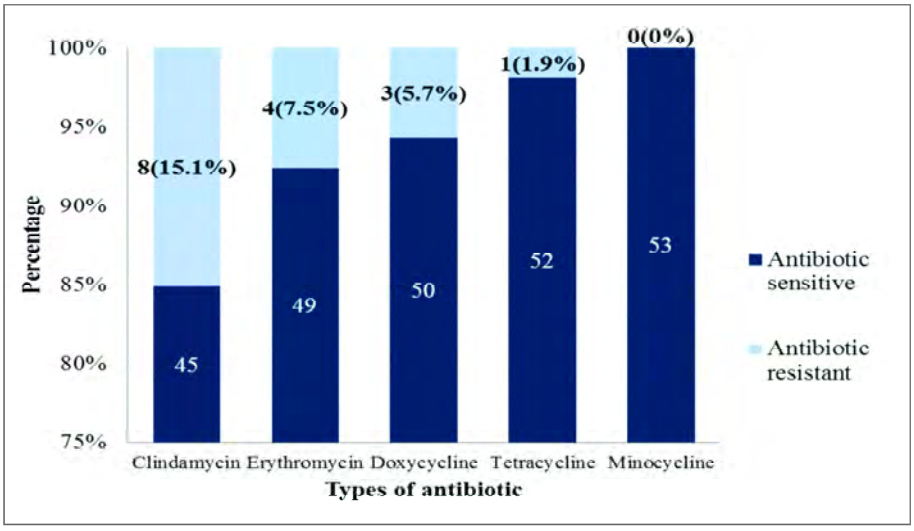

Figure 2 Antibiotic sensitivity pattern of P. acnes according to types of antibiotic

Discussion

Our study showed that 15.1% of *P. acnes* strain was resistant to at least one of the five antibiotics (tetracycline, doxycycline, minocycline, erythromycin and clindamycin). When we compared our study with other studies, we found that our *P. acnes* resistance rate is lower than the studies in Europe countries (ranged from 25% to 94%) but comparable to our neighboring country, Singapore (14.9%). Table 2 shows the comparison of antibiotic sensitivity of *P. acnes* in various studies. A 10-year study at the Leeds General Infirmary in United Kingdom involving 4274 patients reported that the incidence of antibiotic resistance of *P. acnes* increased from 34.5% in 1991 to 55.5% in 2000, with a peak of 64% in 1997.[8] Ross et al conducted a multicentre trial to determine the prevalence of skin colonization by antibiotic-resistant propionibacteria in the United Kingdom, Spain, Italy, Greece, Sweden, and Hungary and showed that the prevalence of carriage of isolates resistant to at least one antibiotic was lowest in Hungary (51%) and highest in Spain (94%)[5]. Similarly, a higher resistance rate was reported by Dumont-Wallon G et al from France which showed that 75.1% of the patients were carriers of antibiotic resistant *P. acnes* strains[9].

Table 2 Comparison of antibiotic sensitivity of P. acnes in various studies

Study	% of overall antibiotic resistance	Top 2 antibiotic resistance	Other antibiotic resistance
Current study 2010 ***Malaysia***	15.1%	† Clin 15% ‡ Ery 7.5%	± Doxy 5.6% + Tetra 1.9% # Mino 0%
Tan HH 2007 [9] *Singapore*	14.9%	Ery 10.3% Clin 7.5%	* Co-T 5.7% Doxy 3.4% Mino 1.7% Tetra 1.7%
El-Mahdy 2007 [10] *Egypt*	≈27%	Clin 26.9% Ery 13.5%	Tetra 3.8%
Kurokawa 1999 [11] *Japan*	≈4%	Clin & Ery 4%	Tetra 2% Doxy 2%
Ross JI 2003 [5]			
Spain	94%	Clin & Ery 91%	Tetra ≈5%
Greece	75%	Clin & Ery ≈75%	Tetra ≈7%
UK	≈56%	Clin & Ery 55.5%	Tetra 26.4%
Italy	≈65%	Clin & Ery ≈58%	Tetra 0%
Hungary	51%	Clin & Ery ≈45%	Tetra 0%
Sweden	≈55%	Clin & Ery ≈49%	Tetra ≈15%
Coates P 2002 [7]			
UK	1991 : 34.5% 1997 : 64% 2000 : 55.5%	1991 : Ery 29% Clin 20% 1997 : Ery 57.6% Clin 49% 2000 : Ery 55% Clin 45%	-
Dumont-WG 2010 [8] *France*	75.1%	Ery 75.1%	Tetra 9.5% Doxy 9.5%

†Clin=Clindamycin ‡Ery=Erythromycin +Tetra=Tetracycline ±Doxy=Doxycycline #Mino=Minocycline *Co-T=Bactrim

We postulate a few explanations why our resistance rate is lower than the European countries. Firstly, majority of our patients (up to 96%) were prescribed topical BPO and retinoid concurrently for their acne. BPO is a powerful non-antibiotic antimicrobial agent that has the ability to suppress emergence and proliferation of antibiotic resistant *P. acnes* and topical retinoid has a complementary mode of action as a comedolytic agent. Hence, routine use of topical BPO and retinoid can actually help to control *P. acnes* resistance. Secondly, topical antibiotics such as erythromycin and clindamycin are not available in our clinic and this helps to further reduce the risk of antibiotic resistance. Thirdly, the low resistance may partly be due to low *P. acnes* isolation rate (53%) in our study.

Our study showed that clindamycin resistance was the most common (15.1%) followed by erythromycin (7.5%), doxycycline (5.7%) and tetracycline (1.9%). There was no *P. acnes* isolates resistant to minocycline. Virtually all the isolates with antibiotic-resistant *P. acnes* were resistant to clindamycin. Even though clindamycin resistance was the highest in our study, there was in fact only 1 patient who was prescribed topical clindamycin in our cohort. We believe some of our patients may have purchased topical clindamycin over the counter and used it prior to this study which led to higher resistance rate towards clindamycin. Our result is in keeping with other studies worldwide which also found the highest resistance rate to erythromycin and clindamycin[5,8,9,10,11,12]. Nevertheless our clindamycin and erythromycin resistance rate as a whole, were still lower than that reported in Europe. In United Kingdom, Coates P et al reported highest resistance to erythromycin which rose steadily from 29% in 1991 to 57.6% in 1997 and the rates of resistance to clindamycin mirrored those for erythromycin but were always slightly lower[8].

It was also been shown by Ross et al that combined resistance to erythromycin and clindamycin was more common in European countries with highest prevalence in Spain (91%) and lowest in Hungary (45%)[5]. In France, Dumont-Wallon G et al also showed that 75.1% of *P. acnes* strains were resistant to erythromycin[9]. Our clindamycin and erythromycin resistance rate was comparable to Singapore which was 7.5% for clindamycin resistance and 10.3% for erythromycin resistance[10]. Erythromycin-resistant *P. acnes* is associated with 3 phenotypes of mutations at 23S rRNA whereas tetracycline resistance is associated with a single mutation at 16S rRNA[1,13]. It has been well described that erythromycin-resistant *P. acnes* may also be cross-resistant to clindamycin and it is common to have resistance to both erythromycin and clindamycin together[8].

The resistance rate towards the tetracycline group in our patients was lower than erythromycin and clindamycin. Among the three drugs in the tetracycline group, doxycycline (5.7%) had the highest resistance in our study, followed by tetracycline (1.9%) and minocycline (0%). This seems to mirror our prescription pattern where doxycycline is the most commonly prescribed oral antibiotic (68%) followed by tetracycline (18%) and minocycline (0%). Most of other studies also reported the lowest resistance rate for minocycline. Results from other studies also showed a lower resistance rate to the tetracycline group as compared to erythromycin and clindamycin. Study by Coates P et al in United Kingdom showed that resistance to tetracycline increased from 12.5% in 1991 to 25.6% in 1996, reaching a peak of 29.9% in 1998[8]. Ross et al reported resistance to tetracyclines as the highest in United Kingdom (26.4%) but no isolates resistant to tetracycline were detected in Italy or Hungary in a multicentre trial in Europe[5]. In France, Dumont-Wallon G et al also showed that resistance to tetracycline (9.5%) was lower than erythromycin (75.1%) and all strains resistant to tetracycline were also resistant to doxycycline[9]. Tan HH et al from Singapore also reported a lower resistance rate to tetracycline group with doxycycline resistance being the most commonly detected, accounting for 3.4% of all isolates while resistance to tetracycline and minocycline were both 1.7%[10]. In general, tetracycline has lower resistance rate because it exerts less selection pressure on antibiotic resistant *P. acnes* as compared with erythromycin/clindamycin[7]. Tetracycline resistant isolates also displayed varying degrees of cross-resistance to doxycycline and minocycline[1,13].

All of the antibiotic resistant *P. acnes* were isolated from patients who were prescribed antibiotic within the last 6 months and the mean duration of antibiotic given within the last 6 months was significantly longer in the group of antibiotic resistant *P. acnes* as compared with antibiotic sensitive *P. acne*. This suggests that the patients who were given longer duration of antibiotic within the last 6 months were at higher risk of developing antibiotic resistant *P. acnes* as compared to those who were on shorter duration of antibiotic. In fact numerous studies have addressed the relationship between antibiotic resistant *P. acnes* and previous antibiotic treatment. Oprica C et al from Sweden found that antibiotics resistant *P. acnes* isolates was significantly higher in the group of patients treated with antibiotic (37%) as compared with non-antibiotic group (13%) of patients (odds ratio, 3.8; p = 0:01)[14]. In France, Dumont-Wallon G et al showed that *P. acnes* resistance to erythromycin was significantly higher in patients who were previously treated with topical erythromycin (p = 0.03) and *P. acnes* resistance to tetracycline was also significantly higher in patients who were previously given systemic cyclines (p= 0.002)[9]. In Singapore, Tan HH et al showed that the isolates of antibiotic resistant *P. acnes* were higher in patients who had been on antibiotics for longer (>18 weeks) periods (21.6%) as compared with patients who had been on short-term (between 6 to 18 weeks) antibiotics (6.25%) or patients who had never been on antibiotics (0%)[6].

It is interesting to note in our study that 11% of swab sampling grew gram negative organism (*Klebsiella species*) which is not a normal commensal on the skin. Further analysis showed 81.8% (9 patients) of the patients had been given antibiotic within the last 6 months with a mean duration of 11.73 weeks. Long term antibiotic therapy will change the normal follicular microbial population and predispose to gram negative bacteria[16]. Gram negative folliculitis should be suspected in patients with acne vulgaris who have been long term antibiotic and present with predominantly inflamed lesions e.g pustules, nodules or papules especially in the perinasal and chin area[16,17]. Our study suggests that long duration of antibiotic may also contribute to emergence of gram negative organism besides antibiotic resistant *P. acnes*. However, the significance of gram negative organism and its relationship to duration of antibiotic therapy are still beyond the scope of our study.

There are a few limitations in our study. We were not able to look into the clinical outcome of patients with antibiotic resistant *P. acnes* in view of the small number of patients with antibiotic resistant *P. acnes*. It would be of clinical relevance to correlate clinical response with antibiotic sensitivity to establish the relevance of colonization with antibiotic resistant *P. acnes*. Our study is a single centre, cross sectional study which does not reflect the overall antibiotic sensitivity pattern of *P. acnes* in Malaysia. Hence, we strongly feel that a multicentre trial involving primary care physicians may be able to address this issue better.

Conclusion

Our study showed that 15.1% of the patients carry antibiotic resistant *P. acnes*. Resistance to clindamycin was the highest followed by erythromycin and doxycycline. Longer duration of antibiotic treatment within the last 6 months predispose to antibiotic resistant *P. acnes*. There is also evidence from our study to suggest emergence of gram negative organism as a result of long duration of antibiotic therapy. Strategies to reduce antibiotic resistance include limiting the duration of therapy, using combination therapy regimens with a rational topical program (Retinoid and BPO) and avoid using oral antibiotics as maintenance. By increasing our understanding of the multifaceted actions of antibiotics and the known clinical implications of antibiotic resistance, we can improve our decision making in prescribing these agents.

References

1. Eady EA, Cove JH, Layton AM. Is antibiotic resistance in cutaneous propionibacteria clinically relevant? Implications of resistance for acne patients and prescribers. Am J Clin Dermatol 2003;4:813-31.
2. Leyden JJ. The evolving role of Propionibacterium acnes in acne. Semin Cutan Med Surg 2001;20(3): 139-143.
3. Kurokawa I, Nishijima S, Asada Y. The antibiotic susceptibility of Propionibacterium acnes: a 15-year bacteriological study and retrospective evaluation. J Dermatol 1988;15:149-54.
4. Oakley A, Rademaker M, Duffill M, Leng R, Shewan J. Propionibacterium: resistance of acne to antibiotics. N Z Med J 1995;108:43-4.
5. Ross JI, Snelling AM, Carnegie E, Coates P, Cunliffe WJ, Bettoli V,Tosti G, Katsambas A, Galvan JI, Pulgar PD, Rollman O, Torok L, Eady EA, Cove JH. Antibiotic-resistant acne: lessons from Europe. Br J Dermatol 2003;148:467-78.
6. Tan HH, Goh CL, Yeo MG, Tan ML. Antibiotic sensitivity of Propionibacterium acnes isolates from patients with acne vulgaris in a tertiary dermatological referral centre in Singapore. Ann Acad Med Singapore 2001;30(1):22-5.
7. Lehmann HP, Robinson KA, Andrews JS, Holloway V, Goodman SN. Acne therapy: A methodologic review. J Am Acad Dermatol 2002;47:231-40.
8. Coates P, Vyakrnam S, Eady EA, Jones CE, Cove JH, Cunliffe WJ. Prevalence of antibiotic-resistant propionibacteria on the skin of acne patients: 10-year surveillance data and snapshot distribution study. Br J Dermatol 2002;146:840-8.
9. Dumont-Wallon G, Moyse D, Blouin E, Dre´no B. Bacterial resistance in French acne patients. Int J Dermatol 2010;49:283-8.
10. Tan HH, Tan AWH, Barkham T, Yan XY, Zhu M. Community-based study of acne vulgaris in adolescents in Singapore. Br J Dermatol 2007;157:547-551.
11. El Mahdy TSM, Abd-Elaziz MM, El-Sayed MH, Ross JI, Abd Allah S, Radwan H. Antibiotic resistance amongst cutaneous propionibacteria from Egyptian acne patients. 17th ECCMID/25th ICC. 2007.
12. Kurokawa I, Nishijima S, Kawabata S. Antimicrobial susceptibility of Propionibacterium acnes isolated from acne vulgaris. Eur J Dermatol 1999;9:25-28.
13. Leyden JJ, Del Rosso JQ, Webster GF. Clinical considerations in the treatment of acne vulgaris and other inflammatory skin disorders: a status report. Dermatol Clin 2009;27:1-15.
14. Oprica C, Emtestam L, Lapins J, Borglund E, Nyberg F, Stenlund K, Lundeberg L, Sillerstrom E, Nord CE. Antibiotic-resistant Propionibacterium acnes on the skin of patients with moderate to severe acne in Stockholm. Anaerobe 2004;10:155-164.
15. Tan HH, Goh CL, Yeo MG, Tan ML. Antibiotic sensitivity of Propionibacterium acnes isolates from patients with acne vulgaris in a tertiary dermatological referral centre in Singapore. Ann Acad Med Singapore 2001;30(1):22-5.
16. Cunliffe WJ, Gollnick HPM. Acne Diagnosis and management. London;Martin Dunitz 2001:1-46.
17. Shalita AR. Acne: Clinical Presentations. Clinics in Dermatology 2004;22:385-386.

GENERAL DERMATOLOGY - Original Article

Comparison of the efficacy and safety of Sungai Buloh Augmented Multiple Drug Therapy (SBA-MDT) and the World Health Organisation Multiple Drug Therapy (WHO-MDT) in the Treatment of Leprosy in Malaysia

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Abstract

Background Multiple drug therapy for leprosy has been in use in Malaysia since 1985. The SBA-MDT is a modified WHO-MDT with an initial intensive phase and a longer duration of treatment.

Objective The aim of the study is to compare the efficacy and safety of SBA-MDT against WHO-MDT in the Treatment of Leprosy in Malaysia.

Methodology A retrospective study was conducted between 1985 and 2009 in thirteen Malaysian dermatology centres. Data collected were analysed for comparison of relapse rates, compliance rates and adverse drug effects between the 2 regimes.

Results A total of 1113 patients were included, of which 966 patients completed the SBA-MDT and 147 patients completed the WHO-MDT. Both the MDT regimes had a treatment failure rate of less than 2%. The relapse rate was 1.7% with SBA-MDT and 1.4% with WHO-MDT ($p = 0.79$). For multibacillary leprosy, the relapse rates were 0.9% with the former and 0 with the latter ($p = 0.32$). For paucibacillary leprosy, it was 3.1% and 5.0% respectively ($p = 0.52$). Patients on SBA-MDT had higher type 1 (16.1% vs. 8.8%, $p = 0.03$) and type 2 lepra reactions (19.2% vs. 6.1%, $p < 0.001$). Similarly, those on SBA-MDT also had higher rate of severe adverse drug reactions (11.1% vs. 5.6%, $p = 0.01$).

Conclusion Both the SBA-MDT and the WHO-MDT regimes were effective in inducing clinical remission. Incidence of lepra reactions and severe adverse drug reactions were higher in patients with SBA-MDT.

Keywords *Hansen's disease, Outcome study, relapse rate, multibacilliary leprosy, paucibacilliary leprosy*

Introduction

Leprosy is a chronic granulomatous infection caused by Mycobacterium leprae affecting mainly the skin and nerves. In Malaysia, leprosy had been eliminated as a public health problem, with prevalence of less than 1 per 10,000 populations since 1994[1]. Nevertheless, it continued to be seen especially among the native populations in particular the Orang Asli and the Penans; and also the immigrant workers from Indonesia, the Phillipines, Myanmar and Nepal[2].

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Dapsone was the first drug to be used in Malaysia for the treatment of leprosy in 1948 by the National Leprosy Control Centre in Sungai Buloh3. However, in 1964, the first case of dapsone resistance was detected[3]. In 1982, the World Health Organisation (WHO) recommended the use of multiple drug therapy (MDT) consisting of rifamipicin, dapsone and clofazimine to prevent the development of drug resistance[4]. In 1985, the WHO-MDT was modified by the National Leprosy Control Centre for use in Malaysia[3]. The differences between the Sungai Buloh Augmented MDT (SBA-MDT), the WHO-MDT 1982 regime and the updated WHO-MDT 1997 regime is shown in Table 1[3,4,5].

Table 1 SBA-MDT, WHO-MDT (1982) and WHO-MDT (1997)

MDT	Regime
Sungai Buloh Augmented	Paucibacillary T Rifampicin 600 mg per month (supervised) T Clofazimine 300 mg per month (supervised) T Dapsone 100 mg per day T Clofazimine 100 mg per day Duration: 1 year Surveillance: 5 years Multibacillary Intensive phase T Rifampicin 600 mg per day (supervised) T Dapsone 100 mg per day (supervised) T Clofazimine 100 mg per day (supervised) Duration: Minimum 3 weeks or until MI = 0 Maintenance phase T Rifampicin 600 mg per month (supervised) T Clofazimine 300 mg per month (supervised) T Dapsone 100 mg per day T Clofazimine 100 mg per day Duration: minimum 3 years or until MI = 0 Surveillance: 10 years
WHO (1982)	Paucibacillary T Rifampicin 600 mg per month (supervised) T Dapsone 100 mg daily Duration: 6 months Surveillance: 5 years Multibacillary T Rifampicin 600 mg per month (supervised) T Clofazimine 300 mg per month (supervised) T Dapsone 100 mg daily T Clofazimine 50 mg daily Duration: 2 years Surveillance: 10 years
WHO (1997)	Paucibacillary T Rifampicin 600 mg per month (supervised) T Dapsone 100 mg daily Duration: 6 months Surveillance: 2 years Multibacillary T Rifampicin 600 mg per month (supervised) T Clofazimine 300 mg per month (supervised) T Dapsone 100 mg daily T Clofazimine 50 mg daily Duration: 1 years Surveillance: 5 years

There were 2 reasons cited for the longer duration of treatment in the SBA-MDT compared to the WHO-MDT. Firstly, funding of longer duration of MDT was not a problem in Malaysia compared to other countries like India. Secondly, most of the patients seen in Malaysia had a high bacteriologic index (BI) and it was noted that there was a high relapse rate associated with shorter duration of treatment, especially in patients with BI > 3[6,7,8].

In Malaysia, the SBA-MDT has been widely used in Peninsular Malaysia. However, in East Malaysia, the WHO-MDT has been adopted since 1993 because of the high number of immigrant workers from Indonesia and the Phillipines having the disease. This is to allow standardization of the MDT treatment when these workers continue their treatment back in their country of origin.

Thus, we aim to determine the efficacy and safety of the SBA-MDT compared with the WHO-MDT used in Malaysia.

Materials and methods

This is a retrospective study to determine the efficacy and safety of the SBA-MDT regime and the WHO-MDT in the treatment of leprosy in Malaysia between January 1985 and December 2009. Thirteen dermatology centres in Malaysia participated in this study i.e. Dermatology Departments of Hospital Kuala Lumpur, Hospital Melaka, Hospital Selayang, Sarawak General Hospital, Queen Elizabeth Hospital, Hospital Pulau Pinang, Hospital Tengku Ampuan Rahimah, Hospital Sultanah Bahiyah, Hospital Sultanah Aminah, Hospital Kota Bahru, Hospital Seremban, Hospital Tengku Ampuan Afzan, and Hospital Tuanku Fauziah.

The inclusion criteria for this study is all the patients with leprosy who successfully completed either the SBA-MDT or the WHO-MDT. The exclusion criteria are patients who failed to complete the MDT, patients given MDT other than the SBA-MDT or the WHO-MDT regime, and patients who were on other antilepromatous treatment before given the SBA-MDT or the WHO-MDT.

Data collection was done using the standardized case report forms. These forms and the study protocol were distributed to all the participating centres. Completed case report forms were returned to the coordinating centre in the Department of Dermatology, Hospital Kuala Lumpur for data processing and analysis. The data collected include sociodemographic characteristics, clinical characteristics, MDT regimes used and outcomes including relapse, treatment failure and side effects of treatment.

In this study, the clinical types of leprosy are defined according to the Ridley-Jopling classification[9]. In addition to the 5 types of leprosy in the Ridley-Jopling classification, we also included indeterminate leprosy and neural leprosy. Neural leprosy is a subtype of leprosy presenting with only nerve involvement without skin manifestations.

MDT treatment failure is defined as failure to respond to the MDT regime in terms of clearance of skin lesion(s) or reduction in the bacteriologic index and morphological index on slit skin smears. Relapse of disease is defined as a patient who successfully completed an adequate course of MDT regime but subsequently develops new signs and symptoms of the disease either during the surveillance period or thereafter[10]. In patients with multibacillary leprosy, relapse is defined by WHO as the multiplication of Mycobacterium leprae, suspected by the marked increase (at least 2+ over the previous value) in the BI at any single site, usually with evidence of clinical deterioration manifested as new skin lesions and/or new nerve damage. In paucibacillary leprosy, relapse is suspected by the evidence of clinical deterioration manifested by development of new skin lesions and/or new nerve damage.

Compliance of treatment is divided into good, moderate, poor and very poor compliance. Good compliance is defined as patients who never or hardly missed their treatment i.e. not more than 1 week in the entire treatment period. Moderate compliance denotes patients who did not take their medications for a period up to 1 month during the entire treatment period. Poor compliance is patients who did not take their

Table 2 Sociodemographic characteristics of the patients who completed the SBA-MDT and the WHO-MDT.

Sociodemographic characteristics	SBA-MDT (N=966)	SBA-MDT (N=966)	p value
Gender			
Male	719 (74.4%)	106 (72.1%)	0.51
Female	243 (25.6%)	41 (27.9%)	
Mean age (years)	39.8 ± 16.30	39.7 ± 17.88	0.98
Ethnicity [n(%)]			
Malay	400 (41.4%)	28 (19.0%)	***<0.001***
Chinese	233 (24.1%)	32 (21.7%)	
Indian	72 (7.5%)	6 (4.0%)	
Bumiputera Sabah	5 (0.5%)	34 (23.0%)	
Bumiputera Sarawak	2 (0.1%)	5 (4.0%)	
Orang Asli	20 (2.1%)	0 (0%)	
Indonesian	198 (20.6%)	15 (10.1%)	
Others	36 (3.7%)	27 (18.2%)	
Nationality [n(%)]			
Malaysian	781 (80.8%)	107 (72.8%)	***0.02***
Others	185 (19.2%)	40 (27.2%)	

Table 3 Clinical characteristics of patients who completed the SBA-MDT and the WHO-MDT.

Clinical characteristics	SBA-MDT (N=966)	WHO-MDT (N=147)	p value
Ridley-Jopling classification [n(%)]			
Indeterminate (Ind)	37 (3.8%)	9 (6.1%)	0.28
Tuberculoid (TT)	175 (18.1%)	31 (21.1%)	
Borderline Tuberculoid (BT)	138 (14.3%)	16 (10.9%)	
Mid Borderline (BB)	61 (6.3%)	7 (4.8%)	
Borderline Lepromatous (BL)	167 (17.3%)	20 (13.6%)	
Lepromatous (LL)	375 (38.8%)	64 (43.5%)	
Neural (Neu)	13 (1.4%)	0 (0%)	
Mean Bacteriologic Index (BI)			
Pre treatment	2.5 ± 1.66	2.6 ± 1.82	0.58
Post Treatment	0 ± 0.07	0.7 ± 1.38	***<0.001***
Mean Morphological Index (MI)			
Pre treatment	2.3 ± 4.01	9.4 ± 15.13	***<0.001***
Post treatment	0 ± 0.06	0.1 ± 0.29	***0.01***

medications for a period of between 1 to 3 months during the entire treatment period. Very poor compliance is patients who did not take their medications for a period of more than 3 months during the entire treatment period. Severe adverse drug reaction is defined as severe unwanted reaction caused by the MDT which might result in the cessation or alteration of the offending drug(s).

Collected data were analysed using SPSS (SPSS Inc., Chicago, IL, USA). Continuous data were described as means and standard deviations. Categorical data were expressed as frequencies and percentages. Statistical comparisons were conducted using Chi-square test or Fisher's exact test for categorical data and t-test for continuous data. The level of significance was set at $p < 0.05$.

Results

There were 1531 patients with leprosy seen within the study period of which 1113 patients fulfilled the inclusion sand exclusion criteria. There were 966 patients who successfully completed the SBA-MDT whereas 147 patients completed the WHO-MDT. Most of the patients who completed the WHO-MDT were from the Dermatology Departments of Sarawak General Hospital and Queen Elizabeth Hospital, both in East Malaysian Borneo.

There were more male patients receiving both MDTs (Table 2). The female to male ratio was higher in patients who completed the SBA-MDT (1:3.0) compared to the WHO-MDT (1:2.6) although the difference was not statistically significant ($p = 0.51$). There were also no significant differences between these two MDTs in terms of age. However, there were more Malaysian receiving the SBA-MDT (80.8% vs. 72.8%, $p = 0.02$). There were also racial differences in both the regimen ($p < 0.001$).

The clinical characteristics of patients on both the MDTs is shown in Table 3. There were no differences in the types of leprosy between patients receiving SBA-MDT and WHO-MDT ($p = 0.28$). The mean pre-treatment morphological index (MI) was significantly higher in patients who completed WHO-MDT (9.4 vs. 2.3, $p < 0.001$). However, the pre treatment bacteriological index (BI) was not significantly different. In the SBA-MDT, all the patients except one were smear negative upon completion of treatment. On the other hand, only 60.9% of patients on WHO-MDT were smear negative after completing treatment.

The mean duration of treatment using the multibacillary SBA-MDT was longer than the multibacillary WHO-MDT (43.1 months vs. 32.1 months, $p < 0.001$). Similarly, the mean duration using the paucibacillary SBA-MDT was also longer than the paucibacillary WHO-MDT (21.4 months vs. 10.6 months, $p < 0.001$).

The mean duration of multibacillary WHO-MDT of 32.1 months was much longer than the standard WHO-MDT protocol of 12 months. It was also surprising to note that the mean duration of the paucibacillary WHO-MDT of 10.6 months was longer than the 6 months recommendation. Similarly, the mean duration of the paucibacillary SBA-MDT of 21.4 months was also longer than the recommended 12 months.

Both the SBA-MDT and WHO-MDT had a failure rate of 1.4%. Surprisingly, 43.5% of patients on SBA-MDT completed the surveillance compared to only 38.1% on WHO-MDT ($p<0.001$) despite the longer surveillance period in the former (Table 4). Patients on WHO-MDT had better compliance to treatment compare to SBA-MDT ($p = 0.03$).

More patients treated with SBA-MDT developed lepra reactions (Table 4). In the SBA-MDT group, 16.1% and 19.2% developed type 1 and type 2 lepra reactions respectively.

In comparison, in the WHO-MDT group, only 8.8% ($p = 0.03$) and 6.1% ($p < 0.001$) respectively developed type 1 and type 2 lepra reaction.

The relapse rate was 1.7% in patients who completed the SBA-MDT compared with only 1.4% in patients who completed WHO-MDT although it was not statistically significant ($p = 0.79$). The relapse rates were 3.1% and 0.9% with paucibacillary and multibacillary leprosy respectively in those who completed SBA-MDT compared to 5.0% ($p = 0.52$) and 0% ($p =0.32$) respectively in those who completed WHO-MDT (Table 5).

Table 4 Treatment characteristics of patient.

Treatment characteristics	SBA-MDT N=966	WHO-MDT N=147	p value
Mean duration of treatment (months)			
Multibacillary	43.1 ± 18.03	32.1 ± 20.89	***< 0.001***
Paucibacillary	21.4 ± 20.64	10.6 ± 9.99	***<0.001***
Treatment failure [n(%)]	14 (1.4%)	2 (1.4%)	0.85
Completed surveillance [n(%)]	420 (43.5%)	56 (38.1%)	***<0.001***
Compliance to treatment			
Good	704 (72.9%)	120 (81.6%)	0.03
Moderate	69 (7.1%)	11 (7.6%)	
Poor	59 (6.1%)	8 (5.4%)	
Very poor	134 (13.9%)	8 (5.4%)	
Leprosy Reactions [n(%)]			
Type 1	156 (16.1%)	13 (8.8%)	0.03
Type 2	185 (19.2%)	9 (6.1%)	***<0.001***

Table 5 Relapse in patients receiving SBA-MDT and WHO-MDT.

Relapse	SBA-MDT N=966	WHO-MDT N=147	p value
Number of patients [n(%)]	16 (1.7%)	2 (1.4%)	0.79
Types of leprosy			
Paucibacillary	10 (3.1%)	2 (5.0%)	0.52
Multibacillary	6 (0.9%)	0 (0%)	0.32

Characteristics of patients with relapse are shown in Table 6.

Severe adverse reactions to drugs to MDT were reported 11.1% of patients given SBA-MDT compared to only 5.6% given WHO-MDT ($p = 0.01$). The most common severe adverse reactions were haemolytic anaemia and hepatitis.

Discussion

It was noted in this study that both the SBA-MDT and WHO-MDT effectively reduced the load of Mycobacterium leprae in patients with leprosy.

Both regimes were equally effective where the treatment failure rates were low (1.4%). However, we found that the relapse rate was higher with SBA-MDT although it was not statistically significant. It is surprising as treatment with SBA-MDT required patients to be on treatment until BI = 0. In Sarawak, East Malaysian Borneo, a similar comparison between SBA-MDT and WHO-MDT failed to detect any relapse in both treatment regimens[11].

Table 6 Characteristics of patients who relapsed during the surveillance period.

No	R-J type	MDT	Type	PreRx SSS *	PostRx SSS *	Rx Duration	Compliance	Relapse Interval	SSS on relapse*
1	Ind	SBA-MDT	PB	0 / 0	0 /0	19 mth	Good	2yr 6mth	+ve
2	TT	SBA-MDT	PB	0 / 0	0 / 0	14 mth	Good	6 mth	0.5 / 0
3	TT	SBA-MDT	PB	0 / 0	0 / 0	34 mth	Moderate	4 mth	0 / 0
4	TT	SBA-MDT	PB	0.1 / 0.1	0 / 0	13 mth	Good	3 mth	0 / 0
5	BT	SBA-MDT	PB	0 / 0	0 / 0	11 mth	Good	5 mth	0 / 0
6	BT	SBA-MDT	PB	0 / 0	0 / 0	25 mth	Good	1yr 9mth	0 / 0
7	BT	SBA-MDT	PB	0 / 0	0 / 0	13 mth	Good	3 mth	0 / 0
8	BT	SBA-MDT	MB	0 / 0	0 / 0	30 mth	Moderate	2 yr 1 mth	0 / 0
9	BT	SBA-MDT	MB	0 / 0	0 / 0	13 mth	Good	2 yr 2 mth	0 / 0
10	BT	SBA-MDT	MB	1.0 / 2.0	0 / 0	37 mth	Good	9 mth	0 / 0
11	BB	SBA-MDT	PB	0 / 0	0 / 0	11 mth	Moderate	1yr 2mth	0 / 0
12	BL	SBA-MDT	MB	3.2 / 4.9	0 / 0	37 mth	Good	1yr 7mth	0 / 0
13	BL	SBA-MDT	MB	3.1 / 0	0 / 0	34 mth	Good	2yr 2mth	2.0 / 0
14	LL	SBA-MDT	MB	2.3 / 1.6	0 / 0	36 mth	Good	2yr 2mth	0 / 0
15	LL	SBA-MDT	MB	3.4 / 4.2	-	34 mth	Very poor	4yr 11mth	0 / 0
16	LL	SBA-MDT	MB	2.1 / 2.7	0 / 0	42 mth	Moderate	3yr 5mth	0 / 0
17	TT	WHO-MDT	PB	0 / 0	0 / 0	5 mth	Moderate	2yr 11mth	0 / 0
18	TT	WHO-MDT	PB	0 / 0	0 / 0	12 mth	Poor	24 mth	0 / 0

Footnote:
Rx = treatment
SSS = slit skin smear
yr = years, mth = months
MB = multibacillary, PB = paucibacillary
R-J = Ridley-Jopling, Ind = indeterminate, TT = tuberculoid, BT = borderline tuberculoid, BB = mid borderline, BL = borderline lepromatous, LL = lepromatous
* indicates BI / MI

respectively in those who completed WHO-MDT (Table 5). Characteristics of patients with relapse are shown in Table 6.

Severe adverse reactions to drugs to MDT were reported 11.1% of patients given SBA-MDT compared to only 5.6% given WHO-MDT ($p = 0.01$). The most common severe adverse reactions were haemolytic anaemia and hepatitis.

Discussion

It was noted in this study that both the SBA-MDT and WHO-MDT effectively reduced the load of Mycobacterium leprae in patients with leprosy.

Both regimes were equally effective where the treatment failure rates were low (1.4%). However, we found that the relapse rate was higher with SBA-MDT although it was not statistically significant. It is surprising as treatment with SBA-MDT required patients to be on treatment until BI = 0. In Sarawak, East Malaysian Borneo, a similar comparison between SBA-MDT and WHO-MDT failed to detect any relapse in both treatment regimens[11].

None of our patients with multibacillary leprosy treated with the WHO-MDT relapsed. This is similarly seen in the Sarawak study[11]. However, studies from other countries showed a relapse rate of between 0.5% and 3% for patients with multibacillary leprosy who had completed the

Table 7 Comparison of the relapse rate among patients with multibacillary leprosy in the current study with other studies.

Reference	Country	Year	Regime	Relapse rate
Current study	Malaysia	2010	SBA-MDT	0.9%
Current study	Malaysia	2010	WHO-MDT (1 year)	0%
Yap et al[11]	Malaysia	2008	Both SBA-MDT and WHO-MDT (1 and 2 years)	0%
Kyaw et al[12]	Myanmar	2008	1 year WHO-MDT	0.5%
Fajardo et al[13]	Philippines	2009	1 year WHO-MDT	3%
Ho & Lo[14]	Hong Kong	2006	2 years WHO-MDT	2.7%
Shen et al[15]	China	2006	2 years WHO-MDT	0.2%
Desikan et al[16]	India	2008	2 years WHO-MDT	0.8%
Poojabylaiah et al[17]	India	2008	2 years WHO-MDT	1.8%
Balagon et al[18]	Philippines	2009	2 years WHO-MDT	4.6%
Fajardo et al[13]	Philippines	2009	2 years WHO-MDT	3%
Medeiros et al[19]	Portugal	2009	2 years WHO-MDT	8.8%
Fajardo et al[13]	Philippines	2009	Intensive daily rifampicin and orfloxacin for a month followed by 1 year WHO-MDT	0%
Fajardo et al[13]	Philippines	2009	Daily rifampicin and orfloxacin for a month	25%

1 year WHO MDT regime and between 0.2% and 8.8% for those who had completed the 2 years WHO MDT regime (Table 7). It is unsure whether the relapse rate of 0% in our study was an underestimation. This might be due to failure to capture relapse because of the short surveillance period of only 5 years for patients with multibacillary leprosy who completed the MDT-WHO. Balagon et al found that most patients relapsed between 6 and 16 years after completion of treatment[18].

The relapse rate of patients with multibacillary leprosy who had completed the SBA-MDT was 0.9%. This figure was within the range of between 0.5% and 8.8% in those who had completed the 1 and 2 years WHO-MDT regimes. However, the relapse rate of this regime was higher than the WHO-MDT although it required patients to be on longer treatment duration until BI = 0. A possible reason for the higher relapse might be due to longer period of surveillance (10 years compared to 5 years) which allowed detection of the relapse. Moreover, higher percentages of patients on SBA-MDT completed surveillance (43.5%) and thus allowed detection of relapse compared to patients on WHO-MDT (38.1%).

We noted that the type 1 and type 2 lepra reactions were significantly higher among patients on Sungai Buloh Augmented MDT. This might be due to the intensive phase of SBA-MDT which might have caused more intense release of mycobacterial antigens. The higher rate of type 1 lepra reaction in patients on SBA-MDT might also be related to the higher proportion of patients (37.9%) in the borderline spectrum of disease (comprising the borderline tuberculoid, mid borderline and borderline lepromatous) compared to those on WHO-MDT (29.3%)[20, 21].

The incidence of adverse drug reactions was higher in patients on the SBA-MDT compared to WHO-MDT. This might be due the use of intensive phase, higher dosage of dapsone and longer duration of treatment in the SBA-MDT. However, the rate of these reactions with SBA-MDT in our study of 11.1% was lower than the rate of 21.1% with similar MDT in Penang[22]. The higher rate of dapsone induced hemolysis and hepatitis with SBA-MDT might be attributed by the higher dosage of dapsone (100 mg daily with SBA-MDT vs. 50 mg daily with WHO-MDT) and the use of intensive phase of rifampicin 600 mg daily for at least 3 weeks respectively.

The limitations in this study are the retrospective nature of the study and the different socio-demographic characteristics of patients receiving the 2 different MDT regimes. The retrospective nature of this study placed a heavy emphasis on the previous documentations in the medical records and also the variation in the interpretation of the data by the investigators from the different participating centres. The differences in clinical characteristics of patients and variable treatment duration in the two MDT regimes might also contribute to the differences in the results.

In conclusion, both the SBA-MDT and the WHO-MDT regimes are effective in inducing clinical remission and reducing bacterial counts. The SBA-MDT regime give a higher relapse rate although not statistically significant. It also contributed to a higher rate of severe adverse drug reactions and leprosy reactions.

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References

1. Fadillah K. Report on a workshop of leprosy elimination in the western Pacific region, Manila, Philippines. 4-7 March 1996.
2. Yap FB. Leprosy in Sarawak, East Malaysian Borneo. Scand J Infect Dis. 2009; 41: 320.
3. Jayalakshmi P. Leprosy in Malaysia. Malaysian J Pathol 1994; 16(1): 7-9.
4. WHO Study Group on Leprosy. Chemotherapy of leprosy control programmes. No. 675 of technical report series. Geneva: World Health Organization; 1982.
5. WHO Expert Committee on Leprosy. 7th report. No.874 of technical report series. Geneva: World Health Organization; 1998.
6. Ganesapillai T. The Augmented Sungei Buloh MDT regime. Guidelines for MDT 1991: 8-15.
7. Ganesapillai T. The Short MDT Regime in Sabah. Cutaneous Mycobacteria an update from Malaysia Lads- JRC Travelling Fellowship lecture 1996: 7 -11.
8. Jamet P, Ji B, the Marchoux Chemotherapy Study Group. Relapse after long term follow up of multibacillary patients treated by WHO multidrug regimen. Int J Lepr 1994; 63: 195-201.
9. Ridley DS, Jopling WH: Classification of leprosy according to immunity. A five-group system. Int J Lepr Other Mycobact Dis 1966; 34(3): 255-273.
10. WHO. Guide to Leprosy Control 1988.
11. Yap FBB, Awang T, Pubalan M. Comparison of multiple drug therapy in leprosy. Malaysian J Dermatol. 2008; 21: 47-51.
12. Kyaw K, Tsoh TM, Swe SYY, Nagaoka Y, Takezaki S, Suzuki K, Ichii N. Clinical analysis of multibacillary leprosy patients after 1-year fixed World Health Organization recommended multidrug therapy at Yangon General Hospital, Myanmar. J Dermatol. 2008; 35: 264-9.
13. Fajardo TT, Villahermosa L, Pardillo FEF, Abalos RM, Burgos J, dela Cruz E, Gerber RH. A comparative clinical trial in multibacillary leprosy with long-term relapse rates of four different multidrug regimens. Am J Trop Med Hyg. 2009; 81(2): 330-4.
14. Lo CK, Ho KK. Epidemiology of leprosy and response to treatment in Hong Kong. Hong Kong Med J 2006; 12: 174-9.
15. Shen J, Liu M, Zhang J, Su W, Ding G. Relapsed in MB leprosy patients treated with 24 months of MDT in South West China: a short report. Lepr Rev 2006; 77: 219-24.
16. Desikan KV, Sundaresh P, Tulasidad I, Rao PVR. 1n 8-12 year follow-up of highly bacillated Indian leprosy patients treated with the WHO multi-drug therapy. Lepr Rev. 2008; 79: 303-10.
17. Poojabylaiah M, Marne RB, Varikkodan R, Bala N, Dandakeri S, Martis J. Relapses in multibacillary leprosy patients after multidrug therapy. Lepr Rev 2008; 79: 320-4.
18. Balagon MF, Cellona RV, dela Cruz E, Burgos JA, Abalos RM, Walsh GP, Saunderson PR, Walsh DS. Long-term relapse risk of multibacillary leprosy after completion of 2 years of multiple drug therapy (WHO-MDT) in Cebu, Philippines. Am J Trop Med Hyg. 2009; 81(5): 895-9.
19. Medeiros S, Cartorze MG, Vieira MR. Hansen's disease in Portugal: multibacillary patients treated between 1988 and 2003. J Eur Acad Dermatol Venereol. 2009; 23: 29-35.
20. Yap FBB, Pubalan M. Risk factors for type 1 leprosy reaction in a tertiary clinic in Sarawak. Malaysian J Dermatol 2009; 22: 29-32.
21. Yap FBB. Clinical characteristics predicting erythema nodosum leprosum (ENL) among patients with multibacillary leprosy (MBL) in Sarawak. Asian Pac J Trop Med. 1009; 2(5): 66-70.
22. Tan WC, Lo Kang SC, Ong CK. Hansen's disease in Penang: a 10 year retrospective analysis. Malaysian J Dermatol 2007; 19: 89-94.

GENERAL DERMATOLOGY - Case Report

Disseminated fusariosis in a patient with acute lymphoblastic leukaemia: A case report and literature review

Tang Jyh Jong

Keywords *disseminated fusariosis, acute Lymphoblastic Leukaemia, fusarium spp, deep fungal infection*

Introduction

Fusarium spp are molds found in the soil and may be saprophytic or facultative plant pathogens. These are rare but important opportunistic pathogens in immunocompromised patients especially those with hematologic malignancies. *Fusarium spp* usually cause local infections such as onychomycosis and infections of surgical and burn wound. However more importantly, these pathogens can lead to severe disseminated infection with involvement of multiple organs including skin. This disseminated form of fusariosis occurs exclusively in patients with prolonged, severe neutropaenia especially in patients with acute leukaemia or those undergoing bone marrow transplantation. Prognosis of disseminated fusariosis is usually guarded if not recognized early. We report a rare case of disseminated fusariosis in a patient with acute lymphoblastic leukaemia.

Case 1

A 21 year-old lady with refractory acute lymphoblastic leukemia on salvage chemotherapy presented to us with multiple painful erythematous papules and nodules involving face, both upper limbs and lower limbs for 10 days prior to admission. The lesions started on both upper limbs and then spread to both lower limbs. These lesions subsequently ulcerated with central necrosis. It was associated with fever and lethargy. There was no history of preceding trauma or animal bite.

On examination, she was febrile and ill looking. She was pale but not jaundiced. Her haemodynamic status was stable. There were multiple erythematous macules as well as tender, indurated erythematous papules and nodules on her face, upper and lower limbs. Some of the lesions were ulcerated and covered with thick black eschar (Figure 1.1, 1.2, 1.3). There were no digital ulcers, paronychia or onychomycosis. There was presence of hepatosplenomegaly but no lymphadenopathy. Examinations of other systems include lung, cardiovascular were all unremarkable.

Our initial differential diagnosis included Leukemia cutis, nodular vasculitis, Sweet's syndrome and disseminated fungal infection. Skin biopsy for histopathological examination showed unremarkable epidermis and dermis. There were focal clusters as well as singly scattered fungal bodies and hyphae (Periodic Acid Schiff and Gomori-Grocott methenamine silver were positive). The fungal bodies were sized 2-3 times larger than RBC and the hyphae were septated, branching and broad (Figure 2.1, 2.2, 2.3). These features were consistent with deep fungal infection. Subsequent skin biopsy for fungal culture grew *Fusarium spp* (Figure 2.4). In addition to that, the blood culture also grew similar *Fusarium spp*. Hence, final diagnosis of disseminated fusariosis was made.

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IV Voriconazole was started subsequently and was given for a total duration of one month. She responded well to IV Voriconazole and all lesions healed well with post inflammatory hyperpigmentation. However this patient passed away few weeks later in the ward due to her nosocomial sepsis secondary to her underlying acute lymphoblastic leukaemia.

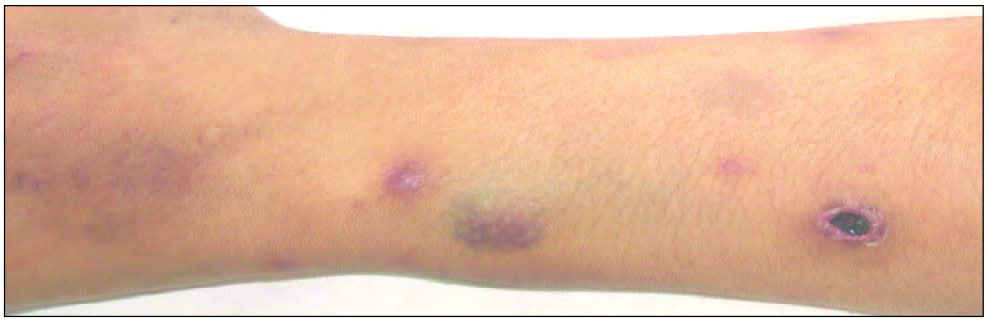

Figure 1.1 Numerous erythematous macules with tender erythematous papules and nodules, some with necrotic centre on left forearm.

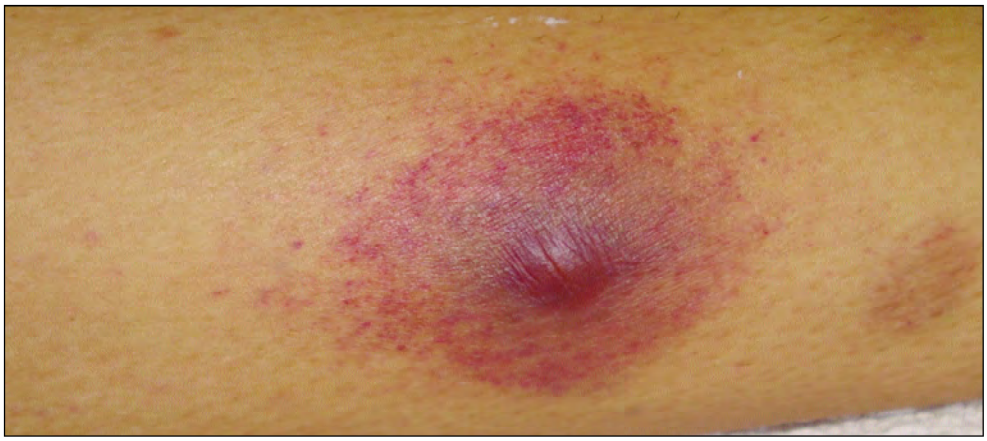

Figure 1.2 Close view of a tender erythematous nodule on leg.

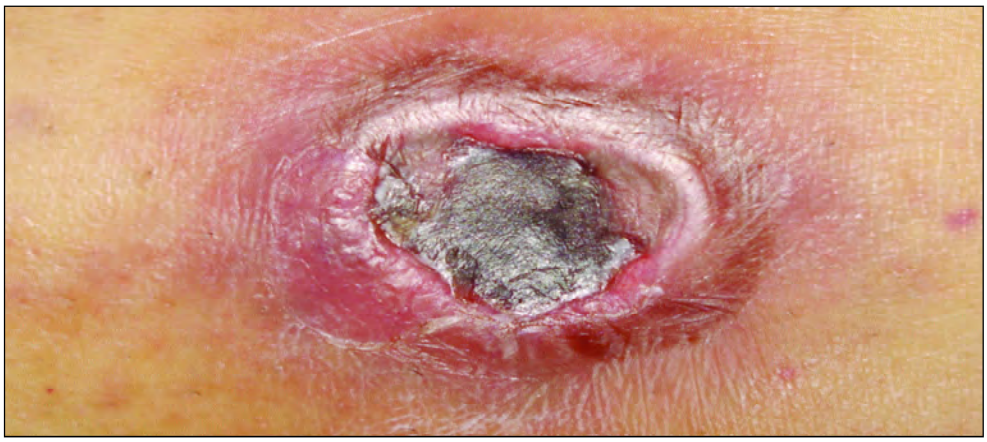

Figure 1.3 Close view of a late stage nodule covered with thick black eschar with a rim of erythema on leg.

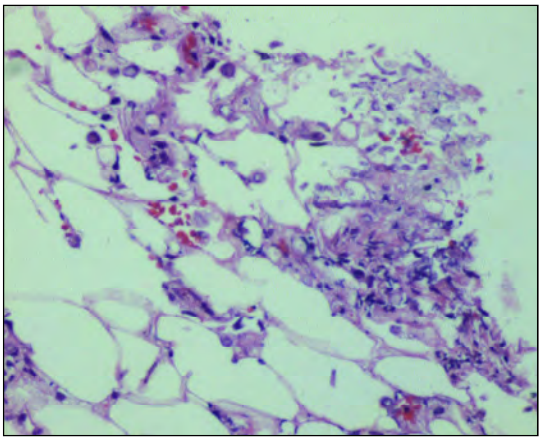

Figure 2.1 Focal clusters as well as singly scattered fungal bodies and hyphae in subcutaneous tissue. (H&E x10)

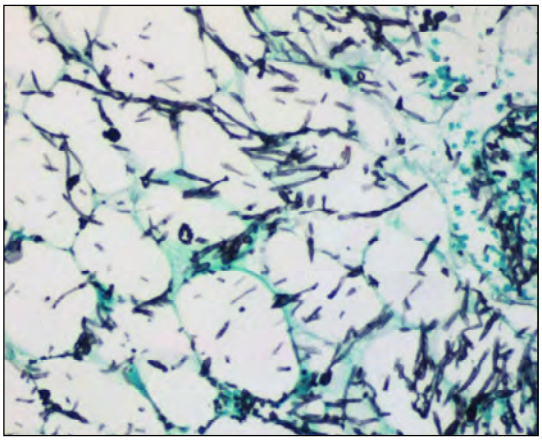

Figure 2.3 Gomori-Grocott methenamine silver stain highlights fungal bodies and septated branching hyphae in the subcutaneous tissue.

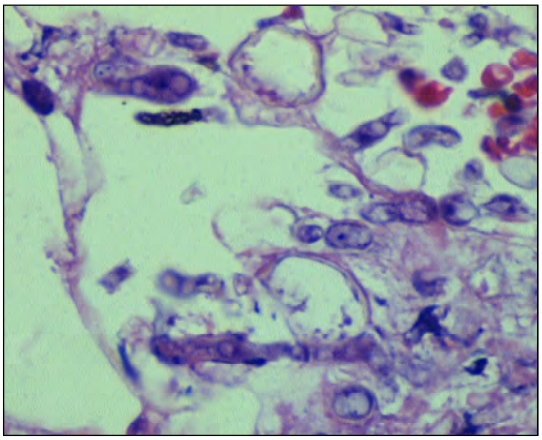

Figure 2.2 Fungal bodies sized 2-3 times larger than RBC with broad, branching and septated hyphae in subcutaneous tissue. (H&E x40).

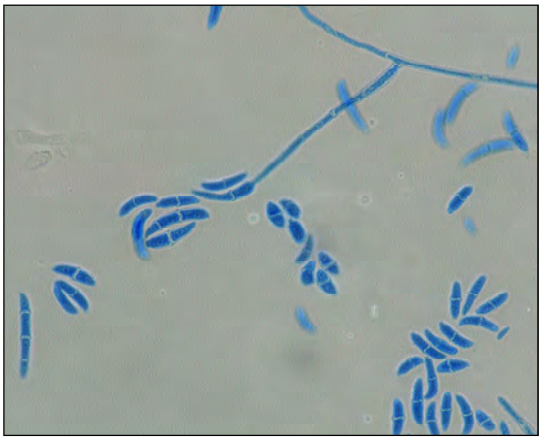

Figure 2.4 Microscopy: large sickle or banana shaped macroconidia (with 3 to 5 septa).

Discussion

Fusarium spp. is saprophytic mould that can be found in the soil and plant[1]. The incidence of disseminated fusariosis is increasing and had been reported in neutropenic patients with hematological malignancies (especially acute leukaemia) and those who had bone marrow transplant[1]. These fungi may cause a variety of cutaneous infection ranging from onychomycosis in healthy individual to widely disseminated infection in immunocompromised patients especially those with haematological malignancy undergoing intensive antileukaemic chemotherapy or allogenic hematopoetic stem cell transplantation[2].

Disseminated fusariosis may infest via inhalation of airborne conidia or the inoculation of conidia through a breach in the skin, especially associated with indwelling catheters, wounds and burns[1,2]. Initial source of disseminated fusariosis is usually sinus or pulmonary infection but skin make up of 33% of initial portal of entry and it is usually related to paronychia or trauma induced digital ulcer[3]. The *Fusarium* spp. most frequently involved in human infections are F. Solani, F. *Oxysporum*, F. *Verticilloides*, and F. *Moniliforme*[3].

Skin lesions are seen in more than 70% of disseminated fusariosis[3]. A variety of skin manifestations are seen in disseminated fusariosis, however, the most prominent feature of the lesion is a red or gray macule with a central ulceration or black eschar[4]. The central ulceration is due to dermal vessel thrombosis caused by hyphae elements. Other manifestation include purpuric papules, pustules and subcutaneous

nodules[4]. Disseminated fusariosis should be suspected in a febrile patient with neutropenia and hematological malignancy who have one or more of the following: 1) a digital paronychia especially with onychomycosis. 2) a digital ulcer or escar 3) suggestive disseminated skin lesions[4]. Our patient had classical presentation of disseminated fusariosis with fever, multiple tender erythematous papules and nodules which were covered with black eschar.

The diagnosis of *Fusarium* is usually based on a high index of suspicion in immunocompromised hosts[5]. Investigations should include skin biopsy for histolopathological examination, culture and immediate fungal stains, blood cultures, radiological evaluation of the lungs and sinuses[4,5]. Skin lesions contribute to the diagnosis of fusariosis in about 60% of patients whereas blood cultures are positive in about 60% of cases[5]. *Fusarium* species can grow rapidly on most conventional fungal medium, but growth is restricted by cycloheximide[1]. The microscopic morphology of *Fusarium* species is characterized by the presence of unbranched or branched conidiophores with phialides that produce multi-septate, banana or sickle-shaped macroconidia[1].

Treatment of fusariosis is especially difficult as *Fusarium* spp is relatively resistant to most antifungal medication[5]. IV Amphotericin B still remains the drug of choice but higher dose is required in treating fusariosis[6]. The new triazole agents (voriconazole, posaconazole, ravuconazole) has shown been to be effective in the treatment of disseminated fusariosis[5,6]. Combination treatment with Amphotericin B and voriconazole or posaconazole have been widely used too[6]. However Ketoconazole, miconazole, terbinafine, and echinocandins have limited activity[5]. Fluconazole, itraconazole and flucytosine have no activity against Fusarium species[5,6]. Apart from antifungal therapy, strategies to improve host immunity and surgical excision of necrotic tissue may help to improve the outcome of disseminated fusariosis[6].

Disseminated fusariosis carries a poor prognosis. Mortality rate in disseminated fusariosis can be as high as 75% which is related to the angiotropism of Fusarium and its ability for adventitious sporulation in tissues[6]. Patients with underlying hematological disease, neutropenia and late diagnosis and treatment contribute further to the poor prognosis of this condition[6]. Hence, it is important to have high index of suspicion in this group of patients so that early empirical intravenous antifungal can be given as early as possible to improve the outcome of this disease.

Conclusion

In conclusion, disseminated fusariosis is not common. The report of this case serves as a reminder of the ability of an innocuous, saprophytic, environmental mould namely *Fusarium spp* to emerge as a clinically significant opportunistic pathogen in the immunocompromised host especially those with haematological malignancy. Failure of early recognition of the disease can be fatal.

References

1. Shelly A Gilroy, Jane Roller, Russell A Rawling et al. Disseminated Fusariosis: an Emerging Opportunistic Infection. Clinical Microbiology Newsletter 2006;28 (22):174-175.
2. Groll A. H., Walsh T. J. Uncommon opportunistic fungi: new nosocomial threats. Clin Microbiol Infect 2001;7 (2):8-24.
3. José-Manuel Vagace, Cesar Sanz-Rodriguez, Maria-Soledad Casado et al. Resolution of disseminated fusariosis in a child with acute leukemia treated with combined antifungal therapy: a case report. BMC Infectious Diseases 2007;7:40.
4. Gerald P. Bodey, Maha Boktour, Steven Mays, Skin lesions associated with Fusarium infection. J Am Acad Dermatol. 2002;47(5):659-666.
5. M. Halpern, E. Balbi, L. Carius. Cellulitis and Nodular Skin Lesions Due to Fusarium spp in Liver Transplant: Case Report. Transplantation Proceedings 2010; 42:599-600.
6. Jossi M., Ambrosioni J., Macedo-Vinas M, Garbino J. Invasive Fusariosis With Prolonged Fungaemia in A Patient with Acute Lymphoblastic Leukaemia: Case Report And Review of the Literature. International Journal of Infectious Diseases. 2010;14:354-356.

PAEDIATRIC DERMATOLOGY - Short Case

Asymptomatic infant with high titre of immunoglobulin *M Mycobacterium Leprae* antibody whose mother has Morbus borderline lepromatous leprosy

Wahyu Lestari, Sri Lestari, Qaira Anum, Zainal H, Satya W

Introduction

Leprosy is a chronic infectious disease with a long incubation period caused by *Mycobacterium leprae*. The average incubation period for tuberculoid and lepromatous cases are 2-5 years and 8-12 years respectively[1,2]. Risk factors for leprosy includes age, sex, household contact and Bacilli Calmette-Guerin (BCG) vaccination[3].

We present an asymptomatic 3 month-old infant with high immunoglobulin M titre mycobacterium leprae antibody whose mother has morbus borderline lepromatous leprosy.

Case report

A 3-month old baby girl whose mother has clinical signs of leprosy was referred to Dermato-Venereology Department of Dr. M. Djamil Hospital on December 15th 2011 to exclude leprosy. She was born per vagina weighing 3.4kg at birth. She had BCG vaccination at one month of age. There was no history of fever, respiratory symptoms or skin signs suggestive of leprosy. She is breast-fed since birth and only cared by her mother. She lives in a small house at Damasraya in a 8x6 m^2 large house and sleeps in the same bed as her parents. Her father earns two million rupiahs per month.

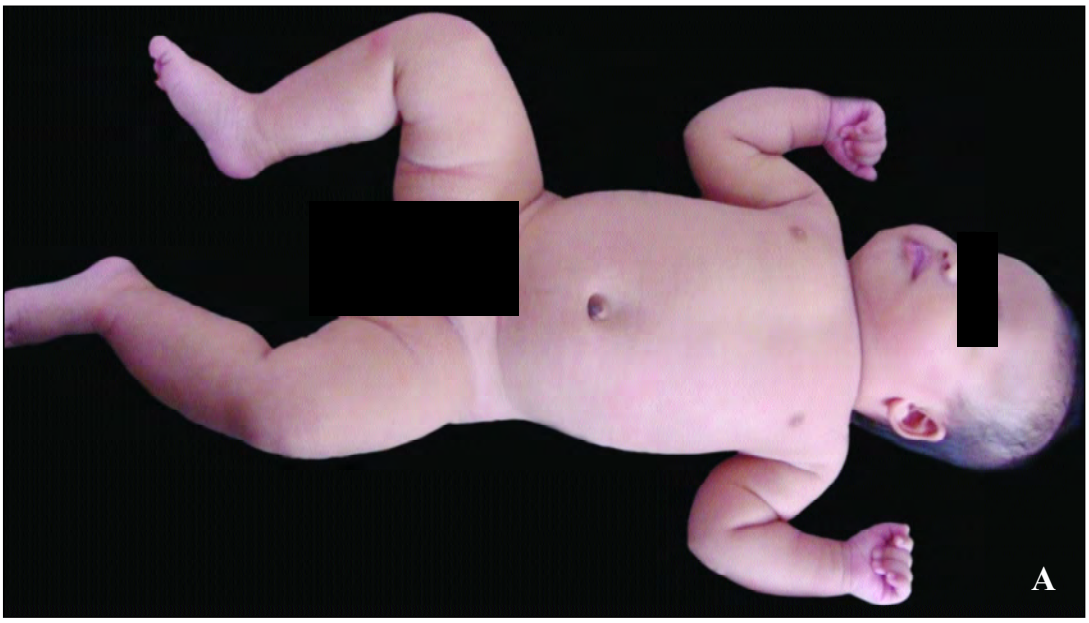

Figure A The patient with a body weight of 5.5kg and height of 68cm.

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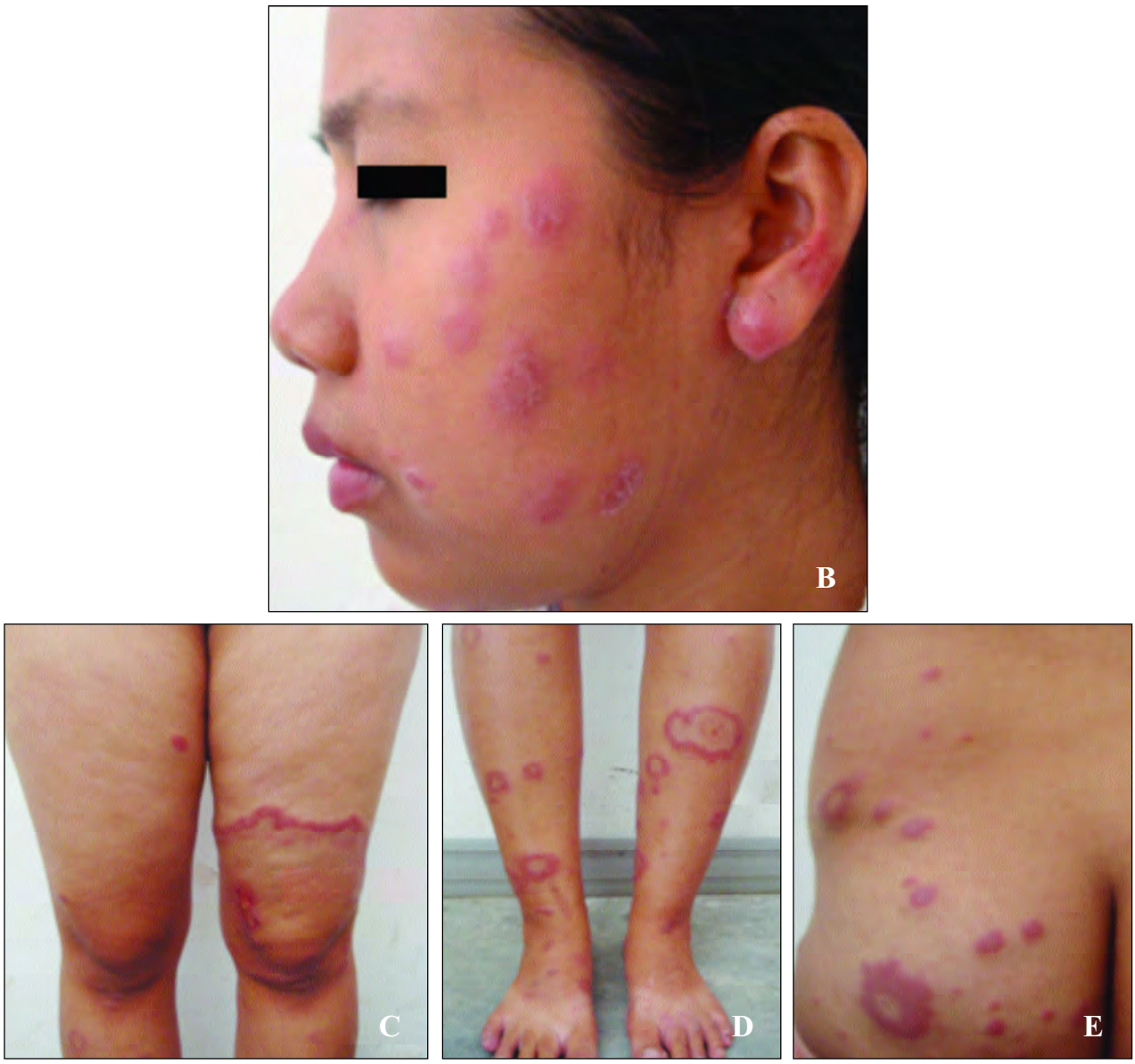

Figure B, C, D and E The patient's mother.

Clinically patient appears well nourished with no signs of cutaneous rash (Figure A). Whereas her mother has multiple facial plaques and nodules on the face and ear lobes. Annular rashes with central hypoaesthesia were noted on the mother's chest, gluteus, abdomen, forearms, hands, legs and feet.

Glove and stocking hypoaesthesia were also noted. Only bilateral ulnar nerves were thickened and tender. Xerosis cutis was noted on the lesions and the extremities. The slit skin smears on both earlobes, leg and gluteus showed acid fast bacilli bacteriology index of +3. No acid fast bacilli noted in the breast milk. The skin biopsy histopathological finding showed features of Virchow's cells and epitheliod cells that was consistent of Morbus borderline lepromatous leprosy.

The infant was diagnosed as having subclinical leprosy and her mother Morbus borderline lepromatous leprosy. Infant's IgM and IgG protein were 174 (normal for her age: 25-100 mg/dl) and 614 (normal for age : 200-700 mg/dl) respectively.

Discussion

This infant has subclinical leprosy. The 65 kd protein is not specific for *M. leprae* and can be cause by other pathogenic *mycobacteria*, such as *M. tuberculosis*[7]. In this case there was no sign of tuberculosis in the infant nor history of tuberculosis in family members. Patient's mother has borderline lepromatous leprosy support subclinicaql leprosy in this patient.

The main mode of transmission in leprosy is via droplet spread. Droplet transmission may be from mother to child or from other family members such as parents, grandparents or siblings and even close friends[4]. In young children, infection may be acquired through placenta or breast milk.

20% of children born to mothers with leprosy may develop leprosy by puberty. Leprosy in young children may resolve spontaneously, Getting pregnant at a young age may trigger leprosy complicated with neuropathy. Thus patient education and awareness of this complication during pregnancy is essential. Close monitoring of pregnant ladies with leprosy to screen for sign of nerve damage associated with MDT reaction[5]. Contact tracing of her children is required to screen for leprosy in her children.

In pregnant woman with active lepromatous leprosy, the placenta is exposed to a high bacteria load of *M. leprae* which can cross the placenta and infect the fetus. Mother's immunoglobulin G can cross the placenta and can be detected in the cord blood. IgM do not cross the placenta. Thus an elevated level of this antibody in the cord may be an indication of the fetal immune system stimulation by antigen transfer in utero.

Normally, IgM in the infant is produced at 6 months of age. Presence of IgM before 6 months of age indicates possibility of infection in the infant[6].

Although leprosy is very rare in infant, 50% of babies of lepromatous mothers have rising titers of IgM antibodies to *M. leprae*, showing that they have been infected[1]. Transplacental transmission of *M. leprae* in mice is well established. Whereas infection in human fetus is only proven recently[4]. In a study for a period of up to two years after birth, Duncan ME (UK,1984) noted acid-fast bacilli present in the cord blood of babies born to women with active lepromatous leprosy and significant increase of IgM antibody activity after birth in babies of mothers with active leprosy compared with the children of normal mothers[7].

Antibody tests can be used as diagnostic tools to detect asymptomatic and subclinical leprosy patient. They have high titers of antibody such as phenolic glycolipid I and arabinomannan and *M. leprae* antigens may be detected in the sera[1,5].

Doughlas JT, et al. (Philippines, 2004) perform a cohort study of contacts of multibacilliary leprosy patients in Philippines with a follow-up time of 11 years. He noted seropositive contacts had a seven times higher risk of developing leprosy and a 24 times higher risk of developing MB leprosy. Household contacts, neighbours, and social contacts have a higher chance of contracting the disease. Whether this is mainly the result of closer contacts to the index case of the infection, similar genetic and immunological background, environmental, or a combination of all, is not yet resolved[8].

Bakker MI, et al. (Indonesia, 2005) screened household contacts and noted an increasing IgM antibodies in 7 out of 122 patients age 0 to 5 years and in 211 out of 219 patients aged 6 to 20 years. Having contact with an infectious patient is a risk factor in harboring antibodies, but to develop MB leprosy genetic factors plays an important role. In Indonesia, people who are seropositive have a 3·8 times higher risk of developing leprosy than negative people9.

Gindhar A, et al. (USA, 1998) reported two cases of leprosy in a 4 and 2 months female infants. On examination there were two small lesions (about 3 cm), ill - defined, hypopigmented patches over the left back near the buttocks. The infant was suspected of having indeterminate leprosy. Skin smears from one ear and one lesion were both negative for acid-fast bacilli (AFB). The serum showed the presence of IgM antibodies, and PGL antibodies were also detected. It is also possible that these infants acquired the infection at postnatal through household contact[10]. In our patient, subclinical leprosy was probably as a result of transmission of bacilli via placenta from her mother who had active lepromatous leprosy during pregnancy.

In a recent prospective study IgM anti *M. leprae* antibody activity was significantly increased in one-third of babies of mothers with lepromatous type taken 3-6 months after birth, but not in any of the sera from babies of mothers with tuberculoid leprosy[10]. Liu D, et al. (Wuhan, 2009) reported during a 5-year follow-up study of a hyperendemic community in Wuhan. These observations suggest that subclinical infection with *Mycobacterium leprae* is common in endemic communities and that antibody seropositivity is a marker of subclinical infection. Detection of subclinical infection may confound control strategies which use screening tests to identify asymptomatic highly infectious cases for earlier therapy[11]. Thus the IgM antibodies *M. leprae* response signifies the presence of active disease, particularly in multi-bacillary cases, and has the potential to be used not only to monitor the response of these patients to therapy, but also to detect subclinical leprosy in high-risk groups such as the relatives of patients with lepromatous disease[11,12].

Patient and her mother could not be tested for anti PGL-1. Anti PGL-1 (phenolic glycolipid) antibodies is a specific test for *Mycobacterium leprae* which measured by ELISA in sera from newly diagnosed and treated leprosy patient. Britton WJ, et al. (Sydney, 1997) reported antibodies to the species-specific phenolic glycolipid (PGL-1) of *Mycobacterium leprae* in sera from newly diagnosed and treated leprosy patients from Sydney and Nepal. IgM anti-PGL-1 antibodies were present in 88-90% of untreated patients at the lepromatous pole of the clinical spectrum and 35-55% of those at the tuberculoid pole[12]. Thus the IgM anti-PGL-1 response signifies the presence of active disease, particularly in multi-bacillary cases, and has the potential to be used not only to monitor the response of these patients to therapy, but also to detect subclinical leprosy in high-risk groups such as the relatives of patients with lepromatous disease[13].

In this case, the prognosis for quo ad sanationam of this patient is dubia ad bonam, according the literature most of the babies will probably control their subclinical leprosy infection without developing clinical signs of leprosy. This will be in agreement with the demonstration of self healing in 75% of early childhood[10]. IgM antibodies against *M. leprae* were present in all the sera examined. Again, the lepromatous leprosy groups had the highest concentration of antibodies. The median value was 140%, with a variation between 10 and 350 % in active lepromatous leprosy[14].

Conclusion

Infant with subclinical leprosy should be examine regularly for sign of leprosy because the risk of suffering from leprosy in childhood and also at the puberty[6]. Contact tracing and screening of all family members for the possibility leprosy.

References

1. Bryceson A, Pfaltzgraff RE. Mycobacterium leprae. In: Bryceson A, Pfaltzgraff RE Leprosy. 3th ed, London: Churchill Livingstone; 1990.
2. Rea TH, Modin RL. Leprosy. In : Wolff K, Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffel DJ eds. Dermatology in general medicine, Fitzpatrick, 7th ed, vol 2, New York: Mc Graw Hill, Medical Publishing Division, 2008: 1786-96.
3. Lockwood DN. Leprosy. In: Burns T, Breatnach S, Cox N, Griffiths CH, editor. Rook's textbook of dermatology; 8th Ed. London: Blackwell publishing; 2010: 32.1-20.
4. Sylvia MR, Castro MCR. Mycobacterial infection. In : Bolognia JL, Jorizzo JL, Rapini R, Horn TD, Mascaro JM editor. Dermatology. 1 th edition, vol 1, London, Mosby, 2004: 1145-50.
5. Duncan ME, Fox H, Harkness RA, Rees JW. The placenta in leprosy. Placenta 1984;189-98.
6. Duncan ME. An historical and clinical review of the interaction of leprosy and pregnancy: a cycle to be broken. Soc. Sci. Med; 1993:457-72.
7. Ochoa MT, Teles R, Haas BE, Zaghi D. A role for interleukin-5 in promoting increased immunoglobulin M at the site of disease in leprosy. Immunology Journal 2010;131: 405-14.
8. Bakker MI, May L, Hatta M, Kwenang A, Klatser. Genetic, household and spatial clustering of leprosy on an island in Indonesia: a population-based study. BMC Medical Genetics; 2005: 1-10.
9. Douglas JT, Cellona RV, Fajardo TT et al. Prospective study of serological conversion as a risk factor for development of leprosy among household contacts. Clin Diagn Lab Immunol, 2004; 11: 897-900.
10. Girdhar A, Mishra B, Lavania RK, Ashok. Leprosy in infants : report of two cases. International journal of leprosy 1998; 57:472-8.

11. Liu D, Li G, Huang W, Gao j.Analysis of newly detected Leprosy cases and misdiagnosis in Wuhan (1990-2004). Lepr Rev 2009; 80: 410-5.
12. Britton WJ, Garsia RJ, Basten A. The serological response to the phenolic glycolipid of Mycobacterium leprae in australian and nepali leprosy patients. Aust NZ J Med 1997:568-74.
13. Melsom R, Harboe M, Duncan ME. IgM and IgG anti M. leprae antibodies in babies of leprosy mothers during the first 2 years of life. Clin. Exp.Immunol 1982: 532-42.
14. Moet FJ, Meima A, Oskam L, Richardus JH. Risk factors for the development of clinical leprosy among contacts, and their relevance for targeted interventions. Lepr Rev, 2004; 75: 310-326.

PAEDIATRIC DERMATOLOGY - Short Case

Cutis marmorata telangiectatica congenita

Sabeera BKI, Mardziah Alias

Keywords *congenital skin anomaly, skin ulceration, skin atrophy*

Introduction

Cutis marmorata telangiectatica congenita (CMTC) is a rare congenital disorder with persistent cutis marmorata, telengiectasia, and phlebectesia, which may be associated with cutaneaus atrophy and ulceration of the involved skin. We herewith report a three month old male baby with CMTC at birth involving left side of the face, upper limbs, both flanks, and left gluteal and left leg with ulceration over the extensor aspects of the left knee joint. The baby had a reticulated bluish purple skin changes all over the body including the face and limb. Although it resembled physiological cutis marmorata, it was strikingly pronounced and definitely was unvarying and permanent. A variety of vascular malformation has been described along with this disorder. Etiology is not very clear. Prognoses in uncomplicated cases are good.

Case report

A three month old Chinese male infant presented with extensive cutis marmorata like lesion involving left side of the face, upper limbs, both flanks, and left gluteal and left leg since birth. The affected left leg was noted to be smaller. The lesions are of the same colour, size and distribution since birth. Some areas of the lesion were ulcerated and healed spontaneously with skin atrophy.

He is otherwise well. His developmental milestones are within normal limit. He is the third child of a non consanguineous marriage. Other 2 siblings are well. Antenatal and postnatal histories were normal. No similar skin problem noted in the family.

On examination there were extensive purplish reticulated vascular network on the left side of body involving the left leg, left flank, right arm, and back (Figure 1 and 2).

There were areas of subcutaneous atrophy and ulceration noted along these vascular lesions. The left lower limb was atrophic but there were no significant limb length discrepancy.

No dysmorphism was noted. His head circumference was above the 90th percentile compare to weight and height which was on the 50th percentile. Other systemic examinations including full neurological examination were normal.

Blood investigations including the autoimmune screening were normal. MRI brain showed normal study. MRI of the left lower limbs showed significant thinning of overlying subcutaneous tissue.

A diagnosis of cutis marmorata telangiectatica congenital was made from the clinical features and investigations. At 1 year follow up, he showed no further clinical improvement of the skin lesions and he was neuro-developmentaly normal.

Discussion

Our patient demonstrates an unusual clinically distinctive cutaneous vascular malformation with cutaneous atrophy and ulceration known as cutis marmorata telangiectatic congenita.

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CUTIS MARMORATA TELANGIECTATICA CONGENITA (CMTC) was first described by the Dutch peadiatrician van Lohuizen in 1922[1]. It is defined as a localized or generalized reticulated, vascular, blue-violet network that is usually present at birth. This marbled pattern is always visible, but may be enhanced by cold temperatures or distress. The skin lesions show a marked improvement over time, with the greatest improvement occurring during the first and second years of life[2].

The pathogenesis of CMTC is unknown. A number of hypotheses have been proposed. These include environmental factors, autosomal dominant inheritance with low or variable penetrance, a multifactorial cause, or a lethal gene surviving by mosaicism[2].

The diagnosis is established on clinical grounds. Histopathologic examination of biopsy specimens may show an increase in the number and the size of capillaries and veins but is usually not necessary to confirm the diagnosis[1,2].

Some overlapping features and clinical similarities to the Klippel-Trenaunay-Weber and Sturge-Weber syndromes have been observed. It has been suggested that these 3 entities should be classified as a group of vascular diseases associated with other developmental defects representing defects of the mesodermal system during embryonic life[3].

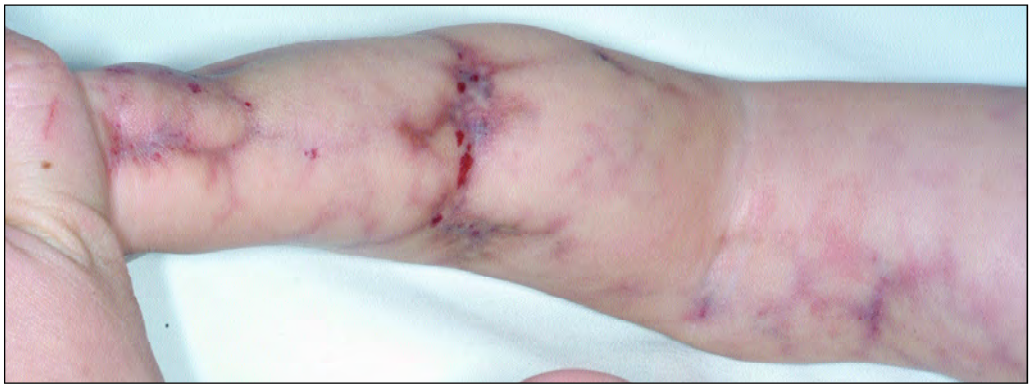

Figure 1 Reticulated, vascular, blue-violet network involving the whole length of right upper limb.

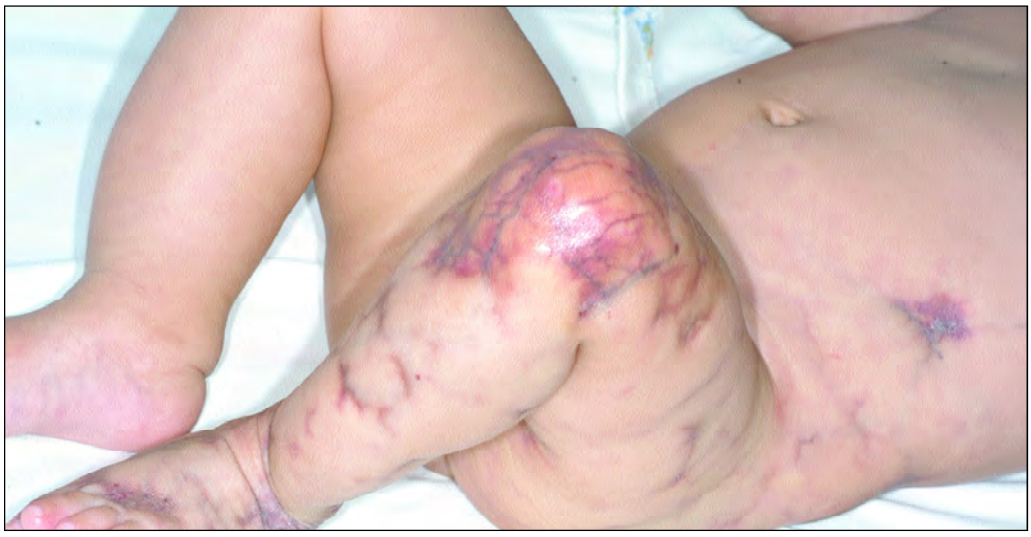

Figure 2 Reticulated, vascular, blue-violet network involving the whole of left lower limb with significant epidermal atrophy over the extensor of the left knee and visible veins.

Additional anomalies have been frequently reported in association with CMTC. The most commonly associated findings include body asymmetry (usually limb hyperplasia or hypoplasia), other vascular anomalies (mostly capillary malformation), glaucoma, hypoplasias or aplasias (ranging from transverse limb defects to localized aplasia cutis congenita to a cleft palate), and, infrequently, psychomotor and/or mental retardation. Cutaneous atrophy and ulcerations may also be observed. These are not always regarded as associated anomalies, but are included in the specific skin findings in CMTC[4,5,6].

For many patients, CMTC is a benign condition, but a full physical examination by a paediatrician and a dermatologist should always be performed. Children with clinically detectable abnormalities must be referred to an appropriate specialist. In the case of a periocular vascular lesion including CMTC, an ophthalmologic examination should be performed to exclude glaucoma or other eye abnormalities. Follow-up for the skin lesions, associated abnormalities and psychomotor development is advisable in patients with CMTC.

For parents, and in later life for the patient, genetic counseling may be necessary. However, almost all reported cases have been sporadic. The segmental distribution, along with the preferred one-sided body involvement, support the hypothesis that CMTC is a disorder to which the lethal gene theory of Happle could be applied, in which he suggests the concept of lethal genes surviving by mosaicism. The mosaic may arise either in an early postzygotic mutation, or from a half chromatid mutation that has occurred before fertilization in one of the two gametes forming the zygote[7].

The differential diagnosis reveals several conditions such as capillary malformation, KTW syndrome, neonatal lupus erythematosus, nevus anemicus, and physiological cutis marmorata, livedo reticularis associated with collagen vascular disorder, nevus flammus, and diffuse phlebectasia.

The prognosis of CMTC is good. Devillers C. A et al observed 35 patients with CMTC, who had rapid improvement of the skin lesions within 2 years either leading to a total disappearance of the lesions or markedly improved residual lesions, a finding that agrees with those of other studies[6].

In conclusion, CMTC is a relatively mild condition. The prognosis is usually good, with minor associated anomalies and an improvement of the mottled, vascular pattern within 2 years. A careful clinical examination of all patients to exclude possible associated anomalies is important.

References

1. Van Lohuizen CHJ. Uber eine seltene angeborene Hautanomalie (Cutis marmorata telangiectatica congenita). Acta Derm Venereol (Stockh). 1922;3: 201-211.
2. Rogers M, Poyzer KG. Cutis marmorata telangiectatica congenita. Arch Dermatol. 1982; 118:895-899.
3. Kennedy C, Oranje AP, Keizer K, van den Heuvel MM, Catsman-Berrevoets CE. Cutis marmorata telangiectatica congenita. Int J Dermatol. 1992;31: 249-252.
4. Pehr K, Moroz B. Cutis marmorata telangiectatica congenita: long-term follow-up, review of the literature, and report of a case in conjunction with congenital hypothyroidism. Pediatr Dermatol. 1993;10:6-11.
5. Devillers, Arjan C. A, De Waard-van der Spek, Flora B, Oranje, Arnold P. Cutis Marmorata Telangiectatica Congenita: Clinical Features in 35 Cases. Archives of Dermatology; 1999 Volume 135(1):pp 34-38.
6. Gerritsen MJP, Steijlen PM, Brunner HG Rieu P. Cutis marmorata telangiectatica congenita: report of 18 cases. British Journal of Dermatology 2000; 142: 366±369.
7. Happle R. Lethal genes surviving by mosaicism: a possible explanation for sporadic birth defects involving the skin. J Am Acad Dermatol. 1987;16: 899-906.

PAEDIATRIC DERMATOLOGY - Short Case

Neonatal lupus erythematosus presenting as multiple photosensitive annular plaques with skin atrophy

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Keywords *congenital skin anomaly, skin ulceration, skin atrophy*

Introduction

Neonatal lupus erythematosus (NLE) is an autoimmune disease affecting the fetus as a result of transplacental transfer of anti-Ro autoantibodies. Typically, it presents in the first few months of life with an annular form of subacute cutaneous lupus erythematosus. We report an infant of NLE presenting at birth with multiple annular erythematous plaques with skin atrophy involving the face, head, and upper trunk. Histopathology of skin biopsy was consistent with subacute cutaneous lupus. The mother was clinically free of disease and had no family history of autoimmune disease. Serology (extra-nuclear antigens) was positive in both the baby and the mother. This is a rare presentation of a rare disease.

Case report

A four month old Chinese baby girl presented with red annular lesions on the forehead, cheek, scalp and chest. These lesions were noted since birth and were regarded as birthmarks. She was described as a difficult baby since she was always crying, irritable and had poor sleep pattern. She is otherwise feeding and thriving well. These lesions appear to be exacerbated by exposure to sun light. Birth history was normal. Her mother is a 28 year old Chinese lady with unremarkable antenatal history.

On examination the baby was haemodynamically stable with normal limit of heart rate and blood pressure. She had annular erythematous plaques with central violaceous hue over the forehead, periorbital region, cheek, scalp and anterior chest. There were peeling of skin at peripheries and some lesions showed areas of skin atrophy (Figure I). Other systemic examinations were normal including CVS and CNS examinations.

Her blood investigation including full blood count, liver enzyme profile, basic chemistry panel, peripheral blood picture, VDRL and TORCH were normal. ESR = 21mm/hr, C3 & C4 were normal. Antinuclear antibody was reactive with titer of 1:1280. Extractable nuclear antigen were detected of which antibodies to Ro and La were >240 units and >320 units respectively. Anti-smooth muscle antibody and Anti-U1RNP were not detected. ECG showed sinus tachycardia with no evidence of heart block and a normal echocardiogram study. Skin biopsy showed: epidermal thining with basal cell vacuolar degeneration, epidermal necrotic keratinocytes and dermal mononuclear infiltrate (Figure 2).

Although the mother was asymptomatic, her investigation showed Antinuclear antibody titer of 1: 2560, with speckled pattern. Extractable nuclear antigen antibodies, both SSA &SSB were detectable.

A diagnosis of **Neonatal lupus erythematosus** was made and the baby was closely monitored. She was treated with topical hydrocortisone 1% cream to be applied on the facial rash and broad spectrum sunblock to the whole face daily.

On follow up, the annular lesions resolved slowly with residual post inflammatory hyperpigmentation and some skin atrophy. Repeat antinuclear antibody at 10 months old was non reactive. The mother was referred to physician for further assessment and follow up.

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Discussion

Neonatal lupus erythematosus (NLE) results from the transfer of maternal autoantibodies usually anti-Ro, to the fetus between the 12th and 16th week of gestation[1]. The most common symptom is rash (90%), which can be distributed over the body and does not necessarily involve the face, followed by congenital heart block (50%), which is the most serious complication and abnormalities in blood findings (10%)[2]. These three symptoms affect children aged up to 6 months, occurring in approximately 1 in 20,000 newborns, and can affect all ethnic groups. Females are more commonly affected by NLE with a ratio of 2:1 for cutaneous lesions[1].

Skin findings occur in nearly half of NLE infants. The eruption, which can occur at birth but more typically within a few weeks after birth, is similar to the lesions of subcutaneous lupus erythematosus. Typically, erythematous scaling and annular plaques appear on sun-exposed areas. After several months, lesions resolve with residual hypopigmentation, epidermal atrophy, and telangiectasia. Commonly, the lesions are in a photodistribution, especially on the head and neck, and often in a malar distribution. Sun exposure is not a prerequisite for the eruption; however, sunlight may initiate or exacerbate the eruption[1]. Rarely, discoid lesions may be seen[3].

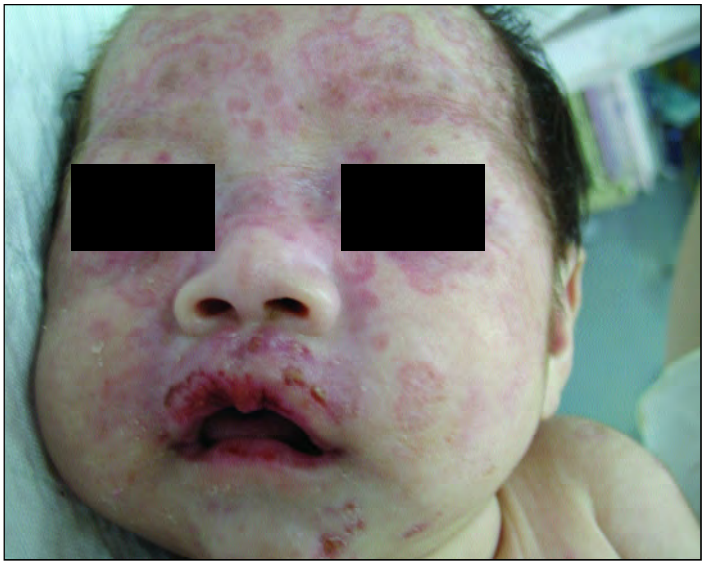

Figure 1 Multiple annular erythematous plaques with central violaceous hue over the forehead, periorbital region, cheek and erythema and crusting of the lips.

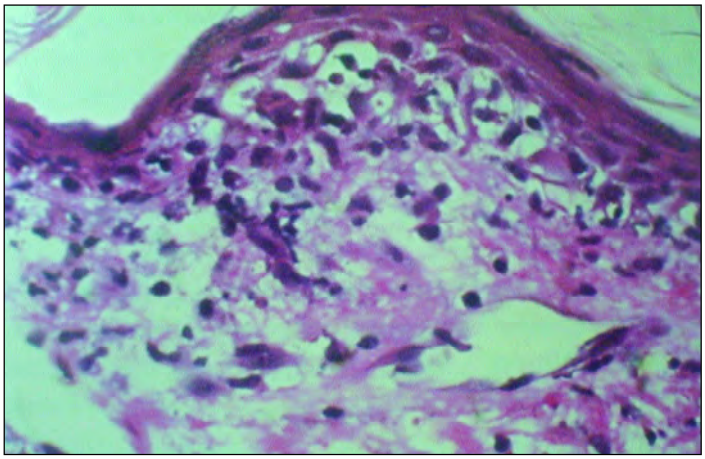

Figure 2 Skin biopsy showed epidermal thining with basal cell vacuolar degeneration, epidermal necrotic keratinocytes and dermal mononuclear infiltrate.

As in adults with SCLE, autoantibodies to RoSSA / La-B antigens correlate with skin lesions. In NLE, autoantibodies are maternal in origin and disappear by 6 months of age. The disappearance of these antibodies parallels the disappearance of the skin lesions. Children with cutaneous neonatal lupus erythematosus need to be evaluated for haematological and hepatic as well as cardiac involvement.

Extra-cutaneous manifestations

By far, the most significant organ involvement in NLE patients is the heart. Irreversible and complete heart block (CHB) occurs in half of the affected infants. It usually presents in utero and may be first detected around 18-24 weeks gestation[4]. NLE appears to be the most common cause of CHB in all patients presenting with this defect. Other conduction defects have been reported, as has congestive heart failure. Immunodeposits of RoSS antibody may result in fibrosis and calcification in and around the atrioventricular node and appears to be responsible for the heart block[1,2].

CHB is associated with significant mortality (20-30%) and morbidity. Early recognition of infants at risk is important.

While thrombocytopenia occurs in 10-20% of patients, it is transient in nature and usually not problematic. Occasionally, gastrointestinal hemorrhage may occur[5].

Approximately 20-40% of patients will have hepatomegaly. This may occur as a result of passive congestion in patients with heart failure or it may be due to extramedullary hematopoiesis. Histologic liver changes include cholestasis, fibrosis, and hepatitis[6].

Other extracutaneous findings have been reported in patients with NLE, but may not be significant and include neurologic abnormalities and anemia.

Pathogenesis

Although the mechanisms responsible for NLE have not been fully characterized, there is strong evidence to support the hypothesis that maternal anti-SSA/Ro and anti-SSB/La autoantibodies are involved in the pathogenesis[7]. How and why maternal autoantibodies affect the target organs in such variable ways is unclear, although it is apparent that the fetal heart is uniquely vulnerable. Boutjdir et al[8] have demonstrated that maternal autoantibodies can interfere with fetal cardiac calcium channels, thus contributing to conduction defects.

Management

Identification of fetuses at risk is paramount. Mothers with a history of autoimmune diseases or with circulating anti-Ro or anti-La antibodies are at highest risk, as are women with a previously affected child. As previously noted, despite having positive anti-Ro antibodies, the risk of developing NLE is low. Detection of maternal Ro/La autoantibodies during pregnancy warrants careful and close monitoring of the fetus.

Skin lesions of affected infants should be treated conservatively with avoidance of sunlight and judicious use of topical corticosteroids. The long-term prognosis of children with skin disease is excellent.

Long term outcome

Although long-term follow-up studies have observed several patients with subsequent development of autoimmune diseases, there does not appear to be any significantly increased risk for developing autoimmune disorders later in life.

Conclusions

NLE is an acquired autoimmune disorder affecting infants of mothers with anti-RoSSA and anti-SSB/La autoantibodies. It represents a prototypical example of passive transfer of autoantibodies and the direct role of these autoantibodies in the development of lupus skin lesions. Babies with NLE have an excellent long-term outcome when only skin lesions are present. Children with CHB also have good long-term outcomes if the heart block is successfully treated. Although uncommon, it is important to recognize early in the gestation period those infants at risk for developing NLE.

References

1. Boh EE. Neonatal lupus erythematosus. Clin Dermatol. 2004;22:125-128.
2. 2. Lee LA. Neonatal lupus erythematosus: clinical findings and pathogenesis. J Investig Dermatol Symp Proc. 2004;9:52-56.
3. N. Lawrence, C. Bligard, J. Storer et al., Neonatal lupus in twins. South Med J 82 (1989), pp. 657-660.
4. Lee LA, Weston WL. Special considerations concerning the cutaneous manifestations of rheumatic disease in children: Cutaneous manifestations of rheumatic diseases. Philadelphia: Williams & Wilkins, 1996:323-42.
5. R. Watson, J.E. Kang, M.May et al. Thrombocytopenia in the neonatal lupus syndrome. Arch Dermatol 1988; 124: 560-563.
6. R.M. Laxer, E.A. Roberts, K.R. Gross et al., Liver disease in neonatal lupus erythematosus. J Pediatr 1990; 116: 238-242.
7. Sontheimer RD, McCauliffe DP. Pathogenesis of anti-Ro/SS-A autoantibody associated cutaneous lupus erythematosus. Dermatol Clin. 1990;8:751-758
8. BoutjdirM, Chen L, Zhang ZH, et al. Arrthymogenicity of IgG and anti-52-kd SSA/Ro affinity-purified antibodies from mothers of children with congenital heart block. Circ Res. 1997; 80:354-362.
9. Multiple Annular Plaques in an Infant. Arch Dermatol 2006;142:1351-1356.

DERMATOLOGY THERAPEUTICS - Original Article

Effect of oral or pulse cyclosphosphamide in recalcitrant pemphigus: an audit of eighteen patients from Hospital Kuala Lumpur

Tang MM, Priya G, Suganthi T

Abstract

Background Autoimmune pemphigus is a potentially life threatening bullous disease. The cornerstone of treatment is systemic corticosteroids. However, adjuvant therapy with immunosuppressant drugs is commonly used to improve disease control and alleviate the high morbidity and mortality associated with the use of corticosteroids. Adjunctive treatment with pulse intravenous cyclophosphamide may be more efficacious and less toxic than other immunosuppressants.

Objective To retrospectively review the clinical outcome of 18 patients with recalcitrant pemphigus who were treated with cyclophosphamide over the past 10 years.

Methodology A retrospective study was conducted between 1985 and 2009 in thirteen Malaysian dermatology centres. Data collected were analysed for comparison of relapse rates, compliance rates and adverse drug effects between the 2 regimes.

Results Eighteen patients were included in this audit of which 12 patients had pemphigus vulgaris and 6 patients had pemphigus foliaceous. Prior to treatment with cyclophosphamide, fourteen patients were on azathioprine, three were given intravenous immunoglobulin, and two were prescribed dapsone; however all these patients were either unresponsive, intolerant or suffered serious side-effects with these drugs. Subsequently, 7 patients (median age: 31 years) received a combination of pulse intravenous cyclophosphamide and either intravenous dexamethasone or methylprednisolone. These seven patients received between 2 to 21 pulses of intravenous cyclophosphamide and steroids at monthly intervals with oral prednisolone and cyclophosphamide (50-100mg) in between pulses. The remaining 11 patients (median age: 46 years) received oral cyclophosphamide and corticosteroids. Of the 18 patients in our cohort, 15 achieved control and consolidation of disease activity at an average of 4 weeks and 10 weeks respectively. The remaining three patients are yet to achieve disease control. The total duration of treatment with cyclophosphamide ranged from 2 to 62 months with a cumulative dose ranging from 2.95g to 93.55g. Four patients achieved partial remission on minimal therapy and 3 achieved complete remission. None of patients experienced serious side effects.

Conclusion Cyclophosphamide may be an alternative treatment option in patients in patients with pemphigus who fail to respond to standard therapy. Controlled trials are needed to further evaluate the efficacy and safety of this therapy.

Keywords *Pemphigus vulgaris, pemphigus foliaceous, cyclophosphamide*

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Introduction

Pemphigus encompasses a group of potentially life-threatening autoimmune diseases with extensive blistering of the skin with or without mucous membrane involvement1. It is characterized by intraepidermal intercellular loss of adhesion caused by autoantibodies against desmoglein 1 and 3 between epidermal keratinocytes.

Systemic corticosteroids remain the forefront in the management of pemphigus. Adjuvant immunosuppressive drugs such as azathioprine, mycophenolate mofetil, dapsone, methotrexate, cyclophosphamide, cyclosporine, intravenous immunoglobulin, rituximab and immunoadsorption have been used to minimize the short- and long-term side effects of systemic corticosteroids[2,3]. Current literature however is insufficient to conclude which is the most effective and safest treatment regime[4]. In addition, the response to treatment may vary between individuals. Cyclophosphamide was found to be both efficacious & successful in maintaining remission[5]. However, its potential serious side effect profile causes a lot of hesitancy among prescribing physicians.

Objective

The objective of this review is to report our experience in the use of oral and pulse intravenous cyclophosphamide in patients with pemphigus vulgaris and pemphigus foliaceous.

Materials and Methods

This is a 10 year retrospective review. The case notes of all patients with confirmed pemphigus vulgaris or pemphigus foliaceous who received cyclophosphamide were reviewed. The diagnosis of pemphigus was made according to the clinical features together with histopathological and direct immunofluorescence study. These patients received either oral or pulse IV cyclophosphamide according to the extent of body surface area involvement using the "rule of nine", oral cyclophosphamide for body surface involvement of less than 20% and pulse cyclophosphamide for body surface involvement of more than 20%.

Oral cyclophosphamide was prescribed at the dose of 0.5-1.5mg/kg/day (ranging from 50-150mg a day) for patients who were unresponsive or developed side effects to other steroid sparing agents. It was given in addition to oral prednisolone in all the cases studied.

Pulse intravenous cyclophosphamide was used in patients with severe rapidly progressive disease which could not be controlled with high doses of systemic corticosteroids. There were 3 phases in the pulse regime. In the first phase, intravenous dexamethasone was given for 3 days with intravenous cyclophosphamide 500mg given on day 2. Oral cyclophosphamide at the dose of 0.5-1.5mg/kg/day and oral prednisolone were given in between. This was repeated every 3-4 weeks until the clinical remission was achieved. During phase II, the above pulse therapy was repeated for another 6 cycles which was then followed by phase III in which the intravenous therapy was discontinued and patients were maintained on oral cyclophosphamide with or without oral prednisolone for another 6-9 months.

We used the consensus guideline recommended by Murell et al[6] for the definition of disease activities (Appendix 1).

Results

The patients' characteristics are shown in Table 1. A total of 18 patients received cyclophosphamide in the past 10 years; 11 were on oral treatment and 7 received pulse intravenous cyclophosphamide. The mean disease duration was about 15 months in both groups prior to the commencement of cyclophosphamide. All patients had refractory disease and had previously been on azathioprine, dapsone and intravenous immunoglobulin.

Table 2 demonstrates the disease response to cyclophosphamide. Patients on oral cyclophosphamide had a median time to disease control of 3 weeks. Disease control was achieved at 25 weeks in patients on pulse cyclophosphamide therapy. In the oral cyclophosphamide group, partial remission was achieved within a median of 10 months, but it took twice as long in the pulse cyclophosphamide group. No patient on pulse therapy achieved complete remission. 2 patients in each group defaulted a number of monitoring visits but they were recommenced on the treatment regimen on subsequent attendance.

Table 1 Characteristics of patients received cyclophosphamide.

		Oral Cyclophosphamide n=11	Pulse Intravenous Cyclophosphamide n=7
Mean age in years (range)		43.7 (35-53)	35.3 (24-51)
Mean duration of disease before cyclophosphamide in months		16.0	14.6
Male : female		4:7	4:3
Type of pemphigus	Vulgaris	8	4
	Foliaceous	3	3
Previous steroid sparing immunosuppressive agents used	Azathioprine	9	5
	Dapsone	1	1
	IVIG	0	3

IVIG - Intravenous immunoglobulin

Table 2 Response to therapy.

		Oral Cyclophosphamide n=11	Pulse Intravenous Cyclophosphamide n=7
Median time to control in weeks (range)		3 (1-8)	25 (4-27) *5 patients
Median time to disease consolidation in weeks (range)		9 (4-13)	20.5 (6-29) *4 patientts
Median time to partial remission on minimal therapy in months (range)		10 (7-26) *7 patients	20 (5-42) * 3 patients
Median time to complete remission on minimal therapy in months (range)		16.2 (11-28) *4 patients	-
Median time to complete remission off therapy in months (2 patients)		55 (49 & 61)	-
Median daily prednisolone dose pre Cyclophosphamide in mg (range)		60 (45-80)	75 (60-80)
Last daily prednisolone dose in mg (range)		5 (0-50)	15 (0-40)
Median duration of cyclophosphamide in months (range)		30.0 (4.2-58.0)	11 (3-42)
Median total cumulative dose in g (range)		48.85 (7.85-90.50)	32.55 (5.32-96.10)
Latest activity	Control of disease	0	1
	Consolidation	3	1
	Partial remission on minimal therapy	3	3
	Complete remission	2 (off therapy) 2 (on minimal therapy)	0
	Still active	1	2

Table 3 The side effects experienced by patients.

Side effects	Oral Cyclophosphamide only n=11	Pulse Intravenous Cyclophosphamide n=7
Transient leucopenia	1	1
Menstrual irregularity	1	2
Pruritus	1	-
Diffuse hyperpigmentation	-	1
Hepatitis	1	-
Infection	3	7

Before cyclophosphamide was initiated, the 11 patients on oral cyclophosphamide were on a median dose of 60mg /day of prednisolone; and the group that received pulse cyclophosphamide therapy was on a higher median dose of 75mg/day of prednisolone. Assessment during the last follow up visit at the end of the study revealed a reduction in dose of prednisolone by about 90% in the oral cyclophosphamide group and 50% in the pulse cyclophosphamide therapy group. The median cumulative dose of cyclophosphamide was notably higher in the oral cyclophosphamide group. When this cohort of patients was last reviewed, 3 patients still had active disease. Four patients who had received oral cyclophosphamide were in complete remission. Of these 4 patients, 2 were completely off treatment and on subsequent follow up, remained disease free for one and three years respectively. The duration of follow-up for our patients ranged from two to nine years with a median of five years.

The side effect profile was similar in both groups. However, there was a slight increase in infection rate among patients on pulse cyclophosphamide (Table 3). These infections included upper respiratory infections, pneumonia, urinary tract infections and cutaneous infections such as folliculitis and furunculosis. One patient died of ischaemic heart disease. He had previously received 30 months of oral cyclophosphamide with cumulative dose of 44g, and was in remission on 2.5 mg of prednisolone at the time of his death.

Discussion

Cyclophosphamide is an alkylating agent approved by the Food and Drug Administration (FDA) in the treatment of acute and chronic leukaemia, advanced staged mycosis fungoides, multiple myeloma, lymphoma, breast carcinoma, ovarian carcinoma and retinoblastoma[7,8]. Pulse treatment in high doses has also been used in systemic lymphoma and systemic lupus erythematosus. It has both cytotoxic and immunosuppressive activities. However, there are no standard practice guidelines to date on the usage of cyclophosphamide be it oral or pulse intravenous therapy.

The use of oral cyclophosphamide in the treatment of pemphigus was first described in 1969 by Ebringer et al[9]. Oral cyclophosphamide has been used at a dosage of 1-2.5mg/kg/day to achieve optimum immunosuppression. The pioneer of pulse cylophosphamide therapy in the management of recalcitrant pemphigus was Parischa et al[10] who has used this regimen for more than 30 years.

Parischa et al[13] recommended the pulse intravenous cyclophosphamide administration for severe pemphigus since 1984. There are 4 phases in this dexamethasone-cyclophosphamide pulse therapy (DCP). In the first phase, intravenous dexamethasone 100mg in 5% glucose is given as slow infusion over a period of 1-2 hour for 3 consecutive days, with co-administration of cyclophosphamide on the 1st day. Oral cyclophosphamide 50mg is given daily between the pulse intravenous therapies. The DCP is repeated every 2-4 weeks depending on the clinical activity. Once the disease is controlled,

patients then enter the second phase in which DCP is repeated monthly for another 6 months. After that, the pulse therapy is stopped and oral cyclophosphamide was continued for a year (phase III). Finally in phase IV, oral cyclophosphamide is stopped altogether. The total duration of treatment is about 2 years.

In our department, all patients with pemphigus were initially prescribed oral prednisolone with adjuvant drugs such as azathioprine, dapsone or intravenous immunoglobulin. The dose of oral prednisolone was initiated at 1mg/kg per day, but in severe cases the patients received up to 1.5 mg/kg/day. However, some patients were unresponsive, intolerant, or developed side effects to conventional first line steroid sparing agents. These patients were continued on oral prednisolone, and prescribed either oral or pulse intravenous cyclophosphamide therapy. In our case series, the cohort with less extensive disease responded more rapidly and we were able to taper their oral prednisolone faster as compared to the group with more extensive body surface area involvement. However, this group also received a higher cumulative dose of cyclophosphamide, although serious side effects was not seen during the follow-up period. The overall response in our patients to oral cyclophosphamide was comparable to studies done by Cummins *et al*[10], Momeni *et al*[11] & Olszewska *et al*[5]. We favoured pulse cyclophosphamide for patients with rapidly progressive disease. The regime described by Parischa et al was modified. The initial part of the regimen with intravenous cyclophosphamide on day 2 was adhered to. However oral prednisolone was not abruptly discontinued but was prescribed at a dose of 0.5-1 mg/kg/day along with oral cyclophosphamide (50-100mg daily) in between pulses. We tapered the oral prednisolone when the patients entered phase II.

This modality was used in 7 patients and our results were comparable with other studies done in Europe and USA (Table 4). Complete remission occurred in only a handful of patients. In most other studies, about 50% of patients improved. The exception to this is the cohort from India described by Parischa *et al*, where complete remission was reported in more than 80% of their patients.

All the patients in our cohort had rapidly progressive, extremely difficult to control and life-threatening disease. Although some of them had yet to complete their families, they were

Table 4 Comparisons of treatment response of pulse intravenous cyclophosphamide.

	Parischa et al 1995 (India)	Fleischli et al 1999 (US)	Rose et al 2005 (Germany)	Saha et al 2010 (UK)	Zivanovic et al 2010 (Serbia)	Tang et al 2010 (Malaysia)
Number of patients	227	9	11	21	72	7
No of pulses	NA	3-24	6	3-22	1-28	3-21
Results	84% CR. 24pt CR still on Rx 13 still active	6pts: ER, 2pts: MinR	5pts: remission 6pts: progression (24 months after treatment initiation)	4pts: CR 7pts: ER 2pts: GR 5pts: ModR 6 pts: MinR 1 pt: NR	59.7% CR 18.1% NR • 50% used as first line • 10pts: 2 courses	3 pt: PR 1 pt: consolidate 1 pt: dis control 2 pts: active

CR - complete remission; ER- Excellent response, GR - Good response; ModR - moderate response; MinR - Minimal response; NR - No response; pt - patient; Cycloph - cyclophosphamide; PR - partial remission, Rx - therapy, pts - patients, pt - patient

offered cyclophosphamide. Prior to administration, the patients were fully counseled about the side effects; after which consent was obtained. None of patients experienced severe side effects while on cyclophosphamide. Haemorrhagic cystitis, which is reported to occur in up to 50% of patients on cyclophosphamide20, was not observed in our patients. No patient developed bladder carcinoma. This is probably because the follow up period was still short, and the average time of development of bladder carcinoma from the first exposure to cyclophosphamide is several years. Thus, long term follow-up and close monitoring is extremely important for patients who have received cyclophosphamide in the past.

Some of our patients relapsed while on therapy. In most cases, this occurred as they defaulted. Our patients cite many reasons for their actions including long distances from hospital, the inconvenience of frequent hospital admissions and the perception of apparent disease improvement causing them to discontinue their medication prematurely. Many other authors reported similar experiences with their patients. Parischa et al observed disease relapse of less than 10% among those who strictly adhered to the pulse intravenous cyclophosphamide.

Conclusion

Cyclophosphamide was beneficial in the management of patients with recalcitrant pemphigus. We were able to reduce the dose of oral corticosteroids and achieve better disease control. Having said that, our results were not as dramatic as other reports, this was probably because our cohort of patients had very stubborn disease and their compliance to treatment left much to be desired.

Appendix 1 Definitions of disease activity.

Term	Definitions
Disease control	The time at which new lesions cease to form and established lesions begin to heal.
End of the consolidation phase	The time at which no new lesions have developed for a minimum of 2 weeks, approximately 80% of lesions have healed and when most clinicians start to taper steroids.
Minimal therapy	Prednisolone at 10mg/d and/or minimal adjuvant therapy for at least 2 months.
Minimal adjuvant therapy	Half of the dose required to be defined as treatment failure.
Partial remission on minimal therapy	Presence of transient new lesions that heal within 1 week while the patient is receiving minimal therapy including topical steroids.
Partial remission off therapy	Presence of transient new lesions that heal within 1 week without treatment & while the patient is off all systemic therapy for at least 2 months.
Complete remission off therapy	Absence of new or established lesions while the patient is off all systemic therapy for at least 2 months.
Complete remission on therapy	The absence of new or established lesions while the patient is receiving minimal therapy.
Relapse	Appearance of $\geq$3 new lesions/month that do not heal spontaneously within 1 week or by the extension of established lesions in a patient who has achieved disease control.

Adapted from Murell et al[6].

References

1. Hertl M, Zillikens D. Clinical and Molecular Characterization of Autoimmune Bullous Diseases. J Invest Dermatol 2008; 128:E19-E21.
2. Meurer M. Immunosuppressive therapy for autoimmune bullous diseases. Clin Dermatol 2012; 30:78-83.
3. Kasperkiewicz M, Schmidt E, Zillikens D. Current therapy of the pemphigus group. Clin Dermatol 2012; 30:84-94.
4. Martin LK, Agero AL, Werth V, Villanueva E, Segall J, Murrell DF. Interventions for pemphigus vulgaris and pemphigus foliaceus. Cochrane Database of Systematic Reviews 2009, Issue 1. Art. No.: CD006263. DOI: 10.1002/14651858.CD006263.pub2.
5. Olszewska M, Kolacinska-Strasz Z, Sulej J, Labecka H et al. Efficacy and Safety of Cyclophosphamide, Azathioprine, and Cyclosporine (Ciclosporin) as Adjuvant Drugs in Pemphigus Vulgaris. Am J Clin Dermatol 2007;8(2): 85-92.
6. Murell DF, Dick S, Ahmed AR, Amagai M et al. Consensus statement on definitions of disease, end points, and therapeutic response for pemphigus. J Am Acad Dermatol 2008;58:1043-6.
7. Ahmad AR, Hombal SM. Cyclophosphamide (Cytoxan). A review on relevant pharmacology and clinical uses. J Am Acad Dermatol 1984; 11: 1115-1126.
8. Ghate J. Immunosuppressive therapies in Dermatology: Cyclophosphamide. Curr Prob Dermatol 2000; 12: 265-267.
9. Ebringer A, Mackay IR. Pemphigus vulgaris successfully treated with cyclophosphamide. Ann Int Med 1969;71:125-127.
10. Pasricha JS, Sood VD, Minocha Y. Treatment of pemphigus with cyclophosphamide. Br J Dermatol 1975; 93:573-576.
11. Cummins DL, Mimouni D, Anhalt GJ, Nousari CH. Oral Cyclophosphamide for the treatment of pemphigus vulgaris and foliaceous. J Am Acad Dermatol 2003;49:276-80.
12. Momeni AZ, Iraji F, Aminjavaheri M, Emami MR et al. The use of oral cyclophosphamide with dexamethasone pulse therapy in the treatment of pemphigus vulgaris. J Dermatolog Treat 2007;18: 275-278.
13. Pasricha JS,Thanzama J, Khan UK. Intermittent high-dose dexamethasone-cyclophosphamide therapy for pemphigus. Br J Dermatol 1988;119:73-77.
14. Pasricha JS, Khaitan BK, Raman RS, Chandra M. Dexamethasone-cyclophosphamide pulse therapy for pemphigus. Int J Dermatol 1995; 34:875-82.
15. Fleischli ME, Valek RH et al. Pulse intravenous cyclophosphamide therapy in pemphigus. Arch Dermatol 1999;135:57-61.
16. Rose E, Wever S, Zilikens D et al. Intravenous dexamethasone-cyclophosphamide pulse therapy in comparison with oral methylprednisolone-azathioprine therapy in patients with pemphigus: results of a multicenter prospectively randomized study. JDDG 2005;3:200-206.
17. Saha M, Powell AM, Bhogal B,Black MM, Groves RW. Pulsed intravenous cyclophosphamide and methylprednisolone therapy in refractory pemphigus. Br J Dermatol 2010:162;790-797.
18. Zivanovic D, Medenica L, Tanasilovic S, Vesic S et al. Dexamethasone-Cyclophosphamide Pulse Therapy in Pemphigus. A Review of 72 cases. Am J Clin Dermatol 2010; 11(2): 123-129.
19. Pandya AG, Sontheimer RD. Treatment of pemphigus vulgaris with pulse intravenous cyclophosphamide. Arch Dermatol 1992; 128:1626-1630.
20. Lawson M, Vasilaras A, De Vries A, Mactaggart P et al. Urological implications of cyclophosphamide and ifosfamide. Scand J Urol Nephrol 2008; 42;309-317.