Original Article

Use of cyclosporine in the treatment of psoriasis

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Abstract

Introduction The efficacy of cyclosporine in the treatment of psoriasis is well established. However widespread use of it has been limited by concerns over adverse effects such as hypertension, renal impairment and the potential risk of malignancy. The aim of this study is to determine the profile of our local psoriasis patients treated with cyclosporine, their response to treatment, their tolerability and the side-effects experienced.

Materials and Methods This is a retrospective study of all psoriasis patients treated with cyclosporine for more than one month from January 1996 to June 2007 at the Department of Dermatology Ipoh Hospital.

Results There were a total 21 patients, 8 males and 13 females. Their mean age was 40 years. There were 7 Malays, 10 Chinese and 4 Indians. Cyclosporine was given as the second or third line of treatment. The average starting dose was 2.76mg/kg and maximum dose was 3.89mg/kg. Best response was noted after 3 months of treatment. Thirteen (61.9%) patients had excellent response, 4(19%) had good response, 3 (14.3%) had moderate response and 1(4.8%) had poor response. Thirteen (61.9%) patients developed raised serum creatinine level exceeding 30% of the baseline while on treatment but all of them improved when the dosages of cyclosporine were reduced. None of them developed renal failure. There were 5 patients who had hypertension while on cyclosporine therapy, 2 of them required antihypertensive agents while for the remaining 3, blood pressure normalized after dosage reduction. Other side effects reported include gastrointestinal upset, gum hypertrophy and hypertrichosis.

Conclusion Cyclosporine is effective in the treatment of psoriasis but close monitoring of serum creatinine and blood pressure is needed.

Keywords Cyclosporine, psoriasis, continuous therapy

Introduction

Cyclosporine (CyA) is an immunomodulator which is now increasingly being used in certain conditions in dermatology such as severe psoriasis, severe atopic eczema and recalcitrant pyoderma gangrenosum. In moderate to severe psoriasis, it can produce marked improvement at dosage between 2.5-5mg/kg/day. However the widespread use of CyA is limited by the well known adverse effects such as hypertension, renal impairment and the potential risk of malignancy.

The objective of this study is to determine the profile of local psoriasis patients treated with CyA at the Department of Dermatology Ipoh Hospital. The clinical response to CyA, tolerability, duration of treatment and side effects experienced were also evaluated.

Materials and Methods

This is a retrospective study of all patients who had completed more than a month of cyclosporine for the treatment of psoriasis from January 1996 to June 2007 at the department of Dermatology Ipoh Hospital. Diagnosis of psoriasis was made clinically by the attending doctors. Study parameters include the patients' biodata, dosage and duration of CyA treatment, baseline & highest blood pressure and serum creatinine during treatment, extent of disease pre-and post-treatment (body surface area).

Response of treatment was assessed by the doctor treating the patients according to the reduction of body surface area involvement. "Excellent" response was defined as more than 75% improvement; "Good" response as improvement of between 50-75%; "Moderate" response as improvement of between 25-50% while "Poor" response as less than 25% improvement or worsening of psoriasis. The data were analyzed using SPSS statistical analysis for Windows 10.

Results

There were a total of 21 patients (8 males and 13 females) given Cyclosporine for more than a month in the treatment of psoriasis during the study period. Most of them had long history of psoriasis with a mean duration of disease of about 12 years. All patients had plaque psoriasis at the outset and 9 went on to develop exfoliative dermatitis/erythroderma. Thirteen patients had associated arthropathy. The demographic data and baseline characteristics of the patients were demonstrated in Table 1.

Cyclosporine was prescribed as the second or third line systemic treatment in all patients. They were all previously using topical treatments. All patients were treated with methotrexate previously. Fourteen patients (66.7%) had phototherapy in the past either with narrowband UVB or PUVA. Eleven patients (52.4%) were given acitretin (Neotigason) and 7 patients (33.3%) were given sulfasalazine before cyclosporine was started.

While the patients were taking CyA, their topical medications were continued. In 13 patients (61.9%) CyA was used alone as systemic treatment. Acitretin was added in 6 cases and isotretinoin was added in 1 case when the CyA dosages were tapered down. In another patient who also had psoriatic arthritis, sulfasalazine was added as CyA alone did not help in controlling the joint pain.

The mean starting dose and maximum dose of CyA was 2.76mg/kg/day (2.11-3.5mg/kg/d) and 3.89mg/kg/day (2.91-5.3mg/kg/day) respectively. The mean total duration of treatment was 16.6 months (3.75-28 months). The maximum clinical improvement was noted after a mean of 3.11 months (0.5-8.5 months). Thirteen patients (61.9%) and 4 patients (19%) achieved excellent and good response respectively at the point of maximum clinical improvement. On the other hand, 3 patients (14.3%) and one patient (4.8%) experienced moderate and poor response respectively. The comparison between the body surface area involvement before and during the maximum clinical response was shown in Figure 1.

Our series of patients experienced raised serum creatinine, new onset hypertension, gastrointestinal upset, gum hypertrophy and hypertrichosis and the frequency of each side effect was shown in Table 2. There were 13 patients who developed elevation of serum creatinine more than 30% from baseline at a mean of 7.4 months (1.25-20 months) after initiation of cyclosporine. The average highest cyclosporine dose used was 3.8mg/kg/day (2.9-5.3mg/kg) and the mean elevation of serum creatinine was 45.2% (30-71.4%) from baseline. All the 13 patients had their serum creatinine level normalized after reducting the dose of CyA.ion.

There were 5 patients who had underlying well-controlled hypertension before cyclosporine was started. Two of them had worsening of control of hypertension requiring adjustment of anti-hypertensive agents. Newly onset hypertension (elevation of blood pressure reading of more than 90mmHg diastolic or more than 140mmHg systolic blood pressure) was experienced by 5 patients (23.8%). Blood pressure readings were normalized after reduction of dosage of cyclosporine in 3 patients while the other 2 patients required anti-hypertensive agent to control their blood pressure. Amlodipine was used in both cases.

At the point of the study in July 2007, cyclosporine treatment was taken off in 15 patients, in which 11 of them had underwent at least 12 months of treatment (13-28 months). Out of the 11 patients, 8 patients had achieved the maximum recommended duration of treatment of 2 years. In the other 3 patients, 1 had achieved remission; while 2 patients had to stop the treatment because the dose of CyA was unable to increase further to achieve better clinical response due to side effects. Out of the 4 patients who took CyA less than a year, one achieved remission; one patient was found to have carcinoma of breast 2 months after initiation of CyA and defaulted follow up in dermatology clinic; one had intolerable hypertrichosis; and another one stopped because her arthritis was not improved with CyA. After cessation of CyA, 6 patients developed a relapse, which is defined as a flare of lesions more than 50% from the time when CyA was ceased. The mean duration of relapse was 1.8 months (range 2 weeks to 5 months).

Discussion

CyA has been proven to be a very effective systemic agent in treating severe plaque psoriasis: 80-90% had rapid and marked improvement or complete clearance of disease when CyA given at the dose of 2.5-5.0mg/kg/d for 12-16 wks[1]. However, its well known side effects namely, renal impairment and hypertension require extreme care during treatment and is not advisable for long term use. Thus, CyA can only be used as second or third line treatment modality in severe form of psoriasis when other systemic treatments such as phototherapy (NBUVB & PUVA), methotrexate or acitretin are not feasible.

The present study demonstrated that long term continuous cyclosporine is effective in treating psoriasis with 81% of patients achieved good and excellent improvement. The effect of CyA could be seen as soon as 2 weeks with the best response noted at about 3 months after initiation of CyA. The side effects experienced in our series of patients were no different from those reported elsewhere. Nonetheless, it is worth mentioning that the rate of raised serum creatinine level of more than 30% from baseline in the present study was higher than reported in similar studies done in other

Table 1. Patient demographics and baseline clinical characteristics

Characteristic		N=21
Mean age in years (range)		40.1 (20-62)
Ethnic	Malay	7 (33.3%)
	Chinese	10 (47.6%)
	Indian	4 (19.0%)
M:F ratio		1:1.63
Duration of Psoriasis (years)		12.1 (3-30)
Severity of Disease (mean BSA)		68.1 (3-100)
Psoriatic arthropathy		13 (61.9%)

Figure 1. Comparison between the Body Surface Area involved with psoriasis before and during the maximum effect of Cyclosporine therapy

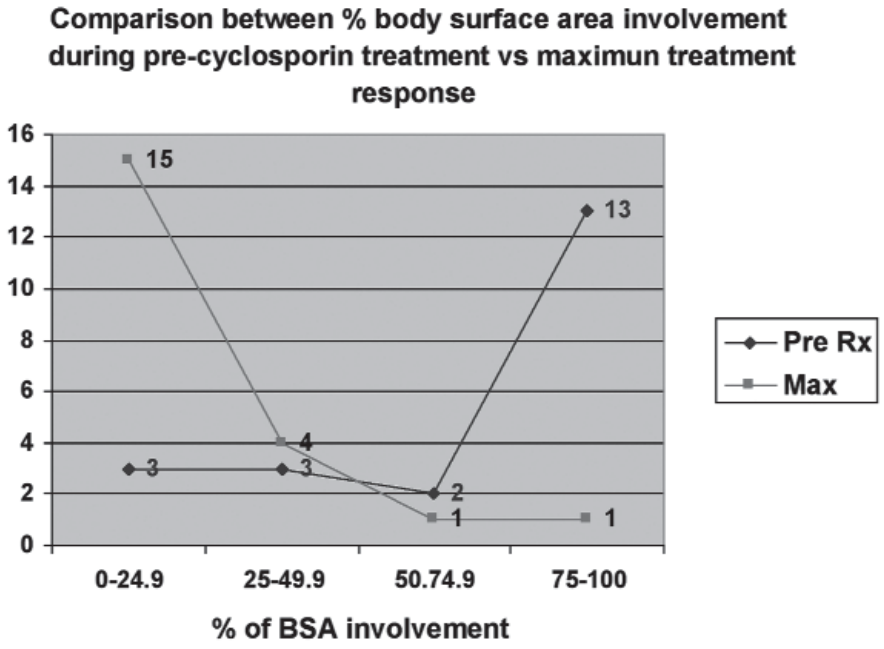

Table 2. Side effects experienced by patients

	Side effects	N (%)
1	Raised serum creatinine >30% from baseline	13 (61.9)
2	New onset hypertension	5 (23.8)
3	Gastrointestinal upset	2 (9.5)
4	Gum hypertrophy	3 (14.3)
5	Hypertrichosis	1 (4.8)

Table 3. Comparison of the use of Cyclosporine in Psoriasis between Skin clinic Hospital Ipoh Malaysia and other centers

	Spain 2004	National Skin Center Singapore 2006	Skin Clinic Hospital Ipoh 2007
Number of patients studied	53	18	21
Study period	1992-1999	1999-2001	Jan 1996-Jun 2007
Mean age (years)	44.49 (18-65)	45 (21-80)	40.1 (20-62)
Mean starting dose (mg/kg/d)	-	2.9 (1.3-4.3)	2.8 (2.1-3.5)
Maximum dose (mg/kg/d)	3.0 (1-5)	3.6 (1.3-5.1)	3.9 (2.9-5.3)
Maximal clinical response (month)	-	4.7 (1.5-9)	2.96 (0.5-8.5)
Total duration of treatment (month)	31.4 (4-95)	8.7 (3-17)	14.5 (3.75-28)
Number & percentage achieved improvement >50%	-	14 (77.8%)	17 (80.9%)
Number & percentage developed elevated serum creatinine >30% from baseline	6 (11.3)	5 (27.7%)	13 (61.9%)
Number & percentage developed hypertension	24 (45.3)	2 (11.1%)	5 (23.8%)

countries (i.e. 61.9% in current study vs 27.7% in National Skin Center (NSC) Singapore[2] vs 11.3% in Spain[3]) as shown in Table 3. As compared to NSC Singapore, our series of patients had a higher rate of hypertension (11.1% vs 23.8%) while taking CyA. On the other hand, the Spanish study showed that 45.3% of their subjects developed hypertension during CyA treatment. This could be attributed to the longer duration of treatment (mean 31.4 months).

As a result of the higher risk of renal impairment (raised serum creatinine of more than 30%) and new onset hypertension in local population, intermittent short course CyA as initiated by Berth-Jones in 1996 might be a better approach. In this regime, patients received CyA 5mg/kg/day until achieving 90% reduction in area affected or for a maximum of 12 weeks. Those failing to demonstrate a satisfactory response were withdrawn. When there was a relapse of lesion 75% or more of affected area compared with baseline, CyA was recommenced. This cycle was repeated up to 3 times. Since then, few reports on the use of intermittent short course CyA at 2.5-5.0mg/kg/d had well demonstrated that this regime is well tolerated and provides effective control of plaque psoriasis[4,5,6,7]. About 80-85% graded overall response as considerable improvement in the studies. The rate of renal impairment and new onset hypertension were 4.4-24% and 1.1-23.7% respectively.

Other studies had shown that longer term use of CyA as maintenance is indicated in a minority of patients with recalcitrant disease[8,9,10,11]. In such cases dose should be adjusted to provide maximum clinical benefit and minimal drug side effect. The dose should not exceed 5.0mg/kg/d (majority <3.5) and the duration of treatment is limited to 2 years or less. One retrospective analysis of long-term CyA therapy for psoriasis (n=122) showed that the percentage of patients who discontinued CyA due to adverse events increased from 14% at 12 months to 41% at 48 months[12]. Reasons for discontinuation included renal dysfunction & hypertension (28% & 19% of all patients, respectively). Due to the risk of potentially serious cumulative toxicities, current guidelines recommend that patients with psoriasis should receive continuous CyA therapy for no more than 2 years[13]. Close monitoring of renal function and blood pressure is needed. Dose reduction is required if serum creatinine raised more than 30% from baseline (even though the reading is still within normal range) or blood pressure rise more than 90mmHg diastolic or 140mHg systolic.

We encountered a patient who discovered carcinoma of the breast 2 months after initiation of CyA. She was 62 years old and had suffered psoriasis for 13 years before starting CyA. Her previous treatment included NBUVB, methotrexate, acitretin and sulfasalazine. We were unsure if there was any family history of breast carcinoma. We believe that the carcinoma of the breast could be a coincidental finding rather than due to CyA therapy. A prospective long term cohort study[14] had shown that patients with psoriasis treated with CyA have a significantly higher risk of non-melanoma skin cancer compared with non-psoriatic population (RR 6:1). This increased risk is observed exclusively in patients who have been exposed previously to PUVA[14,15]. There is no significant increase in risk of non-skin cancer with CyA compared with general population. Prolonged exposure to CyA (>2 yrs cumulative treatment) was not associated with higher risk of non-skin cancer.

Long term continuous cyclosporine is a highly effective treatment modality for severe recalcitrant psoriasis in our experience. However we observed a high rate of reversible renal impairment and new onset hypertension. Furthermore relapses occur frequently and rapidly after cessation of treatment. Therefore, intermittent short-course cyclosporine therapy could be used as a rapid induction of remission for severe psoriasis while another agent such as acitretin or narrow band UVB is added to maintain the remission. Close monitoring of serum creatinine and blood pressure is mandatory.

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Original Article

Predictive values of 10% potassium hydroxide examination for superficial fungal infection of the skin

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Abstract

Introduction Ten percent potassium hydroxide examination is one of the most frequently performed tests in dermatology. It is usually supplemented by fungal culture for detection of superficial fungal infection of the skin and its appendages. We aim to determine the predictive values of 10% potassium hydroxide examination in Sarawak General Hospital.

Materials and Methods A retrospective review of 292 skin scraping results for 10% potassium hydroxide examination and culture was done between October 2003 and December 2004. Data for all the scrapings were analysed for predictive values, specificity, sensitivity and likelihood ratio with fungal culture as the gold standard investigation. Separate data analysis was done for those with onychomycosis.

Results Positive cultures were noted in 80.8% of skin scrapping cases and 85.4% of onychomycosis cases. For the skin scrapping cases, the positive predictive value of 10% potassium hydroxide examination was 67.4%, negative predictive value of 16.9%, sensitivity of 12.3% and specificity of 75%. For those with onychomycosis, the positive predictive value was 75%, negative predictive value 13.6%, specificity 85.7% and sensitivity was 7.3%. The positive likelihood ratio for all cases and onychomycosis cases was 0.5 whereas the negative likelihood ratio was 0.9.

Conclusion Ten percent potassium hydroxide examination has a very low negative predictive value and sensitivity, making it a poor investigative tool in Sarawak General Hospital. Thus, culture of the skin scraping for suspected superficial fungal infection of the skin and its appendages is of utmost importance. Steps to improve the quality of 10% potassium hydroxide examination are important as it is an easy and inexpensive test.

Keywords 10% potassium hydroxide examination, fungal culture, predictive values. Financial interests: Nil

Introduction

Ten percent potassium hydroxide examination is one of the most frequently performed tests in dermatology. This office based investigative tool allows direct visualization of fungal hyphae in keratinized material of the stratum corneum1. It is a rapid and inexpensive test. However, it is operator dependent and can be influenced by topical treatment.

In cases with high suspicion of fungal infection but negative 10% potassium hydroxide examination, culture of the specimen is usually done.

Ten percent potassium hydroxide examinations and fungal cultures are commonly performed among patients with superficial fungal skin infection and its appendages attending the Skin Clinic in Sarawak General Hospital. Thus, we aim to determine the predictive value of 10% potassium hydroxide examination in Sarawak General Hospital.

Materials and methods

A retrospective review of all the suspected fungal infections of the skin and its appendages between October 2003 and December 2004 in the Skin Clinic, Sarawak General Hospital was done. Data regarding fungal culture and 10% potassium hydroxide examination of the skin and its appendages was collected from the central laboratory. Data of patients with onychomycosis was extracted from the pooled data for further analysis.

All the specimens collected were subjected to both 10% potassium hydroxide examination and fungal culture. The 10% potassium hydroxide examination and fungal culture was done by trained microbiology technicians.

Table 1. Culture and 10% potassium hydroxide examination results for all the cases

		Culture		
		Positive	Negative	Total
10% potassium hydroxide examination	Positive	29	14	43
	Negative	207	42	249
	Total	236	56	292

Table 2. Culture and 10% potassium hydroxide examination results for onychomycosis

		Culture		
		Positive	Negative	Total
10% potassium hydroxide examination	Positive	3	1	4
	Negative	38	6	44
	Total	41	7	48

Table 3. Types of fungi grown

Fungus	Superficial skin and its appendages	Onychomycosis	Superficial skin
Trichophyton	98 (41.5%)	16 (39.1%)	82 (42.1%)
Microsporum	45 (19.1%)	3 (7.3%)	42 (21.6%)
Candida albicans	70 (29.7%)	19 (46.3%)	51 (26.1%)
Aspergillus	18 (7.6%)	1 (2.4%)	17 (8.7%)
Penicillium	5 (2.1%)	2 (4.9%)	3 (1.5%)

The gold standard test for fungal detection was fungal culture in this study. The aim was to determine the predictive values for 10% potassium hydroxide compared to fungal culture.

Data collected was compiled into the Microsoft Excel spreadsheet and subjected to descriptive analysis.

Results

From October 2003 to December 2004, we collected 292 scrapings for suspected fungal infection of the skin and its appendages. Tables 1 and 2 showed the results for the 10% potassium hydroxide examination and culture whereas Table 3 showed the type of fungus cultured.

Two hundred and thirty six cases (80.8%) had a positive fungal culture. Of these, 41.5% was Trichophyton, 29.7% Candida albicans and 19.1%Microsporum. No Epidermophyton was cultured during this period.

The 10% potassium hydroxide examination gave a positive predictive value of 67.4% and a negative predictive value of 16.9%. The sensitivity was 12.3% with a specificity of 75%. The positive likelihood ratio was 0.5 whereas the negative likelihood ratio was 0.9.

For onychomycosis, 85.4% of the samples had a positive fungal culture. Candida albicans was the most frequently seen with 46.3%, followed by Trichophyton 39.1% and Microsporum 7.3%.

The 10% potassium hydroxide examination gave a sensitivity of 7.3%, specificity of 85.7%, positive predictive value of 75% and negative predictive value of 13.6%. The positive likelihood ratio was 0.5 and the negative likelihood ratio was 0.9.

Discussion

Sensitivity of 10% potassium hydroxide examination was reported to range from 77% to 88%, and the specificity from 62% to 95%[2,3]. Our sensitivity for the 10% potassium hydroxide examination was very low at 12.3%. However our specificity of 75% was within the range.

The positive predictive value ranges from 59% to 73% and negative predictive value ranges from 79% to 98%[2,3]. We noted that our negative predictive value of 16.9% was far below this range.

We noted a 33.6% false positive rate with an 83.1% false negative rate for the 10% potassium hydroxide examination. This rate is higher than the normally reported 5% to 15% false positive rate reported elsewhere[4]. The high false negative rate explained the low sensitivity and negative predictive value in our study. This low pick up by the 10% potassium hydroxide examination might be due to poor preparation or examination technique by the technicians.

In Tehran, Karemzadegan-Nia noted that the sensitivity of 10% potassium hydroxide examination for onychomycosis was 76.5%, not statistically different from the 80.8% sensitivity of histological examination[5]. We noted a sensitivity of only 7.3% and a negative predictive value of 13.6%. This again is due to the high false negative result of 86.4%.

To improve the 10% potassium hydroxide examination for scraping in Sarawak General Hospital, training of the laboratory technicians for proper preparation and microscopic examination is essential. Besides that, doctors sending patients for this examination should also ensure that these patients have not applied any topical antifungal on the lesions as this will negatively affect the examination. Improving this examination is essential as it is a fast and cheap investigative tool.

In New Delhi, Das and colleagues noted that Trichophyton was the major fungus isolated with over 70% of cases; with Candida only contributing 16% of isolates[6]. We also noted a predominance of dermatophytes especially Trichophyton but with a higher yield of Candida with 33.6%.

Dermatophytes especially Trichophyton and yeasts are the predominant cause of onychomycosis[7,8]. We noted predominant Candida infection among our patients with onychomycosis.

Our mycologic culture results are similar to that observed with other parts of Asia mainly South and Mideastern Asia.

We would like to conclude that 10% potassium hydroxide examination has a high positive predictive value but a very low negative predictive value and sensitivity, making it a poor investigative tool in Sarawak General Hospital. Thus, culture of the suspected fungal infection of the skin and its appendages is of utmost importance. Proper training of the laboratory technicians performing the 10% potassium hydroxide examination is needed to improve the quality of the examination.

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Original Article

Epidemiological characteristics of common secondary bacterial skin infection from patients with atopic dermatitis

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Abstract

Introduction Atopic dermatitis (AD) is a chronic, highly pruritic, inflammatory skin disease that often has a remitting and flaring course, which may be exacerbated by social, environmental, and biological triggers. The estimated incidence of AD in the general population varies between 1% and 5%. Because of compromised skin barrier, AD sufferers frequently develop recurrent bacterial skin infections. These infections can also worsen the disease. The aim of this study is to establish the common types of bacteria found in secondarily infected AD patients who attended Foong Skin Specialist Clinic in year 2005-2007.

Materials and Methods A retrospective study is conducted among all the patients with AD who are seen at the Foong Skin Specialist Clinic in year 2005-2007. Cultures were collected from all AD patients with secondarily infected AD lesions. All their clinical and microbiology laboratory results are recorded and data obtained from these patients whose specimens of infected sites were processed for the presence of types of bacteria.

Results Out of 52 specimens with an equal sex ratio, 43 (82.7%) of them were positive cultures and among these secondarily infected AD patients, 69.2% of them were infected with *Staphylococcus aurues* and 61.9% of *Staphylococcus aurues* were resistant to Penicillin.

Conclusion We found that majority of the AD patients who are clinically diagnosed with secondary bacterial infection have positive cultures of bacteria and the most common organism isolated from eczematous lesion at all sites of body is *Staphylococcus aureus* which is consistent with the results reported by most previous studies. In terms of antibiotic sensitivity, more than half (61.9%) of the *Staphylococcus aureus* infected AD patients are found resistant to penicillin in this study which is considered relatively low as compared to previous studies (>80%).

Keywords Atopic dermatitis, bacterial infection, antibiotic sensitivity

Introduction

Atopic dermatitis (AD) is a chronic inflammatory genetically determined disease of the skin marked by increased ability to form reagin (IgE), with increased susceptibility to allergic rhinitis and asthma, and hereditary disposition to a lowered threshold for pruritus[1]. The estimated incidence of atopic eczema in the general population varies between 1% and 5%[2]. Over the past few decades there has been a steady increase worldwide in the incidence of this disorder[3]. In Malaysia, 3.7% of the general population are diagnosed with atopic dermatitis with the highest prevalence among the Malay with the prevalence of 4.3%[4].

The pathogenesis of AD is multifactorial; resulting from an interaction between genetic susceptibility, the host's environment, skin barrier defects and immunological factors[5]. The condition is characterized by intense pruritus and a course marked by exacerbations and remissions[6]. AD is associated with other atopic diseases such as allergic rhinitis, bronchial asthma[7] and 60% of patients develop AD within the first year of life, 85% by age 5[8]. Although it is an inherited disease, eczema is primarily aggravated by contact with or intake of allergens. It can also be influenced by other factors such as stress or fatigue[9]. The rapid rise in prevalence of AD is thought to be primarily related to changes in our environment[10].

Atopic dermatitis patients are particularly prone to skin infections[11]. The percentage of positive culture from skin swab of AD patients is more than 90%[3,4,8,10,12,13]. Heightened susceptibility occurs because the skin of patients with AD has a defective barrier against organisms, depressed immune function and lacks normal lipophilic bacteria[6]. As a result

AD patients frequently suffer from boils, folliculitis and infected eczema. The infection causes the eczema to worsen and become more resistant to the usual treatment with emollients and topical steroids. Antibiotics are often required to eliminate the infection and control the eczema[11].

The bacteria that cause infection are also commonly found on healthy skin like staphylococci and streptococci[12], Escherichia coli, Enterobacter sp., Klebsiella sp., Acinetobacter sp., Proteus sp[14]. Coagulase-positive staphylococci (Staph. aureus), which are usually not found on normal skin, accounted for the majority of organism isolated from AD patients' skin[15]. According to a study done by Donald Leung et al. in London in 2003, Staphylococcus aureus were found in over 90% of AD skin lesions[5]. Staph. epidermidis which is the predominant organism isolated from the clinically uninvolved skin of AD patients, was second to Staph. aureus to be found in lesional skin[16]. In a study done by Ihsan et al. in Iraq showed that the Staphylococcus epidermidis consisted of 17.13% of bacteria isolated from eczematous lesions of 284 AD patients[10].

In patients with atopic dermatitis, all isolates of S. aureus were sensitive to cloxacillin, cephalexin, clindamycin, and co-trimoxazole; 92% was sensitive to erythromycin, but only 13% was sensitive to penicillin and ampicillin. As 87% of S. aureus is resistant to penicillin and ampicillin, antibiotics such as cloxacillin and cephalexin should be used to eradicate S. aureus in the skin of atopic dermatitis individuals[17].

To date there are very few studies conducted specifically on common secondary bacterial infection of AD patients in Malaysia, especially in Ipoh. In view of that, this study is aimed at determining the bacterial types of each eczematous lesion from patients' skin with AD as well as to correlate them with the sociodemographic data. Since Staphylococcus aureus is the most common organism isolated from AD patients according to previous study, antibiotic sensitivity of Staphylococcus aureus infection among AD patients was determined in this study.

Materials and methods

A retrospective descriptive cross-sectional study was conducted among all the patients with AD complicated by secondary bacterial infection over affected skin lesions who attended Foong Skin Specialist Clinic in year 2005-2007. Patients' medical records were reviewed for basic demographics, clinical diagnosis and bacteriological culture results. Specimens for bacteriological examination and culture were obtained by a sterile swab from the affected skin areas of AD patients. SPSS Student version 11.5 was used for statistical analysis. Descriptive analysis was done on each variable. Chi Square test was employed to compare the qualitative data; while Student's t-test was used to compare the quantitative data, with p value less than 0.05 considered as significant.

Results

A total of 52 specimens were collected from the patients during the study. 26 women and 26 men were enrolled in the study. The age ranges from 2-80 years with a mean of 22 years.

Out of 52 patients, 43 patients (82.7%) were confirmed to have secondary skin infection by skin swab. The remaining 9 patients (17.3%) showed negative results on skin swab culture. 36 patients (69.2%) were infected with a single type of bacteria, compared to 7 patients (13.5%) who had multiple infections.

Figure 1. Distribution of patients according to site of swab

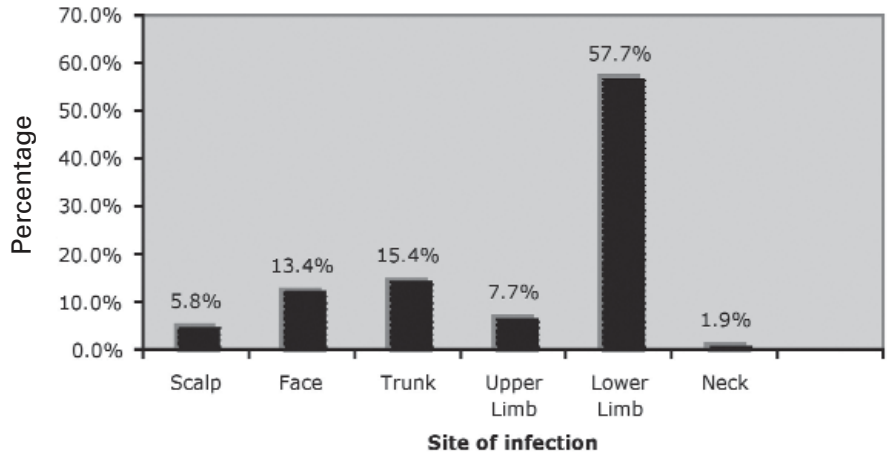

Figure 1 shows the distribution of respondents in relation to site of swab. Most swabs were done on the lower limb 57.7% (n=30). This is followed by trunk 15.4% (n=8). face 13.5% (n=7), upper limb 7.7% (n=4) and scalp 5.8% (n=3).

Table 1. Comparison between age groups, gender and type of infections. Age is categorized into adult (19 year-old and above), schooling (6 to 18 year-old) and pre-schooling (5 year-old and below) groups

Bacteria	Age Groups						Total
	Pre-School		Schooling		Adult		
	Male	Female	Male	Female	Male	Female	
No. examined	1	2	5	10	20	14	52
Non-infected	0 (0.0%)	1 (50.0%)	1 (20%)	0 (0.0%)	2 (10%)	5 (35.7%)	9 (17.3%)
Infected	1 (100.0%)	1 (50.0%)	4 (80%)	10 (100.0%)	18 (90%)	9 (64.3%)	43 (82.7%)
Bacteria							
S. aureus	1 (100.0%)	1 (50.0%)	3 (60.0%)	9 (90.0%)	16 (80%)	6 (42.9%)	36 (69.2%)
S. epidermidis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (7.1%)	1 (1.9%)
S. pyogenes	0 (0.0%)	0 (0.0%)	1 (20%)	1 (10.0%)	0 (0.0%)	1 (7.1%)	3 (5.8%)
Group B Streptococcus	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (14.3%)	2 (3.8%)
P. aeruginosa	0 (0.0%)	0 (0.0%)	1 (20%)	1 (10.0%)	2 (10%)	1 (7.1%)	5 (9.6%)
E. faecalis	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (10%)	1 (7.1%)	3 (5.8%)

Table 1 shows the comparison between age groups, gender and type of infections. Out of 43 patients with secondary bacterial infections, 23 (53.5%) were male, and 20 (46.5%) were female. Female of school going age group had the highest infective rate, with 100% (10/10) shown to be infected. This is followed by adult male (90%) and male of school going age (80%).

In terms of type of infections, majority of infections were caused by *Staph. aureus*, representing 69.2% (n=36). Adult male has the highest prevalence of *Staph. aureus* infection with 16 infected individuals, followed by schooling female (9 infected individuals) and adult female (6 infected individuals). *Pseudomonas aeruginosa* infection is the second highest with 9.6% (n=5). *Strep. pyogenes* and *Enterococcus faecalis* each has three infections (5.8%). Group B streptococci and *Staph. epidermidis* comprising only the minority, with 3.8% (n=2) and 1.9% (n=1) respectively.

Table 2. Multiplicity of infections

Number of bacterial infections	Number examined
Specimens with:	
1. bacteria infection	
Staph aureus	31
Staph epidermidis	0
Strep. pyogenes	1
Group B Streptococcus	2
Pseudomonas aeruginosa	2
Enterococcal faecalis	0
Total specimens with only one infection	**36**
2. bacteria infections	
Staph. aureus + P.aeruginosa	2
Staph. aureus + Strep. pyogenes	2
Staph. aureus + E. faecalis	1
Staph. epidermidis + E. faecalis	1
P. aeruginosa + E. faecalis	1
Total specimens with only two infections	**7**

Table 2 displays the multiplicity of infections among patients with atopic dermatitis. Majority of patients have only one infection. 67.9% (n=36). *Staph. aureus* tops the list with 31 patients being infected, while Group B streptococci and *Pseudomonas aeruginosa* have infected two patients respectively. One patient is infected by *Strep. pyogenes*. Skin specimens from seven patients showed multiple infections. The common combinations of bacteria are *Staph. aureus* with *Pseudomonas aeruginosa* and *Staph. aureus* with *Strep. pyogenes*. Other combinations include: *Staph. aureus* with *E. faecalis*; *S. epidermidis* with *E. faecalis* and *P. aeruginosa* with *E. faecalis*.

Association between number of infection and age group is not significant statistically since p=0.656. Similar result is obtained when associating number of infection with gender (p=0.452), hence difference in number of infection between male and female was statistically insignificant.

Table 3. Comparison between age groups and antibiotic sensitivity to *Staph. aureus*

Antibiotics	Status	Age Groups				
		Pre-school	Schooling	Adult	Total	p-value
Augmentin	Not Done Sensitive Resistant	0 (0.0%) 1 (2.8%) 1 (2.8%)	1 (2.8%) 11 (30.6%) 0 (0.0%)	7 (19.4%) 15 (41.7%) 0 (0.0%)	8 (22.2%) 27 (75.0%) 1 (2.8%)	0.001*
Cefuroxime	Not Done Sensitive Resistant	0 (0.0%) 1 (2.8%) 1 (2.8%)	1 (2.8%) 11 (30.6%) 0 (0.0%)	6 (16.7%) 16 (44.4%) 0 (0.0%)	7 (19.4%) 28 (77.8%) 1 (2.8%)	0.001*
Erythromycin	Not Done Sensitive Resistant	0 (0.0%) 2 (5.6%) 0 (0.0%)	0 (0.0%) 10 (27.8%) 2 (5.6%)	0 (0.0%) 17 (47.2%) 5 (13.9%)	0 (0.0%) 29 (80.6%) 7 (19.4%)	0.707
Fusidic Acid	Not Done Sensitive Resistant	0 (0.0%) 1 (2.8%) 1 (2.8%)	0 (0.0%) 10 (27.8%) 2 (5.6%)	0 (0.0%) 22 (61.1%) 0 (0.0%)	0 (0.0%) 33 (91.7%) 3 (8.3%)	0.022
Methicilin	Not Done Sensitive Resistant	0 (0.0%) 2 (5.6%) 0 (0.0%)	0 (0.0%) 12 (33.3%) 0 (0.0%)	0 (0.0%) 22 (61.1%) 0 (0.0%)	0 (0.0%) 36 (100.0%) 0 (0.0%)	-
Penicillin	Not Done Sensitive Resistant	0 (0.0%) 0 (0.0%) 2 (5.6%)	0 (0.0%) 2 (5.6%) 10 (27.8%)	0 (0.0%) 3 (8.3%) 19 (52.8%)	0 (0.0%) 5 (13.9%) 31 (86.1%)	0.818
Tetracyclin	Not Done Sensitive Resistant	0 (0.0%) 2 (5.6%) 0 (0.0%)	0 (0.0%) 9 (25.0%) 3 (8.3%)	0 (0.0%) 16 (44.4%) 6 (16.7%)	0 (0.0%) 27 (75.0%) 9 (25.0%)	0.695
Vancomycin	Not Done Sensitive Resistant	1 (2.8%) 1 (2.8%) 0 (0.0%)	1 (2.8%) 11 (30.6%) 0 (0.0%)	1 (2.8%) 21 (58.3%) 0 (0.0%)	3 (8.3%) 33 (91.7%) 0 (0.0%)	0.084
Total		**2 (5.6%)**	**12 (33.3%)**	**22 (61.1%)**	**36 (100%)**	

Table 3 shows the cross-tabulation between age groups with antibiotic sensitivity to *Staphylococcus aureus*. Out of 33 individuals infected with *S. aureus*, penicillin shows highest incidence of resistance (86.1%), followed by tetracycline (25%), erythromycin (19.4%), fusidic acid (8.3%), augmentin (2.8%) and cefuroxime (2.8%). There is no methicilin-resistant *S. aureus* (MRSA) or vancomycin-resistant *S. aureus* (VRSA) infections in this population.

In term of age groups, adult has the highest infective rate (22 out of 36 patients), followed by schooling and pre-school age groups. Among adult patients, *S. aureus* is most sensitive against methicilin, vancomycin, fusidic acid, cefuroxime and augmentin. Erythromycin and tetracycline are less sensitive, while penicillin is almost not effective. School age group had almost similar profile as adults. Pre-school age group had higher resistant rate to most antibiotic than other age groups. Augmentin, cefuroxime and fusidic acid are all less effective among pre-school patients while methicilin and vancomycin remain resistance-free.

Discussion

Atopic dermatitis is a chronic relapsing, pruritic inflammation of the skin, affecting 10-20% of children and 1-3% adults worldwide, with increasing prevalence in highly industrialized countries[18]. In Malaysia, it is estimated that one-third of the population is currently suffering from some form of allergy. A study by Jaafar et a[l4] in 1993 reported that out of 13,524 patients, 4.3% was noted to be affected by atopic dermatitis and Malays were the highest affected among all races. If this trend continues, by the year 2020 it is expected that half of the population will be involved. However, allergy is still not accorded the attention and priority that it needs[19].

Table 4. Comparison of infection prevalence with previous studies

Prevalence in this study (%)	Sample size	Bacterial					
		Staph. aurues	*Staph. epidermidis*	*S. pyogenes*	*Group B Streptococci*	*P. aeruginosa*	*E.faecalis*
	52	**69.2%**	**1.9%**	**5.8%**	**3.8%**	**9.6%**	**5.8%**
Prevalence in Other Studies (%)							
Marwa Abdullah et. al. (2007, Egypt)[20]	37	37	N/A	40.0%	N/A	N/A	20.0%
Ihsan et al. (2006, Iran)[10]	40	40	17.2%	17.1%	N/A	17.5%	23.1%
JQ. Gong et al. (2006, China)[21]	119	119	38.4%	N/A	4.1%	N/A	N/A
Yong Kwang Tay et al. (1999, Singapore)[3]	492	492	5.0%	N/A	N/A	N/A	N/A
Mustafa et al. (1996, Malatya)[22]	60	60	N/A	3.3%	N/A	N/A	N/A

Most previous studies reported that *Staph. aureus* is the most common organism isolated from atopic dermatitis skin lesion[3,8,10,12,20-22]. *Staph. epidermidis*, *Strep. pyogenes*, *Enterococcus faecalis* and *Pseudomonas aeruginosa* infections are other common organisms throughout literature review. However, *Staph. epidermidis* infection is relatively uncommon in this study with only one patient infected (1.9%).

Antibiotic sensitivity profile of *Staph. aureus* in this study is compared with the literature and tabulated below. It is noted that penicillin has the highest resistance among all antibiotics in this study as well as various previous studies. Commonly used macrolides such as erythromycin is also shown to have high resistant rate ranging from 19.2% to 77%. Hence, it is recommended that penicillinase-resistant penicillin (dicloxacillin, oxacillin, or cloxacillin) and first-generation cephalosporins might be preferred in the management of secondarily infected atopic dermatitis[5].

Table 5. Comparison of antibiotic sensitivity of *Staph. aureus* with previous studies

Prevalence in this study (%)	Antibiotic Resistance						
	Erythromycin	Fusidic Acid	Methicillin	Penicillin	Rifampicin	Tetracyclin	Vancomycin
	19.2%	**7.7%**	**1.9%**	**61.9%**	**1.9%**	**25%**	**1.9%**
Prevalence in Other Studies (%)							
Marwa Abdullah et. al (2007, Egypt)[20]	77.0%	12.9%	9.7%	100.0%	7.1%	N/A	6.5%
Brook I et al. (1996, LA)[23]	35.9%	22.6%	N/A	90.0%	N/A	N/A	N/A
Mustafa et al. (1996,Malatya)[22]	N/A	N/A	N/A	85.9%	18.7%	N/A	4.7%

Staph. aureus is recognized as an important triggering factor for the maintenance of skin inflammation and acute exacerbations of the genetically determined skin disease such as atopic dermatitis[23-24]. *Breuer K. et al* (2000)[25] demonstrated that the colonization density of eczematous lesions can reach up to 107 CFU/cm^2. Many modern studies illustrated the factors whose relevance to the increased colonization of atopic dermatitis skin with *Staph. aureus* such as ability to produce exotoxins, ability of bacteria to adhere to host cells and optimal pH activity[10]. Another research reported that up of 65% of all *Staph. aureus* strains isolated from skin lesion have been shown to produce exotoxins with superantigenic properties[26].

From this study, we found that majority of the AD patients who were clinically diagnosed with secondary bacterial infection had positive cultures of bacteria. The most common organism isolated from eczematous lesion at all sites of body was *Staphylococcus aureus*. This result is similar to those of the previous studies conducted in various parts of the world including developed and developing countries. Hence antibiotics may have a role in the treatment of atopic dermatitis. Although the prevalence of resistance of *Staphylococcus aureus* to Penicillin is relatively low compared to previous studies, more than half of the *Staphylococcus aureus* infected AD patients were found resistant to penicillin in this study. Thus, antibiotics such as cloxacillin and cephalexin should be used to eradicate *Staphylococcus aureus* in the skin of atopic dermatitis individuals.

Therefore, further studies on a large scale to estimate the exact incidence of the different bacterial organisms found in secondary infection of AD patients as well as bacterial culture of specimens should be performed to confirm the bacterial etiology so that suitable treatment can be provided.

In order to limit the misuse of antimicrobials and prevent emergence of resistant bacterial strains, antimicrobial susceptibility testing should be considered when prescribing antimicrobial therapy.

Advances are likely to need better definitions for the various clinical phenotypes of atopic dermatitis, a better understanding of the immunoregulatory abnormalities underlying it, and new paradigms for preventing relapses of this skin disorder. Recently fillagrin gene mutation mapped at the loci 1q21 is responsible for the skin barrier defect. Such advances may lead to the development of pharmacogenetics and targeting of effective treatments to subsets of patients with atopic dermatitis.

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Original Article

Cutaneous tuberculosis in Penang: A 12-year retrospective study

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Abstract

Background Cutaneous tuberculosis (TB) is a form of extra-pulmonary tuberculosis. Diagnosis of cutaneous TB is often difficult because of the diverse clinical presentations. The positive yields from cultures are often low. To describe the demographic, clinical, histopathological and bacteriological aspects of cutaneous TB.

Materials and Methods This retrospective review looked at cases of cutaneous tuberculosis treated at the Respiratory and Dermatology unit, Penang Hospital from 1996 to 2007. Data were analysed with SPSS 13.0 version.

Results A total of 23 cases of cutaneous tuberculosis were reviewed. The male to female ratio was 2.3 to 1. The mean age was 37.7 ± 20.7 years. There were 10 Malays, 9 Chinese, 2 Indians and 2 Indonesian. The types of cutaneous tuberculosis observed were lupus vulgaris (47.8%), tuberculides (17.5%), tuberculosis verrucosa cutis (13.0%), scrofuloderma (13.0%) and primary inoculation TB (8.7%). 43.5% of patients had systemic involvement. Mantoux tests were positive in 85.0% of cases. Skin biopsies were performed in 91.3% of patients and 71.4% of them showed classical histopathologic findings suggestive of tuberculosis. Mycobacterium tuberculosis was isolated in the culture from 28.6% of patients. Localized diseases were found more often in BCG-vaccinated individuals. Regional lymphadenopathy was noted more often in patients with disseminated disease. No correlation was found between Mantoux reactivity and the extent of disease.

Conclusion Lupus vulgaris was the commonest form of cutaneous tuberculosis. Cultures were positive in only a small proportion of patients. Almost half of our patients had systemic involvement. The presence of regional lymphadenopathy often indicates disseminated disease. Patients without BCG vaccination were at higher risk of disease dissemination.

Keywords Tuberculosis, Cutaneous tuberculosis, Lupus vulgaris, Scrofuloderma, Tuberculide

Introduction

Tuberculosis is a chronic granulomatous infection caused by Mycobacterium tuberculosis. Cutaneous tuberculosis (TB) is one of the rarer forms of extra-pulmonary tuberculosis. Diagnosis of cutaneous TB is difficult because of the protean clinical presentation and the poor yield from culture.

Despite the attention given to pulmonary tuberculosis, there was very limited data on the epidemiology of cutaneous tuberculosis especially in this part of the world. We describe the clinical, histopathological and bacteriological findings of patients diagnosed with cutaneous tuberculosis in our centre.

Materials and methods

This retrospective study looked at cases of cutaneous tuberculosis presented to respiratory and dermatology units, Penang Hospital from 1996 to 2007. Case records, histological reports and culture results of confirmed cases were retrieved and reviewed. The demographic details, clinical features, results of investigation including chest radiograph, Mantoux test were recorded and analysed.

We have also included cases with negative tissue culture but with clinical features and histological findings compatible with cutaneous tuberculosis, which showed good clinical response to anti-tuberculous treatment.

Those patients with *Mycobacterium leprae* and non-tuberculous mycobacterial disease were excluded from this study. Patients with tuberculous lymphadenitis without evidence of skin involvement were also excluded from the study.

Results

23 cases of cutaneous tuberculosis were included. The male to female ratio was 2.3:1. The mean age of patients was 37.7 ± 20.7 years (range from 1 to 78 years old). Only 2 children (Age <12 years old) were diagnosed to have cutaneous TB during study period. There were 10 Malays, 9 Chinese, 2 Indians and 2 Indonesian.

The types of cutaneous tuberculosis observed in our cohort were lupus vulgaris (47.8%), tuberculides (17.5%), tuberculosis verrucosa cutis (13.0%), scrofuloderma (13.0%) and primary inoculation TB (8.7%). Among the tuberculides that observed in our study, there were 2 cases of erythema induratum and 2 cases of papulonecrotic tuberculide. (Refer figure 1 & 4)

9 (39.1%) patients have a contact history of tuberculosis and 2 (8.7%) patients had had a past history of tuberculosis. Only 9 (39.1%) patients were brought to medical attention within a year of onset of the disease and 5 (21.7%) patients were diagnosed after more than 5 years of the onset of the illness. All our patients were tested for HIV[3]. (13.0%) out of 23 patients had concomitant HIV infection.

Systemic organ involvement

Systemic involvement was seen in 10 (43.5%) patients. The lung was the most common organ involved, in 5 (50.0%) patients, followed by lymph nodes in 4 (40.0%) and bone in 1 (10.0%). There were no cases of TB involving the gastrointestinal tract, genitourinary tract, CNS and heart. Regional lymphadenopathy was noted more often in patients with disseminated disease. (Refer figure 3)

BCG vaccination

Of the 23 patients, 11 (47.8%) had been vaccinated and 12 (52.2%) had no documented BCG vaccination. Among the vaccinated group, only 3 patients (27.3%) had disseminated disease. 7 patients (58.3%) in the non-vaccinated group had disseminated disease. Patients with disseminated disease were less often found in those with BCG vaccination. (Refer figure 3)

Mantoux reactivity

Information regarding Mantoux reactivity was available in 20 (87.0%) patients, 11 (55.0%) with localized disease and 9 (45.5%) with disseminated disease. Of the 11 patients with localized disease, 9 (81.8%) were Mantoux positive. 8 (88.9%) patients with disseminated disease had positive Mantoux test. No correlation was found between Mantoux reactivity and the extent of disease. (Refer figure 2 & 3)

Histopathology

Histopathological reports were available for evaluation in 21 patients (91.3%). Out of which, 15 (71.4%) showed classical histological findings of TB (epithelioid granuloma ± caseation). Tubercle bacilli has been demonstrated in 1/11 (9.1%) cases with LV and 2/3 (66.7%) cases of SFD. (Refer figure 2)

AFB culture

AFB cultures were done for 21 patients (91.3%) but Mycobacterium tuberculosis was isolated in only 28.6% of cases. (Refer figure 2)

Conclusion

Cutaneous tuberculosis is a rare form of extrapulmonary tuberculosis. It was reported in 1.0 - 4.4% of all cases of TB[1-2]. In Morocco, cutaneous tuberculosis ranks fifth in frequency after pleural, lymph node, genitourinary and intestinal tuberculosis[3]. Although cutaneous TB only comprises a small proportion of cases, the absolute number may be high, given the high prevalence of TB in many developing countries.

In our centre, we observed 23 cases of cutaneous TB over a 12 years period. It is interesting to compare this figures with various case series around the world: Farina (Spain)[4], 11 cases in 14 years; Chong (Hong Kong)[5], 176 cases in 10 years; Jerajani, Mumbai (India), 291 cases in 10 years and Kumar in Chandigarh (India), 402 cases in 25 years. The numbers in these series may reflect true incidence or in certain communities underreporting - a well-known problem in resource-poor areas with a high burden of disease.

Factors contributing to increasing prevalence of cutaneous TB include HIV co-infection, multidrug-resistance, immigrants from countries of higher prevalence and the neglect of preventive measures[6-8]. HIV infection has led to a 20% increase in the incidence of extra-pulmonary tuberculosis in the United States[6], of which 1.5% comprised of cutaneous tuberculosis[9]. Although the skin remained a relatively uncommon site of dissemination, several cases of cutaneous miliary tuberculosis, scrofuloderma, tuberculous ulcer, subcutaneous tuberculous abscess and tuberculide in HIV-seropositive individuals have been reported. 3 out of 23 (13.0%) cases from our cohort were HIV infected patients.

Tuberculosis of the skin was most commonly reported in young adults[10]. In our study, 43.5% of patients were under 30 years of age. This may be explained by the study methodology. We only looked at the data retrieved from the respiratory unit and dermatology unit which are mainly seeing the adult patients. The data in paediatric clinic were not captured in this study. We observed a male predominance as noted in other studies[4-5,11].

Figure 1. Characteristics of patients with cutaneous TB seen at respiratory unit, Penang Hospital (1996 to 2007)

	N (%) of patients
Sex	
Male	16 (69.6)
Female	7 (30.4)
Ethnic	
Malay	10 (43.5)
Chinese	9 (39.1)
Indian	2 (8.7)
Foreigner	2 (8.7)
Age (Mean: 37.7 ± 20.7 yrs)	
≤12	2 (8.7)
13-20	2 (8.7)
21-30	6 (26.1)
31-40	3 (13.0)
41-50	4 (17.4)
51-60	1 (4.3)
> 60	5 (21.8)
Type of cutaneous TB	
True cutaneous TBb	19 (82.5)
LV	11(57.9)
TVC	3 (15.8)
SFD	3 (15.8)
Primary inoculation TB	2 (10.5)
Tuberculides	4 (17.5)
EI	2 (50.0)
PNT	2 (50.0)

LV, lupus vulgaris; TVC, tuberculosis verrucosa cutis; SFD, scrofuloderma; EI, erythema induratum; PNT, papulonecrotic tuberculide.

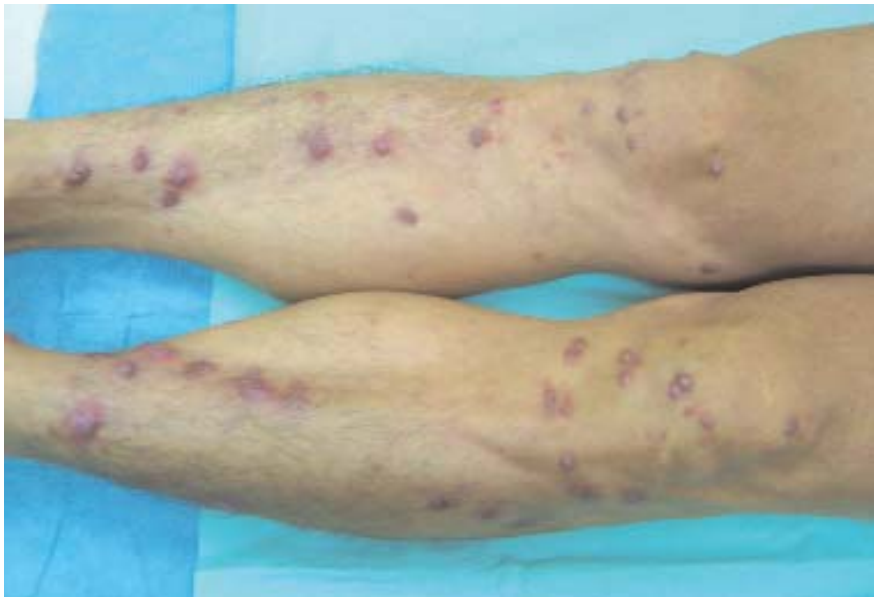
Figure 2. Mantoux's test, skin biopsy and AFB culture findings in our cohort

Test	Performed (%)	Positive (%)
Mantoux Reactivity	87	85
Histopathology	91.3	71.4
AFB Culture	91.3	28.6

Figure 3. Clinical predictors of disseminated

Parametres	Disease spectrum	
	Localised (N=13)	**Disseminated (N=10)**
BCG Vaccination Status		
- Vaccinated	8	3
- Non Vaccinated	5	7
Regional Lymphadenopathy		
- Yes	6	10
- No	7	0
Type of Cutaneous TB		
- True Cutaneous TB	13	6
- Tuberculides	0	4
Mantoux Reactivity		
- Positive	9	8
- Negative	2	1
- Not done	3	1

Figure 4. Papulonecrotic tuberculide



The development of cutaneous TB depends on several factors, including the patient's immune status, route of inoculation and past sensitization with TB[12]. In relation to host immunity, cutaneous tuberculosis represents a continuous spectrum with lupus vulgaris (high degree of immunity) at one end of the spectrum, scrofuloderma and tuberculous gumma (low degree of immunity) at the other[13].

There are two general categories of manifestation of cutaneous TB. The first is true tuberculosis, a disease evolving from a proliferation of tuberculosis bacilli in the skin such as lupus vulgaris, scrofuloderma, tuberculosis verrucosa cutis, cutaneous primary tuberculosis, tuberculosis cutis orificialis and cutaneous miliary tuberculosis. In true infections, the bacilli reach the skin either from an exogenous route or an endogenous focus. Apart from miliary tuberculosis, lesions are mostly single or few in number and mycobacteria can usually be detected. The second category is tuberculide, which is diagnosed when the skin is involved as a reaction to tuberculous infections in other organs. Erythema induratum (Bazin's disease), papulonecrotic tuberculide and lichen scrofulosorum are different forms of tuberculide described. Tuberculides typically manifest as recurrent skin eruptions that are usually disseminated, symmetrical and show a tendency to spontaneous involution. Organisms cannot be isolated from these sites.

Lupus vulgaris (LV) is the commonest form of cutaneous TB reported in our cohort. However some studies have reported a higher incidence of SCD or equal number of cases of LV and SCD[4,11]. Scrofuloderma is most often associated with active tuberculous lymphadenitis and pulmonary TB. We observed a similar pattern in our study population. 17.5% of cutaneous TB cases in our cohort were tuberculides. There were an increasing number of tuberculide cases being reported in Japan[14] and Hong Kong[15].

Disseminated form of tuberculosis has been reported in 5% to 22.1% of patients with cutaneous tuberculosis[3,5,16]. We found a substantially higher percentage of active extracutaneous disease (systemic involvement) in our patients (43.5%). Disseminated forms of TB were observed in all clinical variants except in tuberculous verrucosa cutis.

Localized disease is more commonly seen in a BCG-vaccinated individual. Regional lymphadenopathy was noted more often in patients with disseminated disease. No correlation was found between Mantoux reactivity and the extent of disease. Similar findings were also reported by Kumar B et al[10].

Cutaneous tuberculosis continues to be one of the most elusive and difficult diagnoses to make for dermatologists practicing in developing countries. Not only because they have to consider a wide range of differential diagnoses but also because of the difficulty in obtaining a microbiological confirmation. The culture provides only small diagnostic yield in patients with cutaneous TB[11,17] as noted in our series.

A diagnosis of cutaneous TB is typically made presumptively based on the presence of active tuberculosis elsewhere, clinical history and physical signs, a positive purified protein derivative (PPD) skin test reaction, typical histological findings and a therapeutic response to antituberculous treatment[3,18]. Several case reports indicate the usefulness of polymerase chain reaction (PCR) in the diagnosis of cutaneous TB[19-20].

Majority of our patients responded satisfactorily to anti-tuberculous therapy. Because most of the cutaneous TB cases were related to tuberculous disease of other organs, standard TB treatment regimens is usually sufficient. A clinical response could be expected by week 4 or 6 of the therapeutic trial, with lupus vulgaris showing a faster response than scrofuloderma[18]. In areas of high TB prevalence like Malaysia, a therapeutic trial of anti-TB chemotherapy should be considered.

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Original Article

Comparison of BBL chromagar MRSA to conventional media for the detection of methicillin resistant staphylococcus aureus in surveillance nasal swabs

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Abstract

Objectives This study aims to detect MRSA nasal carriers among medical staff and patients in Dermatology ward Hospital Kuala Lumpur by using two methods, the conventional blood sheep agar (BSA) and the novel BBL CHROMagar MRSA (C-MRSA). It also aims to compare the BSA medium with the C-MRSA medium in terms of specificity, sensitivity and time to detection to MRSA.

Method A single centre, prospective study where 100 nasal swab samples were taken from medical staff and inpatients, then plated on to both BSA and C-MRSA. After 24 hours incubation, the plates were examined for presence of bacterial colonies, then incubated for another 24 hours if no colonies were present. All colonies on C-MRSA and BSA were subjected to coagulase and susceptibility testing for confirmation of MRSA. MRSA strains produce mauve colonies on C-MRSA from hydrolysis of the chromogenic substance, thus C-MRSA uses colour as a diagnostic tool.

Results Mauve colonies were present on nine C-MRSA plates in the first 24 hours which were all confirmed to be MRSA. Another nine C-MRSA plates isolated bluish colonies which were not MRSA. There were colonies on 96 BSA plates, nine of which were MRSA. C-MRSA medium has 100% sensitivity and specificity in detecting MRSA. Both culture media had similar detection rates of MRSA from nasal swabs, however C-MRSA allows for earlier detection of MRSA within 24 hours compared to BSA which takes 48 hours. 2.2% of ward staff and 15.7% of inpatients were found to be MRSA carriers.

Conclusion CHROMagar MRSA allows for more rapid identification of MRSA carriers within 24 hours compared to the conventional BSA which takes 48 hours. This allows earlier action to be taken to reduce the spread of MRSA infection.

Keywords MRSA, CHROMagar, nasal carrier

Introduction

MRSA was first reported in 1961 and its prevalence is believed to be increasing worldwide[1]. According to the National Nosocomial Infection Surveillance System, the mean prevalence of MRSA in US hospitals increased from 2.4% in 1975 to 36% in 1999 as a percentage of all staphylococcus aureus strains isolated[2]. In Hospital Kuala Lumpur the incidence of MRSA infection was reported as 0.22-0.7% for every 100 admissions a month in 2006, which was amongst the highest of the government hospitals in Malaysia.

Methicillin resistant Staphylococcus aureus (MRSA) is an important pathogen causing serious nosocomial infections. Infections caused by MRSA are associated with increased morbidity and mortality, longer hospital stay, longer course of antibiotics therapy and higher costs compared with infections caused by Methicillin susceptible Staphylococcus aureus (MSSA)[3]. MRSA infection is often highly transmissible and 20-60% of hospitalized patients who are MRSA nasal carriers eventually have MRSA infection[4].

Active surveillance for MRSA in the nares of those at risk is an important component of the Society for Healthcare Epidemiology of America recommendations for the control of nosocomial transmission of MRSA[5]. Many centres screen for staphylococci in particular MRSA in the nares of at-risk populations, to control nosocomial transmission of MRSA. Identification of patients and healthcare workers colonized with MRSA during outbreaks, as well as contact precautions and strict hand hygiene have reduced the transmission and controlled the spread of MRSA.

Figure 1.

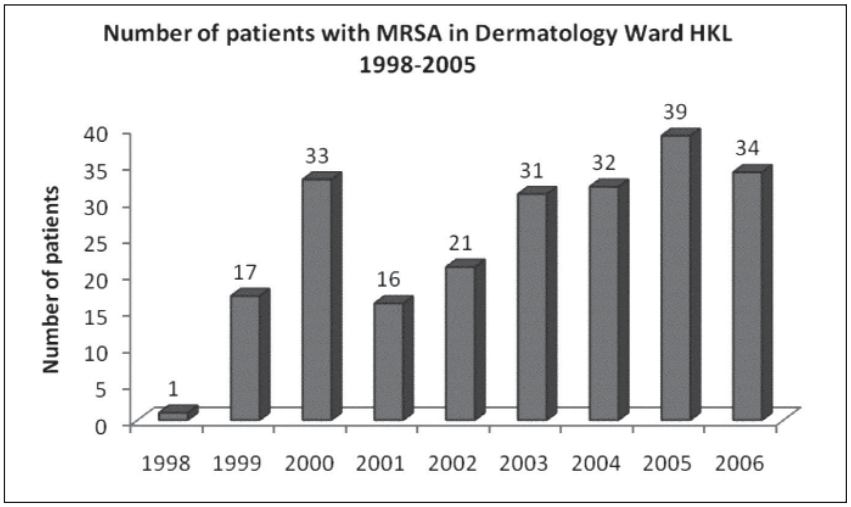


Figure 2. BBL CHROMagar MRSA showing the growth of MRSA which appears as mauve colonies - visual identification

The number of patients with MRSA infection in the Dermatology Ward, HKL has increased over the years despite pro-active measures to actively treat MRSA nasal carriers among healthcare personnel and inpatients (Figure 1). Hence it is of prime importance to develop rapid, highly sensitive and cost-effective surveillance methods to identify MRSA carriers and take necessary actions to control the spread.

BBL CHROMagar MRSA (C-MRSA) is a selective and differential medium for the qualitative direct detection of nasal colonization by MRSA. C-MRSA medium permits the direct detection and identification of MRSA through the incorporation of specific chromogenic substrates and cefoxitin. MRSA strains will grow in the presence of cefoxitin and produce mauve-coloured colonies resulting from hydrolysis of the chromogenic substrate (Figure 2).

Objectives

This study aims to detect MRSA nasal carriers among 100 healthcare workers and patients in the Dermatology Ward HKL by using two methods, the conventional blood sheep agar (BSA) and the novel BBL CHROMagar MRSA. It also aims to compare the BSA medium with the C-MRSA medium in terms of specificity, sensitivity and time to detection to MRSA. The C-MRSA is currently approved for use with nasal swabs.

Material and Methods

This was a single centre, prospective study which was carried out from 14th February to 17th March 2006 until the target sample size of 100 was reached. All healthcare workers and inpatients of Dermatology Ward HKL were included in the study. Healthcare workers included doctors, nurses, medical assistants, attendants and hospital support services staff.

Inpatients included all patients warded in the Dermatology Ward during the study period. The length of hospital stay was noted at the time the nasal swabs were taken. The patients' case notes were also reviewed to obtain information on the number of ward admissions and clinic visits.

There were altogether 100 subjects. A research nurse obtained the nasal swabs from all the subjects to ensure consistency and to minimize sampling error. Each subject had two swabs taken from the nares. The swab was initially moistened with sterile saline, then inserted into both the anterior nares in a gentle rotating manner and immediately put into the Amies transport medium. These samples were sent to the microbiology lab, where each sample was plated onto the conventional BSA and C-MRSA medium.

After 24 hours of incubation, C-MRSA plates were examined for the presence of mauve-coloured colonies. These colonies were subjected to coagulase and susceptibility testing. Colonies of other colours were also subjected to the same tests to identify the organisms. Colonies on BSA also underwent coagulase and susceptibility testing. If there were no colonies in the first 24 hours, the plates would be reincubated for another 24 hours, and colonies which grew after that would also be subjected to similar tests (Figure 3).

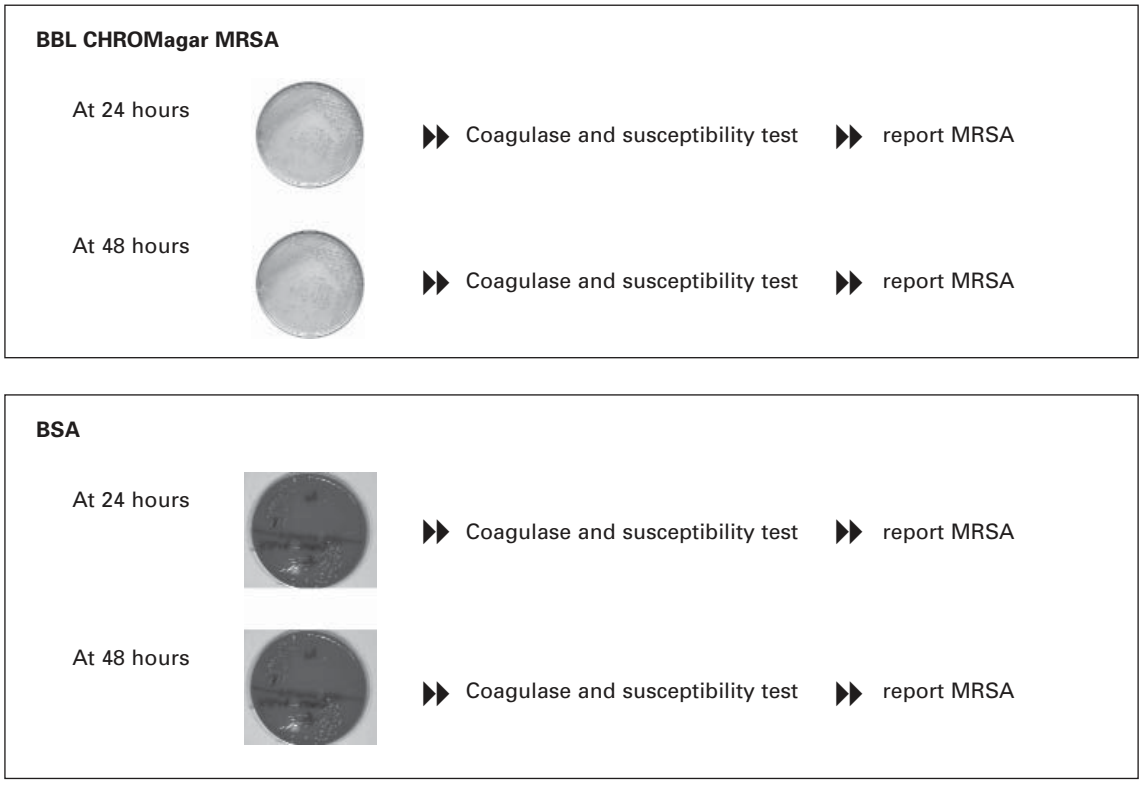
Tube coagulase test

A Gram smear was done from colonies to confirm that it was a Gram positive cocci. This was followed by the coagulase test which was performed by mixing anticoagulated pooled human plasma or rabbit plasma with Staph aureus culture. Free (extracellular) coagulase clots plasma in the absence of calcium. The tube coagulase test was determined by looking for clot formation after incubation for 4 hours. If negative, it was re-examined at 24 hours because a few strains required a longer time for clot formation.

Susceptibility Test

Susceptibility to common antibiotics was determined by disc diffusion method according to the Clinical Laboratory Standards Institute. The following antibiotic discs were used: Erythromycin 15 mcg, Cotrimoxazole 25 mcg, Fucidic acid 10 mcg, Rifampicin 5 mcg, Vancomycin 30 mcg, Oxacillin 1 mcg, Mupirocin 10 mcg, Teicoplanin 30 mcg, Linezolid 30 mcg and Clindamycin 2 mcg. Parameters such as temperature of 350 C, colony suspension equivalent to 0.5 McFarland and prolonged incubation period of 18 to 24 hours were employed to improve the sensitivity and specificity of the tests. The antibiotic discs were placed on Mueller Hinton agar plate containing Staph aureus inoculum. The diameter of zone surrounding the antibiotic discs was measured using the Biomic Vision Microbiology Analyser.

Figure 3. Workflow and identification of MRSA from CHROMagar MRSA and BSA



The detection of methicillin resistance was done by performing the oxacillin disc diffusion test. A 6 mcg Oxacillin disc was placed on the entire surface of Mueller Hinton agar plate covered with colony suspension and after overnight incubation, the diameter of the zone around it was measured. Measurement of less than 10mm indicated that the Staph aureus colonies were resistant to methicillin.

Results

There were a total of 46 ward staff, 51 patients and 3 caregivers in this study (Figure 4). The ward staff comprised of twenty doctors, seventeen nurses, two Medical Assistants, five attendants and two support services staff.

There were non-specific colonies on 96 BSA plates within the first 24 hours (Table 1), the organisms isolated are shown in Table 2. Mauve colonies were present on 9 C-MRSA plates in the first 24 hours, another 9 C-MRSA plates had dark purplish and bluish colonies .Coagulase and susceptibility tests confirmed that all the mauve colonies on C-MRSA were MRSA. The dark purplish and bluish colonies on C-MRSA were Staph species (resistant to oxacillin).

Table 2 shows all the organisms isolated and interestingly both BSA and C- MRSA detected all the MRSA isolates. The BSA medium also isolated MSSA and other non MRSA organisms. The growth of MSSA and other non MRSA species except for Staph species (resistant to oxacillin) were suppressed on the C-MRSA medium. The sensitivity and specificity of C-MRSA in detecting MRSA is 100%

Nine percent (9/100) of the total population studied were MRSA nasal carriers. On further analysis, 2.2% (1/46) of ward staff and 15.7% (8/51) of patients were MRSA carriers. Out of the nine MRSA carriers, eight were patients and one was a nurse (Figure 5). Six patients had been in the ward for more than 72 hours whereas two patients were admitted for less than 72 hours. In the first six patients, two had been on steroids, another two had previous hospitalization and the last two were never admitted before. The other two patients had history of hospitalization with recurrent clinic visits in the past one year and had been on steroids.

Figure 4.

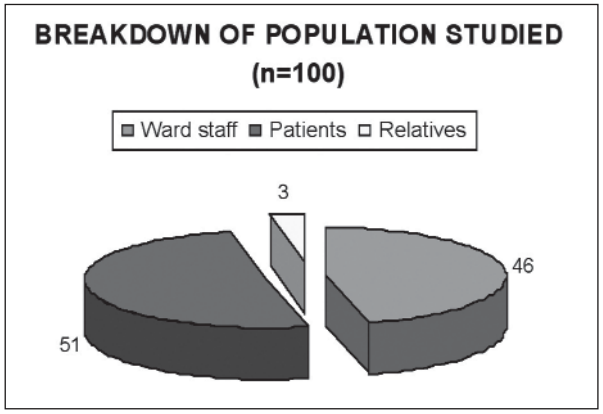


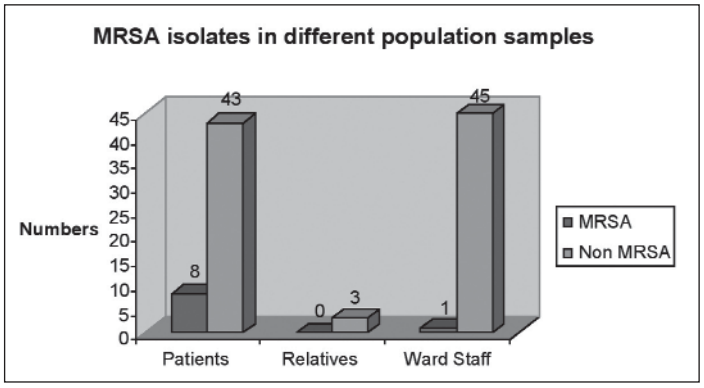
Table 1.

Media	Appearance (after 24 H)	Appearance (after 48 H)
BSA	96 plates - Colonies	
	4 plates - No colonies	4 plates - No colonies
C-MRSA	9 plates - Mauve colonies	
	9 plates - Dark purplish and bluish colonies	
	82 plates - No colonies	82 plates - No colonies

Table 2.

Organisms isolated	BSA	C- MRSA
MRSA	9	9
Staph aureus	15	0
Staph species (sensitive to oxacillin)	47	0
Staph species (resistant to oxacillin)	12	9
Diphtheroids	13	0
No growth	4	0

Figure 5.



Discussion

This was the first study done in HKL to evaluate the performance of the novel C-MRSA in detecting MRSA from nasal swabs. It showed that the sensitivity and specificity of C-MRSA in detecting MRSA is 100%. Thus it may not be necessary to do coagulase and susceptibility tests if mauve-coloured colonies are present on C-MRSA, as all the mauve colonies were MRSA in this study. This would save money and reduce labour requirements as no further confirmatory tests are needed. Even if confirmatory tests are done for the C-MRSA plates, the number will be far less than the conventional medium (18 C-MRSA plates as opposed to 96 BSA plates) as C-MRSA suppresses the growth of non MRSA species. The conventional BSA still requires coagulase and susceptibility tests for confirmation of MRSA. Thus C-MRSA can potentially reduce the number of confirmatory tests and allows identification of MRSA in a single step.

C-MRSA also allows for rapid identification of MRSA within 24 hours compared to the traditional BSA which takes 48 hours. This would mean that necessary actions could be taken earlier as MRSA could be identified within 24 hours. This includes initiating contact precaution which will potentially reduce the spread of MRSA.

There was no further recovery of MRSA after reincubating specimens for another 24 hours. Thus an individual may be declared non MRSA carrier within 24 hours provided no mauve colonies were grown on C-MRSA. However due to the small number of specimens in the study, the results need to be interpreted with caution. A few other studies with larger sample sizes have shown additional isolates of MRSA on C-MRSA after 48 hours incubation[6]. Based on these earlier studies, it is still recommended to incubate the medium for 48 hours if there are no colonies present in the first 24 hours to increase the recovery of MRSA isolates.

Detecting MRSA nasal carriers is important because relative to other body sites, MRSA nasal colonization poses a higher risk for subsequent infection in at risk subjects[7]. Those at risk include patients on haemodialysis as well as continuous ambulatory peritoneal dialysis[8]. A few studies have monitored MRSA nasal colonization rates in patients on admission to the hospital. MRSA nasal colonization rates were 0.03% in Netherlands, 7.3% in major hospitals in the United States and 7.9% in major hospitals in France[9]. In our study 15.7% of dermatology inpatients were MRSA nasal carriers. The number is high as this study was conducted during MRSA outbreak in the ward. This study also found that MRSA carriage was more common in patients with longer hospital stay, recurrent clinic visits and

on steroids. Many studies have shown that decreasing the length and frequency of hospital stays reduces the risk for nosocomial MRSA transmission[10,11]. Netherlands is among a few countries with very low nosocomial and community levels of MRSA attributed to the "search and destroy" policy for prevention of MRSA transmission and policy of restrictive antibiotic use[9,12].

Healthcare workers who are MRSA nasal carriers are also at risk of transmitting it to their patients. The colonization rate in healthcare workers was 2.5% in the United States and 6.2% in France. In our dermatology ward, the colonization rate in healthcare workers was found to be 2.2%.

Carriers were treated topically with mupirocin ointment three times a day for 5 consecutive days[13] for nasal decolonization to prevent spread to others. Mupirocin is very effective in eradicating nasal carriage and preventing infection over a short term period but long term results are less impressive[14].

Certain practices need to be put into place to prevent the spread of MRSA. Patients who are colonized or infected with MRSA need to be isolated. There should be use of barrier precautions which include gloves and gowns as well as hand washing. Active screening of patients for MRSA carriage should be carried out with patients selection determined by local infection control team and discussed with appropriate clinical teams. Screening of staff is not recommended routinely unless there is an outbreak of MRSA infection in the ward.

Conclusion

Nine percent of the population studied which comprises healthcare workers and patients of dermatology ward HKL were MRSA nasal carriers. Active surveillance for MRSA in the anterior nares of those at risk is important to control the nosocomial transmission of MRSA.

The novel C-MRSA is as sensitive as BSA in the detection of MRSA. C-MRSA also allows identification of MRSA isolates within 24 hours with 100% sensitivity and specificity as compared with the conventional BSA which takes 48 hours and requires further coagulase and sensitivity tests. This translates into rapid identification of MRSA nasal carriers and initiating contact precautions, all of which will potentially reduce the spread of MRSA.

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Case Report

D-penicillamine - induced pemphigus in a patient with Wilson disease

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Pemphigus is an autoimmune blistering disease characterized by circulating autoantibodies directed against the keratinocyte cell surface. Majority of patients with pemphigus develop the disease spontaneously. However, there is a small group of patients who develop pemphigus after treatment with certain medications, of which D-penicillamine (DPA) and captopril are the best documented. We report a case of DPA-induced pemphigus vulgaris in a young Chinese lady treated with DPA for Wilson disease.

Case Report

A 26-year-old Chinese lady was referred to the skin clinic in June 2003 when she developed blisters on her abdomen, arms and legs.. She was diagnosed to have Wilson disease following an episode of severe hepatitis in January 2000 and started on D-penicillamine 250mg QDS. She remained well with good control of her Wilson disease until November 2002 when she developed painful blisters and ulcers on her buccal mucosa, tongue and lips. She was seen in the dental department and treated with dexamethasone mouth rinse and fluocononide cream. Her mouth lesions persisted and she lost 7 kg within 6 months due to poor oral intake secondary to painful mouth lesions. In April 2003 she complained of recurrent painful red eyes and was treated as conjunctivitis by the ophthalmologist.

On further enquiry, apart from ongoing mouth ulcers and conjunctivitis, the blisters on her abdomen were only present for 2 weeks and new lesions were developing on the arms and legs. The lesions were initially small fluid-filled vesicles and gradually increased in size. They remained tense unless traumatized and became crusted and painful. Apart from D-penicillamine, she admitted to taking prednisolone 5mg daily given by a family physician for the past few days for her newly developed blisters. There was no other positive past medical history, allergy or family history. Systemic enquiry was normal except for weight loss secondary to poor oral intake due to painful mouth lesions.

On examination, there were a few discrete tense blisters ranging from 8 to 12 mm diameter scattered on the abdomen, arms and legs. There were also a few crusted lesions. Examination of vulva showed some erosion on the labia majora. Mild injected conjunctivae were noted and erosion and ulcers were detected on the lips, tongue and oral mucosae. Differential diagnosis included D-penicillamine induced pemphigus and erythema multiforme.

A skin biopsy was carried out and histopathology report showed mild acanthosis and focal perivascular collection of lymphocytes and plasma cells. Direct immunofluorescence was positive for IgG and complement was positive in the intercellular areas of the lower half of the epidermis. The features were consistent with pemphigus vulgaris. A biopsy of buccal mucosa carried out in July 2003 was also consistent with pemphigus vulgaris. (Figure 3a) Direct immunofluorescence was positive for IgG with intercellular distribution (Figure 3b).

Diagnosis of D-penicillamine induced pemphigus was explained to the patient and D-penicillamine was stopped. She was started on zinc sulphate 50mg TDS for Wilson disease and prednisolone 30mg OD for the pemphigus. Her pemphigus was controlled with slow tapering dose of prednisolone which was eventually stopped in Oct 2004. She had no further flare-up of her pemphigus on the subsequent follow up and was eventually discharged from the skin clinic in 2006.

Discussion

Wilson disease is a recessively inherited, rare disorder of copper metabolism that results in accumulation of copper in the liver and subsequently other organs, mainly the central nervous system and kidneys. Treatment of Wilson disease includes chelation therapy using D-penicillamine (DPA)[1], trientine and more recently, use of zinc acid.

DPA was first recognised as a degradation product of penicillin more than half a century ago[2] . It was first used clinically as a copper-chelating agent in the treatment of Wilson disease[1] and in lead poisoning. Subsequently it has been a therapy for a variety of diseases such as rheumatoid arthritis, cystinuria, systemic sclerosis, primary biliary cirrhosis and many others. However the use of DPA has been hindered by its many adverse effects. The reported noncutaneous side effects include renal, gastrointestinal, haematologic, pulmonary and autoimmune involvement.

The skin reactions are the most common adverse effects of DPA. It affects 25% to 50% of patients taking DPA. The cutaneous side effects may be divided into several categories, according to their induction mechanisms[3]. 1. Dermatoses that result from interference with collagen and elastin (penicillamine dermopathy, elastosis perforans serpiginosa, excessive wrinkling, cutis laxa, pseudoxanthoma elasticum.) 2. Acute sensitivity reactions (urticaria, maculopapular eruptions.) 3. Lesions caused by autoimmune mechanisms (bullous pemphigus and pemphigoid, eruptions of systemic lupus erythematosus and dermatomyositis.) 4. Dermatoses that result from an uncertain mechanism (lichen planus, psoriasiform dermatitis, seborrhoeic dermatitis like, alopecia, hypertrichosis and nail changes).

Figure 1. Erosions on oral mucosa

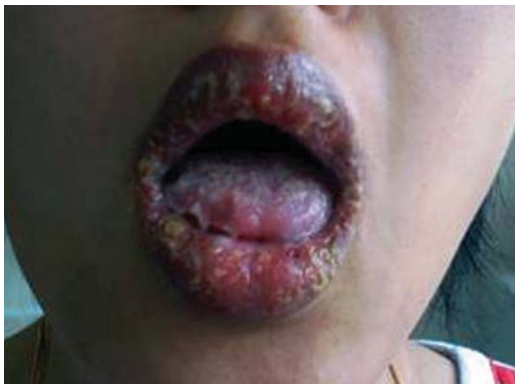


Figure 2. Tense blisters on left forearm

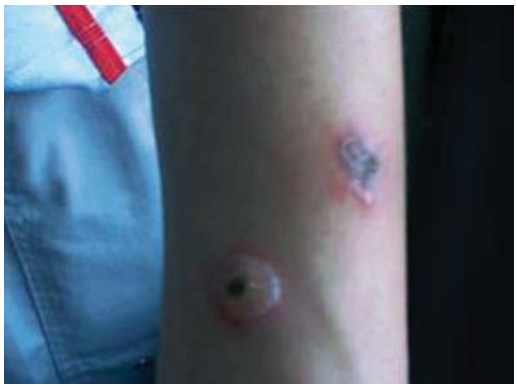
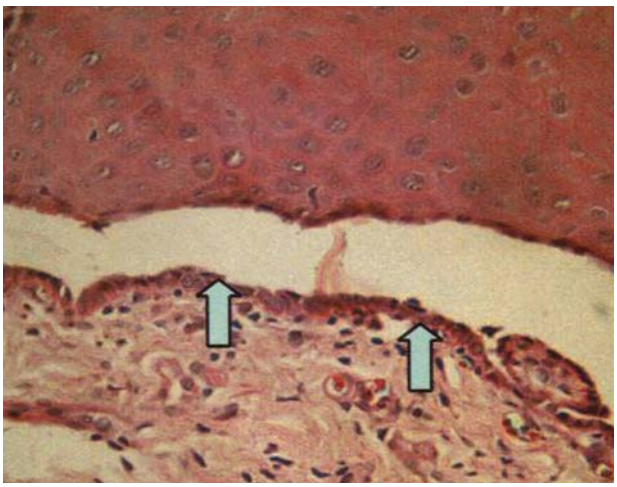


Figure 3. IIntraepithelial split in pemphigus vulgaris



Pemphigus is an autoimmune blistering disease characterized by circulating autoantibodies directed against the keratinocyte cell surface. The large majority of patients with pemphigus develop the disease spontaneously. However, there is a small group of patients who develop pemphigus after treatment with certain medications, of which DPA and captopril are the best documented 4 .

DPA-induced pemphigus was first described by Dego et al in 1969.5 It is estimated that up to 7% of patients treated with DPA for at least 6 months will acquire pemphigus. Most cases of DPA-induced pemphigus appear after an average of 11.7 months (range from 4 weeks to 3 years) 3 . In our patient, it took about three years of treatment with DPA before she presented with pemphigus.

Pemphigus foliaceus accounts for 46% of all DPA-induced pemphigus cases. Approximately one third of the cases are of the vulgaris variant, and pemphigus erythematosus accounts for up to 20% of the cases 6 . Clinical presentation of our patient was one of pemphigus vulgaris. The average age of patients with DPA-induced pemphigus was 57 years (range from 24 to 78 years old), with a male to female ratio of 1.7:1. Blistering was frequently preceded by a pruritic urticarial eruption. Oral involvement occured in only 18% of DPA-induced pemphigus cases. However, oral mucosal involvement as the sole manifestation of DPA-induced pemphigus has been reported 7 . Our patient had oral involvement of DPA-induced pemphigus which preceeded the cutaneous involvement by more than six months.

The histopathology finding that characterizes many cases of DPA-induced pemphigus is diffuse acantholysis throughout the epidermis. The cleavage level may vary in different lesions as suprabasilar or a high level of intraepidermal splitting. In some reports, dermal infiltrates of DPA-induced pemphigus may consist of neutrophils or lymphocytes in a perivascular or diffuse pattern. This is atypical of spontaneously occurring pemphigus which are characterized by a mild infiltrate of oesinophils and lymphocyte 8 . Most patients with drug induced pemphigus have tissue-bound and/or low-titre circulating autoantibodies with the same antigenic specificities at a molecular level as autoantibodies from patients with other forms of idiopathic pemphigus. Positive direct immunofluorescence in DPA-induced pemphigus is found in about 72.6% while positive indirect immunofluorescence was 52.1% 9 . It is suggested that DPA might exacerbate subclinical pemphigus foliaceus which is associated with HLA-DR4. Alleles of HLA-DR4 predispose to pemphigus vulgaris and a susceptibility allele is also carried by individuals with drug-induced pemphigus 10 .

It is reported that 80% of DPA-induced pemphigus resolve within 1 year of drug withdrawal, with or without treatment 6 . Our patient's DPA-induced pemphigus took more than a year to resolve despite cessation of DPA and treatment with prednisolone.

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Case Report

Cutaneous B-cell pseudolymphoma: Case reports and literature review

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Keywords Cutaneous B-cell pseudolymphoma, lymphocytoma cutis, cutaneous lymphoid hyperplasia

Cutaneous B-cell pseudolymphoma (CBPL) is a reactive B-cell hyperplasia that clinically and histologically mimics cutaneous B-cell lymphoma (CBCL). Many different terms have been used to describe this condition such as lymphocytoma cutis and cutaneous lymphoid hyperplasia. This condition typically present as a solitary nodule or papule over face (cheek, nose and ear lobe), chest and upper extremities, but multiple lesions may also be present. A variety of stimuli are known to induce this condition but most cases have an unknown cause. We report 2 cases of CBPL, the causes of which could not be ascertained.

Case Reports

Case 1

A 60-year-old Indian lady presented with multiple asymptomatic erythematous nodules and plaques over her face for 3 months. There was no history of any insect bite or trauma. She had no fever, loss of appetite or loss of weight. She was diagnosed to have hypertension for 8 years and has been on atenolol, prazosin and chlorothiazide. On examination, there were multiple erythematous plaques and nodules over her forehead and upper lip (Fig1). Systemic examination was unremarkable. Baseline blood investigations and chest X-ray were all normal. Skin biopsy revealed dense mature lymphocytes in dermis with widespread lymphoid follicles, some with a germinal center formation. (Fig 3a). The germinal centre showed plentiful tingible body macrophages (Fig 3b). Immunohistochemical studies revealed a predominantly CD 20+ B-cells in germinal centre and mantle zone area while CD 3+ and CD 45R0+ cells were present in paracortical area. The B-cells expressed both κ and λ light chains with κ/λ ratio of 4:1. The diagnosis of cutaneous B-cell pseudolymphoma was made and she was started on mometasone furoate 0.1% cream. However, the response to treatment was slow and she was subsequently given intralesional triamcinolone acetonide and hydroxychloroquine. Her lesions improved significantly with the treatment but she developed some new eruptions 4 months later which required further intralesional corticosteroid injection. Since then, she did not have any recurrences.

Case 2

A 57-year-old Malay man presented with multiple asymptomatic, slowly progressive, erythematous nodules over his face for 1 year. He denied any history of insect bite or trauma and did not report any constitutional symptoms. His medical history includes hypertension of 5 years duration and was on atenolol. On examination, there were erythematous plaques and nodules over his nose, right cheek and above his upper lip (Fig 2). He had no lymphadenopathy or hepatosplenomegaly. Other systems were normal. Baseline blood investigations and chest X-ray were all normal. Skin biopsy showed that the dermis was infiltrated by a nodular pattern of mature lymphocytes, macrophages, few plasma cell and eosinophils. The lymphocytic infiltrates formed follicles with germinal centers and tingible body macrophages which were surrounded by a mantle of small lymphocytes. Immunohistochemical studies revealed a mixed B- and T-lymphocytes. He was diagnosed as cutaneous B-cell pseudolymphoma and was started on topical mometasone furoate 0.1% cream. However he did not respond to topical treatment and subsequently intralesional triamcinolone acetonide and hydroxychloroquine were added. The lesions started to improve 6 weeks later and almost disappeared after 9 months of treatment.

Figure 1. Case 1. A 60-year-old lady with erythematous plaques and nodules on her forehead and upper lip

Figure 2. Case 2. A 57 year-old-man with erythematous plaques and nodules on his nose, upper lip and right cheek.

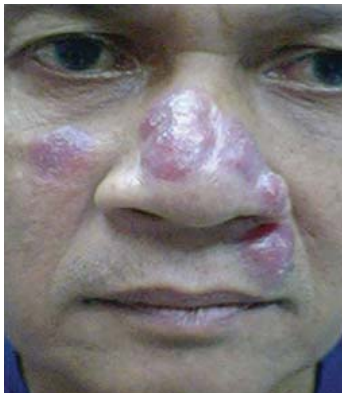
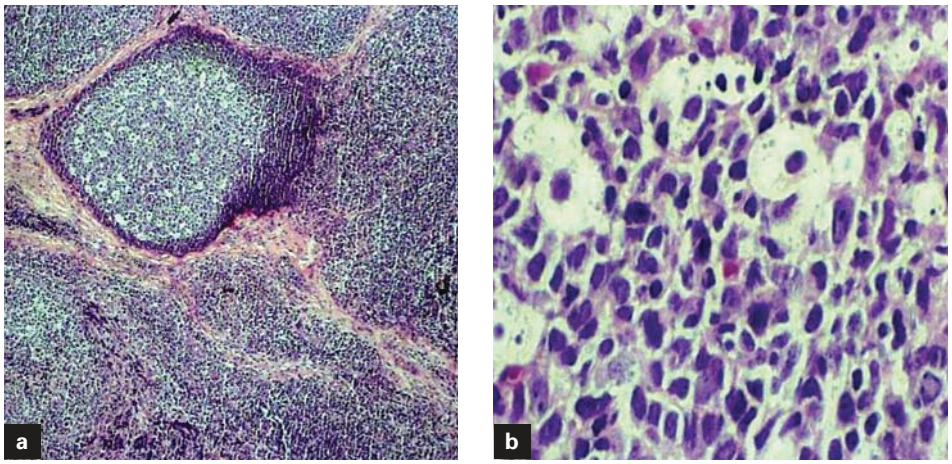


Figure 3. (a). Widespread lymphoid follicles with germinal centre formation in dermis and (b). The germinal centre shows plentiful tangible body macrophages



Discussion

Cutaneous pseudolymphoma (CPL) is a group of benign T or B lymphocytic infiltrate of the skin which clinically and/or histologically simulate cutaneous lymphomas. It can be further divided into T- and B-cell pseudolymphoma depending on the predominant cell type in the infiltrate. CPL represents the benign end of a lymphoproliferative continuum eventuating in true lymphoma at its malignant extreme.

This condition was first described as sarcomatosis cutis by Kaposi in 1891. Subsequently various terms have been used to describe this condition such as lymphocytoma cutis, lymphadenosis benigna cutis, cutaneous lymphoid hyperplasia, pseudolymphoma of Spiegler and Fendt. It was finally known as cutaneous pseudolymphoma by Burg et al in 1982. Cutaneous pseudolymphoma is a preferred designation to describe the whole group as it always alerts one to differentiate these conditions from malignant cutaneous lymphoma. Van Vloten et al suggested that it is best to avoid all the various names and to use only cutaneous B- or T-cell pseudolymphoma.

Cutaneous B-cell pseudolymphoma (CBPL) is known to be induced by a variety of stimuli. These include Borrelia burgdorferi infection, insect bites, tattoo (predominantly red colours), drugs reactions (injected drugs), acupuncture, trauma, vaccination and gold piercing earrings. However, most cases have an unknown cause, as in our 2 patients, and they are termed as idiopathic CBPL. Clinically, CBPL often presents as a single nodule or papule (flesh-colored to plum-red dermal) commonly located on face (cheek, nose and ear lobe), chest and upper extremities. Scale and ulceration are generally absent. Multiple lesions and generalized form is rather infrequent . Both of our patients presented with multiple erythematous nodules and plaques over the face, which were are rather uncommon. There were no identifiable triggering factors in both cases.

It may be extremely difficult to differentiate between CBPL and cutaneous B-cell lymphoma (CBCL) and a skin biopsy is often necessary to differentiate these two conditions. CBPL can be differentiated from CBCL by the mixed-cell infiltrate with small mature lymphocytes mainly involving the upper dermis, so called "top heavy", in contrast to CBCL where the infiltrate is monomorphous, composed of medium to large lymphocytes mainly involving the reticular dermis, so called "bottom heavy". Follicular germinal centers and tingible body macrophages are often present in CBPL but are rarely found in CBCL. Furthermore, the epithelial and adnexal structures are preserved in CBPL but they are often obliterated in CBCL.

Immunohistochemical and molecular biological techniques enables us more precisely to distinguish CBPLs from cutaneous malignant B-cell lymphomas. Immunohistochemistry in CBPL will show predominance of CD 20+ B-cells within reactive follicles and a variable number of CD3+ T-cells at interfollicular area. Immunostaining for kappa (κ) or lambda (λ) light chains will show both chains present in CBPL (polyclonality) while only one of these will be present in CBCL (monoclonality) (κ:λ ratio greater than 10:1 or less than 0.5:1)[2]. In our patients, both had the typical histopathological features suggestive of CBPL which include mature lymphocytic infiltrates in dermis with multiple follicular germinal centers and tingible body macrophages. Immunohistochemical staining also showed that predominance of CD20+ B cells in the germinal centre. We were able to demonstrate polyclonal κ and λ light chains in the B-cells in Case 1 while staining for κ and λ light chains was not done in Case 2.

In some cases, the possibility of lymphoma cannot be excluded by means of histologic analysis. In such cases, molecular biologic studies which consist of immunoglobulin or T-cell receptor genetic rearrangements may provide additional helpful information. If a clone is identified, it increases the likelihood of CBCL. The results of this test should not be considered definitive as clonality is reported in occasional pseudolymphomas. This intermediate condition is known as "clonal cutaneous lymphoid hyperplasia" which is capable of eventuating into overt lymphoma. Antibodies to B burgdorferi may be identified in 50% of patients with borrelial lymphocytoma[2].

In treatment of CBPL, identification of the causative agent is very important as removal of the cause generally leads to resolution. In cases in which the cause is unknown, the course varies considerably, but it tends to be chronic and indolent. For localized persistent lesions, treatment options include topical or intralesional corticosteroids, topical tacrolimus , cryosurgery, interferon alfa, local radiation and surgical excision. Treatment options for widespread lesions include antimalarials (Hydroxychloroquine), photodynamic therapy (PDT) with topical 5 aminolevulinic acid (ALA), thalidomide and cytotoxic agents. Borrelia lymphocytoma cutis can be treated with oral penicillin 1 gm tds or doxycycline 100 mg bd for 2 weeks. In our case, both patients showed good response to combination of hydroxychloroquine, topical and intralesional corticosteroid therapy.

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