Original Article

Acute generalized exanthematous pustulosis: A histologic study of forty-five cases

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Abstract

Background Literature on acute generalized exanthematous pustulosis (AGEP) is restricted to case reports, with only one prior series study. More importantly, a detailed histologic comparison to pustular psoriasis has not been done.

Objective To identify discriminatory characteristics, we compared the histologic features of 45 cases of AGEP and 19 cases of pustular psoriasis.

Methods Demographic, historical, clinical, and histologic features of AGEP and pustular psoriasis were compared using specimens from 5 tertiary medical centers.

Results The age of patients with AGEP ranged from 12 to 91 years (mean, 53 years) with a nearly equal M:F ratio. All 45 patients presented with a generalized erythematous, pustular eruption (mean duration of pustules, 12 days) and fever (present in 25/31 patients). Recent drug ingestion was documented in 36/38 (95%) patients. Of the 5 pediatric cases, two had prior upper respiratory tract infection, but were without a history of recent drug ingestion. No patient with AGEP had a history of psoriasis. AGEP was distinguished from pustular psoriasis based upon the following histologic features: necrotic keratinocytes, papillary dermal edema, presence of eosinophils within the dermis, and absence of parakeratosis with neutrophils ($p < 0.05$).

Conclusion While the precise etiology of AGEP remains unknown, our findings confirm that most AGEP cases in adults are drug-related. Certain histologic features appear to reliably discriminate AGEP from pustular psoriasis, and awareness of them may increase diagnostic accuracy.

Keywords acute generalized exanthematous pustulosis, AGEP, pustular psoriasis.

Introduction

In 1968, Baker and Ryan[1] reported 104 cases of generalized pustular psoriasis; 5 of which occurred in patients without a history of psoriasis, raising the possibility of infection or drug as a possible etiology. In 1980, Beylot et al[2]. introduced the term acute generalized exanthematous pustulosis (AGEP) to describe pustular eruptions with the following characteristics: (1) an acute onset without a history of psoriasis, infection, or drug ingestion less than one day prior; (2) spontaneous resolution of the eruption within 15 days; and (3) histologically, non-follicular subcorneal pustules.

The published literature on AGEP exists primarily as case reports. A case series has not been described since 1991, when Roujeau et al. reported on 63 cases[3]. While textbooks may occasionally note the histologic features of AGEP to be indistinguishable from pustular psoriasis, a detailed comparison between AGEP and pustular psoriasis has never been performed. In this study, we compared the histological features of 45 cases of AGEP and 19 cases of pustular psoriasis derived from 5 tertiary medical centers.

Materials and methods

This study was approved by the institutional review boards. All cases with the histologic diagnosis of a pustular eruption consistent with AGEP and pustular psoriasis were obtained using computerized database searches. The clinical history of these cases was reviewed. The cases were classified as

either AGEP or pustular psoriasis based upon the corresponding clinical findings. Histologic specimens of 45 AGEP and 19 pustular psoriasis cases from 1992 to 2007 were retrieved from the pathology files of Massachusetts General Hospital and Boston University Medical School, Boston, MA; UMass Memorial Medical Center, Worcester, MA; University of Texas Southwestern Medical Center, Dallas, TX; and University of Colorado Health Sciences Center, Aurora, CO. Clinical and histological patient data were catalogued and de-identified.

Clinical Evaluation
For all cases, the following information was extracted from the medical records: presentation and distribution of the rash; duration of erythema and pustulosis; presence of fever; and a history of recent use of medications, prior drug reaction(s), psoriasis, recent infection(s), and other relevant underlying diseases.

Histologic Evaluation
Histologic sections of all cases were re-reviewed and the diagnoses confirmed independently by two dermatopathologists (MPH and MM). For each of 64 cases, the histologic features outlined in Table 3 were graded as either present or absent. The dermal inflammatory infiltrate was graded as sparse (1+), non-brisk (2+) and brisk (3+).

Statistical Analysis
Statistical differences were confirmed using the Pearson's chi-squared test for non-continuous variables, or where a category contained less than 5 observations, using the Fisher's exact test for non-continuous variables. P-values of less than 0.05 were considered significant.

Results

Demographic Data
The demographic data of 45 AGEP cases from 44 patients are summarized in Table 1. All patients presented with a generalized erythematous and pustular eruption. Most often the eruption began upon the face or in the intertriginous areas (Figures 1-3). The age of patients with AGEP ranged from 12 to 91 years (median, 65 years; mean, 53 years). The male to female ratio was 4:3.
Additional clinical information was available for 38 patients. Fever was present in 25/31 (81%) patients. The duration of pustules was documented in 17 patients (range, 4 to 30 days; median, 10 days; mean, 12 days). Recent drug ingestion was documented in 36/38 (95%) patients, with 13 of these 36 patients having had a prior drug reaction. Two pediatric patients (Table 2) had a prior upper respiratory tract infection, but were without a history of recent drug ingestion. No patient with AGEP had a history of psoriasis (0/38). A family history of psoriasis was not noted (0/13).
For the cases of pustular psoriasis, patient age ranged from 3 to 84 years (median, 60 years; mean, 51 years). The male to female ratio was 6:13. Nine of 19 patients had a prior history of psoriasis. The duration of pustules was documented in 5 patients and it ranged from 3 weeks to 4 months (median, 3 months).

Histologic Evaluation
The histologic features of AGEP and pustular psoriasis are summarized in Table 3. Necrotic keratinocytes, papillary dermal edema, and a significant (>1+) dermal infiltrate of eosinophils were features more often observed with AGEP ($p < 0.05$) (Figure 4). Follicular involvement was noted in four cases (Figure 4). Fibrin thrombi were rare in AGEP. Parakeratosis containing neutrophils was observed with greater frequency in pustular psoriasis ($p < 0.05$).

Discussion

In the prior series of patients with AGEP, Roujeau et al[3]. noted significant differences between patients with AGEP and pustular psoriasis including: (1) a history of drug eruption(s), (2) recent drug administration, (3) duration of pustules, and (4) duration of fever. Further, it was noted that AGEP most often began upon the face or intertriginous areas and disseminated within a few hours of ingestion of the offending substance. Non-follicular pustules of < 5mm diameter arose upon edematous and erythematous skin. Pruritis and/or a burning sensation were often noted. Most patients (46/63) had more than 100 pustules, and the mean duration of the pustules was 9.7 days (range, 4 to 30 days). Typically, desquamation followed within a few days.

Because of the retrospective nature of our study, we were not able to retrieve complete clinical data for all the AGEP and pustular psoriasis cases studied herein. However, for AGEP cases with available clinical information, we noted similar distinguishing features including: the presence of fever (81%), the mean duration of the pustules (12 days), and a recent history of drug ingestion (95%). One patient had 2 episodes of AGEP within a 2-year period (Cases 43 and 44).

Four of our cases occurred in children. Interestingly, only approximately 12 cases of pediatric AGEP have been reported in the world literature[4-11]. The clinical features of our 4 pediatric cases of AGEP, as compared to the 8 pediatric cases already described in the English-language literature, are summarized in Table 2[4-7]. In our pediatric cases the age ranged from 5 months to 16 years (median, 7 years). Interestingly, a male predominance was noted among pediatric AGEP cases. A family history of psoriasis was not noted in two (0/2) pediatric patients. Development of psoriasis was not observed 3 years after presentation in one patient with available follow-up. Recognized etiologic agents for AGEP in children include drugs, infections, mercury exposure, and pneumococcal vaccination (table 2)[4-7]. In contrast to our adult population with AGEP, in which drug ingestion was the predominant association, infection was equally implicated in our pediatric cases.

Table 1. Clinical data of 45 cases of acute generalized exanthematous pustulosis

Case #	Age/ Sex	Clinical presentation	Fever	Duration of pustules	H/o drug intake	Previous drug reaction	H/o	H/o infection	Underlying disease
1	32F	Gyeneralized vesiculopustular rash	yes	5d	Clarithromycin	none	psoriasis	none	none
2	32F	Generalized erythema and pustules	no	ND	Penicillin/ ampicillin	none	none	none	postpartum
3	21M	Generalized erythema and pustules	yes	ND	Amoxicillin	yes	none	Viral versus mononucleosis	none
4	21M	Diffuse maculopapular rash	yes	ND	Vancomycin	none	none	osteomyelitis	Status post motor vehicle accident
5	48M	Generalized erythema and pustules	yes	ND	Ibuprofen	none	none	none	Acute renal failure
6	84F	Generalized erythema and pustules	yes	ND	Clindamycin	none	none	none	none
7	13M	Generalized erythema and pustules	yes	ND	none	none	none	Viral upper respiratory tract infection	eczema
8	35M	Generalized erythema and pustules	yes	ND	Penicillin/ cefipime	none	none	none	Synovial sarcoma with multiple lung metastases
9	24M	Diffuse maculopapular rash	yes	9d	Tegretol	none	none	none	Status post motor vehicle accident
10	70M	Generalized erythema and pustules	yes	ND	Vancomycin	yes	none	Streptococcal liver abscess	Chronic obstructive pulmonary disease
11	82F	Pustular eruption on trunk and extremities	yes	23d	Bactrim/dilantin	none	none	none	Glioblastoma multiforme
12	69M	Generalized	yes	ND	Vancomycin	yes	none	none	Aortic dissection, right empyema
13	15M	Diffuse pruritic eruption with subcorneal pustules	yes	ND	none	none	none	upper respiratory tract infection	none
14	72F	Diffuse pustules on an erythematous base	yes	ND	Penicillin	yes	none	none	Rheumatic fever, aortic and mitral valves impairment
15	19M	Generalized	yes	10d	Ibuprofen	none	none	Urinary tract infection, mononucleosis	Asthma, obesity
16	38M	Generalized	yes	ND	Amoxicillin	yes	none	none	none
17	86F	Diffuse rash	yes	ND	Vancomycin	yes	none	none	Bilateral lower leg cellulitis
18	77M	Diffuse erythematous and dusky rash	yes	21d	Cefepime	yes	none	none	Clostridium difficile colitis
19	72F	Generalized	yes	5d	Plavix	yes	none	none	Acute myocardial infarction
20	69M	Generalized	yes	ND	Vancomycin	yes	none	Bacterial infection	Right ankle fracture

Case #	Age/ Sex	Clinical presentation	Fever	Duration of pustules	H/o drug intake	Previous drug reaction	H/o	H/o infection	Underlying disease
21	75F	Generalized	yes	13 d	Zometa (zoledronic acid)	yes	none	none	Metastatic breast carcinoma
22	59F	Generalized	yes	6 d	Cardizem	none	none	none	Diabetes mellitus, endometrial carcinoma
23	12M	Diffuse erythematous papules and pustules	yes	4d	Acetaminophen; ibuprofen	none	none	none	none
24	16M	Diffuse pustules	yes	14d	Azithromycin	none	none	none	none
25	30F	Generalized	yes	30d	Isoniazid	yes	none	none	Sezary syndrome/ mycosis fungoides
26	48F	Generalized	no	ND	Zoloft, trazodone	none	none	none	Diabetes mellitus, hypertension
27	44F	Generalized	no	13 d	Lamisil	none	none	none	Asthma, hypertension
28	28F	Generalized	yes	7 d	hydroxychloroquine	yes	none	none	ND
29	36F	Generalized	ND	ND	Ampicillin	none	none	none	Status post caesarean section
30	91F	Generalized	ND	5d	Cephalexin	none	none	none	ND
31	58M	Generalized	ND	ND	Itarubicin, araC, allopurinol	ND	none	none	Acute myelogenous leukemia
32	86M	Generalized	ND	ND	Meclizine, clonzazepam, timolol, Lanoxin, coumadin, paxil, flonase	ND	none	none	ND
33	31F	Generalized	ND	NA	Lovenox, coumadin, heparin, TPA, vicodin	ND	ND	ND	ND
34	88M	Generalized	NA	NA	NA	NA	NA	NA	NA
35	81F	Generalized	NA	ND	NA	NA	NA	NA	NA
36	71M	Generalized	ND	ND	Lipitor	none	none	none	ND
37	86M	Generalized	ND	ND	Ultram	none	none	none	ND
38	88F	Generalized	ND	NA	Plaquenil	none	none	none	Lupus erythematosus
39	35F	Generalized	NA	NA	NA	NA	NA	NA	NA
40	82F	Generalized	NA	NA	NA	NA	NA	NA	NA
41	79F	Generalized	NA	no	NA	NA	NA	NA	NA

Case #	Age/ Sex	Clinical presentation	Fever	Duration of pustules	H/o drug intake	Previous drug reaction	H/o	H/o infection	Underlying disease
42	82F	Generalized	no	7d	Allopurinol, citalopram, torsemide, protonix, toprol, albuterol, protoniz, Vantin, Norvasc, coumadin, oxycodone, heparin, synthroid	none	none	none	hypothyroidism
43	42F	Generalized	no	14d	Cipro, ceftriaxone	yes	none	none	none
44		generalized (same pt, 2 years later)	no	14d	Levofloxacin	yes	none	none	none
45	71M	Generalized	NA	NA	NA	NA	NA	NA	NA

NA : not available; ND : not documented

Table 2. Summary of pediatric AGEP cases in the English literature

Case # (reference)	Age / Sex	History of drug intake	History of infection
Case[7]	13yr/M	none	Viral upper respiratory tract infection
Case[13]	15yr/M	none	upper respiratory tract infection
Case[23]	12yr/M	Acetaminophen; ibuprofen	None
Case[24]	16yr/M	Azithromycin	None
Ersoy #1[4]	5mo/M	None	rhinorrhea
Ersoy #2[4]	15mo/M	None	Diarrhea, vaccine (measles, mumps, rubella, diphtheria, pertussis, tetanus and pneumococcal vaccinations)
Ersoy #3[4]	8yr/M	None	Non-group A beta-hemolytic streptococcal tonsillitis
Ersoy #4[4]	15mo/M	None	otitis media
Ersoy #5[4]	13yr/M	Labetolol Vancomycin	None
Sezer[5]	6yr/M	Acetaminophen	None
Lee[6]	6yr/M	NA	NA
Meadows[7]	17mo/M	Amoxicillin	None

NA: not available

Table 3. Summary of histologic comparison

	AGEP	Pustular psoriasis	P value
Number of Cases	**45**	**19**	
Parakeratosis with neutrophils and serum	7/45 (15.6%)	1/19 (5.3%)	NS
Parakeratosis with neutrophils	4/45 (8.9%)	16/19 (84.2%)	0.0001
Subcorneal pustules	45/45 (100%)	18/19 (94.7%)	NS
Intraepidermal pustules	40/45 (88.9%)	18/19 (94.7%)	NS
Eosinophils within pustule	14/45 (31.1%)	1/19 (5.3%)	NS
Epidermal spongiosis	45/45 (100%)	14/19 (73.7%)	NS
Acanthosis	44/45 (97.8%)	19/19 (100%)	NS
Psoriasiform hyperplasia	8/45 (17.8%)	9/19 (47.4%)	NS
Basal mitoses (> 1per 10HPFs)	30/43 (69.8%)	11/19 (57.9%)	NS
Exocytosis of eosinophils	16/45 (35.6%)	1/19 (5.3%)	NS
Necrotic keratinocytes	41/45 (91.1%)	1/19 (5.3%)	0.0006
Papillary dermal edema	43/45 (95.6%)	7/19 (36.8%)	0.0477
Vasculitis	0/44 (0%)	0/18 (0%)	NS
Fibrinoid necrosis	1/44 (2.3%)	0/18 (0%)	NS
Extravasation of erythrocytes	42/45 (93.3%)	10/19 (52.6%)	NS
Follicular involvement	4/45 (8.9%)	1/19 (5.3%)	NS
Dermal eosinophils (>1+)	19/44 (43.1 %)	0/18 (0%)	0.0089
Dermal neutrophils (>1+)	25/44 (56.8%)	6/18 (33.3%)	NS
Dermal lymphocytes (>1+)	25/44 (56.8%)	12/18 (66.7%)	NS

AGEP, acute generalized exanthematous pustulosis; HPF, high power field; NS, not statistically significant

Figure 1. Involvement of the face is frequently seen in AGEP cases whereas it is rarely seen in pustular psoriasis.

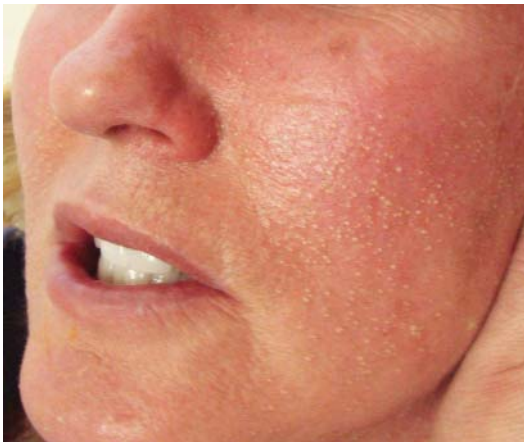


Figure 2. Involvement of the body folds is common including the neck of one patient.

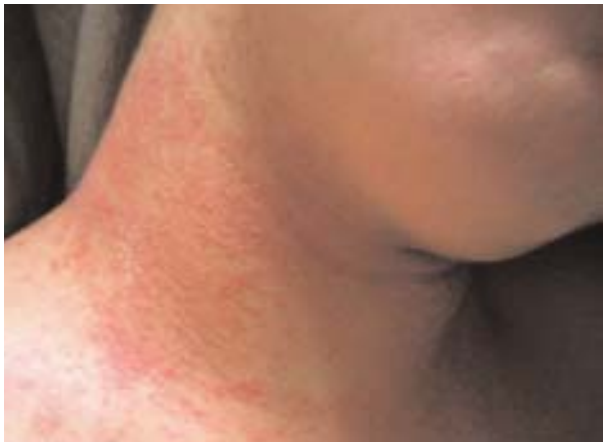


Table 4. Drugs as causes of acute generalized exanthematous pustulosis (in alphabetical order)

acetaminophen[3]	ciprofloxacin[28]	isoniazid[48]	prostaglandin[63]
allopurinol[12]	co-amoxiclav[29]	itraconazole[49]	pseudoephedrine[64]
amoxapine[13]	corticosteroids[30]	labetolol[4]	PUVA[65]
amoxicillin[14]	cytarabine[31]	lansoprazole[50]	pyrimethamine[40]
amphotericin B[15]	dalteparin[32]	lincomycin[51]	quinidine[3]
azathioprine[16]	dextropropoxyphene[33]	macrolides antibiotics[3]	quinolones[66]
anti-HIV protease inhibitors[17]	diaphenylsulfone[27]	metamizole[52]	rifampicin[67]
beta-lactam antibiotics[3]	diltiazem[34]	metronidazole[53]	ranitidine hydrochloride[68]
bamifylline[18]	disulfiram[35]	minocycline[54]	salazosulfapyridine[69]
bleomycin[19]	doxycycline[36]	morphine[55]	sertraline[70]
bufexamac[3]	enalapril[37]	nadoxolol[3]	simvastatin[71]
buphenine[20]	eprazinone[38]	nifedipine[3]	STI571[72]
carbamazepine[3]	fluconazole[39]	nifuroxazide[56]	sulfamethoxazole[73]
carbutamide[3]	furosemide[40]	nimesulide[57]	teicoplanin[74]
chemotherapy (high dose)[21]	gefitinib[41]	nystatin[58]	terbinafine[75]
chloramphenicol[22]	gentamicin[42]	paracetamol[59]	tetracycline[3]
chromium picolinate[23]	griseofulvin[37]	piperacillin/tazobactam[60]	thalidomide[76]
clemastine[24]	hydrochlorothiazide[43]	piperazine ethionamide[40]	thallium[77]
clindamycin[25]	hydroxychloroquine[44]	sulbutiamine[3]	ticlopidine[78]
clobazam[3]	ibuprofen[45]	propafenone[61]	valdecoxib[79]
clozapine[26]	icodextrin[46]	propicillin[62]	vancomycin[3]
cimetidine[27]	imatinib[47]		

Figure 3. Involvement of the thigh inferior to the inguinal fold.

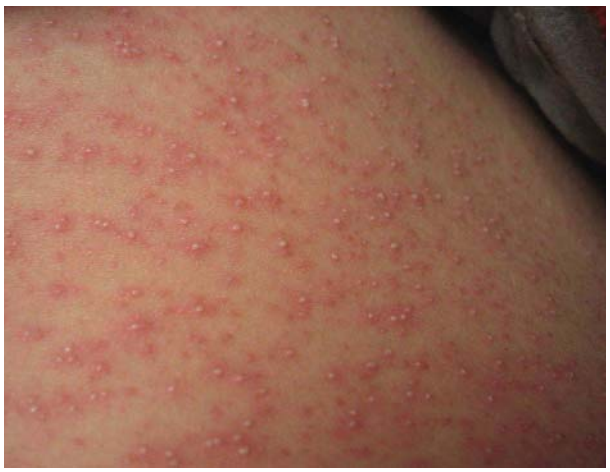
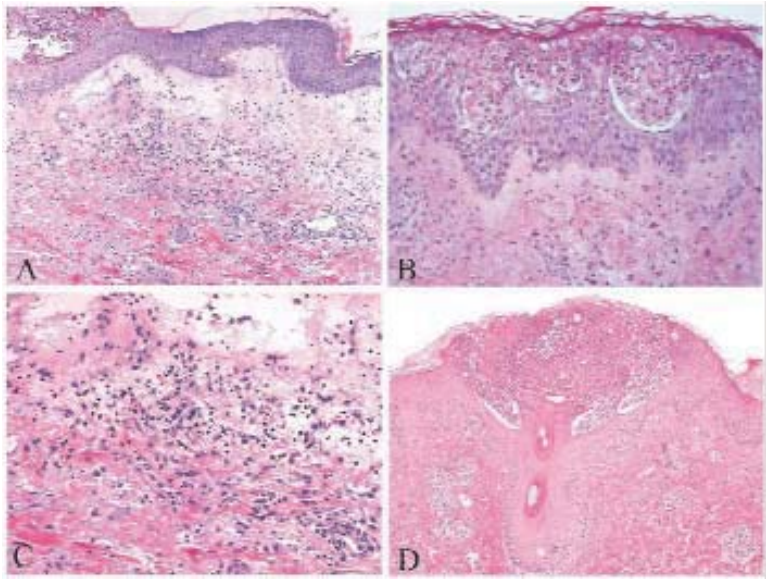


Figure 4. Salient histologic features of acute generalized exanthematous pustulosis include: papillary dermal edema (A, original magnification X 100), necrotic keratinocytes (B, original magnification X 200), prominent dermal infiltrate of eosinophils (C, original magnification X 100). Follicular involvement was noted in occasional cases (D, original magnification X 100) (Hematoxylin-eosin)



It appears greater than 90% of all AGEP cases in the literature are drug-related, with a wide variety of medications suspected to engender this reaction pattern (Table 4)[3,4,12-79]. AGEP has also been associated with viral infections (specifically adenovirus[3], coxsackie B4 virus[8], cytomegalovirus[80], Epstein-Barr virus[3], enterovirus[3], hepatitis B virus[3], and human parvovirus B1981) and also infections with mycoplasma pneumoniae[3] and echinococcosis[82]. Exposure to mercury was a suspected cause for 8 of 63 patients reported by Roujeau et al[3]. Vaccinations[4,83], illicit drug use[84], herbal medications[85], spider bite[86], intravenous contrast media[87], lacquer chicken[88], and progesterone[89] have also been associated with AGEP.

Roujeau et al.[3] described the main histologic findings of AGEP to be spongiform superficial pustules (66%), papillary dermal edema (61%), a polymorphous perivascular infiltrate with eosinophils (34%), leukocytoclastic vasculitis with fibrinoid necrosis (20%), and necrotic keratinocytes (25%). In most cases, the epidermis was uninvolved or exhibited spongiosis without psoriasiform hyperplasia (61%). In our large series we found that the presence of necrotic keratinocytes, papillary dermal edema, and dermal eosinophils were discriminatory features, capable of distinguishing AGEP from pustular psoriasis. In contradiction to the findings of Roujeau et al.[3] vasculitis and fibrinoid necrosis of the vessel walls were decidedly uncommon in our series. Although Beylot et al[2] included a "non-follicular" eruption as one criterion of AGEP, four of our 45 cases (10%) exhibited follicular involvement histologically, two of which were observed in pediatric patients (2/5).

The differential diagnosis of AGEP includes subcorneal pustular dermatosis, pustular contact dermatitis, bullous leukocytoclastic vasculitis, drug hypersensitivity syndrome, and IgA pemphigus. Subcorneal pustular dermatosis (Sneddon-Wilkinson disease) exhibits only subcorneal pustules; whereas intraepidermal pustules are often noted in AGEP. A few cases of pustular contact dermatitis have been reported in the literature[90,91]. While pustular lesions may arise in some cases of leukocytoclastic vasculitis, we found vasculitis to be an uncommon feature of AGEP in our large series. Drug hypersensitivity syndrome, or DRESS (drug rash with eosinophilia and systemic syndrome), may present with pustules, but these typically are less pronounced than

those seen in AGEP. In addition, patients with drug hypersensitivity often have lymphadenopathy, eosinophilia, mononucleosis, and significant visceral involvement, including hepatitis, nephritis, pneumonitis, and/or myocarditis. Mild acanthosis would usually be noted in cases of IgA pemphigus. In addition, direct immunofluorescence would demonstrate intercellular IgA deposition.

Although the pathogenesis of AGEP is not well understood, a combination of different mechanisms likely contributes to its development. It has been suggested that an immunologic recall phenomenon, in which particular memory T-cells produce neutrophil-attracting cytokines such as interleukins 3 and 8 (IL-3, IL-8) may play an important role[92]. Britschgi et al.[93] showed that significantly more IL-8 is produced from drug-specific T-cells taken from patients with AGEP in comparison with similar cells taken from patients with other exanthems. Schmid et al.[94] demonstrated that drug-specific CD4+ cytotoxic CD8+ T-cells are activated in AGEP. In addition, perforin or granzyme B, and to a variable degree the Fas/FasL-killing mechanism, are involved in the formation of vesicles in AGEP. Additional secretion of IL-8 by T cells and keratinocytes attracts neutrophils, filling the vesicles and transforming them into pustules.

Treatment for AGEP is chiefly symptomatic and supportive. The offending drug must be identified and discontinued. Antibiotics are not to be given unless there is well-documented associated infection. The overall prognosis is good, although high fever or superinfection of skin lesions may rarely be life-threatening, particularly in the elderly or in immunocompromised individuals.

Ultimately, although the precise etiology of AGEP remains unknown, our findings support the theory that most cases of AGEP in adults are drug-related, while in pediatric cases infection and drugs appear equally implicated. Salient histologic features of AGEP include necrotic keratinocytes, papillary dermal edema, and eosinophils within the dermis. In comparison, these histologic features are reduced or absent in pustular psoriasis, and an awareness of these features may likely increase the diagnostic accuracy for AGEP.

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Original Article

A 4-year retrospective study of Stevens-Johnson syndrome and toxic epidermal necrolysis

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Abstract

Background Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare bullous mucocutaneous disease usually caused by drugs. We aim to determine the demographics, causes and outcomes of patients admitted with SJS, TEN and SJS-TEN overlap in Sarawak General Hospital.

Materials and Methods A retrospective review of cases admitted to Sarawak General Hospital with SJS, TEN and SJS-TEN overlap from January 2004 to December 2007 was undertaken. Data regarding the demographic, causes and outcomes were collected from the case folders and subjected to descriptive statistical analysis using Microsoft Excel.

Results Twenty four cases were admitted with 54.2% having SJS, 25% having SJS-TEN Overlap and 20.8% having TEN. With the mean ages of more than 40 years, patients with SJS and SJS-TEN overlap were older than patients with TEN, with a mean age of only 25.4 years. Seventy nine percent of cases were drugs induced. Anticonvulsants were the main culprit constituting 29.2% followed by allopurinol with 20.8%. Cases with SJS had the longest incubation period with mean of 21.6 days whereas cases with TEN had the longest mean hospital stay with 12.4 days. A 12.5% mortality rate was recorded with 2 deaths in the SJS-TEN overlap group and one death in the TEN group. All cases who were given intravenous immunoglobulin (IVIg) survived.

Conclusion SSJS, SJS-TEN Overlap and TEN were mainly drug induced and have high mortality. IVIg treatment seems promising. Early recognition and optimal care in institution with dermatology service is essential in reducing morbidities and mortalities.

Keywords Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), intravenous immunoglobulin (IVIg).

Introduction

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare bullous mucocutaneous disease. Although rare with an incidence of 0.05 to 2 persons per 1 million populations per year, it has significant impact on the public health in view of its high morbidity and mortality[1,2]. Majority of cases were drug induced[3,4,5]. They are also grossly under reported worldwide.

Few studies on SJS and TEN are available in Malaysia due to its rarity[4]. There are no reported studies from East Malaysia. Hence, our study aim to determine the causes and management outcome of cases with SJS, SJS-TEN Overlap and TEN admitted to Sarawak General Hospital for a 4 year period from January 2004 to December 2007.

Materials and methods

A retrospective review of cases admitted to the Sarawak General Hospital with SJS, SJS-TEN Overlap and TEN was done for a period of 4 years from January 2004 to December 2007. Data were retrieved from clinical notes in the Medical Records Department.

A clinical diagnosis of SJS, SJS-TEN and TEN was done based on the clinical features of the cases. No skin biopsy was performed. They were classified as SJS, SJS-TEN Overlap and TEN based on Bastuji-Garin et al[6]. SJS is characterized by widespread small blisters and skin detachment levels of less than 10% of the body surface area, SJS-TEN Overlap by skin detachment levels of 10% to 30% of the body surface area, and TEN by skin detachment levels of more than 30% of the body surface area.

Clinical notes were studied in detail regarding the demographics, causative drugs implicated, clinical course and management outcome.

Data collected were compiled on a Microsoft Excel sheet and subjected to descriptive statistical analysis.

Results

Table I shows the demographics of patients admitted to Sarawak General Hospital from January 2004 to December 2007. A total of 24 cases were admitted with 54.2% having SJS, 25% having SJS-TEN Overlap and 20.8% having TEN. There was a male preponderance of 58%. The mean age for cases with TEN was 23.3, SJS-TEN Overlap 44.5 and SJS 40.3 years. They range from 8 to 73 years.

Seventy nine percent of the cases were due to drugs. Anticonvulsants and allopurinol were the major culprits, contributing to 7 and 5 cases respectively. Traditional medications were implicated in 2 cases. Other drugs included antibiotics, non steroidal anti-inflammatory drugs, sulpha drugs and antihelmintics (Table II).

Four cases were given anticonvulsants for pain disorders while 2 were given for seizure prophylaxis for intracranial haemorrhage. Only one case was on anticonvulsants for epilepsy. All the cases on allopurinol were given for asymptomatic hyperuricaemia.

The mean incubation time i.e. time from drug initiation to onset of disease ranging from 4.7 days in TEN to 21.6 days in SJS. The hospital stay in cases with TEN were also longer with a mean of 12.4 days compared to only 8.9 days in cases with SJS.

Table III represents the treatment administered. All the patients with SJS and two third of cases with SJS-TEN Overlap were given corticosteroids. Eighty percent of cases with TEN were given intravenous immunoglobulins.

There were only 3 deaths noted with a mortality rate of 12.5%. They succumbed to acute respiratory distress syndrome (ARDS) and sepsis. The culprit drug was Jamu Asam Urat containing phenylbutazone (a type of nonsteroidal antiinlammatory drugs) in one case whereas no drug was implicated in the other two. They were given corticosteroids and cyclosporine on admission. All the cases with TEN given intravenous immunoglobulin (IVIg) survived.

Morbidities seen include skin dyspigmentation (52%), nail dystrophies (10%) and ophthalmic complications (10%). 2 patients had visual impairment as a result of severe keratitis.

Discussion

The spectrum of disease from SJS to TEN is mainly drug induced. We have found that almost 4 out of 5 cases admitted to our centre were drug induced. Regional and international studies quoted a rate of 50% to 90% of cases[3,4,5,7].

Anticonvulsant is one of the commonest culprit agents implicated[4,8]. The estimated incidence per 10,000 new users is 1 to 10 depending on the agents used[9]. The drug reactions are more commonly seen in slow drug metabolizer due of genetic polymorphism. In carbamazepine hypersensitivity, the polymorphism is in position 308 and 328 of the promoter region of TNF-a gene[10]. SJS and TEN are considered T cell mediated disorders in which activation of CD8 T lymphocytes lead to destruction and apoptosis of keratinocytes[11]. Drugs can activate T cells by acting as a hapten, as a prohapten or by direct pharmacologic interaction among the drug, Major Histocompatibility Complex (MHC) molecule and a T cell receptor. It is postulated that carbamazepine in its chemically inert form can bind with the MHC and T cell receptor causing activation of T cells contributing to SJS and TEN[12].

We found that 36% of our cases were due to anticonvulsant. Among the anticonvulsant, the majority of cases (71%) were due to carbamazepine. This trend was also seen in India, Taiwan, Singapore and northeastern Malaysia[4,8,13]. The increasing utilization of anticonvulsants in pain management and in prophylaxis in neurosurgical patients might explain this. The benefit of prophylactic anticonvulsants in neurologic critical care is controversial and is often not evidence based[14]. Carbamazepine induced SJS and TEN was also found to be more common in Han Chinese with HLA-B1502 phenotype in Taiwan[15]. This might explain the trend in Singapore and some of our cases although no phenotyping was done.

Cases developing adverse drug reactions to carbamazepine should not be given other aromatic anticonvulsants namely phenytoin and phenobarbitone because of cross reaction among the drugs. Mockenhaupt et al found that SJS and TEN occurred in 1 to 10 per 1000 new user of aromatic anticonvulsants and 2.5 per 1000 new user of Lamotrigine, a newer class of anticonvulsant[9]. Sodium valproate and other newer anticonvulsants rarely cause adverse cutaneous drug reactions. Therefore, we would suggest that aromatic anticonvulsants be used cautiously. Safer alternatives for pain management should be used. They should also be used with care in those with Han Chinese lineage.

Allopurinol contributed to 26% our cases. Halevy et al found that in Europe and Isreal, allopurinol is the most common cause of SJS and TEN. They found an increased risk with dosage 200 mg per day or more16. All our cases had taken 300mg per day as it is the only form available in Malaysia. Halevy et al also did not find an increased risk of allopurinol induced SJS and TEN with comedications with diuretics, aminopenicillins, angiotensin converting enzymes inhibitors (ACEI), nonsteroidal anti-inflammatory drugs (NSAIDs) and aspirin[16]. In Han Chinese, HLA-B5801 allele was strongly associated with severe cutaneous adverse reactions to allopurinol[17]. Allopurinol was administered in all our cases for asymptomatic hyperuricaemia. Other published studies also revealed inappropriate indications for

Table 1. Demographic of Patients

	SJS	SJS-TEN Overlap	TEN
Cases	13	6	5
Male	10/13	2/6	2/5
Female	3/13	4/6	3/5
Mean Age (Years)	40.3	44.5	25.4
Range Age (Years)	13-70	8-73	10-42
Chinese	4/13	2/6	1/5
Malay	3/13	3/6	2/5
Iban	4/13	0/6	1/5
Bidayuh	2/13	1/6	1/5

Table 2. Drugs Implicated

	SJS (n=11)	SJS-TEN Overlap (n=5)	TEN (n=3)
Anticonvulsant			
Carbamazepine	2	2	1
Phenytoin	2	2	0
NSAIDs			
Ibuprofen	0	0	0
Mefenemic Acid	0	0	1
Traditional Medications			
Asam Urat	0	0	0
Chinese Herbs	0	0	1
Anti Gout			
Allopurinol	4	4	0
Others			
Sulfasalazine	1	1	0
Amoxycillin	1	1	0
Albendazole	1	1	0

Table 3. Incubation Period of Drugs

	SJS	SJS-TEN Overlap	TEN
Mean (Days)	21.6	12.4	4.7
Range (Days)	2-40	1-21	2-10

Table 4. Duration of Hospital Stay

	SJS	SJS-TEN Overlap	TEN
Mean (Days)	8.9	9.2	12.4
Range (Days)	2-46	2-23	7-19

Table 5. Treatment Outcome

	SJS (n=13)	SJS-TEN Overlap (n=6)	TEN (n=5)
Treatment			
Corticosteroids	13	4	1
IVIg	0	0	4
Cyclosporine	0	1	0
Nursing Care only	0	1	0
Outcome			
Survive	13	4	4
Succumb	0	2	1

allopurinol in up to 86% of patients[18,19]. So, we recommend judicious prescription of allopurinol. A proper guideline on prescription of allopurinol should be established in Malaysia to prevent such inappropriate usage. This will hopefully reduce the allopurinol related life threatening adverse drug reactions.

The highest risk for development of SJS and TEN with drug use occurs within 2 months of initiation[9,16]. We also noted a similar trend with longest incubation period of only 40 days. Interestingly, we also observed that the shorter mean incubation period was associated with more severe clinical presentation. This observation need to be further clarified by future studies as it has prognostic significance.

Our overall mortality was 12.5% with mortality for SJS-TEN Overlap of 33.3% and TEN of 20%. The reported mortality rate range from 5% to 40%[4,5,7,8,20]. Two of our 3 deaths were children with no apparent drug related cause. We postulate that they had very severe viral infection and probably had secondary bacterial sepsis. Their immunity was further depressed by the administration of corticosteroids and cyclosporine leading to their death. Hence, immunosuppressive drugs should be used cautiously especially in those with suspected underlying infection. Systemic corticosteroids has unproven benefit in early cases of SJS and TEN and deleterious in the advanced forms[19,20].

We noted a 100% survival of the TEN cases given intravenous immunoglobulin (IVIg). IVIg is derived from plasma pool of several thousand donors and consists mainly of IgG. It interferes with Fas-Fas Ligand interactions by blocking the Fas binding to its ligand thereby blocking the apoptosis of the keratinocytes[21]. Stella et al in Turin noted a reduction in mortality from 75% to 26% with the use of IVIg[22]. In a review of 8 studies on the use of IVIG in SJS and TEN, French et al found that 6 studies points towards a benefit of IVIg on mortality associated with TEN[23]. Thus, the use of IVIg in TEN is very promising. Prospective studies should be done in Malaysia to determine the efficacy of IVIg as a first line treatment in TEN.

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Original Article

Lepra reactions: A 10-year retrospective analysis

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Abstract

Introduction Leprosy is a chronic granulomatous infection caused by Mycobacterium leprae. Drug treatment is effective in eradicating the bacilli but does not prevent lepra reaction. Despite much attention being focused on the problem of lepra reactions, very limited data has been published on the epidemiology of lepra reactions especially this part of the world. The aim of the study is to improve the understanding of lepra reaction and to determine the demographics and clinical patterns of lepra reactions in Penang General Hospital.

Materials and Methods This retrospective study covers a 10-year period from 1997 to 2006. Demographic characteristic and clinical patterns of lepra reactions were analysed with SPSS 13.0 version.

Results Of the 95 patients who were enrolled in the study, 67 (70.5%) were male and 28 (29.5%) were females. The mean age at presentation was 40.4 ± 17.9 years (range 3-91 years). There were 35 Malays (36.8%), 34 Chinese (35.8%), 5 Indians (5.2%) and 21 foreigners (22.2%). 35.8% of patients presented with LL (n=34), 18.9% BT (n=18), 17.9% TT (n=17), 13.7% BB (n=13) and 13.7% BL (n=13). In our series, the lepra reaction rate among leprosy patient was 51.6% (n=49). Among those with lepra reaction, 53.1% cases were type 1 reaction (n=26), 44.9% cases were type 2 reaction (n=22) and 2.0% cases were Lucio phenomenon (n=1). Common manifestations observed in lepra reaction were worsening of skin lesions (100%), inflammatory oedema of hands, feet and face (53.1%), nerve pain (46.9%), fever (20.8%) and nerve tenderness (20.4%). Only 4 cases had involvement of other organs like the eye and joint. 30.6% of the reactions observed in our cohort were severe. Type 1 reaction commonly involved those in borderline spectrum whereas type 2 reaction commonly involved those in the lepromatous spectrum. Lepra reactions occurred before treatment (24.5%), during treatment (71.4%) or even after treatment has been stopped (4.1%). Most of the lepra reactions occurred during the treatment period especially the first 12 months of therapy.

Conclusion Our study showed a more severe and higher reaction rate compared to other studies. Lepra reaction is a common presentation of leprosy. Type 1 reaction commonly involved those with borderline disease but type 2 reaction commonly involved those with lepromatous spectrum of disease. Lepra reaction occurred before, during and even after the treatment has stopped. Most of the lepra reactions occurred during treatment period especially the first 12 months of therapy.

Keywords Leprosy, Lepra Reaction, Reversal reaction, Erythema nodosum leprosum, Lucio phenomenon

Introduction

Leprosy is a chronic granulomatous infection caused by Mycobacterium leprae. The principal manifestations are skin lesions and peripheral neuropathy. Drug treatment is effective in eradicating the bacilli, but does not prevent reactions. Despite much attention being focused on the problem of lepra reactions, very limited data has been published on the epidemiology of lepra reactions especially this part of the world. The aim of the study is to improve the understanding of lepra reaction and to determine the demographics and clinical patterns of lepra reaction in Penang general hospital.

Materials and Methods

This retrospective study covered a 10 year period from 1997 to 2006. Reporting forms were filled up by doctor in-charge. Demographic characteristic and clinical patterns of lepra reaction were noted and analysed.

All patients (inpatient and outpatient) in the Department of Dermatology Penang General Hospital, with the diagnosis of leprosy within this period were included. Due to paucity of cases and difficulty in doing biopsy in young children, some cases were diagnosed clinically without a biopsy. Skin smears were taken from site of lesion and stained with Ziehl-Neelsen's staining method. Skin biopsy from the site of lesion was taken after obtaining an informed consent. The tissue specimens were processed for routine histopathological examination (i.e. staining with Hematoxylin-Eosin and Fite-Faraco stains).

The diagnosis of leprosy is primarily clinical. Anaesthetic / hypoesthetic skin lesions with or without thickened peripheral nerves are virtually pathognomonic of leprosy. A full thickness skin biopsy from an anaesthetic lesion showing granuloma and lymphocytic infiltration of nerves essentially confirms the diagnosis.

Leprosy is categorized as TT (Tuberculoid Leprosy), BT (Borderline Tuberculoid), BB (Borderline Borderline), BL (Borderline Lepromatous) and LL (Lepromatous Leprosy) types according to the Ridley Jopling classification.

Lepra reaction is the term given to a violent but often ineffective tissue response presenting as an acute deterioration in the clinical lesions of the patient undergoing treatment for leprosy.

Severe reaction is defined as presence of one or more of the following signs or symptoms:

- Sensory or motor impairment
- Ulcerating skin lesions
- > 10 reactional skin lesions
- Oedema that impair function
- Nerve tenderness on palpation
- Paraesthesia or nerve pain disturbing sleep or impairing function
- Involvement of other organs like eye, joints or testis

Inclusion Criteria:

- Patients who were diagnosed to have Leprosy
  By one or more of the following symptoms and signs:
  1. Hypopigmented or erythematous skin lesion(s) with definite loss of sensation.
  2. Damage to the peripheral nerves as demonstrated by palpable thickening with or without impairment of sensation and/or weakness of the muscles of hands, feet or face
  3. Presence of acid-fast bacilli in slit skin smears
  4. Histological changes diagnostic of leprosy in skin biopsy
- Receiving standard MDT treatment for leprosy or completed treatment for leprosy

Exclusion Criteria:

- Presence of other skin disorders that may be confused with the clinical picture of leprosy.
- On oral corticosteroid or other immunosuppressive treatment for other disorder, not for the purpose of the treatment of lepra reaction.

Statistical analysis:
All analyses were performed using SPSS 13.0 version.

Results

A total of 95 patients were diagnosed to have leprosy during this period (1997-2006) in the Dermatology Clinic, Penang Hospital. The mean age at presentation was 40.4 ± 17.9 years (Range3- 91). Of the 95 patients who were enrolled in the study, 67 (70.5%) were male and 28 (29.5%) were females There were 35 Malays (36.8%), 34 Chinese (35.8%), 5 Indians (5.2%) and 21 foreigners (22.2%). Foreigners are mainly from our neighbouring countries (Indonesia, Nepal, Bangladesh and Philippines).

Patients experienced symptoms for a mean of 21.4 months before being referred to our clinic. At presentation, patients had a mean Bacteriological Index (BI) of 1.38±1.5 and a mean Morphological Index (MI) of 1.00±1.29. Most of them have no family history of leprosy (n=66, 69.5%). 35.8% of patients presented with lepromatous leprosy (n=34), 18.9% BT (n=18), 17.9% TT (n=17), 13.7% BB (n=13) and 13.7% BL (n=13).

In our series, the lepra reaction rate among leprosy patient was 51.6% (n=49). Among those with a lepra reaction, 26 cases are type 1 reaction (53.1%), 22 cases are type 2 reaction (44.9%) and 1 case is Lucio phenomenon (2%). 49.0% of lepra reactions involved LL patients. Those with BT, 16.3% of them developed reaction, followed by BL, BB and TT (14.3%, 14.3% and 6.1% respectively).

Common manifestations observed in patients who developed lepra reaction were worsening of skin lesions (100%), inflammatory oedema of hand, feet and face (53.1%), nerve pain (46.9%), fever (20.8%) and nerve tenderness (20.4%). Only 4 cases had involvement of other organs like eye and joint. 30.6% of the reactions observed in our cohort were severe, requiring high dose and prolonged course of systemic corticosteroid and other immunosuppressive agents (Figure 1).

Lepra reactions occurred before, during and even after the treatment has stopped. At presentation, 12 patients (12.6%) had ongoing lepra reaction, majority of them had type 2 reaction. During treatment, 35 patients experienced a reaction, and following treatment cessation an additional 2 patients experienced a reaction. Lepra reactions seen during treatment were mainly type 1 reaction. Majority of reactions occurred within 12 months of MDT and were rarely seen among those already on MDT for more than 12 months (Figure 2, 3 & 4).

Type 1 reaction commonly involved those with borderline spectrum. They commonly presented with worsening of pre-existing skin lesions (i.e the lesion becomes more erythematous and oedematous), oedema and tenderness of peripheral nerves. The peak time for type I reactions was during the first 3 months of therapy and for up to 12 months. Type 2 reaction mainly involved those with lepromatous spectrum of disease. They presented with crops of painful erythematous nodules of the skin and subcutaneous tissue. It was associated with fever, malaise, arthralgias, neuralgia, dactylitis and orchitis. The peak time for type 2 reaction was during the first 6 months and frequently occurred before treatment was started.

Figure 1. Reactional signs and symptoms observed in the subjects

Signs And Symptoms	N	%
Skin Lesions		
None	0	0
New site	22	44.9
Pre-existing site	26	55.1
Degree Of Inflammation		
None	0	0
Erythema	26	53.1
Erythema and raised plaque or nodules	22	44.9
Ulceration*	2	4
Reactional Oedema		
None	23	46.9
Minimal	18	36.8
Visible	8	16.3
Affecting function*	0	0
Fever Due To Reaction		
< 37.5°C	15	30.6
37.6 - 38.9°C	10	20.4
39.0°C*	2	4
Involvement Of Other Organ (Eye / Joint / Testis)		
None	45	91.8
Mild	3	6.1
Definite*	1	2.1
Nerve Pain / Paraesthesia		
Presence*	23	46.9
Absence	26	53.1
Nerve Tenderness		
Presence*	10	20.4
Absence	39	79.6
Severity Of Reaction		
Mild	34	69.4
Severe*	15	30.6

Figure 2. Lepra reaction observed among the subjects in the cohort

	NUMBER OF PATIENTS					
	ALL	TT	BT	BB	BL	LL
Type 1	26	3	8	5	4	6
Before treatment	4	0	2	1	1	0
During treatment	21	3	6	3	3	6
First 3/12	13	1	4	3	3	2
3/12-6/12	6	1	2	0	0	3
6/12-12/12	2	1	0	0	0	1
> 1 Yrs	0	0	0	0	0	0
After treatment	1	0	0	1	0	0
Type 2	22	0	0	2	3	17
Before treatment	7	0	0	0	1	6
During treatment	14	0	0	2	2	10
First 3/12	7	0	0	1	2	4
3/12-6/12	3	0	0	1	0	2
6/12-12/12	2	0	0	0	0	2
> 1 Yrs	2	0	0	0	0	2
After treatment	1	0	0	0	0	1
Lucio Phenomenon	1	0	0	0	0	1
No Reaction	46	14	10	6	4	12

Figure 3. Lepra reactions according to classification of leprosy

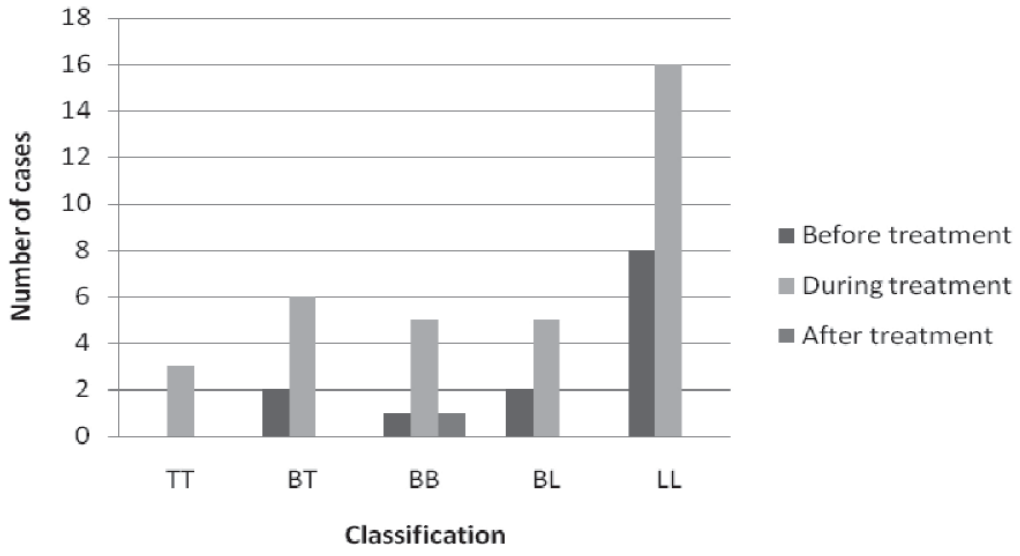
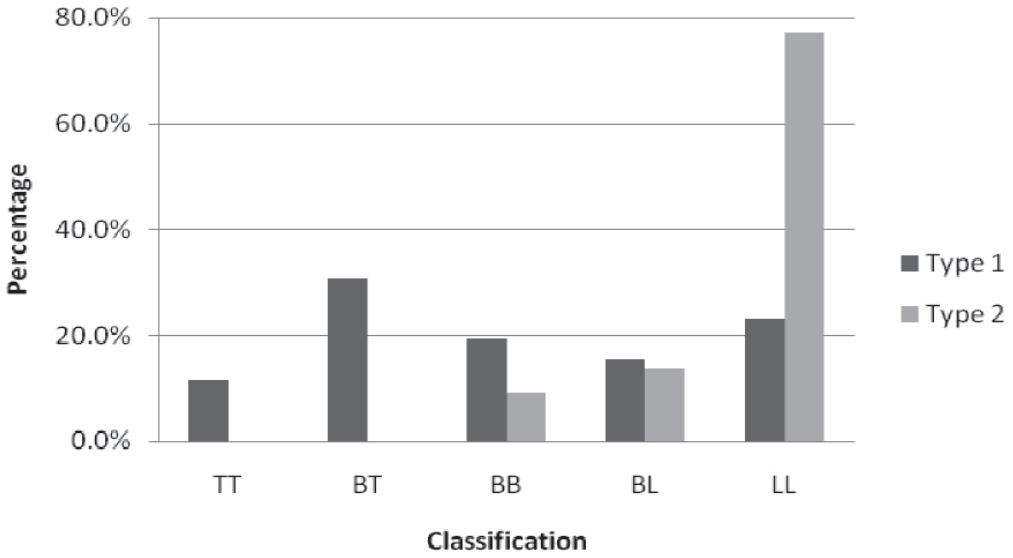


Figure 4. Lepra reaction in relation to timing of treatment and classification of leprosy



Discussion

Malaysia achieved WHO's target for control and elimination of leprosy in 1994[1]. However, Leprosy is still being considered as a public health problem in Malaysia because of the potential permanent physical disabilities it may cause and social stigma.

Leprosy is an infectious disease caused by Mycobacterium leprae. It is often complicated by the host's intermittent hypersensitivity reactions (the so-called lepra reactions). The skin, superficial peripheral nerves, anterior chamber of the eyes, and testes are the most frequently affected organs[2-3].

Leprosy demonstrates a wide spectrum of immunological, microbiological, histological and clinical sequelae as classified by Ridley and Jopling in 1962[4]. Based on the immunologic response of the host to Mycobacterium leprae, Leprosy is classified into a five groups: TT (polar tuberculoid), BT (borderline tuberculoid), BB (borderline), BL (borderline lepromatous), and LL (polar lepromatous). In 1982, the WHO study group of chemotherapy for control programs recommended that the classification of all patients be based on Ridley-Jopling classification and the positivity of bacilli in skin-slit smears. The type of leprosy varies in different populations. In India and Africa, 90% of patients are tuberculoid spectrum of diseases. While in Mexico 90% are lepromatous spectrum. In our cohort, about 50% of leprosy patients are in lepromatous spectrum.

Indolent course of leprosy is sometimes punctuated by acute exacerbation of the clinical condition of the patient, in terms of worsening of older lesions and appearance of new lesions, or other symptoms ("Lepra reaction"). Most of the studies reported 20 - 30% rates of lepra reaction of varying degrees of severity during the course of their illness. Our cohort had shown a relatively higher reaction rate of 51.6%. Similar findings were also observed in northern India and other countries[3-4,16].

Lepra reactions consist of type 1 (reversal reaction), type 2 (Erythema Nodosum Leprosum) and Lucio phenomenon reactions. They can cause considerable morbidity and mortality. They are also a potential source of confusion to patients and clinicians who expect improvement after starting MDT. They may be precipitated by drug therapy (MDT/antimicrobial), intercurrent infection, immunization, pregnancy, parturition or stress[5-8]. It is interesting to note that there are 6 patients (12.2%) who had preceding history of broad spectrum antibiotic use prior to the lepra reaction. Our cohort did not reveal any other obvious precipitating factors.

Type 1 reaction / Reversal reaction is the most common type of reaction. It is mediated by delayed-type hypersensitivity directed against M. leprae antigens which usually localized to skin and nerve and result in mycobacterial elimination. These reactions typically occur in 'immunologically unstable BT, BB and BL leprosy patients[2-3]. A similar pattern was observed in our cohort (76.9% of type 1 reaction occurred among these groups). They manifest clinically as acutely inflamed skin lesions and acute neuritis. Type 1 reactions are usually not associated with systemic symptoms such as fever or arthralgias. The nerve lesions can manifest as acute painful nerve palsies within 24–36 hours. Involved nerves are usually enlarged and tender. Reversal reactions occur most frequently within 6 to 12 months after starting treatment[16].

Type 2 (erythema nodosum leprosum, ENL) reactions occur as a result of immune-complex deposition in the vascular endothelium and tissues and mediated by type 3 immune reactions (immune-complex mediated). ENL tends to occur in patients with high antigen load as a result of improved / enhanced antibody production in BL and LL leprosy. This is not protective in terms of limiting the infection and killing Mycobacterium leprae but it helps to clear the tissue of accumulated mycobacterial antigens9. ENL is usually a systemic disorder. Patients with ENL present with fever, malaise, anorexia, leukocytosis and anaemia. Classical clinical manifestations include crops of erythematous painful nodules in the skin and subcutaneous tissue anywhere in the body but mainly in the face, forearms, torso and medial thighs. There may be accompanying nerve, ocular, hepatic, splenic, joint, musculoskeletal, reticuloendothelial, testicular (in males), cardiac and renal involvement[2-3,10-12].The reaction is a manifestation of the disease and not always a complication of its therapy[4].

ENL is an episodic reaction which occurs in about half of borderline lepromatous and lepromatous leprosy patients. It frequently develops within the first 2 years of drug treatment. It may persist and exacerbate even after 5–10 years in patients who are presumed to be bacteriologically negative. 90.9% of type 2 reaction cases in our cohort belonging to BL and LL leprosy. Data from Brazil show that 30% of the patients diagnosed with MB developed ENL (Pereira 2003)[13], paralleling data from other countries such as Nepal (Van Brakel & Khawas 1994)[14], China (Li et al. 1990)[15] and north India (Kumar et al. 2004)[16]. ENL is certainly not rare.

Lucio Phenomenon is a rare occurrence found mainly in Latin Americans, especially Mexicans. The condition has also been reported from our region like Singapore[20] and Malaysia. Patients present as a form of lepromatous leprosy described as diffuse lepromatosis, resulting in necrotic lesions that ulcerate, especially below the knees. Lesions are the result of dermal ischemic infarction resulting from endothelial proliferation and/or thrombosis in small vessels. Bacilli are often present along with endothelial cells. Unlike ENL, Lucio is present at the time of initial diagnosis[6,17-19].

Our study showed a more severe and higher reaction rate compared to other studies. Lepra reaction is a common complication of leprosy. Type 1 reaction commonly involved those with borderline diseases whereas type 2 reaction commonly involved those with lepromatous spectrum of disease. Lepra reaction occurred before, during and even after the treatment has stopped. Most of the lepra reactions occurred during treatment period especially the first 12 months of therapy.

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Original Article

Comparison of multiple drug therapy in leprosy

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Abstract

Introduction Multiple drug therapy (MDT) was utilized for the treatment of Hansen's disease in Sarawak since 1989. MDT Sungai Buloh and MDT Sarawak were the 2 major MDT regimens used. Hence, we aim to compare the outcomes of MDT Sungai Buloh and MDT Sarawak.

Materials and Methods A retrospective review of 40 cases receiving MDT Sungai Buloh and MDT Sarawak from 1993 to 2006 was performed. Data regarding demographics and outcomes were collected and analysed. Primary outcome was cure and secondary outcomes were relapse, reactivation, death, leprosy reactions and deformities.

Results There were no statistically significant differences in the primary outcome among patients on MDT Sungai Buloh and MDT Sarawak (p=0.41) after adjustment for surveillance rate. We noted that significantly more patients on MDT Sarawak (40.9%) were still under surveillance compared to MDT Sungai Buloh (5.6%, p=0.01). We also noted a higher rate of erythema nodosum leprosum (ENL) (16.7%) and deformities (22.2%) in patients receiving MDT Sungai Buloh compared to 9.1% ENL and 9.1% deformity rate among those on MDT Sarawak. However, this did not reach statistical significance. Other secondary outcomes were not significantly different between the two regimens. No recurrence was reported with the two treatment regimens. Subanalysis for multibacillary patients did not reveal any significant differences between the two regimens in the primary outcome of cure after adjustment for surveillance rate (p=0.35). Both ENL and deformity rates of 25% each for MDT Sungai Buloh were higher than the rate of 13.3% each for MDT Sarawak although they did not reach statistical significance. Analysis for paucibacillary patients did not show superiority of any one regimen.

Conclusion Both the MDT Sungai Buloh and MDT Sarawak were effective in leprosy treatment. Selection of the best treatment regimens will depend on the cost effectiveness, ease of administration and duration of treatment that patients can tolerate.

Introduction

Leprosy is one of the oldest diseases in mankind. It was reported as early as 600 BC in India and 400 BC in China[1]. It is caused by Mycobacterium leprae, an acid fast, pleomorphic, rod-like Gram positive bacteria.

Multiple drug therapy (MDT) has been introduced by the World Health Organisation (WHO) in the fight against leprosy. In Malaysia, use of MDT was launched in the 1980s. In Sarawak, the first MDT regime utilized was the MDT Sungai Buloh regime in 1989. It was used until 1994 when the MDT Sarawak regime, a modification of the 1981 WHO MDT regime was introduced. Since 2006, the WHO 1997 MDT regime has replaced the MDT Sarawak until today.

Here, we aim to compare the outcomes of MDT Sungai Buloh and MDT Sarawak, 2 of the most commonly used MDT in Sarawak over the years.

Materials and Methods

This retrospective review aims to compare the outcomes of patients receiving MDT Sungai Buloh and MDT Sarawak in the Skin Clinic, Sarawak General Hospital from 1993 to 2006.

All the leprosy patients seen between 1993 and 2006 were reviewed. Of the 74 cases reviewed, 14 were excluded because they did not receive either MDT Sungai Buloh or MDT Sarawak. Of the remaining 60 patients who were receiving either MDT Sungai Buloh or MDT Sarawak, another 20 patients were excluded as they were transferred to other institutions for completion of their treatment. These patients were excluded as we were unable to determine their treatment outcomes.

We collected data on demographics and treatment outcomes. The primary outcome was cure. The secondary outcomes were recurrence, death, leprosy reactions and deformity.

The patients were classified into multibacillary or paucibacillary based on 1988 World Health Organisation (WHO) classification[2,3]. The MDT Sungai Buloh and MDT Sarawak protocol is shown in Table 1.

We define cure as release from surveillance of leprosy without signs and symptoms of active disease; and bacteriologic index (BI) of < 2. The duration of surveillance depends on the MDT regime used (Table 1). Recurrence of disease is defined as appearance of new skin lesions consistent with leprosy and a BI of 2 at any site (21). Recurrence of disease during surveillance is termed reactivation, whereas recurrence after the surveillance period is termed relapse.

Leprosy reactions consist of Erythema Nodosum Leprosum (ENL) and lepra reaction. ENL is defined as appearance of tender erythematous nodules or plaques on the body associated with constitutional symptoms during and after treatment. Lepra reaction is inflammation of existing lesions during and after treatment.

All the patients seen between 1989 and 1994 were given MDT Sungai Buloh. Those seen after 1994 were all given MDT Sarawak.

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Data collected were analysed with SPSS version 10. Means, standard deviations (SD) and frequencies were computed for demographic variables. Exploratory analysis using chi-square test was done to compare the outcomes between the two MDT regimens. The level of significance was set at 0.05.

Results

Table 2 showed the characteristics of the 40 patients who received MDT Sungai Buloh and MDT Sarawak. There were 18 patients on MDT Sungai Buloh and 22 receiving MDT Sarawak. The baseline characteristics of patients on both MDT regimens were almost similar. Male outnumber female patients in both the regimens. Almost two third of the patients in both regimens had multibacillary leprosy. Both regimens had predominant Chinese patients. Only 5 (27.8%) patients on MDT Sungai Buloh were new treatment naïve patients. The rest had had dapsone as a single agent treatment previously. However, 14 (63.6%) patients on MDT Sarawak were treatment naïve on presentation.

Table 3 compared the outcomes of patients treated with MDT Sungai Buloh and MDT Sarawak. There was a significantly better cure rate with MDT Sungai Buloh at 83.3% compared to MDT Sarawak at 45.5% (p=0.01). However, significantly more patients on MDT Sarawak (40.9%) were under surveillance (p=0.01). Therefore, after adjusting for patients who were still under surveillance, we noted that the cure rate between both arms were not significant (p=0.41). Other outcomes were statistically not significant although we noted a higher rate of ENL and deformities in patients receiving MDT Sungai Buloh. The ENL rate was 16.7% among those on MDT Sungai Buloh compared to 9.1% on MDT Sarawak, whereas the deformity rate was 22.2% and 9.1% respectively. There was no reported recurrence in both regimens. Two patients on MDT Sungai Buloh and 3 on MDT Sarawak succumbed to the disease.

In the subanalysis of multibacillary patients, we also noted that the cure rate of 66.7% with MDT Sungai Buloh was superior to MDT Sarawak at 25% (p=0.02). Again, because significantly more patients on MDT Sarawak (46.7% versus 8.3%) were still under surveillance, adjustment for this variable was done. After the adjustment, the cure rate between the two regimens were not statistically significant (p=0.35). There was also no significant difference in other outcome measures. We noted that the ENL and deformity rates of 25% each with MDT Sungai Buloh were higher than those of MDT Sarawak with 13.3% each. However, these variables did not reach statistical significant difference. In paucibacillary patients, comparison between the two MDT regimens did not show superiority of any one agent.

Discussion

Gallo et al compared 2 multibacillary MDT regimens i.e. regime 1 containing 600mg rifampicin with 100mg dapsone daily for three consecutive months followed by self-administered 100mg dapsone daily for 21 months and regime 2 containing 600mg rifampicin with 300mg clofazimine once a month under supervision plus self-administered doses of 50mg clofazimine with 100mg dapsone daily for 24 months and showed no statistically meaningful differences (p>0.05) in terms of bacilloscopic, histopathological and neuromotor evaluation parameters between the two regimens[4]. However, they found that those on regimen 2 had fewer reaction frequency (p<0.05). This implied that daily rifampicin for 3 months was of no benefit. Jadhav et al also noted that there were no difference in the 2 year multibacillary MDT regimen containing daily rifampicin for 9 months and the 2 year WHO regimen[5]. However, the MDT regimen containing daily rifampicin for 9 months conferred a significantly greater fall in bacteriologic index (BI). In our comparison, we also did not find any significant difference between MDT Sungai Buloh which utilized an intensive 1 month daily rifampicin and the MDT Sarawak regimen which was without. We also noted a higher reaction rate with MDT Sungai Buloh which utilized 1 month intensive rifampicin therapy.

Table 1. MDT regimes used in Sarawak

Regime	Medications	Durations	Surveillance
MDT Sg Buloh*			
Paucibacillary		1 year	5 years
Monthly pulse dose	Rifampicin 600 mg		
	Clofazimine 300 mg		
Daily dose	Clofazimine 50 mg		
	Dapsone 100 mg		
Multibacillary		3 years	10 years
Intensive phase treatment		1 month or MI^{r} = 0	
Daily dose	Rifampicin 600 mg		
	Clofazimine 100 mg		
	Dapsone 100 mg		
Maintenance treatment		3 years	
Monthly pulse dose	Rifampicin 600 mg		
	Clofazimine 300 mg		
Daily dose	Clofazimine 50 mg		
	Dapsone 100 mg		
MDT Sarawak			
Paucibacillary		6 months	5 years
Monthly pulse dose	Rifampicin 600 mg		
	Clofazimine 300 mg		
Daily dose	Dapsone 100 mg		
Multibacillary		2 years	10 years
Monthly pulse dose	Rifampicin 600 mg		
	Clofazimine 300 mg		
Daily dose	Clofazimine 100 mg		
	Dapsone 100 mg		

MDT Sg Buloh = MDT Sungai Buloh* *MI^{r} = morphological inde*

Li et al in Nanjing, China showed that 64.7% of their 303 multibacillary patients receiving a 3-year treatment using rifampicin, clofazimine and dapsone showed negative skin smears and clinical inactivity[6]. The rest showed different degree of improvements. 9 out of 11 patients (81.8%) of patients in Cebu, Philippines who received the 2 year WHO MDT assessed at five or more years after completion of treatment had no evidence of relapse[7]. These 2 studies showed that both the 2 and 3 years regimen were effective in leprosy control. In our study, we noted that the cure rate after adjustment for surveillance rate were not significantly different between the 2 year MDT Sarawak regimen and the 3 year MDT Sungai Buloh regimen. Moreover, none of our patients had relapse.

Girhdar BK et al found that relapse rates in patients with BI of 4 or higher was significantly higher ($p < 0.01$) in the fixed dose regimen of 2 years WHO MDT group as compared to those receiving treatment till the point of smear negativity[8]. All the relapsed patients responded to retreatment with the same drug combination, indicating that the exacerbation in their condition was because of insufficient treatment. They suggested that treatment be continued till smear negativity, at least in patients with high BI to prevent or reduce relapses. In Cebu, Cellona et al found that the absolute relapse rate was 3% with a cumulative risk estimate of 3.9% at 15 yrs among multibacillary patients receiving the 2 year WHO MDT regimen. In our study, we did not find any relapses among all our patients on both MDT regimens during the surveillance period of 10 years. All these patients were not followed up after they were discharged from surveillance. As the peak period of relapse is between 12 to 15 years post treatment, we would not be certain if our patients actually have relapse. Thus, as the relapse rate is highest with a high BI, we recommend that multibacillary patients with BI of 4 or higher on presentation be administered MDT Sungai Buloh which employed a longer duration of treatment and those with lower BI be put on MDT Sarawak.

Table 2. Baseline demographics and classifications of leprosy cases

	MDT Sg Buloh	MDT Sarawak
Sex		
Male	16 (88.9%)	15 (68.2%)
Female	2 (11.1%)	7 (31.8%)
Age (years)		
Mean	36.6	37.7
SD	17.6	20.6
Min, max	10,74	8,94
Race		
Chinese	10 (55.6%)	14 (63.6%)
Malay	3 (16.8%)	6 (27.3%)
Iban	1 (5.5%)	1 (4.5%)
Indonesians	1 (5.5%)	0
Penan	0	1 (4.5%)
Kenyah	1 (5.5%)	0
Bidayuh	1 (5.5%)	0
Kayan	1 (5.5%)	0
WHO		
Multibacillary	12 (66.7%)	15 (68.2%)
Paucibacillary	6 (33.3%)	7 (31.8%)
New Cases	5 (27.8%)	14 (63.6%)

Katoch et al compared 3 paucibacillary MDT regimens i.e. regimen 1 consisting of rifampin 600mg once a month for 6 months with dapsone 100mg daily for 6 months, regimen 2 with an additional 6 months treatment with dapsone 100 mg daily on top of regimen 1 and regimen 3 with rifampicin administered daily for the first 7 days on top of regimen 29. They found that 72.2% of the patients in regimen 1, 94.9% of the patients in regimen 2, and 97.1% in regimen 3 became inactive. On follow-up for 1 1/2 years, three regimen 1 patients and none of the regimen 2 or regimen 3 patients showed relapses. In our comparison, we noted that there was no statistically significant difference between the 2 regimens both on cure rate and the relapse rate during the 5 years surveillance period. We did not see any relapse among our patients. Both the MDT Sungai Buloh and MDT Sarawak had included clofazimine in the regimens. The addition of clofazimine might be the crucial link in the success of these treatments in the paucibacillary patients.

Limitation of the study

We had a small number of patients who received MDT Sungai Buloh and MDT Sarawak. This affected the statistical power of the study. As this was a retrospective review, a head to head comparison was difficult. Moreover, patients received the two MDT regimens on a different time frame; from 1989 to 1994, patients were given MDT Sungai Buloh and thereafter, were given MDT Sarawak. This might be significant as the pattern and responsiveness of the disease might have changed with time. In addition, 72.2% of patients on MDT Sungai Buloh had dapsone monotherapy previously whereas 63.6% of patients on MDT Sarawak were treatment naïve on presentation.

Conclusion

We would like to conclude that both the MDT Sungai Buloh and MDT Sarawak were effective in leprosy treatment. We would recommend that multibacillary patients with BI of 4 or higher on presentation be put on MDT Sungai Buloh to prevent recurrence. Otherwise, the selection of the treatment regimens will depend on the cost effectiveness, ease of administration and duration of treatment that patients can tolerate.

Table 3. Outcomes by MDT regimes

	MDT Sg Buloh	MDT Sarawak	p value
Overall	18	22	
Cured	15 (83.3%)	10 (45.5%)	*0.01*
Died	2 (11.1%)	3 (13.6%)	0.81
Under surveillance	1 (5.6%)	9 (40.9%)	*0.01*
Reactivation/relapse	0	0	0
ENL	3 (16.7%)	2 (9.1%)	0.47
Lepra reaction	0	1 (4.5%)	0.36
Deformities	4 (22.2%)	2 (9.1%)	0.25
Multibacillary	12	15	
Cured	10 (83.3%)	6 (40.0%)	*0.02*
Died	1 (8.3%)	2 (13.3%)	0.68
Under surveillance	1 (8.3%)	7 (46.7%)	*0.03*
Reactivation/relapse	0	0	0
ENL	3 (25%)	2 (13.3%)	0.44
Lepra reaction	0	1 (6.7%)	0.36
Deformities	3 (25%)	2 (13.3%)	0.44
Paucibacillary	6	7	0
Cured	5 (83.3%)	4 (57.1%)	0.31
Died	1 (16.7%)	1 (14.3%)	0.91
Under surveillance	0	2 (28.6%)	0.16
Reactivation/relapse	0	0	0
ENL	0	0	0
Lepra reaction	0	0	0
Deformities	1 (16.7%)	0	0.26

MDT Sg Buloh = MDT Sungai Buloh MI^ = morphological index*

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Original Article

Granular cell tumour - A case series of 9 patients and literature review

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Abstract

Granular cell tumours are uncommon benign lesions with a predilection for the head and neck region. We report 9 cases of this rare tumour seen at the National Skin Centre, Singapore, between 1996 and 2006. Five patients were female and four were male. Patient ages were between 15 to 66 years, with a mean of 37.1 years. All 9 patients presented with an asymptomatic painless mass varying from a 1 year to 10 years duration, with a mean duration of 4 years. 6 of the patients were Chinese, 2 were Indian and 1 was Sri Lankan. Five tumors were in the head and neck, three were in the groin or genital regions, and one was in the limb. The tumours ranged in size from 0.3 cm (in the scrotum) to 2.5 cm (in the neck). On examination, none of the lesions had any features of malignancy. The pre-operative diagnosis was dermatofibroma in 3 patients, epidermal cyst in 5 patients, and adnexal tumour in 1 case. For 1 of the patients, there were 2 synchronous tumours present in the scrotum. Excision biopsy was performed for all patients and histology confirmed the diagnosis.

Introduction

Granular cell tumours are relatively rare benign soft tissue neoplasms first described by Abrikossoff[1] in 1926. They appear in two forms: the adult type more commonly found in the head and neck region, which occurs more frequently in women and blacks; and the congenital type usually occuring on the gingiva of the anterior maxillary ridge. The granular cell component of both lesions is identical, consisting of a diffuse infiltrate of large polyhedral cells with abundant eosinophilic granular cytoplasm and small central nuclei.

The origin of granular cell tumours is not completely understood. They were originally thought to stem from striated muscle cells, macrophages or undifferentiated mesenchymal cells, but now are thought to arise from neural tissue or Schwann cells. Malignant transformation is rare, but metastatic granular cell myoblastomas have been reported[2,6].

Granular cell tumours predominantly arise from the head and neck region, with a predilection for the tongue and buccal mucosa[3,4]. Tumours may be bilateral. Granular cell tumours can also uncommonly occur in internal sites e.g. muscle, lip, jaws, parotid gland, pharynx, larynx, trachea, bronchus, lung, chest wall, breast, lacrimal sac, orbit, heart, oesophagus, common bile duct, urinary bladder, spermatic cord, male urethra, perineum, anal region, vulva and ovary[5]. The sites involved are typically superficial tissues, such as the dermis and subcutis, but deep tissue such as muscle and abdominal organs may rarely be involved. Because of various sites of presentation, these tumors are documented in the literature of different specialties, including dermatology, thoracic surgery[7], dental surgery, otolaryngology, orthopaedic surgery and pathology publications.

Materials and methods

We report a case series of 9 patients with granular cell tumour seen from 1996 to 2006 in our centre. Data for this case series was obtained by the medical and histological records of the National Skin Centre, Singapore.

Case Series

Nine patients were referred to National Skin Centre, Singapore during a 10-year period from 1996 to 2006 (Table 1). Five patients were female and four were male. Patient ages were 15 to 66 years, with a mean of 37.1 years. All 9 patients presented with a primary symptom of an asymptomatic painless mass varying from a 1 year to 10 years duration, with a mean duration of 4 years. 6 of the patients were Chinese, 2 were Indian and 1 was Sri Lankan. Five tumors were in the head and neck, three were in the groin (Figure 1) or genital regions, and one was in the forearm. The tumours ranged in size from 0.3 cm (in the scrotum) to 2.5 cm (in the neck). On examination, none of the lesions had any features of malignancy which included rapid growth, large size (> 4 cm), local invasion and regional metastases. The pre-operative diagnosis was dermatofibroma in 3 patients, epidermal cyst in 5 patients, and adnexal tumour in 1 case. For 1 of the patients, there were 2 synchronous tumours present in the scrotum. Excision biopsy was performed for all patients.

Table 1. Characteristics of patients with Granular Cell Tumour

Case	Sex	Race	Age	Family Hx	No.	Site	Duration (years)	Pre-operative diagnosis	Longest diameter (cm)	Features of Malignancy	Recurrence?
1	Male	Chinese	56	nil	1	Neck	4	Epidermal Cyst	2.5	No	No
2	Female	Chinese	17	nil	1	Lip	2	Epidermal Cyst	0.8	No	No
3	Male	Chinese	52	nil	1	Neck	5	Dermatofibroma	1	No	No
4	Female	Sri Lankan	12	nil	1	Labia Majora	1	Epidermal cyst	1	No	No
5	Female	Chinese	35	nil	1	Lip	3	Epidermal cyst	2	No	No
6	Female	Chinese	59	nil	1	Groin	6	Adnexal tumour	3.5	No	No
7	Male	Indian	22	nil	2	Scrotum and Pubis	10	Epidermal cyst	0.3 (scrotum), 0.4 (pubis)	No	No
8	Female	Chinese	66	nil	1	Nose	3	Dermatofibroma	0.3	No	No
9	Male	Indian	15	nil	1	Forearm	2	Dermatofibroma	1.5	No	No

Figure 1. Granular Cell Tumour in the Groin. A punch biopsy was carried out which confirmed the diagnosis. The patient opted for excision of the lesion

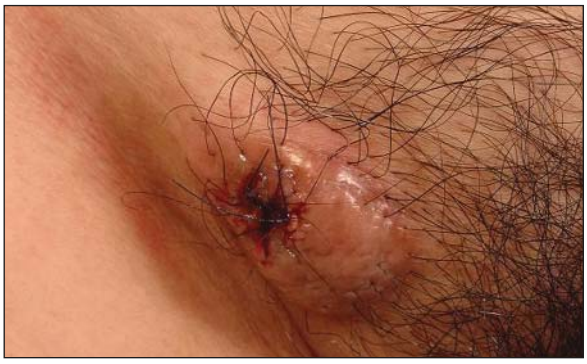
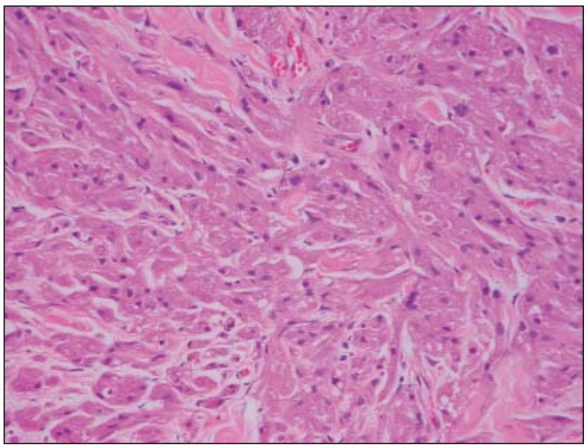


Figure 2. Granular cell tumour. A diffuse infiltrate of large polyhedral cells with abundant eosinophilic granular cytoplasm and small central nuclei is seen



All patient information was obtained from their computerized and written medical records, and telephone contact was made with all the patients to determine whether they had any evidence of recurrence. All patients contacted over the phone were asymptomatic at the time of the interview.

Biopsy material was fixed in 10% neutral buffered formalin, embedded in paraffin, and cut into 5-µm sections. All interpretations of fine biopsy histologic samples were performed by experienced pathologists, and final pathologic diagnoses were made by histologic examination of hematoxylin and eosin stained specimens. The diagnosis was based on the presence of sheets of polygonal cells with small central pyknotic nuclei and abundant granular eosinophilic cytoplasm (Figure 2). These eosinophilic granules were periodic acid-Schiff positive and diastase resistant. S100 staining was positive in all cases. Epidermal acanthosis was noted especially in the more superficial tumours. The tumour cells were arranged in lobules or trabeculae in the mid-dermis. Nuclear pleomorphism, multinucleation, and evidence of increased mitoses were not noted in any of the biopsy specimens.

Discussion

Granular cell tumors can be found in several sites, which include the upper respiratory and gastrointestinal tract, skin and viscera[3,4]. The majority of granular cell tumours are found in the head, neck, trunk and extremities. Genital and multifocal lesions are rare.

In our series, all of the lesions were unifocal except one patient who had two synchronous granular cell tumours of the scrotum. Only a few cases of scrotal granular tumours have been reported in the literature[8,9,10,11,12] and only one out of the five reports featured a second synchronous tumour involving an anatomically adjacent site (the penis)[9]. The rest of the tumours were solitary.

The tumour cells almost always stain positively for S-100 protein, neuron-specific enolase and NK1-C3, reflecting their Schwann cell origin[13-14]. Positivity with stains for myelin-associated P0 and P2 proteins, myelin basic protein and Leu-7 is variable. These stains may also be positive in a variety of benign and malignant neurogenic tumours, including neurofibroma, neurofibrosarcoma, neurilemmoma and malignant spindle cell sarcoma[15]. Granular cells are non-immunoreactive for epithelial, muscle and endotheilial cell markers.

Rarely, granular cell tumours may be malignant. Approximately 0.5% to 2% of granular cell tumours are malignant[4,6]. Fewer than 40 cases have been reported in the literature[6,16]. These occur more often in deep-seated regions in adults, with the lesions usually larger (4-15 cm) and locally destructive. They differ from their benign counterparts in that histologically, they have increased nuclear and cellular pleomorphism, increased mitotic figures, necrosis, wide cellular sheets, and spindle cell structure[16-18]. Clinically, decreased rates of survival are correlated with tumour diameter greater than 4 cm, female gender, presence in the lower extremities, intramuscular location, rapid recent growth, advanced patient age, local recurrence, metastases, Ki67 values greater than 10%, and p53 immunoreactivity[16-18].

In benign lesions, recurrence rates are 2-8%, even when the resection margins are deemed free of tumour infiltration[19]. The rates can rise to 21-50% when the margins are positive for tumour involvement. Malignant lesions behave aggressively and are difficult to eradicate with surgery. Metastases are usually detected within 2 years with 40% 3-year survival[16,19]. Thus, all lesions should ideally undergo a wide excision with regular follow-up and examination for recurrence. However, all the cases in our series only underwent an excision biopsy, as granular cell tumours are frequently diagnosed as a benign soft tissue condition (e.g. epidermal cyst, dermatofibroma) based on their appearance.

Granular cell tumour is a rare benign tumour. The presence of two synchronous granular cell tumours of the scrotum is a rare finding. Because of the risk of recurrence and the low risk of malignant transformation, patients should ideally be followed up regularly with serial physical examinations.

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