Pyoderma Gangrenosum in Asian Population: A retrospective case series of clinical features and diagnostic challenges

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Abstract

Introduction:
Pyoderma Gangrenosum (PG) is a rare neutrophillic dermatosis characterised by rapidly progressive and painful cutaneous ulceration. PG is commonly seen in association with various malignant and autoimmune conditions, such as haematological malignancies, inflammatory bowel disease (IBD) and inflammatory arthritis. Diagnosis of PG is often delayed and the management is challenging.

Objective:
To describe the epidemiology, co-morbidities and diagnosis challenges of PG in a retrospective hospital-based study

Methodology:
A retrospective review of all PG cases diagnosed over 10-year duration between 1 January 2005 and 31 December 2014 at the Singapore General Hospital was conducted. Patient data were retrieved from computer-coded record and medical notes. Inclusion of cases were based on the modified criteria published by Philipp et al. [5] Details on patient demographics, comorbidities, clinical characteristics and outcomes were collected.

Results:
20 cases of PG were identified, including 11 female and 9 male with a mean age of 56 (26 – 80). The most common subtype of PG was ulcerative PG (n= 16; (80.0%)) and associated diseases include hematological disorders (n=8; (40.0%), inflammatory arthritis (n=4; (20.0%)), inflammatory bowel diseases (n=2; (10.0%)) and others (n= 3; (15.0%)). 70% of patients had more than 1 lesion and lesions were predominantly located on the limbs. The mean diagnostic delay was 11 weeks and 7 patients had surgical interventions prior to the establishment of PG diagnosis (surgical debridement (n=7) and autologous skin grafting (n=1)). The one-year-mortality rate was 27.8%.

Conclusion:
PG is rare in the Asian population. Our series demonstrated a strong association of PG with haematological disorders which may explain for the high mortality rate in our cohort. The association of PG with IBD was, however, less profound. PG is associated with long diagnostic delay, frequent misdiagnosis, unnecessary surgical interventions and prolonged inpatient admissions. A better understanding of the epidemiology and presentation of PG in the Asian population is important to aid clinicians in making prompt diagnosis and commencing effective treatment for the disease.

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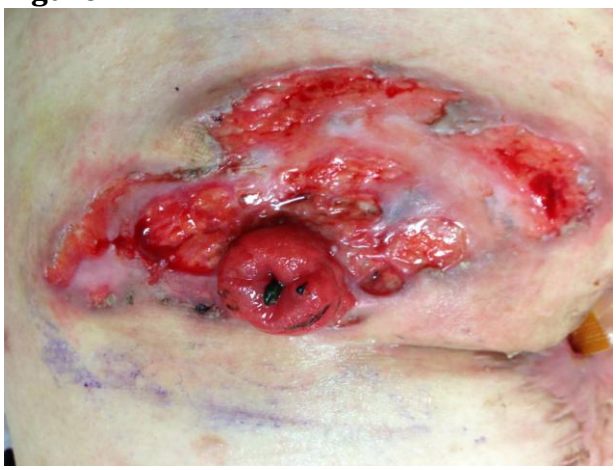
Introduction:

Pyoderma Gangrenosum (PG) is a rare neutrophillic dermatosis that is commonly seen in association with various malignant and autoimmune conditions such as haematological malignancies, inflammatory bowel diseases and inflammatory arthritis. Although classical PG often presents with a distinctive lesion that is characterized by an inflammatory ulcer with purulent undermined border, the presentation may mimic other conditions such as cutaneous infections, cutaneous vasculitis and other non-inflammatory ulcers, often resulting in delayed diagnosis, inappropriate interventions and poor patient outcomes. [3] The incidence of PG and its associations varies in different populations. To date, the literature of PG in Asian populations remains limited. [9-11] The objective of our study is to describe the epidemiology and clinical features of PG among the Asian population as well as to highlight the diagnostic challenges of PG in a hospital setting.

Figure 1



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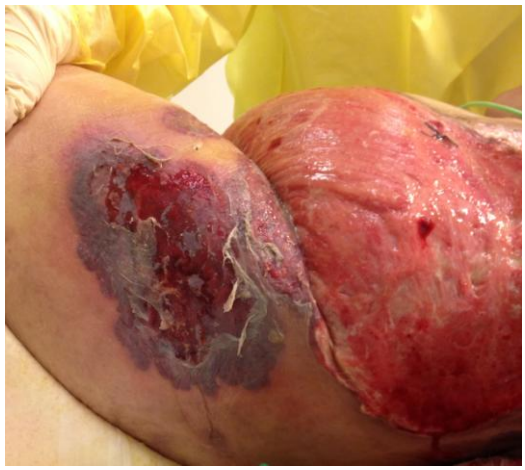

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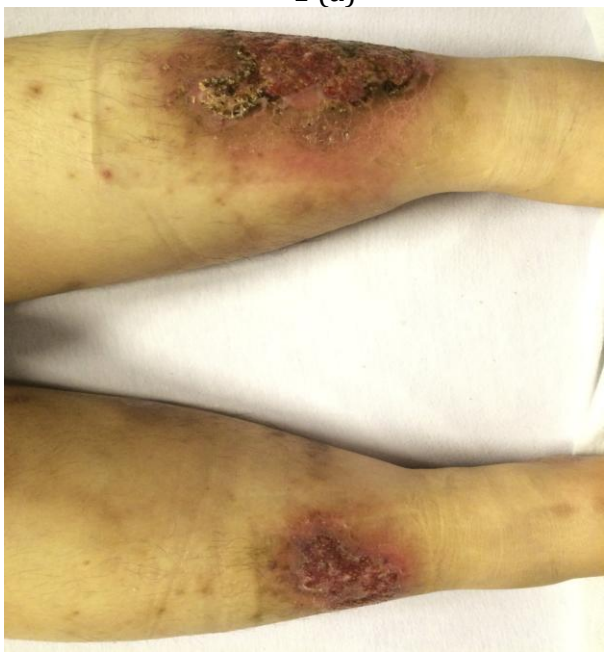

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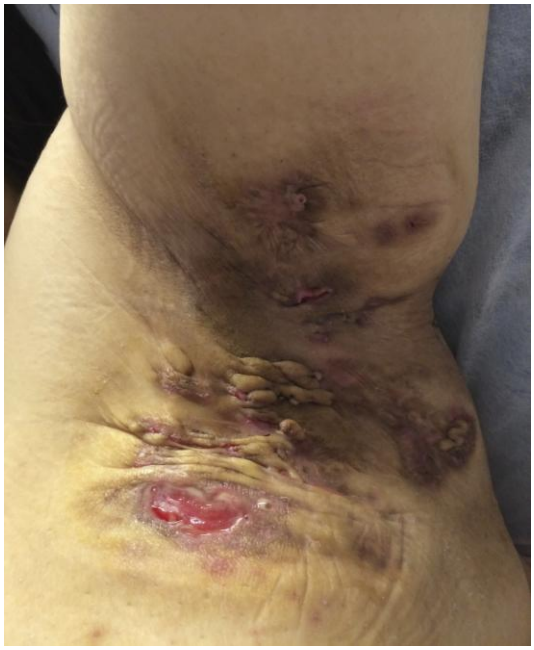

1 (d)

Figure 1 (a) Peristomal PG in a patient with Crohn's disease
Figure 1 (b) Extension of bullous PG at the margins of surgical debridement wounds.
Figure 1 (c) Bilateral classical PG on a patient with Pyoderma gangrenosum, Acne, and suppurative hidradenitis syndrome (PASH).
Figure 1 (d) Associated severe hidradenitis suppurativa in patient with PASH

Materials and methods:

A retrospective review of PG cases diagnosed over 10-year duration between 1 January 2005 and 31 December 2014 at the Dermatology Department of Singapore General Hospital (SGH) was conducted. Patient data were obtained from computer-coded records and medical notes. The modified criteria for PG (Table 1), published by Philipp et al, was used to diagnose PG with at least one from the main criteria and at least two from the additional criteria. Data on patient demographics, comorbidities, clinical and histology findings, treatments, patient outcomes, and characteristics of PG lesions including number, size, site and variants were collected. All patients' information was anonymised to maintain confidentiality.

Table 1 Modified diagnostic criteria for PG. [5]

I. Main criteria	Primary sterile pustule or ulcer with livid, undermined wound-border Exclusion of other relevant differential diagnoses like chronic venous/arterial leg ulcer, pyodermatitis, vasculitis
II. Additional criteria	Histology of the wound-border: neutrophilic infiltration of the dermis with signs of vasculitis and accumulation of immunglobulins and/or complement factors beside the vessels Existence of relevant, associated concomitant diseases like chronic inflammatory bowel diseases, arthropathies, haematological disorders, neoplasia, endocrine dysfunctions, metabolic syndrome Response to a systemic immunosuppressive therapy or no response to a conventional ulcer-therapy Triggering of a PG by pathergy-phenomenon Extremely painful ulcer (VAS > 4 points)

Results:

Patient Characteristics

There were a total of 20 cases of PG which fulfilled the diagnostic criteria over the study period. 19 patients were diagnosed/managed in the inpatient setting. The total number of inpatient admissions in the same period was 839, 456. The incidence of PG was estimated to be 23 per 1,000,000 as estimated from the study population. The patient demographics and disease characteristics are shown in table 1.

The most common subtype observed was classical (ulcerative) PG presenting in 17 patients (85%). Bullous (15.0%) and pustular (5.0%) variants were less common and no vegetating subtypes were seen. Pain was a predominant feature occurring in 17 patients (85.0%) and pathergy was observed in 8 (40.0%) patients. Fever and raised inflammatory markers were noted in 13 (65.0%) patients. Ulcers were noted most commonly on the lower limbs (70.0%), followed by the upper limbs (30.0%), abdomen (20.0%) and head & neck (5.0%). The average number of ulcers documented was 2.5 ± 1.6 (range 1-7) and multiple lesions were noted in 14 patients (70.0 %).

Associated Diseases and outcomes

In this case series, we included the commonly reported disease associations (inflammatory bowel disease, haematological maglinancy and inflammatory arthritis) as well as new potential associations (endocrine disorders, hepatitis, anaemia) described in the recent literatures. [4, 5] Of the 20 patients, 8 had haematological malignancy (4 Myelofibrosis, 2MDS, 2 AML), 4 had inflammatory arthritis (4 RA), 2 had inflammatory bowel disease (2 Crohn's Disease) and one had solid organ malignancy (Breast Cancer). 3 patients were reported to have hepatitis and all three patients were diagnosed with viral hepatitis. 5 patients were noted to have some form of endocrine disorders, including 3 Type 2 Diabetes Mellitus, 1 Grave's Disease and 1 Polycyctic Ovarian Syndrome. 4 patients were reported to have anaemia. Of significance, 2 of the patients with Pyoderma Gangrenosum had them as part of an autoinflammatory syndrome (PASH & PAPA syndrome). Only one patient had none of the listed comorbidities. (Table 4)

The average inpatient duration was 25 days. Four patients died during the admission and one patient died four months following discharge. All of the 5 who died had underlying haematological malignancy. The one-year-mortality was 27.8% (n=18). Data on one-year-mortality could not be identified in 2 patients at the point of data collection.

Table 2 Patient Characteristics

	Total (n = 20)
Gender Distribution	
Age at onset (years) Mean ± SD	56.2 ± 14.6
Race, n (%)	
Chinese	20 (100.0%)
Malay	-
Indian	-
Others	-
Ulcer number, Mean ± SD	2.5 ± 1.6
Two or more, n (%)	14 (70.0%)
Three or more, n (%)	7 (35.0%)
Localization, n (%)	
Lower limb	14 (70.0%)
Upper limb	6 (30.0%)
Abdominal/Peristomal	5 (25.0%)
Head and neck	1 (5.0%)
Clinical Subtype	
Classic Ulcerative	16 (80.0%)
Bullous	3(15.0%)
Pustular	1(5.0%)
Vegetans	-
Associated Clinical Findings	
Tenderness	17 (85.0%)
Fever	13 (65.0%)
Raised Inflammatory markers	13 (65.0%)
Pathergy	8 (40.0%)

Age/ Sex	Type of PG	Site	Dur. of disease (month)	Previous Diagnosis	Raised inflam. marker	Pathergy	Skin Biopsy Done	Conclusive Biopsy	Major Assoc. Disease	Assoc. Disease	Treatment	Outcome
64 F	Classical	LL	4	Infected ulcer	N	Y	Y	N	N	Anaemia	OP DB	**Improved**
60 M	Classical	LL	2	-	Y	Y	Y	N	RA	N	OP MC IFx DB	**Improved**
60 F	Classical	LL	6	-	N	N	Y	N	RA	T2DM	OP CS ETx HT	**Improved**
63 M	Bullous	LL	3	Infected ulcer	Y	Y	Y	C	MF AML	AE	OP DC THx DB	**Improved**
55 M	Bullous	UL, ABD	-	Nec. Fasciitis	Y	Y	N	NA	MF AML	Hep. B	OP DB	**Died**
63 F	Classical	UL	2	Nec. Fasciitis	N	Y	Y	N	MF	Anaemia	OP DB	**Improved**
26 F	Classical	LL	1	-	Y	N	Y	N	PASH syndrome	Anaemia, T2DM, PCOS, AE, HS	OP IFx TT	**Improved**
45 F	Classical	LL	1	Cellulitis	Y	N	N	NA	Breast CA.	N	OP	**Improved**
67 M	Classical	UL	1	Cellulitis	N	N	Y	C	AML	T2DM, Hep.B	OP TT	**Improved**
29 F	Classical	LL	3	-	N	N	Y	N	PAPA Syndrome	Grave's, Pyogenic Arthritis, AE	OP AZ TT	**Improved**
41 F	Classical	LL ABD	6	Cellulitis	Y	N	Y	C	Crohn's	N	OP AZ TT IFx	**Improved**
77 M	Classical	LL, ABD	2	-	N	N	Y	N	N	N	OP	**Improved**
61 F	Classical	LL	-	Infected Ulcer	N	Y	Y	N	MF	Anaemia	DB SG	**Died**
68 F	Classical	ABD	-	Nec. Fasciitis	Y	N	Y	C	MDS	Anaemia Azacitadine drug therapy	TS	**Died**
80 M	Bullous	UL	-	Cellulitis	Y	N	Y	N	MDS	N	N	**Died**
61 M	Classical	H&N	-	Drug Reaction	Y	Y	Y	C	AML	N	OP DB	**Died**
64 F	Classical	LL	11	Infected Ulcer	Y	Y	Y	N	RA	N	OP	**Improved**
46 M	Classical	LL	4	Infected Ulcer	N	N	Y	N	RA	N	OP	**Improved**
36 F	Classical	LL	3	-	N	N	Y	N	N	RP AE	OP	**Improved**
57 M	Pustular	UL, ABD	2	-	N	N	Y	N	Crohn's	N	OP CS	**Improved**

Table 3 Clinical profile and associated diseases.

ABD, Abdomen, AE, Acneform Eruption, AML, Acute Myeloid Leukemia, AZ, Azathioprine, CA, Cancer, CS, Ciclosporin, CTD, Connective tissue disease, DB, Debridement, H&N, Head and Neck, HT Hyperbaric Oxygen Therapy, IFx, Infliximab, LL, Lower Limb, MC, Minocycline, MDS,Myelodysplastic Syndrome, MF, Myelofibrosis, NF, Necrotizing Fasciitis, OP, Oral Prednislone, PCOS, Polycystic Ovarian Syndrome, RA, Rheumatoid Arthritis, RP Relapsing polychondritis, SG, Skin Graft, T2DM, Type 2 Diabetes Mellitus, THx, Thalidomide, Topical Steroid, TT, Topical Tacrolimus,UL, Upper Limb.

Misdiagnosis and diagnostic delay

The average diagnostic delay was 10.8 ± 18.3 (range 1-72) weeks. The diagnostic delay was defined by the duration from the date of the onset of lesion to the date of the first secondary care appointment with the dermatologist when the clinical diagnosis of PG was made. In addition, 13 patients were misdiagnosed as other conditions. Of the 13 patients, 5 patients were diagnosed as infected ulcer, 4 patients were diagnosed as cellulitis, 3 patients were diagnosed as necrotising fasciitis and 1 patient was diagnosed as drug reaction. These misdiagnoses led to 10 patients being referred for surgical opinions. 7 patients actually had surgical debridement performed, of which 5 had repeated debridements due to extension of wound as a result of pathergy. One patient had skin graft and one patient had hyperbaric oxygen therapy for the ulcer. Vacuum dressing was used in 4 patients.

Treatment

The treatment modality were summarised in table 4. 17 (85.0%) patients were initiated with systemic therapy. Of the 17 patients, all were started on high dose systemic steroids. Other immune-modulating agents, such as Ciclosporin, Azathioprine, Minocycline and Doxycycline were administered as second line therapy. 4 patients received either Ciclosporin or Azathioprine treatment and 2 patients received either Minocycline or Doxycycline. Infliximab, Thalidomide and Etanercept were used as third line therapy or in patients with very poor response to systemic steroids. 3 patients received Infliximab treatment, 1 patient received Thalidomide treatment and 1 patient received Etanercept treatment. 11 (55.0%) patients achieved disease control with steroid monotherapy, whereas 2 (10.0%) patients required dual therapy and 4 (20.0%) patients required more than 2 systemic agents. Topical Tacrolimus was the most commonly used local treatment. 4 patients had topical Tacrolimus and only one patient had topical steroids.

Table 4 Treatment modalities

Treatment	Total (n = 20) n(%)
Systemic treatment	
Steroids	17 (85.0%)
Infliximab	3 (15.0%)
Minocycline	1 (5.0%)
Doxycycline	1 (5.0%)
Ciclosporin	2 (10.0%)
Azathioprine	2 (10.0%)
Etanercept	1 (5.0%)
Thalidomide	1 (5.0%)
Tried one	11 (55.0%)
Tried two	2 (10.0%)
Tried three or more	4 (20.0%)
Local treatment	
Topical steroid	1 (5.0%)
Topical Tacrolimus	4 (20.0%)
Others	-

Discussion

Pyoderma Gangrenosum is a rare skin condition in the Asian population. Literature of PG in the Asian population is limited. [9,10,11] One case series of 18 patients on Indian population was published in 2011. [9] By far, there is no case series of PG focusing on Asian Chinese population. Singapore is a multiracial country, with its population constituted by 75% Chinese, 13% Malays, 9% Indians and 3% others. [12] The diversity of genetic make-up in the population is interesting and allow for an evaluation of the epidemiology of PG in different ethnicity with dissimilar disease prevalence. The incidences of PG were highest among the Chinese ethnicity. Of the 20 patients, all of them were Asian Chinese. No cases of PG were reported in the Malay, Indian or other immigrant community. Our case series reported a mean age of 56 with a slight female predominance. This was fairly consistent with the result published by Philipp et al, which was by far one of the largest case series. The incidence of PG was estimated to be 2.3 per 1,000,000 in the study population. Classical (ulcerative) PG was noted to be the most common type of PG in this case series. 3 cases of Bullous PG were reported, two cases were associated with myelofibrosis and one case was associated with myelodysplastic syndrome. One case of pustular PG associated with Crohn's disease was reported. In this case series, the pattern of disease associations was observed to be different from the results reported in 2 of the larger case series published recently.

Table 5 Comparison of data from different case series

	IBD, n (%)	**Haematological disorders, n (%)**	**Inflammatory Arthritis, n (%)**
Binus et al Pyoderma gangrenosum: a retrospective review of patient characteristics, comorbidities and therapy in 103 patients. Boston, USA. 2011 (n = 103)	35 (34.0%) UC: 18 CD: 17	21 (20.4%)	30 (29.1%)
Philipp et al Associated factors and comorbidities in patients with pyoderma gangrenosum in Germany: a retrospective multicentric analysis in 259 patients. 2013 (n = 259)	24 (9.3%) UC: 17 CD: 7	10 (3.9%)	27 (10.4%)
Our data (n = 20)	2 (10.0%) UC: - CD: 2	8 (40.0%)	4 (20.0%)

Our case series demonstrated a strong association of PG with haematological disorders in the Asian population. The association of PG with IBD was less profound. Both PG cases associated with IBD in this case series were Crohn's disease. None of the PG cases was associated with ulcerative colitis. This observation is consistent with the data published by Singapore Hospital records and combined data from survey of gastroenterologists in 2004. The disease prevalence of Crohn's disease is 7.2 per 100, 000 person-years and no ulcerative colitis case was reported for the study period. In North America, the incidence rate for Crohn's disease ranges from 3.1 to 14.6 cases per 100,000 person-years and from 2.2 to 14.3 cases per 100,000 person-years for ulcerative colitis. [8] The incidences of PG associated with IBD were noted to be higher in the region. In Europe, the incidence rate for Crohn's disease ranges from 0.7 to 9.8 cases per 100,000 person-years and from 1.5 to 20.3 cases per 100,000 person-years for ulcerative colitis. [8] However, the data may not be a good representation due to vast geographical and population variations in the European regions. Our case series elucidates the variability of disease associations in different population, which has been an important diagnostic clue for PG.

Our case series reported higher incidences of PG cases associated with haematological disorders. In contrast to the previous studies [13], the mortality rate reported in this case series was higher. The associated disease could be an important prognostic indicator. The prognosis of PG patients with haematological malignancy was poor with one-year-mortality of 71.4% and rapid disease progression was observed in these patients. No mortality was reported in patients with other associated disease. It was also noted that the onset of PG in 2 patients with myelofibrosis occurred concurrently with the progression to Acute Myeloid Leukemia (AML). Our case series suggest a possible correlation between the onset of PG and disease progression in haematological malignancy, which has never been reported in the literature. Prompt diagnosis of PG is essential and early systemic steroid treatment needs to be considered in these patients. In addition, patients with haematological malignancy who presented with ulcers should always prompt thorough investigation and close monitoring of the associated disease status.

Table 5 Incidence of Inflammatory Bowel Disease in different populations

		UC (n/100,000)	Crohn's (n/100,000)
Thia et al [7] Singapore Hospital records and combined data from survey of gastroenterologists 2004	Singapore	-	7.2
Loftus et al [8] Clinical epidemiology of inflammatory bowel disease: incidence, prevalence, and environmental influence. Gastroenterology 2004	Europe	1.5-20.3	0.7-9.8
	North America	2.2-14.3	3.1-14.6

In this case series, we also documented data on the new potential associations (endocrine disorders, hepatitis, anaemia) described in the recent literature. [4,5] 3 (15.0%) patients were reported to have viral hepatitis. It was also worth noticing that these patients have Hepatits B infection rather than Hepatitis C infection as described in the previous study. [4] 5 patients were noted to have some form of endocrine

disorders, 3 were diagnosed with type 2 diabetes mellitus and 4 patients were reported to have anaemia. However, the sample size was not conclusive to confirm these associations. 4 patients were noted to have concurrent acneform eruption and 2 were reported to have Hidradenitis Suppurativa. It was also worth noticing that these patients were mostly younger female. Similar presentations were previously reported in one of the PG case series from America. [14] Our study also confirms the new autoinflammatory syndrome previously described by Braun et al. [15] 2 of the patients with Pyoderma Gangrenosum had them as part of an autoinflammatory syndrome (PASH & PAPA syndrome).

PG is a challenging disease to diagnose and manage. This is even more difficult when the epidemiology of PG in the population is poorly understood. In our case series, 15 (75.0%) cases of PG were diagnosed clinically and only 5 (25.0%) patients had biopsy findings suggestive of PG. As highlighted in the previous study, [4] the pathology finding of PG is rarely conclusive. The yield of the biopsy depends largely on the timing and the site of biopsy. Clinically, the morphology of PG lesion resembled infective lesion and could be challenging to differentiate even for experienced clinicians. This case series documented the diagnostic delays and the common misdiagnosis made by clinicians. Infective causes were the most common misdiagnosis. The rate of misdiagnosis was as high as 65.0%. The average diagnostic delay was 11 weeks. This resulted in delay in treatment and significant physical and mental stress on the patients. 10 patients were referred previously for surgical opinion and 7 patients had surgical debridement performed. Of the 7 patients who had debridement, 3 did not improve and subsequently died. Prompt and accurate diagnosis of PG is crucial in preventing unnecessary procedure performed on patients and improving patient outcome. Interestingly, it was noted that short healing duration was seen in patients with minimal diagnostic delay.

By far, there is very limited number of randomised controlled trials on the treatment modalities of PG. The treatment of PG is often empirical. Systemic corticosteroids remain the most frequently used systemic treatment. [16] Oral prednisolone was noted to be the first line of treatment in this case series. 17 patients were started on high dose systemic steroids and 53% of these patients responded to high dose systemic steroids. Other immune-modulating agents, such as Ciclosporin, Azathioprine, Minocycline and Doxycycline were administered as second line therapy. 30.0% of the patients received one of these treatments. Infliximab, Thalidomide and Etanercept were used as third line therapy or in patients who had very poor response to systemic steroids. A randomized, placebo-controlled trial of Infliximab in 30 patients with PG was published in 2006. [17] It was demonstrated to be clinically effective in treating new PG and remitting PG. [17] Etanercept worked similarly as another TNF-a antagonist. Charles et al reported complete healing of 73% of ulcers in 7 PG patients with an average healing duration of 12.5 weeks. [18] Albeit the fact that these treatments were proven efficacious, many aspects needed to be put into considerations before initiating these treatments. Majority of the patients in this case series were older individuals with multiple co-morbidities, such as haematological malignancy and poor renal function. The risk of developing acute renal failure and infection in these individuals was therefore higher compared to general population. The STOP GAP trial (a multi-centred randomised controlled trial of prednisolone versus ciclosporin in PG treatment) is anticipated to provide more concrete knowledge about the treatment of PG. [19]

Statistical analysis was not conducted due to small sample size. In addition, inpatient recruitment of patients could raise the possibility of selection bias. This is minimised by following a strict set of criteria to diagnose PG. Nevertheless, this case series has a well-defined cohort and all patients were followed up closely.

Conclusions

PG is a rare cutaneous condition in the Asian population. By far, this is the largest case series from Asia, focusing on Asian Chinese population. There were few contrasting differences in the pattern of disease associations of PG in our case series compared to data from the Western literature. Our case series demonstrated a strong association of PG with haematological disorders in the Asian population. The association of PG with IBD was, however, less profound. PG is associated with long diagnostic delay, frequent misdiagnosis, prolonged inpatient admission duration and high mortality rate. A better understanding of the epidemiology of PG in the Asian population is important to aid clinicians in making prompt diagnosis and commencing effective treatment for the disease.

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