Sweet's syndrome: A review from two tertiary hospitals in Malaysia

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ABSTRACT

Introduction: Sweet's syndrome (SS) also known as acute febrile neutrophilic dermatosis, is an uncommon disease characterised by acute onset of tender, violaceous or erythematous, oedematous papules, nodules or plaques, with fever. It is classified into classic, malignancy-associated, and drug-induced subtypes.The aims of this study is to evaluate the subtypes, clinical features, laboratory profiles, and treatment of patients with SS.

Materials and methods: We did a retrospective medical record review of all patients with SS from July 2014 to July 2018 at Hospital Queen Elizabeth and Hospital Pulau Pinang, both tertiary hospitals in Malaysia.

Results: Twenty-nine patients were included. Approximately half of the patients (15) were females with a mean age of onset of 50.93 (± 11.52) years. The most common subtype was classic (62.0%) followed by malignancy-associated (31.0%) and drug-induced (6.9%). Among the patients with the classic subtype, infective-related causes (50.0%) were the most common. Among the patients with malignancy, eight had haematological malignancy and one had a solid tumour. Two-third of the malignancies were diagnosed within a year after the diagnosis of SS. Eight of our patients in Sabah had mycobacterial infections with three having concomitant haematological malignancies. Patients with malignancy-associated SS had lower mean haemoglobin (p=0.018) and mean platelet count (p=0.031). Itch was associated with the presence of pustules (p=0.038). Histopathological examination of all skin lesions showed dermal neutrophilic infiltrates and 25 (86.2%) of them had papillary dermal oedema. The study was limited by its retrospective design. The sample size was small likely due to the uncommon occurrence of this condition.

Conclusion: SS is an uncommon dermatosis with distinctive clinical and histopathological features. Screening for underlying malignancy is essential especially for those who present with anaemia, thrombocytopenia, and pathergy phenomenon. Mycobacterial infection should be considered in this region due to high tuberculosis burden.

KEYWORDS:
Sweet's syndrome, acute febrile neutrophilic dermatosis, malignancy-associated, mycobacterial infection, paraneoplastic

INTRODUCTION

Sweet's syndrome (SS), also known as acute febrile neutrophilic dermatosis, is an uncommon disease that was first described by Dr Robert Douglas Sweet in 1964. SS is characterized by acute onset of tender, violaceous or erythematous, edematous papules, nodules, or plaques with predilection for the head, neck and upper extremities. These skin eruptions are often accompanied by fever. It is associated with neutrophilia and may have systemic involvement.[1] Histologically, the distinctive feature is the presence of neutrophilic infiltrate in the upper dermis and papillary dermal oedema. The first diagnostic criteria for SS was proposed by Su and Liu in 1986, which was then modified by von den Driesch in 1994 (Table I).[2] Walker and Cohen proposed the criteria for drug-induced SS in 1996.[1]

SS is classified into three subtypes – Classical, malignancy-associated, and drug-induced. Current literature reported that classical SS is the most common subtype. Classical SS may be associated with infection, connective tissue disease, pregnancy, inflammatory bowel disease, or idiopathic.[1] This is followed by malignancy-related SS which accounts for about a quarter of cases, with 85% related to haematological malignancy, with the most common being acute myelogenous leukemia.[3] The remaining 15% is related to solid tumours which include breast adenocarcinoma, gastrointestinal, or genitourinary carcinoma.[1] The association of SS with systemic diseases needs to be investigated as it may signify an undiagnosed malignancy or a relapse of a previously treated malignancy. Most patients with malignancy-associated SS were diagnosed with the malignancy prior to onset of SS.[4] For drug-induced SS, the most frequently associated drug is granulocyte-colony stimulating factor (G-CSF).[1]

Although the treatment is straightforward, the diagnosis may not be. There are broad differential diagnoses which include infections, reactive erythema, vasculitis, and neoplasms.[5,6] A study published in The Hand Surgery Journal reported that almost half of their Sweet's syndrome cases were referred as non-healing wound and that one of the patient had four previous surgeries to treat the condition.[7]

This review aimed to evaluate the subtypes, clinical features, laboratory profiles, and treatment of patients with SS presenting to Hospital Queen Elizabeth and Hospital Pulau Pinang.

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MATERIALS AND METHODS

We performed a retrospective medical record review of all patients with SS at Hospital Queen Elizabeth and Hospital Pulau Pinang from July 2014 to July 2018. The diagnosis of SS was made by the treating dermatologists, with the criteria established by Su and Lui and revised by von den Driesch[2] (Table I). Drug-induced SS was diagnosed using the diagnostic criteria proposed by Cohen et al.[1] Approval from the Medical Research & Ethics Committee (MREC), Ministry of Health Malaysia was obtained prior to commencement of the study.

Data collection

Demographic data, clinical presentations, lesion morphology and distribution, subtypes, laboratory and histopathological findings, treatment, and outcomes were extracted using a structured data collection form.

Statistical analysis

All data were analyzed using SPSS version 22.0. Parametric data were expressed as mean ± standard deviation (SD). Non-parametric data were expressed as median and interquartile range. Descriptive statistics were provided for the numerical and categorical variables using mean ± SD and percentage distribution where appropriate. For analysis of numerical variables between subgroups, Mann–Whitney test or independent t-test was used. For analysis of nominal variables between subgroups, Chi-square test or Fisher exact test was used. p value < 0.05 was considered statistically significant.

RESULTS

Clinical characteristics

A total of 29 patients were included. There were 14 (48.3%) males and 15 (51.7%) females. The mean age was 50.93 (± 11.52) years (range 27-70 years). Of the 29 patients, 11 (37.9%) were indigenous group of Sabah, eight (27.6%) were Chinese, seven (24.1%) were Malays, and one (3.4%) was an Indonesian. Majority of the patients (65.5%) had documented fever associated with skin lesions. The skin lesions were described as erythematous or violaceous plaques (100.0%) (Figure 1), pseudo-vesicles (48.3%) (Figure 2), papules (37.9%), nodules (34.5%), or pustules (24.1%). More than 90% of the patients had upper limbs involvement. The lesions were reported to be infiltrated (79.3%), tender (65.5%), and had associated pruritus (24.1%). Pruritus was associated with the presence of pustules (p=0.038), which was reported in four patients. Fifteen patients were checked for pathergy phenomenon, and it was present in 6 (40%) patients with five of them in the malignancy subgroup.

Subtypes of SS

The most common subtype was the classical type (18 cases, 62.1%) which was subclassified into infection-related (9 cases), idiopathic (8 cases), and pregnancy (1 case). Of those patients with infections, two had respiratory infection and gastrointestinal infection, respectively, three had mycobacterium tuberculosis (MTB) infection and two had non-tuberculous mycobacterial (NTM) infection. This was followed by the malignancy subtype (9 patients, 31.0%) with eight patients with hematological malignancy and one patient with a solid tumour. Of those with hematological malignancy, five had acute myeloid leukemia, two had lymphoma and one had myelodysplastic syndrome. The patient with the solid tumour had nasopharyngeal cancer. Three patients were diagnosed with malignancy prior to SS while six patients were diagnosed with malignancy within a year after diagnosis of SS. Three patients with malignancy had concurrent infection with two patients having MTB infection and one with NTM infection. Two patients had drug-induced SS. The causative drug was radio-contrast and sulfamethoxazole-trimethoprim, respectively.

Of all patients, five patients had MTB infection (two with TB lymphadenitis, three with disseminated TB) and three patients had NTM infection. In the MTB group, two patients were diagnosed based on culture, another two patients based on caseating granulomatous inflammation on histopathological examination with positive Ziehl–Neelsen stains and one patient based on TB QuantiFERON. The patients in the NTM group were initially treated for MTB, however had poor response to treatment thus was empirically treated for NTM and all of them responded well to NTM treatment.

Laboratory Investigation Findings

Twenty-four (82.8%) of our patients had neutrophilia. Two patients had leukopenia, and both had malignancy-associated SS. Anaemia was present in 23 (79.3%) patients. Eighteen of 25 patients (72.0%) had elevated C-reactive protein (CRP). Erythrocyte sedimentation rate (ESR) was recorded in 20 patients and 17 (85.0%) had raised ESR.

Histopathological Findings

All skin lesions demonstrated neutrophilic dermal infiltrate. Twenty-five (86.2%) of them had papillary dermal oedema. Other cell types were also observed in the specimens namely lymphocytes (69.0%), histiocytes (69.0%), and eosinophils (31.0%). Most of the specimens had no epidermal changes (86.2%). Perivascular neutrophilic infiltration was observed in 12 specimens (41.4%) and there was leukocytoclastic vasculitis in four specimens (13.8%). Four of the patients with malignancy-associated SS in Hospital Queen Elizabeth had dermal infiltrate of histiocytoid cells of myeloid origin. These cells were positive for CD68 and myeloperoxidase and negative for CD34 and CD117, supporting the diagnosis of histiocytoid SS.

Clinicopathological Features in Patients with or without Concurrent Malignancy

A comparison between the clinicopathological features in patients with or without concurrent malignancy is shown in Table II. The mean hemoglobin level was 9.69 g/dl in those with malignancy-associated SS compared to 11.36 g/dl in the subgroups that were not associated with malignancy (p=0.018). The mean platelet count was 142.7 x 10^9/L in those with malignancy-associated SS compared to 329.7 x 10^9/L in those without malignancy (p=0.0310).

Treatment and Outcomes

The treatment and outcomes were summarized in Table III. Data on treatment response was available for 28 patients. Of these, 11 (39.2%) patients had complete response within 4 weeks, 8 (28.5%) within 8 weeks, 7 (24.1%) within 12 weeks, and the remaining 2 (6.9%) patients within 16 weeks of

Table I: Modified diagnostic criteria for Sweet's Syndrome as proposed by von den Driesch[2]

Diagnosis established with the presence of two major and two minor criteria	
Major	**Minor**
1. Abrupt onset of painful erythematous plaques and nodules 2. Histology features of a dense neutrophilic inflammatory infiltrate without leukocytoclastic vasculitis	1. Preceded by a non-specific respiratory or gastrointestinal tract infection or vaccination or associated with: • Inflammatory diseases such as chronic autoimmune disorders and infections • Hemoproliferative disorders or solid malignant tumours • Pregnancy 2. Fever > 38°C 3. Abnormal laboratory values at presentation (three of four) • Erythrocyte sedimentation rate > 20 mm/h • Elevated C-reactive protein levels • Leucocytosis > 8,000 per microlitre • Neutrophilia > 70% 4. Excellent response to treatment with systemic corticosteroids or potassium iodide

Table II: Characteristics of patients with Sweet Syndrome with or without malignancy

Characteristics	Malignancy, N (%) n = 9	No malignancy, N (%) n = 20	*p* value*
Male	4 (44)	10 (50)	1.000
Symptoms/signs			
Fever	8 (89)	11 (55)	0.107
Constitutional symptoms	7 (78)	12 (60)	0.431
Painful lesions	8 (89)	11 (55)	0.107
Pruritus	2 (22)	5 (25)	1.000
Pathergy	5 (56)†	2 (10)‡	0.035
Morphology			
Papule	4 (44)	7 (35)	0.694
Plaque	8 (89)	20 (100)	0.310
Nodule	5 (55)	5 (25)	0.205
Pseudo-vesicles	5 (55)	9 (45)	0.700
Pustule	1 (11)	6 (30)	0.382
Infiltration	9 (100)	20 (100)	0.633
Distribution			
Upper limbs	7 (78)	20 (100)	0.089
Lower limbs	3 (33)	14 (70)	0.106
Trunk	7 (78)	17 (85)	0.633
Head	6 (67)	8 (40)	0.245
Histology			
Eosinophilic infiltrate	1 (11)	8 (40)	0.201
Leukocytoclasia	5 (56)	7 (35)	0.422
Treatment			
Systemic corticosteroids	8 (89)§	18 (90)	1.000
Topical corticosteroids	8 (89)§	18 (90)	1.000
Colchicine	0 (0)§	3 (15)	0.536
Dapsone	0 (0)§	1 (5)	1.000
Duration of systemic steroids			
> 6 weeks	5 (63)§	7 (35)	0.231
Recurrence	2 (25)§	5 (25)	1.000

*Fisher-exact test; †n = 6; ‡n = 7; §n = 8

treatment. Twenty-eight (96.5%) patients achieved remission except one patient who succumbed to malignancy prior to treatment response. Median duration of follow-up was 9 months (interquartile range 15 months). There was no difference between the duration of treatment to remission between patients with or without malignancy (*p*=0.231).

Seven (24.1%) patients had recurrence of SS which were successfully treated. There was no association between leukocytoclasia (*p*=0.665) with recurrence. There was no association between the patients with malignancy or mycobacterial infection compared to patients with other subtypes in terms of recurrence of SS (p = 1.000).

DISCUSSION

The slight female preponderance[8-11] and onset at middle age[8,9,12] in our patients corroborate with previous reports. Most of the patients had fever,[9,10] erythematous or violaceous infiltrated plaques, followed by papules and pseudo-vesicles,[8,10,11,13,14] leucocytosis, neutrophilia,[8,15] anemia[16] and raised inflammatory markers,[8] in line with the previous studies. Notably, 23 (80%) patients suffered from anaemia which was much higher compared to the previous studies. This may be due to the high prevalence of anaemia among the population in Malaysia, which was reported to be 24.2% in a nationwide population survey. Factors associated with

Table III: Comparison of present study with previous studies of patients with Sweet's Syndrome

	Present Study	Nelson C,[16] USA 2017	Casarin Costa,[8] San Paulo 2017	Marcoval J,[9] Spain 2016	Amouri M,[10] Tunisia 2016
Total (n)	29	83	83	138	90
Mean age (years)	50.9	57.0	48.0	51.2	46.5
Age range	27-70		7-84	18-84	4-84
Gender (Male/Female)	14/15	42/41	15/68	66/72	15/75
Subtypes					
Classic (total)	18 (62.1%)	25 (30.1%)	43 (51.8%)	97 (70.3%)	83 (92.2%)
• Idiopathic	8	-	11	54	62
• Pregnancy	1	-	2	0	3
• Infection	9	-	24	23	14
• Autoimmune/ Inflammatory	0	-	6	20	4
Malignancy (total)	9 (31.0%)	36 (43.4%)	14 (16.9%)	35 (25.4%)	6 (6.7%)
• Haematological	8	26	5	31	5
• Solid tumour	1	10	9	4	1
Drug-induced	2 (6.9%)	22 (26.5%)	26 (31.3%)	6 (4.3%)	1 (1.1%)
Presentation					
Fever	19 (65.5%)	60 (72.3%)	27 (32.5%)	81 (58.7%)	55 (61.1%)
Painful lesions	19 (65.5%)	32 (38.6%)	26 (31.3%)	36 (26.1%)	-
Pruritus	7 (24.1%)	24 (28.9%)	-	-	-
Distribution					
Upper limbs	27 (93.1%)	60 (72.3%)	73 (88.0%)	103 (74.6%)	75 (83.3%)
Lower limbs	17 (58.6%)	58 (69.9%)	35 (42.2%)	74 (53.6%)	67 (74.4%)
Trunk	24 (82.8%)	69 (83.1%)	56 (67.5%)	73 (52.9%)	12 (13.3%)
Head	14 (48.2%)	33 (39.8%)	27 (32.5%)	41 (29.7%)	25 (27.7%)
Lab Investigations					
Neutrophilia	27 (93.1%)	-	32 (38.6%)	61 (44.2%)	74 (100.0%)*
Anaemia	23 (79.3%)	64 (77.1%)	39 (47.0%)	61 (44.2%)	7 (7.8%)
Thrombocytopenia	8 (27.6%)	43 (51.8%)	-	25 (18.1%)	-
Raised ESR	17 (85.0%)†	-	64 (77.1%)	101 (73.2%)	74 (100.0%)‡
Treatment					
Systemic steroids	26 (92.9%)‖	49 (59.0%)	75 (90.3%)	99 (71.7%)	30 (33.3%)
Topical steroids	26 (92.9%)‖	32 (38.6%)	3 (3.6%)	-	4 (4.4%)
Colchicine	3 (10.7%)‖	6 (7.2%)	1 (1.2%)	-	44 (48.9%)
Dapsone	1 (3.4%)‖	14 (16.9%)	1 (1.2%)	-	-
Others	COX-2 inhibitor 3 (10.7%) NSAIDS 2 (7.1%)	Supersaturated potassium iodide 6 (7.2%)	NSAIDS 2 (2.4%)	-	-
Recurrence	7 (24.1%)‖	-	19 (22.9%)	22 (15.9%)	26 (28.9%)
Associations with malignancy	Anaemia, thrombocytopaenia, pathergy	Anaemia, thrombocytopaenia, leukopenia, absence of arthralgia, histiocytoid and subcutaneous histopathology	Anaemia, higher ESR	Older age, anaemia, thrombocytopenia, absence of arthralgia	Vesiculobullous lesions
Association with recurrence	-	-	Leukocytoclasia	-	-

*n = 74; †n = 20; ‡n = 74; ‖n = 28
Abbreviations: COX-2, cyclooxygenase-2; NSAIDS, non-steroidal anti-inflammatory drugs; ESR, erythrocyte sedimentation rate

the risk of anaemia were females, older age, and ethnicity.[17] A comparison of the features in the present study with other studies is shown in Table III.

The pathogenesis of SS remains largely unknown. It is postulated to be due to hypersensitivity reactions to infections, neoplasms, autoimmune or inflammatory diseases, and drugs. This is further supported by rapid response to systemic corticosteroids. In addition, circulating autoantibodies, cytokines, dermal dendrocytes, human leucocyte antigen serotypes, immune complexes, and leukotactic mechanisms may be contributory factors.[1] T helper 1 (Th1) cells and inflammatory cell markers such as CD3, CD163, myeloperoxidase, metalloproteinases, and vascular endothelial growth factors were found to be in higher levels in skin lesions in SS compared to other neutrophilic dermatoses.[18] Furthermore, malignancy-associated SS is postulated to be due to overproduction or impaired regulation of inflammatory cytokines such as IL-1, IL-3, IL-6, IL-8, G-CSF, and granulocyte macrophage colony stimulating factor (GM-CSF). This is further supported by SS occurrence in patients that received G-CSF or patients with neoplasms that were capable of producing G-CSF.[1,3]

Seven patients had pruritus (24.1%) in our study. Pruritus was also reported by Rochet et al[13] in one fifth of their

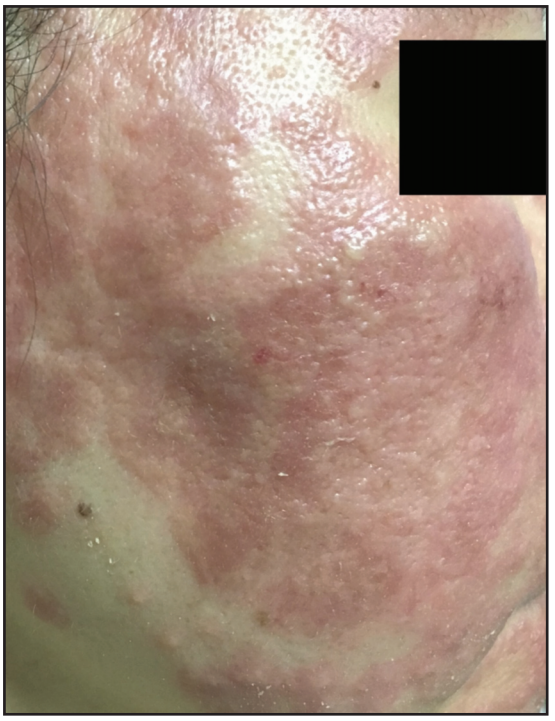

Fig. 1: Edematous, erythematous plaque on the right cheek

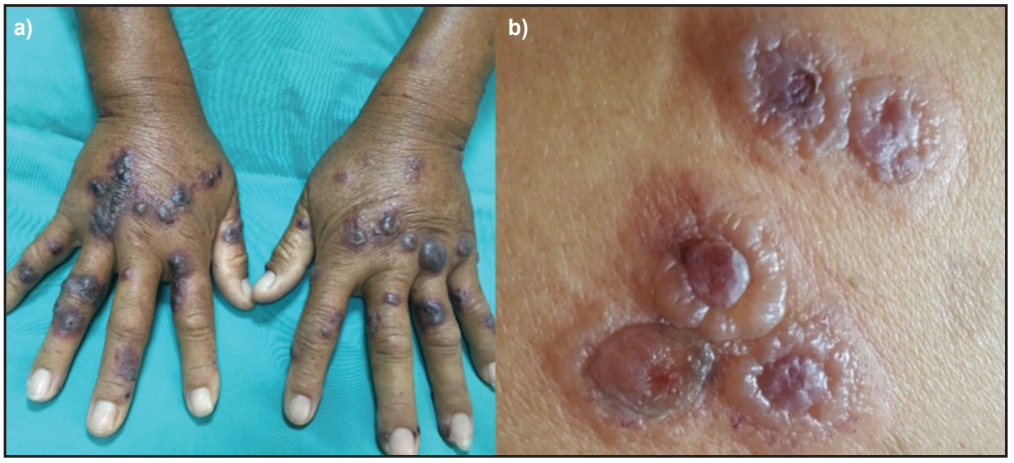

Fig. 2: a) Discrete purplish pseudo-vesicles and papules on the dorsal hands. b) Red-purplish pseudo-vesicles arranged in an annular configuration

patients (18.2%) and by Nelson et al[16] in a third of their patients. We found that pruritus was associated with pustules (p=0.038). The pruritus might be due to pruritogens secreted by the neutrophils in the pustular infiltrates. Neutrophils have been found to produce and release pruritogens such as histamine, proteases, prostaglandin E2, leukotriene B4, and S100 proteins. Hashimoto et al[19] postulated that SS is not associated with itch although it is a neutrophilic dermatosis as the neutrophilic infiltrate are deep within the dermis. However, we postulate those patients with pustules experienced itch because the pustules were more superficially located in the skin. In addition, Heath et al[20] found that apart from Th1 cells, T helper 17 (Th17) cells also play a significant role in SS. Th17 cytokines have been implicated in itch in conditions such as psoriasis and acute phase of atopic dermatitis.[21]

The main histological characteristic of SS is neutrophilic infiltrate in the dermis without evidence of leukocytoclastic vasculitis. However, several reports have described the presence of perivascular neutrophilic infiltrate with changes consistent with leukocytoclastic vasculitis with reported occurrence between 8.8 and 74.2%.[10,22,23] The presence of leukocytoclastic vasculitis was related to secondary changes as a result of massive release of toxic metabolites from activated neutrophils leading to vessel wall damage rather than primary vasculitis.[1,22,23] Furthermore, Malone et al[22] described that lesions that were present for a longer duration (median 17.5 days) were significantly associated with vasculitis compared to lesions that were present for a shorter duration (median 6 days). Additionally, direct immunofluorescence study failed to detect any immune complex or complement deposition within the vessel walls, which is commonly seen in leukocytoclastic vasculitis.[22]

In the present study, classical subtype was the most common, followed by malignancy-associated and drug-induced SS, similar to other studies.[9,10,13,24] For the classical subtype, the majority of our patients had underlying infection, which differ from the previous reports whereby idiopathic cause was more common.[9,10,24] The most common infection in our patients was mycobacterial infection. Eight (five classical SS, three malignancy-associated SS) of our patients in Hospital Queen Elizabeth were diagnosed with mycobacterial infection around the time of diagnosis of SS. Previous case series reported the association of mycobacterial infection with SS whereby majority of them had extrapulmonary or disseminated involvement. Infection with NTM was more commonly reported compared to MTB infection.[25,26] The high number of MTB infection in our patients may be explained by the fact that Sabah has the highest incidence of MTB in Malaysia.[27]

Haematological malignancy was the most common malignancy associated SS and acute myeloid leukaemia was the most frequently occurring cancer in our patients which is consistent with previous studies.[9,16] Anaemia and thrombocytopenia were associated with malignancy, in accordance with the results from the previous studies.[9,12,16]

The histiocytoid variant of SS (HSS) was first described by Requena et al[28] in 2005. The lesions in this variant demonstrate inflammatory infiltrate that resemble histiocytic mononuclear cells but are in fact immature myeloid cells. It is postulated that the immature myeloid cells are released from the bone marrow during the acute stage of the disease and are subsequently replaced by mature neutrophils as the disease evolves. These cells may be difficult to distinguish morphologically from leukemic cutis. These immature myeloid cells stain positively with myeloperoxidase (MPO) and CD68.[28] On the other hand, most of the leukemic cutis cases are immunoreactive to CD34 or CD117. However, not all cases can be distinguished reliably as some cases of hematological malignancy do not possess the markers. A summary of published cases by Bush et al.[29] reported an association of histiocytoid variant with hematological malignancy, with the most common being myelodysplastic syndrome. A review by Alegria-Lande et al.[30] did not demonstrate this association but concurred with the finding that myelodysplastic syndrome was the most common hematological malignancy encountered with the histiocytoid variant. All (4) of the patients with malignancy- associated SS in Hospital Queen Elizabeth had histiocytoid variant and were positive for MPO and CD68 and negative for CD34 and CD117. Two patients had acute myeloid leukemia, one had myelodysplastic syndrome and one had Hodgkin's lymphoma. We were not able to study the association between histiocytoid variant and malignancy as the markers were not performed on patients with other subtypes.

Studies have showed that fluorescence in situ hybridisation (FISH) analysis of the cutaneous infiltrates may aid in the differentiation between SS and leukemic cutis. Carvan et al.[31] reported that six patients with haematological malignancy associated SS had chromosomal aberrations of the bone marrow biopsy specimens. FISH analysis was performed on five of the skin biopsy samples of these patients and the same cytogenetic abnormalities were identified in four of the samples and one had equivocal results. This suggests that the patients had leukemic cutis rather than SS. In a case series by Alegria-Landa et al.,[30] seven patients with FISH analysis of bone marrow specimens underwent FISH of the cutaneous biopsy specimens. Only one patient with chronic myelogenous leukaemia had similar chromosomal aberrations in the bone marrow and cutaneous specimens. In this case, there were scattered cells with the chromosomal aberrations in the dermis which suggests the coexistence of leukemic cutis and histiocytoid SS. Both papers concurred that the use of FISH to identify leukemic cutis is only possible if appropriate probes are available for the specific cytogenetic abnormality.[30,31] Unfortunately, FISH was not performed in our patients who had histiocytoid variant as the test is not readily available.

With regard to drug-induced SS, the most frequently associated drug is G-CSF.[1] Other drugs include antibiotics (minocycline, nitrofurantoin, trimethoprim-sulfamethoxazole), antiepileptic (carbamazepine), antihypertensive (hydralazine), oral contraceptives and retinoids.[32] Our patient who was given radiocontrast for a computed tomography (CT) scan developed SS a day after the procedure. Recurrence occurred a year later when he underwent another CT scan with contrast. The association of SS and radiocontrast has been reported in two case reports and both patients had vesiculobullous presentation,[33,34] which was also seen in our patient.

LIMITATIONS

The study was limited by its retrospective design. The sample size was small likely due to the uncommon occurrence of this condition. Furthermore, patients with mild SS might have received treatment at primary care and thus were not referred to us. As FISH was not performed in patients with histiocytoid SS, leukemic cutis cannot be excluded with absolute certainty.

CONCLUSION

In summary, all patients with SS should have a comprehensive history and clinical examination to evaluate for systemic disorders. Mycobacterial infection should be considered in this region due to high TB burden. Anaemia and thrombocytopenia presage an occult malignancy.

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