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Original Research Article

Sweet's syndrome: disease spectrum from an Indian perspective

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ABSTRACT

Background: Sweet's syndrome is characterized by sudden onset of tender, erythematous papules, nodules, and plaques with a characteristic histopathology. It arises in three clinical settings- idiopathic, drug induced and malignancy induced. It has several clinical and histopathologic variants. Newer entities have been recently described in literature, thereby, emphasizing the need for continuous research. So, this study was conducted to add to scant data published in Indian literature with respect to this uncommon disease. The aims of the study were to bring insights into this rarely seen condition with special emphasis on histopathology; to highlight association of Sweet's syndrome with other systemic diseases, and its extra-cutaneous manifestations.
Methods: A retrospective analysis of medical records from January 2013 to February 2017 of patients with Sweet's syndrome was done in our dermatology department in a tertiary care hospital.
Results: Out of total 13 patients, 6 (46%) were males and 7 (54%) were females. The age of patients ranged from 33 to 82 years. Five (39%) had idiopathic Sweet's syndrome, while 8 (61%) had non-idiopathic Sweet's syndrome, out of which three were associated with autoimmune diseases (ulcerative colitis, interstitial lung disease and crohn's disease in 1 patient each), 3 cases were associated with malignancy (chronic neutrophilic leukemia, chronic myeloid leukemia and acute myelogenous leukemia in 1 patient each) and 2 cases were linked with infection. Bullous Sweet's syndrome was seen in 2 (15%) while neutrophilic dermatosis of dorsal hands was diagnosed in 5 (39%) cases. Four patients developed uncommon extracutaneous manifestations of Sweet's syndrome. In addition to classical histopathological findings of Sweet's syndrome, one case showed presence of immature neutrophils (histiocytoid Sweet's syndrome), fibrinoid necrosis was evident in 2 (15.4%), leucocytoclasia in 6 (46.2%), RBC extravasation in 3 (23.1%) and neutrophilic infiltration into vessel wall in 3 (23.1%) patients.
Conclusions: Several unique variants were observed in the current study.

Keywords: Sweet's syndrome, Malignancy, Histiocytoid Sweet's

INTRODUCTION

Sweet's syndrome (SS) or acute febrile neutrophilic dermatoses was originally described by Robert Douglas Sweet in 1964.[1] It is characterized by fever, leucocytosis, and sudden onset of painful, erythematous papules, nodules or plaques histopathologically characterized by a dense dermal infiltrate of neutrophils with prominent papillary dermal oedema sometimes severe enough to produce subepidermal vesiculation or bullae. This condition is highly responsive to corticosteroids.[2] There are various clinical subtypes of SS which include classical or idiopathic, respiratory or gastrointestinal tract infection related, drug induced, autoimmune disease

associated, malignancy associated, and pregnancy associated.[2,3] Sweet's syndrome may be related with both solid organ tumors and hematological malignancies.[3] Many new variants have recently been described in the literature including neutrophilic dermatosis of dorsal hands (NDDH), neutrophilic panniculitis, histiocytoid SS, SS associated leukemia cutis, and necrotizing SS.[4] Also, newer concepts related to various aspects of SS such as variation in inflammatory infiltrate, vascular changes, extracutaneous involvement, and new drugs associated with SS have been recently introduced in the literature.[5] This highlights the need of continuous research in SS. We, hereby, describe a series of 13 cases of SS and review their clinical presentation, histopathological features especially vasculitic component, response to treatment, associations and course of disease.

METHODS

A retrospective analysis of SS cases was done from January 2013 to February 2017 in our dermatology department in a tertiary care hospital in North India. The diagnosis of SS was made on the basis of abrupt onset of erythematous tender lesions and dense neutrophilic dermal infiltration on histopathology with rapid dramatic response to systemic corticosteroids. Medical and histopathological records were retrieved. Data of all patients including age, gender, duration, affected sites, morphology of lesions, extracutaneous manifestations, co-morbidities, underlying cause, and investigations such as complete hemogram, peripheral blood film, liver function tests, renal function tests, erythrocyte sedimentation rate, C-reactive protein, viral markers, urinalysis, ANA profile, skin biopsy, culture studies, radiological and bone marrow studies wherever performed was gathered. Details of histopathology findings were gathered in the form of epidermal and dermal inflammatory infiltration, composition of infiltrate, dermal vessel changes, subcutaneous tissue involvement, and immunofluorescence and immunohistochemistry wherever indicated. Clinical subtype and response to therapy was noted in every patient. Cases lacking any of these data were excluded from the study. Patients fulfilling all of these requirements made up a total of 13 cases.

Two out of these cases have been already published as individual case reports.[12,13]

RESULTS

Clinical details

The study included 13 patients, of whom 6 (46%) were males and 7 (54%) were females. The age of patients at the time of presentation ranged from 33 to 82 years (mean of 54.5 years). Majority of patients (77%) were aged ≥50 years. The duration of lesions before presenting to hospital ranged from 1 day to 1½ year with majority of patients seeking medical advice (72%) within 10 days of onset of lesions. Only two patients had history of prior recurrent episodes of lesions prior to presentation. Most of the patients had lesions consisting of tender erythematous to violaceous papules and plaques (Figure 1). The usual sites of involvement were upper limbs, lower limbs, and upper trunk. Five patients (39%) had lesions confined to dorsae of hands (NDDH) (Figure 2). Face was affected in only four patients (31%). Thighs were involved in 3 cases (23%). Constitutional symptoms such as fever, malaise, myalgias etc. were complained by 7 (54%) patients. Ocular manifestations were seen in the form of conjunctival congestion in one patient and another patient had uveitis. Extracutaneous features were seen in 4 (31%) cases, of which one patient had joint pains, another was having pulmonary manifestations in the form of cough and dyspnea with left sided pleural effusion, third patient developed submandibular lymphadenopathy with joint pains, and fourth suffered from uveitis. One patient was positive for Hepatitis C virus (HCV). Some of the patients had co-morbid ailments in the form of hypertension (3 patients), diabetes mellitus (5 cases), and bronchial asthma (1 patient). One female patient had ovarian cyst with hydrosalpinx. Erythema nodosum was associated in one case. The details of patient characteristics are depicted in Table 1.

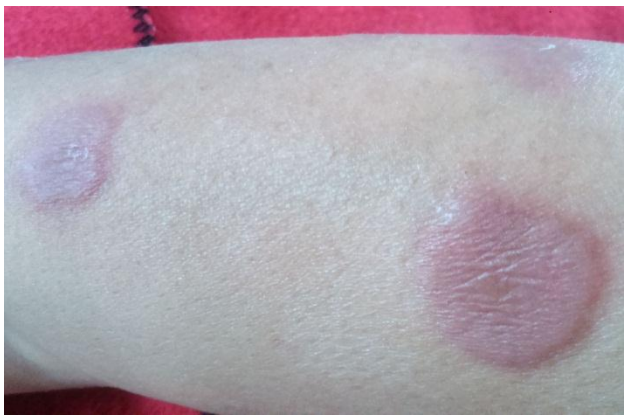

Figure 1: Well defined erythematous plaques on forearm.

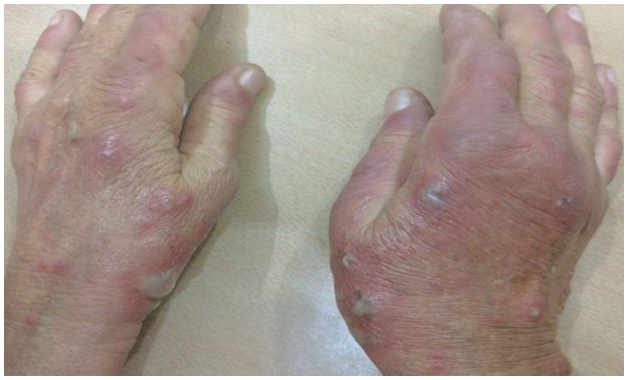

Figure 2: Multiple coalescing erythematous boggy plaques and few pustules over dorsum of hands, and fingers of neutrophilic dermatosis of dorsal hands (patient no 10).

Table 1: Clinical characteristics of patients with Sweet's syndrome.

S. No	Age/ Sex	Duration	Sites	Underlying disorder	Extracutaneous involvement	Final diagnosis	Clinical outcome
1	50/M	3 days	Hands, fingers	Erythema nodosum	-	NDDH	Clinical remission
2	33/M	3 weeks	Face, upper & lower limbs, Hands, Feet	Chronic neutrophilic leukemia	Conjunctival congestion, HSM	Paraneoplastic	Died after 1 year of diagnosis
3	82/F	1 day	Back, Arms	-	Cough, dyspnea, pleural effusion	Bullous SS with pulmonary involvement	Died after 1 year of diagnosis
4	65/M	8 days	Hands, Fingers	-	-	NDDH	Clinical remission
5	45/F	1 year	Upper limbs, Trunk	Ulcerative colitis	-	Autoimmune associated	Clinical remission
6	50/F	1½ years	Face, Upper & lower limbs, Trunk	-	Uveitis	Idiopathic	Clinical remission
7	51/F	7 days	Face, Upper Limbs	Crohn's disease	Submandibular lymphadenopathy, Joint pains	Autoimmune associated	Clinical remission
8	55/M	2 days	Back, Chest, Arms	Chronic myeloid leukemia (received nilotinib)	-	Paraneoplastic	Died due to treatment resistant leukemia
9	38/F	10 days	Hands, Face	Hepatitis C virus positive	Joint pains	NDDH, infection associated	Clinical remission
10	65/F	3 days	Hands, ears, elbows	Interstitial lung disease (Scl70 +ve)	-	NDDH and Autoimmune associated	Clinical remission
11	66/M	2 days	Forearms, Back	Acute myelogenous leukemia	-	Paraneoplastic (Histiocytoid SS)	Clinical remission
12	55/F	15 days	Hands, Feet	-	-	NDDH	Clinical remission
13	80/M	2 days	Right forearm, Arm, thigh, lower abdomen	-	-	Bullous SS, infection associated	Lost to followup

Out of the 13 patients, 5 (39%) had idiopathic SS, while 3 (23%) had paraneoplastic SS. Three were associated with autoimmune disease (ulcerative colitis in one, interstitial lung disease in one and Crohn's disease in one), two cases were linked with infections (HCV-1 patient and UTI-1 patient). The clinical variants are shown in Table 2.

Table 2: Clinical variants of Sweet's syndrome.

Variants	Sub-types	n	%
Idiopathic/classic		5	39
Non-classical	Malignancy associated	3	23
	Autoimmune associated	3	23
	Infection associated	2	15
	Drug induced	0	0
	Bullous SS	2	15
	NDDH	5	39

Neutrophilic dermatosis of the dorsal hands

Five (39%) patients had lesions confined to hands. Females (3) outnumbered males (2) among cases of NDDH (Figure 2). Though lesions were predominantly located on hands in these cases, few lesions were also evident on other parts of the body including feet, elbows, and ears. Two patients had exclusive involvement of hands only. Two patients presented with typical lesions of SS over face and retroauricular area, two with bullous lesions, and one patient developed gangrene of bilateral feet. Histopathologically, all cases showed classic neutrophilic dermal infiltrate. In addition, vasculitis was observed in 3 patients. Subcutaneous tissue infiltration was seen in one case of NDDH.

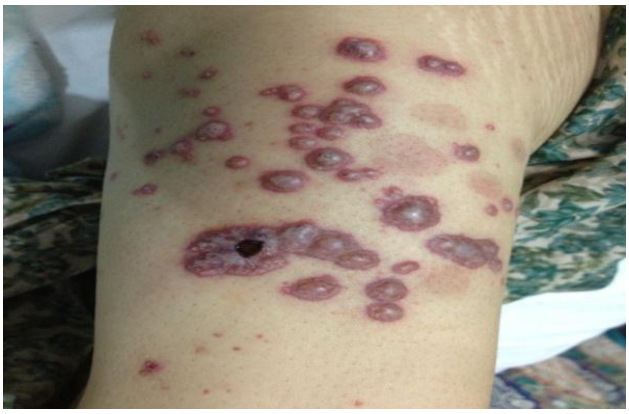

Figure 3: Multiple bullous lesions of Sweets syndrome on forearm (patient no 3).

Bullous Sweet's syndrome

Two (15%) patients presented with lesions predominantly consisting of bullae (Figure 3). Of these, one patient was also suffering from hypertension and diabetes mellitus, and the other had hypertension, bronchial asthma, benign prostate hypertrophy and urinary tract infection. One had bullous SS along with pulmonary manifestations in the form of pleural effusion and cough. Both the cases had dermal neutrophilic infiltration on microscopic examination. In addition, one showed neutrophilic infiltration within the vessel wall and subcutaneous tissue. Direct immunofluorescence of skin biopsy was negative for immunoreactants in both of our patients.

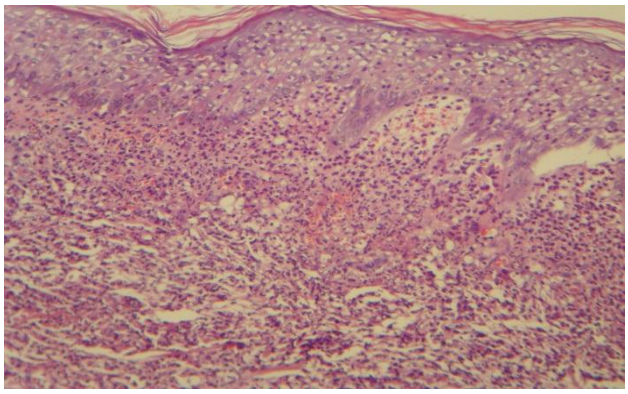

Figure 4: Dense neutrophilic infiltrate in the upper dermis and neutrophils infiltrating the epidermis (H and E; 200X).

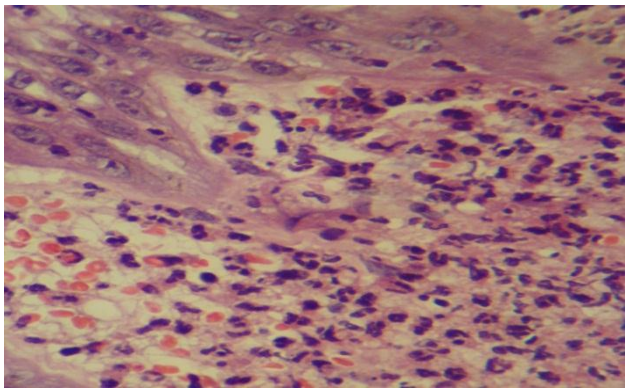

Figure 5: Dense dermal neutrophilic infiltrate in dermis with extravasation of erythrocytes (H and E; 400X).

Malignancy associated SS

Three (23%) had paraneoplastic SS (chronic neutrophilic leukemia in one, chronic myelogenous leukemia in blast crisis in one, acute myelogenous leukemia in one). Two patients with paraneoplastic SS were known to have malignancy prior to onset of SS while one case developed SS as the presenting symptom of CNL. Patient with CML was receiving Nilotinib for four months prior to the onset of SS, but causal association of Nilotinib with SS could not be definitely established due to retrospective nature of the study. Skin biopsies showed infiltration of neutrophils in the dermis in all of these cases. In addition, the patient with CNL had subcutaneous neutrophilic inflammatory infiltrate. Of these, two patients (CML: treatment resistant disease and CNL: progressive disease) died due to the underlying malignancy.

Laboratory findings

Seven (54%) patients were found to be anaemic, they had either malignancy or inflammatory bowel disease. Leucocytosis was observed in all the patients except for one patient with CML in blast crisis (92%). Neutrophilia was seen in 77% (10) patients. Myelocytes and metamyelocytes were present in peripheral blood film of one patient with chronic neutrophilic leukemia. Thrombocytopenia was noted in 3 (23%) patients. Acute inflammatory mediators such as ESR and CRP were elevated in all the patients. One patient had proteinuria. Three patients had positive ANA. One patient was positive for Scl 70 and CENP B was borderline positive in one case. The patient with chronic neutrophilic leukemia had raised LDH (lactate dehydrogenase) and CT abdomen showed marked splenomegaly with peripheral hypodense non enhancing areas suggestive of infarcts, bone marrow aspiration revealed hypercellular marrow with myeloid hyperplasia, M:E ratio 8:1, normoblastic erythroid maturation. Chronic myeloid leukemia was excluded by a negative BCR/ABL gene translocation and JAK2 gene mutation (Onquest Laboratory).

Histopathological features

Refer to Table 3 for detailed histopathological features.

Table 3: Histopathological features of Sweet's syndrome.

Histopathological findings		n	%
Epidermal changes	Spongiosis	6	46.2
	Exocytosis	7	53.8
Dermal infiltrate	Neutrophils	13	100
	Immature neutrophils	1	7.7
Dermal oedema		7	53.8
Vasculitis	Fibrinoid necrosis	2	15.4
	Leucocytoclasia	6	46.2
	Extravasation of RBC	3	23.1
	Infiltration of vessel wall with neutrophils	3	23.1
Subcutaneous tissue infiltration with neutrophils		3	23.1

Histiocytoid Sweet's syndrome (HSS)

Immature neutrophils resembling histiocytes along with typical neutrophilic infiltration was seen in one patient with AML (Figure 6 and 7). Immunohistochemistry revealed positivity of MPO and CD68 while CD117 and CD34 were negative, thus confirming the diagnosis of Histiocytoid SS (Figure 8). The patient has been in clinical remission till date and is undergoing chemotherapy.

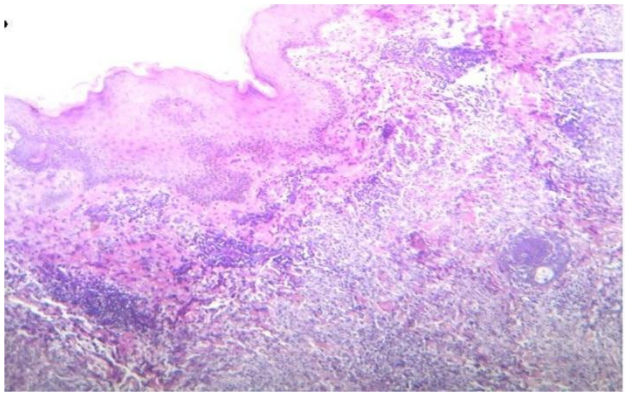

Figure 6: Dermal infiltrate of neutrophils in the upper dermis (H and E; 100X).

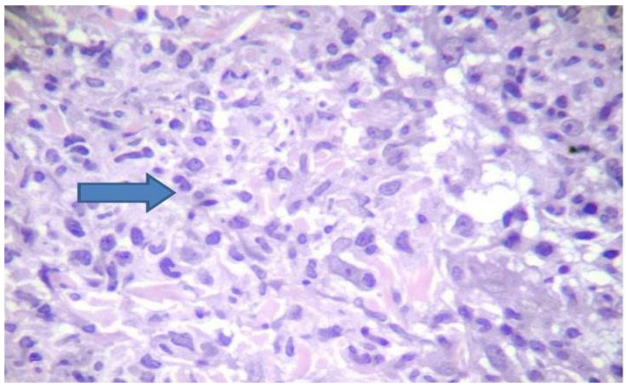

Figure 7: Infiltrate of mature neutrophils and immature neutrophils in the dermis (H and E; 400X).

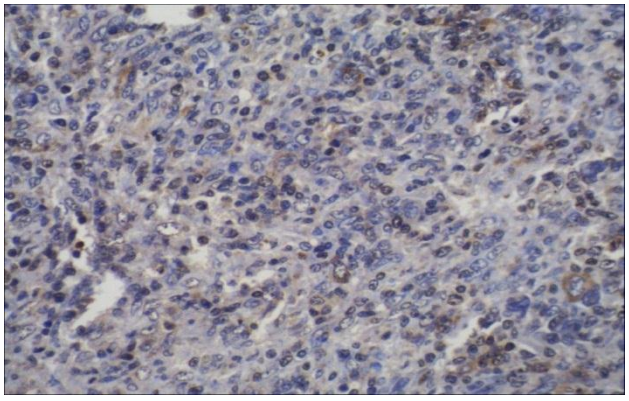

Figure 8: Dermal Infiltrate of immature neutrophils showing CD 68 positivity (IHC; 400X).

Treatment and clinical course

All the patients received tapering dose of prednisolone 1 mg/kg which led to gradual improvement in majority of patients. One patient in addition was given dapsone 100 mg/day. Three patients (one due to chronic neutrophilic leukemia, second case of treatment resistant CML, and third due to old age) died after 1 year of diagnosis. The rest of the patients have been in remission till date.

DISCUSSION

Majority of the patients in our study presented with typical clinical picture consisting of abrupt onset of tender erythematous to violaceous papules and plaques over the face, neck, trunk and proximal extremities. In a recent review by Neoh et al, from Singapore, several unusual and distinct clinical and pathological variants of Sweets syndrome have been described. The subtypes or variants as described by them were also observed in the present analysis.[7] A site-specific variant of SS, known as neutrophilic dermatosis of dorsal hands (NDDH), localized to hands was seen in 5 cases (39%). A female predominance has been described in NDDH in literature, similar finding was seen in our study. The lesions of NDDH are usually restricted to the dorsal hands; however, lesions on oral mucosa, lip, gingiva, arm, legs, back, and face have also been reported.[8]

Malignancy associated SS was seen in 23% of the patients which is comparable to study published by Abbas et al.[9] Females outnumbered males in our study which is similar to that reported by Abbas et al. None of the patients belonged to the pediatric age group which is in contrast to the frequency reported in the literature (5%).[10]

Sweet's syndrome has been reported in association with both hematologic malignancies and solid organ tumors.[11] Three of our patients had hematological malignancies, out of which one had CNL. In this case, SS preceded the diagnosis of CNL. Chronic Neutrophilic Leukemia is a very rare hematological malignancy and to the best of our knowledge, only one case has been reported in association with CNL so far in literature and our case of SS associated with CNL is the second patient published till date.[12] Although there are no well established criteria to identify risk of neoplasia in SS; however, Gille and Woodrow have recommended search for malignancy in patients presenting with features such as recurrent episodes, painful or polymorphic skin lesions, oral involvement, abnormal CBC and absence of fever or neutrophilia.[14,15]

Drug-induced SS has been seen with all-trans retinoic acid, granulocyte colony-stimulating factor, trimethoprim-sulfamethoxazole, carbamazepine, imatinib, and nilotinib.[16,17] Our patient with CML received nilotinib for 4 months prior to onset of SS. Although drug-induced SS has been described with imatinib in patients with hematological malignancies, nilotinib has rarely been reported.

Laboratory findings such as leucocytosis, neutrophilia, raised ESR and CRP were seen in more than 80% patients which is similar to studies published by other authors.[9] Seven cases showed anemia, of which 50% cases were associated with hematological malignancy.

Histopathologically, most of the patients had the typical features of SS comprising of diffuse dermal infiltration of neutrophils with dermal edema. Although mature neutrophilic infiltration is the prominent feature, abnormal or immature myeloid cells have also been reported.[2] Histiocytoid SS is a histopathological variant of SS. Histologically, HSS can present with an infiltrate consisting predominantly of mononuclear cells with large, slightly eccentric kidney-shaped or elongated nuclei with single indistinct nucleoli and slightly eosinophilic cytoplasm accompanied by numerous mature neutrophils; these cells may be mistaken as histiocytes. These cells actually represent immature granulocytes.[18,19] It was reported by Requena *et al* that HSS tends to follow a benign course with no relationship to hematopoietic diseases.[19] However, Bush and Wick have reported that 36% of patients with HSS have an association with hematological disorders (including Myelodysplastic Syndromes, myeloproliferative disorders and acute myelogenous leukemia).[20] They have analyzed 100 cases of HSS reported in the literature till 2016.[20] Our patient with AML presented with classic lesions of SS, but with unusual histopathological features of immature neutrophils admixed with typical polymorphonuclear leucocytes in the dermis. Histopathological differential diagnosis of leukemia cutis was considered which was excluded on the basis of immunohistochemisty as the cells lacked CD117 and CD34. An attempt to exclude underlying hematological disorder and long term follow up of patients with HSS is warranted in all cases.[20]

A considerable number of patients (n=8; 62%) in our study showed histological evidence of vasculitis as has been reported in other studies too.[21] Although diagnostic criteria excludes presence of vasculitis in SS, its presence should not exclude the possibility of SS as it may occur as an epiphenomenon secondary to extensive neutrophilic dermal infiltration in SS.[21]

Subcutaneous infiltration of neutrophils was seen in 3 (23.1%) cases in our study. Whether it is a separate entity or subcutaneous SS, is not well understood. Some researchers have proposed it as a distinct entity featured by lobular panniculitis histopathologically, an association with myelodysplasia, and good response to steroids.[22] But others are in favor of subcutaneous SS characterized by pathological changes in adipose tissue or involving both the dermis and subcutaneous fat.[23]

The gold standard treatment of SS is systemic corticosteroids.[24] Other first line drugs also include potassium iodide and colchicine, especially useful where corticosteroids are contraindicated or corticosteroid side effects are intolerable.

Limitations of our study include a small sample size, its retrospective nature.

CONCLUSION

In a nutshell, the epidemiological, clinical, laboratory, and histopathological findings of the study population in our study was comparable to that published in the literature, but with prominent vasculitic changes in considerable number of patients and a higher than reported incidence of NDDH among patients of SS.

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Ethical approval: The study was approved by the institutional ethics committee

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