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Sweet's Syndrome: Clinicopathological Study of 16 Cases

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Background: Sweet's syndrome is a subject of interest regarding its pathogenesis, clinical and pathological presentations because it is a dermatological condition with systemic manifestations and malignant associations.

Objective: Our aim is to study and analyze the clinical, pathological presentations and associations of Sweet's syndrome in a group of our patients.

Methods: Sixteen patients who have been diagnosed as Sweet's syndrome for the last 5 years were studied and analyzed.

Results: The majority of our patients (14 out of 16) were females. Four out of the 16 patients had hematological malignancies.

Conclusion: Sweet's syndrome should be kept in mind in any patient with acute illness and tender acral skin lesions and these patients should be investigated and followed up to rule out associated malignancy.

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Sweet's syndrome was initially described in 1964 as an acute febrile neutrophilic dermatosis by Robert Douglas Sweet[1]. It is characterized by fever, neutrophilia, multiple raised asymmetric, erythematous painful cutaneous plaques, a dense dermal neutrophilic inflammatory cell infiltrate, and a rapid response to steroid therapy. It usually occurs in middle aged women and often is preceded by an upper respiratory tract infection but rarely, it can occur in men and children[2-4]. Additional associated features include arthritis and arthralgia, conjunctivits and episcleritis, proteinuria .and rarely oral ulceration[5,6] .The skin lesions are usually expulsive tender with acral location (extremities and head neck) and if untreated heal within one to three months without scarring, but residual post-inflammatory hyperpigmentation may remain[3,7]. Malignancy has been reported in 15% of patients with Sweet's syndrome[3].

METHODS

All patients diagnosed as Sweet's syndrome at King Hussein Medical Center through our dermatology clinic for the last 5 years, were included in this study. A total number of 16 patients were included; 14 females and 2 males with age range

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from 20 to 75 years. In all patients, the clinical diagnosis was proved by a skin biopsy using the wedge incisional method. The medical files and skin biopsy slides for all patients were retrieved, reviewed and analysed. Hemotoxilyn and Eosin stain was used as a routine stain for skin biopsy sections and Gram and PAS stains were used as special stains to rule out the possibility of infections.

RESULTS

The vast majority of patients in our study were females, 14 female patients with age range from 20 to 75 years old and 2 male patients with ages of 30 and 55 years. In four patients out of the sixteen in this study, there was an associated hematological malignancy, three of them had acute myelogenous leukemia and one has had non-Hodgkin's lymphoma. Another patient had diabetes mellitus and three patients had non-specific upper respiratory tract infection. Fever was absent in one patient and leukocytosis was absent in two patients. Neutrophils were present histologically in the dermal inflammatory cell infiltrate of all patients and predominated in the dermal infiltrate of 14 patients. While in the other two patients mononuclear lymphoid cells were predominant. Gram stain and PAS stain were negative for bacterial and fungal infections in all cases. Fifteen patients responded very well to systemic steroids and one patient responded well too to Dapsone. Table 1 shows the results.

Table 1. **Clinicopathological results**

Case	Sex	Age (years)	Site	Associated disease	Dermal infiltrate	Leuko-cytosis	Fever
1	Female	48	Forearms Face	AML +	Neutrophils* Lymphocytes Histiocytes Eosinophils	Present	Present
2	Female	60	Legs Wrists	URTI + +	Neutrophils* Lymphocytes Eosinophils	Present	Present
3	Female	50	Palms	AML +	Neutrophils*	Present	Present
4	Female	67	Dorsum of Hands	DM + + +	Neutrophils*	Absent	Present
5	Female	53	Dorsum of Hands	---	Neutrophils*	Present	Absent
6	Female	45	Dorsum of Hands	---	Neutrophils*	Absent	Present
7	Female	52	Hands	---	Lymphocytes* Histiocytes* Neutrophils	Present	Present
8	Female	61	Hands Legs Feet	---	Neutrophils* Eosinophils*	Present	Present
9	Male	30	Hands Feet	---	Neutrophils*	Present	Present
10	Female	75	Palms	URTI + +	Neutrophils*	Present	Present

11	Female	38	Forearms	---	Lympocytes* Histiocytes* Neutrophils	Present	Present
12	Female	37	Hand	Non Hodgkin's lymphoma	Neutrophils*	Present	Present
13	Female	35	Face	---	Neutrophils*	Present	Present
14	Male	55	Hands	URTI + +	Neutrophils*	Present	Present
15	Female	56	Palms	---	Neutrophils*	Present	Present
16	Female	20	Forearms legs	AML +	Neutrophils*	Present	Present

AML+ = acute myelogenous leukemia.
URTI+ + = Non spespecific upper respiratory tract infection.
DM+++ = Diabetes mellitus.
* = *Predominant cell in the dermal infiltrate.*

DISCUSSION

Sweet's syndrome is considered to belong to the complex group of neutrophilic dermatosis and it is a well-defined entity clinically and histologically[8]. Sweet's syndrome may be associated with a number of systemic diseases and has been divided into four broad subgroups, which are as follows: Idiopathic (classic); parainflammatory including infection and autoimmune diseases; paraneoplastic including hematological malignancies and solid tumors and those associated with pregnancy[9].

Classical Sweet's syndrome is more common in middle-aged women after a non-specific infection of the respiratory or gastrointestinal tracts[1,10]. Typically the skin lesions in Sweet's syndrome are multiple, sometimes single, irregular well-defined dull red or plum-coloured, painful, tender nodules and plaques[10.11]. Most patients complain of pain or burning sensation, but no itching[10,11]. The typical sites for skin lesions are, extremities, face, neck and upper trunk[9,12]. Mucous membranes may be affected[6,12]. Extracutaneous manifestations involving the lung, liver and kidneys have also been described[9,13,14]. Histologically, Sweet's syndrome is typically characterized by upper and middermal predominantly neutrophilic inflammatory cell infiltrate containing mononuclear cells and eosinophils with endothelial swelling. Sometimes there is leukocytoclasia and extravasation of red blood cells, but usually there is no vasculitis[15]. Other histological features include epidermal hyperplasia and upper dermal edema[8]. Sometimes in the late stage mononuclear cells including lymphocytes and histiocytes may predominate, but some of these mononuclear cells could be an immature mononuclear neutrophils (promyelocytes)[8,15]. In all our patients neutrophils were present in the dermal infiltrate and predominated in 14 patients while only two patients showed predominance of mononuclear cells in the dermal infiltrate.

The diagnosis criteria proposed in 1986 have generally been accepted[16]. For the diagnosis of Sweet's syndrome, two major criteria consisting of typical skin lesions and a neutrophilic dermal infiltrate without vasculitis have to be present. In addition to that 2 of 4 minor criteria should be present: (l) preceding non-specific

respiratory or gastrointestinal infection, vaccination, hematoproliferative disease, chronic infection or autoimmune disease; (2) fever and malaise; (3) raised erythrocyte sedimentation rate, C-reactive protein, leukocytosis or neutrophilia; (4) response to systemic steroids. All patients in this study met the criteria required for a definitive diagnosis. Cases without fever or neutrophilic leukocytosis have been reported[17,18]. In one of our patient fever was absent and two others did not have neutrophilic leukocytosis.

The pathogenesis of Sweet's syndrome is still unclear, but recently it has been suggested that interlukin-1 (IL-1) might play a key role in Sweet's syndrome[19]. IL-1 possesses endogenous pyrogen activity, is chemotactic for neutrophils, induces a neutrophil leukocytosis and stimulates synthesis of prostaglandin-E2[20]. IL-l could, therefore account for many of the features of Sweet's syndrome[21].

The differential diagnosis of Sweet's syndrome includes; erythema multiforme, erythema nodosum, erythema elvatum diutinum, pyoderma gangenosum[23], neutrophilic eccrine hidradenitis, and Behcet's disease[8,15,22-25].

As mentioned earlier different associations have been reported in patients with Sweet's syndrome, including malignancies, the majority of which are hematological in approximately 15% of cases, and the most common hematological malignancy is AML (acute myelogenous leukemia)[3,26,27]. Three of our patients in this study had AML. In the majority of Sweet's syndrome patients, the diagnosis is made concurrently with or before the diagnosis of the hematological disorder[3]. In two of our patients Sweet's syndrome was diagnosed concurrently with AML and in one patient it was diagnosed before the diagnosis of Non- Hodgkin's lymphoma.

Drug-induced Sweet's syndrome is not common. Different drugs have been reported to cause drug-induced Sweet's syndrome, these include: all trans-retinoic acid, granulocyte colony-stimulating factor (G-CSF) hydralazine, nitrofurantion, minocycline, oral contraceptives, lithium, trimethoprin-sulfonamide and celecoxib[28-35].

The treatment of choice for Sweet's syndrome is systemic steroids, which produce rapid resolution in the majority of cases[1]. Dapsone, colchicine, Indomethacin, clofazimine, potassium iodide and cyclosporine have also been reported to be effective in the management of Sweet's syndrome[1,21,35,36]. In one of our patients Dapsone was used effectively.

CONCLUSION

Sweet's syndrome should be kept in mind in any patient with acute illness and tender acral skin lesions and these patients should be investigated and followed up to rule out associated malignancy.

REFERENCES

1. Sweet's RD. An Acute Febrile Neutrophilic Dermatosis. Br J Dermatol 1964;76:349-56.

2. Storer JS, Nesbitt LT Jr, Galen WK, et al. Sweet's Syndrome. Int J Dermatol 1983;22:8-12.
3. Cohen PR, Kurzrock R. Sweet's Syndrome and Malignancy. Am J Med 1987;82:1220-6.
4. Hazen PG, Kark EC, Davis BR, et al. Acute Febrile Neutrophilic Dermatosis in Children: Report of Two Cases in Male Infants. Arch Dermatol 1983;119:998-1002 .
5. Gunawardena DA, Gunawardena KA, Ratnayaka RMRS, et al. The Clinical Spectrum of Sweet's Syndrome (Acute Febrile Neutrophilic Dermatosis). A report of 18 Cases. Br J Dermatol 1975;92:363-73.
6. Kemmett D, Hunter JAA. Sweet's Syndrome. A clinicopathological review of twenty cases. J Am Acad Dermatol 1990;23:503-7.
7. Champion RH, Burton JL, Burns DA, et al. Textbook of Dermatology. Vol.3. 6th edn. Black Well Science, 1998:2192-3 .
8. Elder D, Elenitsas R, Jaworsky C, et al. Liver's Histopathology of the Skin. 8th edn. Lippencott –Ravan, 1997:204-7 & 358.
9. Driesch VP. Sweet's Syndrome (Acute Neutrophilic Dermatosis). J Am Acad Dermatol 1994;31:353-6.
10. Sitjas D, Puig L, Cuatrecases M, et al. Acute Febrile Neutropilic Dermatosis (Sweet's Syndrome). Int J Dermatol 1993;32:261-8 .
11. Greer KE, Pruitt JL, Bishop GF. Acute Febrile Neutrophilic Dermatosis (Sweet's Syndrome). Arch Dermatol 1975;111:1461-3.
12. Sommer S, Stephen M, Wilkinson WJ, et al. Sweet's Syndrome Presenting as Palmoplantar Pustulosis. J Am Acad Dermatol 2001;42:332-4.
13. Fitzgerad RL, Mcburneyei, Nestbitt LT. Sweet's Syndrome. BJM 1996;35:9-15.
14. Longo MI, Pico M, Bueno C, et al. .Sweet's Syndrome and bronchiolitis Obliterans Organizing Pneumonia. Am J MED 2001;111:80.
15. Bernard A, Akerman et al. Histologic Diagnosis of Inflammatory Skin Diseases. An Algorithmic Method Based on Pattern Analysis. 2nd edn. Williams and Wilkins A Waveriy Company, 1997:202-14, 682,740-1.
16. Siu WPD, Liu HNH. Diagnostic criteria for Sweet's Syndrome. Cutis 1986;37:167-74.
17. Sweet RD. Acute Febrile Neutrohilic Dermatosis. Br J Dermatol 1979;100:93-9.
18. Sweet RD. Further Observation on Acute Febrile Neutrophilic Dermatosis Br J Dermatol 1968;8:800-5.
19. Going JJ. Is the Pathogenesis of Sweet's Syndrome Mediated By Interleukin-I? Br J Dermatol 1987;116:282-3 .
20. Dinarello CA. Interleukin-I and the Pathogenesis of the Acute Phase Response. New Engl J Med 1984;311:1413-80.
21. Bourke JF, Berth-Jones J, Graham-Brown RAC. Sweet's Syndrome

Responding to Cyclosporin. Br J Dermatol 1992;127:36-8.
22. Muff JC, et Al. Erythema Multiforme: A critical Review of Characteristics,
Diagnostic Criteria, and Causes. J Am Acad Dermatol 1993;8:763.
23. Sheretz EF. Pyoderma Gangrenosum Versus Acute Febrile Neutrophilic Dermatosis (Sweet's Syndrome). Am J Med 1987;83:1031-4.
24. Harrist TJ, Fine JD, Berman RS, et al. Neutrophilic Dermatosis. Arch Dermatol 1982;118:263-6.
25. Arbesfeld SJ, Kurban AK. Behcets Disease. JAAD 1988;19:767-76.
26. Naz E, Mruano G, Vidaurrazage, et al. Sweet's Syndrome as Life - Threatening Dermatosis. Am J Med 2000;109:73-4.
27. Morgan KW, Callen JP. Sweet's Syndrome in Acute Myelogenous Leukemia Presenting as Periobital Cellulitis with An Infiltrate of Leukemic Cells. J Am Acad Dermatol 2001;45:590-5 .
28. Arun B, Berberia B, Azumi N, et Al. Sweet's Syndrome During Treatment With All -Trans Retinoic Acid in a Patient with Acute Promyelocytic Leukemia. Leuk Lymphoma 1998;31:613-5 .
29. Reuss-Borst MA, Muller CA, Waller HD. The Possible Role of G-CSF in the Pathogenesis of Sweet's Syndrome. Leuk Lymphoma 1994;15:261-4 .
30. Gilmour E, Chamers PJG, Rowlands DJ. Drug Induced Sweet's Syndrome (Acute Febrile Neutrophilic Dermatosis) Associated With Hydralazine. Br J Dermatol 1995;133:490-1 .
31. Retief CR, Malkinson FD. Nitrofurantoin Associated Sweet's Syndrome . Cutis 1999;63:177-9.
32. Thibault MJ, Billick RC, Srolovitz H. Minocycline-Induced Sweet's Syndrome. J Am Acad Dermatol 1992;27:801-4 .
33. Tefany FJ, Georgourask K. A neutrophilic Reaction of Sweet's Syndrome Type Associated With the Oral Contraceptive. Aust J Dermatol 1991;32; 55-9.
34. Walker DC, Chen PR. Trimethoprin -Sulfa Methoxazole -Associated Acute Febrile Neutrophilic Dermatosis; Case Report and Review of Drug -Induced Sweet's Syndrome. J Am Acad Dermatol 1996;34:918-22.
35. Fye KH, Crowley E, Berger TG, et al. Celecoxib –Induced Sweet's Syndrome. J Am Acad Dermatol 2001; 45:300-2.
36. Myatt AC, Baker DJ, Byfield DM. Sweet's Syndrome: A report on The Use of Potassium Iodide. Clin EXP Dermatol 1987;12:9-11.