

Sweet's syndrome

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Abstract

Sweet's syndrome is a neutrophilic dermatosis. It is characterized by fever, neutrophilia, tender erythematous skin lesions (papules, nodules and plaques) and a diffuse infiltrate consisting predominantly of mature neutrophils that are typically located in the upper dermis. The classical or idiopathic form of the condition usually presents in women between the age of 30 to 50 years and is preceded by an upper respiratory tract infection. Initiation of systemic corticosteroids triggers a dramatic response of both the symptoms and skin lesions; approximately one-third of patients experience recurrence of the dermatosis. In addition to streptococcal infections of the upper respiratory tract (streptococcosis) and the gastrointestinal tract (salmonellosis and yersiniosis), the dermatosis may be associated with inflammatory bowel disease (Crohn's disease and ulcerative colitis). Sweet's syndrome can also present as either a paraneoplastic syndrome (malignancy-associated form of the condition which is most commonly related to acute myelogenous leukemia) or as a medication-related disorder (drug-induced form of the condition which most commonly occurs after the patient has received treatment with granulocyte-colony stimulating factor therapy). The pathogenesis of Sweet's syndrome remains to be definitively determined; however, it has been postulated that cytokines may—directly or indirectly—have an etiologic role in the development of the dermatosis. Although systemic corticosteroids are the therapeutic gold standard, potassium iodide and colchicine are also first-line therapeutic alternatives. And, in smaller studies, indomethacin and clofazimine have also been observed to be effective for treating Sweet's syndrome.

Keywords: acute febrile neutrophilic dermatosis, arthritis, Behcet's disease, inflammatory bowel disease, cancer, carcinoma, clofazimine, colchicine, ulcerative colitis, corticosteroid, Crohn's disease, cutaneous, cyclosporin, dapsone, erythema nodosum, etanercept, fever, gastrointestinal, GCSF, Grave's disease, Hashimoto's thyroiditis, infliximab, indomethacin, myelogenous leukemia, leukocytosis, neoplasm, neutrophilia, relapsing polychondritis, potassium iodide, prednisone, pregnancy, skin rash, rheumatoid factor, sarcoidosis, Sweet's syndrome, thalidomide, solid tumor

Disease name and synonyms

- Sweet's syndrome
- Acute febrile neutrophilic dermatosis

The syndrome was originally described by Dr Robert Douglas Sweet as an "acute febrile neutrophilic dermatosis" in 1964. In his report, Dr Sweet mentioned that "in eponymous honor

of the first 2 patients, the condition was known in my department as the Gomm-Button disease, a title some may still prefer to that which heads this paper." He subsequently suggested that the name of the "distinctive and fairly severe illness" that he observed in 8 women from 1949 to 1964 remain descriptive; yet, in spite of his recommendation, "Sweet's syndrome" has become the established eponym for this condition.

Definition

Classical Sweet's syndrome

Sweet's syndrome is characterized by pyrexia, elevated neutrophil count, tender erythematous skin lesions (papules, nodules, and plaques) and a diffuse infiltrate consisting predominantly of mature neutrophils typically located in the upper dermis.

Malignancy-associated Sweet's syndrome

The first patient with solid tumor-associated Sweet's syndrome, a 58-year-old man with testicular carcinoma, was reported by Shapiro *et al.* in 1971. However, several authors acknowledge that the 16-year-old girl with acute myelogenous leukemia and recurrent cutaneous lesions of variable morphologies, described by Costello *et al.* in 1955, represents the initial report of malignancy-associated Sweet's syndrome.

Subsequently in 1973, two women with Sweet's syndrome lesions confirmed by biopsy were described. These lesions were the presenting manifestation of their previously unsuspected acute leukemia.

Drug-induced Sweet's syndrome

The first patient with drug-induced Sweet's syndrome (associated with trimethoprim-sulfamethoxazole) was reported by Su and Liu in 1986. At this time, they also proposed diagnostic criteria for Sweet's syndrome.

Diagnostic criteria

The diagnostic criteria for classical (or idiopathic) Sweet's syndrome were modified by von den Driesch in 1994. Although these criteria include malignancy-associated Sweet's syndrome as a subset of classical Sweet's syndrome, several authors choose to distinguish between the classical form and the malignancy-associated form since many of the cases of Sweet's syndrome are cancer-related. Diagnostic criteria for drug-induced Sweet's syndrome were proposed by Walker and Cohen in 1996.

Diagnostic criteria for classical Sweet's syndrome (see Table 1)

Criteria consist of major and minor criteria. Both major criteria and 2 of the 4 minor criteria are required to establish the diagnosis of classical Sweet's syndrome.

Table 1. Diagnostic criteria for classical Sweet's syndrome

Major criteria	<ul style="list-style-type: none"> <input type="checkbox"/> Abrupt onset of painful erythematous plaques or nodules <input type="checkbox"/> Histopathologic evidence of a dense neutrophilic infiltrate without evidence of primary leukocytoclastic vasculitis
Minor criteria	<ul style="list-style-type: none"> <input type="checkbox"/> Pyrexia (greater than 38°C) <input type="checkbox"/> Association with an underlying hematological or visceral malignancy, inflammatory disease, or pregnancy or preceded by an upper respiratory or gastrointestinal infection or vaccination <input type="checkbox"/> Excellent response to treatment with systemic corticosteroids, potassium iodide, or colchicines <input type="checkbox"/> Abnormal laboratory values at presentation (3 of the following 4): erythrocyte sedimentation rate greater than 20 mm/hr, positive C-reactive protein, greater than 8000 leukocytes, and greater than 70% neutrophils

Criteria for drug-induced Sweet's syndrome

Several medications have been associated with drug-induced Sweet's syndrome. The most

frequently incriminated drug is granulocyte-colony stimulating factor (GCSF); other dermatosis-inducing medications that have been

implicated include all-trans retinoic acid, carbamazepine, celecoxib, diazepam, diclofenac, hydralazine, levonorgestrel/ethinyl estradiol, minocycline, nitrofurantoin, propylthiouracil, and trimethoprim-sulfamethoxazole.

The diagnostic criteria for this variant of Sweet's syndrome are:

- (1) Abrupt onset of painful erythematous plaques or nodules,
- (2) Histopathological evidence of a dense neutrophilic infiltrate without evidence of primary leukocytoclastic vasculitis,
- (3) Pyrexia greater than 38 degrees Centigrade,
- (4) Temporal relationship between drug ingestion or injection a clinical presentation, or temporally related recurrence after either oral or intravenous challenge, and
- (5) temporally related resolution of lesions after drug withdrawal or treatment with systemic corticosteroids.

All 5 of these criteria must be present to confirm the diagnosis of drug-induced Sweet's syndrome.

Differential diagnosis

The mucocutaneous and systemic disorders whose dermatological manifestations can morphologically mimic those of Sweet's syndrome are numerous.

These disorders consist of not only cutaneous conditions and systemic diseases, but also infectious and inflammatory disorders, neoplastic conditions, reactive erythemas and vasculitis.

Clinical differential diagnosis

The clinical differential diagnosis includes acne vulgaris, acral erythema, bacterial sepsis, Behcet's disease, bowel (intestinal) bypass syndrome, cellulitis, chloroma, dermatomyositis, drug eruptions, eruptive xanthomas, erysipelas, erythema elevatum diutinum, erythema multiforme, erythema nodosum, familial Mediterranean fever, granuloma faciale, halogenodermas, herpes simplex virus infection, leprosy, leukemia cutis, leukocytoclastic vasculitis, lupus erythematosus, lymphangitis, lymphoma, metastatic tumor, panniculitis, periarteritis nodosa, pustular eruption of ulcerative colitis, pyoderma gangrenosum, sporotrichosis, syphilis, systemic mycosis, thrombophlebitis, tuberculosis, urticaria, varicella-zoster virus infection, vesicular eruption associated with hepatobiliary disease, and viral exanthem.

Histological differential diagnosis

The histological differential diagnosis of Sweet's syndrome includes conditions microscopically characterized by either neutrophilic dermatoses

or neutrophilic panniculitis. Neutrophilic dermatoses include abscess or cellulitis, bowel (intestinal) bypass syndrome, erythema elevatum diutinum, granuloma faciale, halogenoderma, leukocytoclastic vasculitis, neutrophilic eccrine hidradenitis, pyoderma gangrenosum, and rheumatoid neutrophilic dermatitis.

Leukemia cutis can not only occur concurrently with Sweet's syndrome, but also mimic the dermal changes of Sweet's syndrome; yet, in contrast to Sweet's syndrome, in leukemia cutis the dermal infiltrate consists of malignant immature leukocytes instead of mature neutrophils. The adipose tissue changes of subcutaneous Sweet's syndrome are similar to those of other conditions characterized by a neutrophilic lobular panniculitis: alpha 1-antitrypsin deficiency, factitial panniculitis, infection, pancreatitis, and rheumatoid arthritis.

Frequency

Classical or idiopathic Sweet's syndrome

Classical or idiopathic Sweet's syndrome predominantly affects in women; the initial episode occurs between the ages of 30 to 50 years most frequently.

However, Sweet's syndrome has been reported in children (as young as 7 weeks of age) and younger adults.

A preceding upper respiratory tract infection is common and recurrence of the dermatosis is noted in approximately one-third of individuals.

Malignancy-associated Sweet's syndrome

Malignancy-associated Sweet's syndrome has mostly been described in single case reports or small series of patients. Cohen and Kurzrock attempted to more accurately define the incidence of malignancy-associated Sweet's syndrome by reviewing and combining the data from several published series of patients with Sweet's syndrome. After evaluating 15 studies (each containing between 10 to 48 individuals), they found that 21% of the patients with Sweet's syndrome (96 of 448 individuals) had either a hematological malignancy or a solid tumor. Malignancy-associated Sweet's syndrome occurs as frequently in men as in women and is less often preceded by an upper respiratory tract infection.

Clinical description

Fever

Fever is the most frequent symptom in patients with Sweet's syndrome. The cutaneous manifestations may be preceded by fever; alternatively, pyrexia can concurrently be

present throughout the duration of the dermatosis. However, in some patients with biopsy-confirmed malignancy-associated Sweet's syndrome, fever may be absent. Arthralgia, general malaise, headache, and myalgia are other Sweet's syndrome-associated symptoms that may also be present. Indeed, patients with this condition may appear dramatically ill.

Skin lesions

Sweet's syndrome skin lesions are typically tender and often painful. They appear as red or purple-red papules and nodules. The pronounced edema in the upper dermis of the lesions results in their transparent, vesicle-like appearance; in patients with malignancy-associated Sweet's syndrome, the lesions may appear bullous, become ulcerated, and/or mimic the morphologic features of pyoderma gangrenosum. Over a period of days to weeks, the individual lesions enlarge and may coalesce to form irregular, sharply border plaques. The upper extremities, face and neck are the most frequent lesion locations.

Cutaneous lesions of Sweet's syndrome may appear at sites of trauma to the skin, such as locations where procedures have been performed (biopsies, intravenous catheter placement, or venipuncture), sites where either bites (insect) or scratches (cat) have occurred, areas that have received radiation therapy, or places that have been contacted by sensitizing antigens; this dermatosis-associated feature is referred to a skin hypersensitivity or cutaneous pathway. Occasionally, the distribution of the skin lesions has been noted to occur in sun-exposed areas or the location of a prior sunburn (phototoxic reaction).

Less commonly, the lesions of Sweet's syndrome present as a pustular dermatosis—either as tiny pustules on the tops of the red papules or as erythematous-based pustules. Many investigators consider those patients who have previously been reported to have either “neutrophilic dermatosis of the dorsal hands” or “pustular vasculitis of the dorsal hands” to be included in this clinical variant of Sweet's syndrome. In addition, it is likely that some of the patients who were described as having “pustular eruption of ulcerative colitis” also should be included as patients with the pustular variant of Sweet's syndrome.

Extracutaneous manifestations

Extracutaneous manifestations of Sweet's syndrome may involve the following sites: bone, central nervous system, eyes, kidneys, intestines, liver, heart, lung, mouth, muscles, and spleen.

Dermatosis-related sterile osteomyelitis has been reported in children. Mucosal involvement of the mouth, presenting as oral ulcers, is uncommon in classical Sweet's syndrome; however, this is more frequently noted in patients with Sweet's syndrome and hematological disorders.

The reported incidence of ocular involvement (such as conjunctivitis) is variable in classical Sweet's syndrome and uncommon in the malignancy-associated and drug-induced forms of the dermatosis; however, in some patients with Sweet's syndrome, ocular manifestations have been observed to be the presenting feature of the condition.

Associated diseases

Several conditions have been observed to occur either before, concurrent with or following the diagnosis. Hence it is reasonable to conclude that the occurrence of Sweet's syndrome may be associated with the development of some of these conditions.

Specifically, a bonafide association between Sweet's syndrome and the following conditions probably exists (see **Table 2**): cancer (both hematological malignancies—most commonly acute myelogenous leukemia—and solid tumors—most commonly carcinomas of the genitourinary organs, breasts, and gastrointestinal tract), infections (most commonly of the upper respiratory tract—streptococcosis—and the gastrointestinal tract—salmonellosis and yersiniosis), inflammatory bowel disease (Crohn's disease and ulcerative colitis), medications (with granulocyte-colony stimulating factor being the most commonly reported drug), and pregnancy. In addition, it is also possible that a bonafied association exists between Sweet's syndrome and the following conditions: Behcet's disease, erythema nodosum, relapsing polychondritis, rheumatoid arthritis, sarcoidosis, and thyroid disease (Grave's disease and Hashimoto's thyroiditis). However, for many of the conditions that have been observed in patients with Sweet's syndrome, the presence of that disorder in a patient with Sweet's syndrome is likely to represent a coincidental occurrence. However, for many of the conditions that have been observed in patients with Sweet's syndrome, the presence of that disorder is likely to be coincidental.

Management

Sweet's syndrome lesions may persist for weeks to months. However, in some patients with classical Sweet's syndrome, the dermatosis-related symptoms and cutaneous lesions eventually resolved without any therapeutic intervention. Successful management of the

dermatosis-related cancer in patients with malignancy-associated Sweet's syndrome occasionally resulted in clearing of the condition. And, in patients with drug-induced Sweet's syndrome, discontinuation of the associated medication was typically followed by

spontaneous improvement and subsequent resolution of the syndrome. Some of the patients with Sweet's syndrome associated tonsillitis, solid tumors, or renal failure experienced resolution of the dermatosis following appropriate surgical intervention.

Table 2. Reported associations in Sweet's syndrome

<p>Cancer (21%)</p>	<ul style="list-style-type: none"> ❑ Hematological malignancies (15%) most commonly acute myelogenous leukemia ❑ Solid tumors (6%) most commonly carcinomas of the genitourinary organs, breast and gastrointestinal tract
<p>Infections</p>	<ul style="list-style-type: none"> ❑ Mostly of the upper respiratory tract (75 to 90% in patients with classical or idiopathic Sweet's syndrome) Streptococcosis ❑ Gastrointestinal tract Salmonellosis and Yersiniosis
<p>Inflammatory bowel disease</p>	<ul style="list-style-type: none"> ❑ Crohn's disease and ulcerative colitis
<p>Pregnancy</p>	
<p>Other conditions for which there is a possible bonafied association</p>	<ul style="list-style-type: none"> ❑ Behçet's disease, ❑ Erythema nodosum, ❑ Relapsing polychondritis, ❑ Rheumatoid arthritis, ❑ Sarcoidosis, ❑ Thyroid disease (Grave's disease and Hashimoto's thyroiditis)
<p>Medications</p>	<ul style="list-style-type: none"> ❑ Granulocyte-colony stimulating factor The most commonly reported drug

Systemic corticosteroids

Systemic corticosteroids are the “gold standard” of therapy for Sweet’s syndrome. Dermatitis-associated symptoms improve promptly after treatment has been started and the cutaneous lesions resolve subsequently. Systemic corticosteroid therapy often begins with 1 mg/kg/day of prednisone as a single oral morning dose. The dose can usually be tapered to 10 mg/day within 4 to 6 weeks. However, some patients may require treatment for 2 to 3 months or intravenous therapy. In patients whose dermatosis has been refractory to other treatments, daily pulse intravenous methylprednisolone sodium succinate (at a dose of up to 1000 mg/day) over 1 or more hours for 3 to 5 days has been given; this has usually been followed by a tapering oral dose of corticosteroid or another immunosuppressant agent.

Topical or intralesional corticosteroids

Topical or intralesional corticosteroids can be used to treat patients with localized Sweet’s syndrome lesions as either monotherapy or concurrently with another therapy. High potency topical corticosteroids (such as 0.05% clobetasol propionate) in either a cream base or an ointment base can be applied to the lesions. Individual lesions have improved following a single injection or multiple intralesional treatments with triamcinolone acetonide when used at a dose ranging from 3 mg/ml to 10 mg/ml.

Potassium iodide and colchicine

In addition to systemic corticosteroids, potassium iodide and colchicine are also considered to be first-line agents for the treatment of Sweet’s syndrome. Horio *et al.* originally described the dramatic improvement in patients with Sweet’s syndrome who were treated with potassium iodide in 1980. He confirmed his earlier observations with a larger study in 1983. Subsequently, several other investigators have also observed similar improvement when using potassium iodide to treat patients with Sweet’s syndrome.

After the initiation of potassium iodide therapy, symptoms of the dermatosis typically resolve within 1 to 2 days and skin lesions subside within 3 to 5 days. Potassium iodide, when available as a 300 mg enteric-coated tablet, can be administered orally 3 times each day (for a total daily dose of 900 mg). Alternatively, when the drug is available as a saturated solution (1 gram/ml of water) of potassium iodide (SSKI - saturated solution of potassium iodide-, which is also referred to as Lugol’s solution), it is initially given at a dose of 3 drops 3 times each day. When a “standard” medicine dropper (which

dispenses 20 drops per ml) is used, 1 drop equals 0.05 ml (or 50 mg when the concentration of potassium iodide is 1000 mg/ml). Therefore, the initial dose is 9 drops per day which equals 450 mg of potassium iodide per day. The dose is increased by 1 drop 3 times each day, typically to a final dose between 21 drops per day (1,050 mg) to 30 drops per day (1,500 mg).

The efficacy of colchicine for Sweet’s syndrome was initially reported by Suehisa and Tagami in 1981. Two years later, in 1983, Suehisa *et al.* reported 3 additional patients with Sweet’s syndrome who were successfully treated with colchicine. Several larger studies have subsequently confirmed that colchicine is an effective agent for the successful management of patients with Sweet’s syndrome. For example, Maillard *et al.* presented 20 patients with Sweet’s syndrome of whom 90% (18 individuals) responded to colchicine therapy: fever resolved within 2 to 3 days, skin lesions attenuated within 2 to 5 days, arthralgia disappeared within 2 to 4 days, and leukocytosis normalized within 8 to 14 days. Similar to earlier studies, the starting dose of colchicine was 0.5 mg orally 3 times each day (for a total daily dose of 1.5 mg); treatment ranged from 10 to 21 days (mean = 15 days). Colchicine may cause diarrhea, abdominal pain, nausea and vomiting; therefore, some investigators have recommended lower daily doses.

Indomethacin and clofazimine

In individual case reports and in a single larger study, indomethacin and clofazimine have each been described to be effective. In 1997, Jeanfils *et al.* reported therapeutic efficacy for 17 of the 18 patients with Sweet’s syndrome who received indomethacin as first-line monotherapy: an oral daily dose of 150 mg for 7 days and then 100 mg per day for 14 days. Von den Driesch reported “almost complete remission” in 6 patients who were treated with clofazimine. The patients had chronic and relapsing Sweet’s syndrome and had previously been unsuccessfully treated with methylprednisolone; they received an oral daily dose of 200 mg of clofazimine for 4 weeks and then 100 mg per day for 4 more weeks. None of the 6 patients required systemic treatment of their Sweet’s syndrome after the clofazimine was discontinued.

Cyclosporin and dapsone

Cyclosporin and dapsone have been used either as monotherapy or in combination with other agents. The initial oral dose of cyclosporin ranged from 2 mg/kg/day to 10 mg/kg/day; for the patient who was receiving 10 mg/kg/day, the dose was reduced by 2 mg/kg/day every 2 days and discontinued on day 21. The initial oral

dose of dapsons ranged from 100 mg per day to 200 mg per day.

There are individual case reports of patients with Sweet's syndrome whose dermatosis has improved after systemic therapy with antibiotics such as doxycycline, minocycline, tetracycline; dermatosis-related *Yersinia* or *Chlamydia* infections were present in some of these patients. The symptoms and lesions of Sweet's syndrome also resolved in other patients after they were treated with either ciprofloxacin, metronidazole, penicillin, or pyrimethamine and sulfonamide; some of these patients also had Sweet's syndrome-associated infections caused by either *Salmonella typhimurium*, *Streptococcus*, *Helicobacter pylori*, or *Toxoplasma*. Lesions of Sweet's syndrome often become secondarily impetiginized; therefore, when patients with Sweet's syndrome receive systemic therapy directed toward *Staphylococcus aureus* their dermatosis-related skin lesion often partially improve.

The effective treatment of Sweet's syndrome has also been observed after using intralesional and systemic interferon alpha, etretinate, cytotoxic chemotherapeutics and antimetabolites. However, these agents have only been described in uncontrolled studies and single case reports. Pentoxifylline, although postulated to be of therapeutic benefit in Sweet's syndrome, has not been found to be an effective monotherapy for this dermatosis.

Recently, the tumor necrosis factor alpha-neutralizing agent, infliximab, has been used to treat Sweet's syndrome. Matzkies *et al.* reported a 51-year-old man with insulin dependent diabetes mellitus and relapsing polychondritis (whose "immunologic activity"..."appeared to be insufficiently controlled" while receiving glucocorticoids, methotrexate, and azathioprine) who developed Sweet's syndrome. His manifestations of Sweet's syndrome were initially treated with an intravenous infusion of infliximab (at a dose of 3 mg/kg) after the azathioprine was discontinued; his dermatosis-related symptoms (arthritis) resolved rapidly and the Sweet's syndrome-associated cutaneous lesions disappeared. When Sweet's syndrome symptoms (fever) and skin lesions reappeared 14 days later, the glucocorticoid was increased to 80 mg and a second infliximab infusion (at the same dose of 3 mg/kg) was given; again, there was resolution of his Sweet's syndrome. He developed infection and subsequent multisystem failure; 11 weeks after his second infusion he died. Prior to his death the lesions of Sweet's syndrome reappeared. Based on this patient's dramatic—although temporary—resolution of his Sweet's syndrome manifestations following each infliximab infusion, it has been suggested that

additional investigation using infliximab and other tumor necrosis factor alpha-altering drugs (such as etanercept and thalidomide) as monotherapy for patients with Sweet's syndrome should be considered for those individuals whose dermatosis is unresponsive to standard therapy.

Etiology

The pathogenesis of Sweet's syndrome remains to be definitively determined. Many etiologies—not necessarily mutually exclusive—have been postulated.

Several features of Sweet's syndrome suggest that the dermatosis results from a hypersensitivity reaction to an eliciting antigen; and, the source of that antigen may be diverse, such as bacterial, viral, or tumoral. In addition to the appearance, histopathology and course of the skin lesions, the prompt response of both the symptoms and the lesions to corticosteroids support this hypothesis.

Several investigators believe that the effects of cytokines—either directly or indirectly or both—have an etiologic role in the development of Sweet's syndrome. Potential cytokine candidates include GCSF, granulocyte macrophage colony stimulating factor, interferon-gamma, interleukin-1, interleukin-3, interleukin-6, and interleukin-8. For example, elevated levels of serum GCSF and interleukin-6 and detectable levels of intra-articular synovial fluid granulocyte macrophage-colony stimulating factor have been observed in a patient with myelodysplastic syndrome-associated (non-GCSF induced) Sweet's syndrome and an infant with classical Sweet's syndrome, respectively. The results of an immunohistochemical evaluation of the epidermis of Sweet's syndrome lesions suggests the importance of interleukin-1 as a potential cytokine mediator in Sweet's syndrome: the researchers concluded that the decreased epidermal staining for interleukin-1 and interleukin-6 was due to the release of these cytokines into the dermis. The investigators of another study concluded that interleukin-2 and interferon-gamma (helper T-cell type 1 cytokines)—rather than interleukin-4 (a helper T-cell type 2 cytokine)—were probable cytokine mediators in the etiology of Sweet's syndrome when they observed significantly elevated levels of interleukin-1-alpha, interleukin-1-beta, interleukin-2, and interferon-gamma and normal levels of interleukin-4 in the sera of Sweet's syndrome patients.

Pathology

The spectrum of pathological changes described in cutaneous lesions of Sweet's syndrome has expanded since the initial description by Dr

Sweet. In addition to variability of the composition or the location of the inflammatory infiltrate, concurrent leukemia cutis may be present in the skin lesions in patients with hematological malignancy-associated Sweet's syndrome. Characteristically, a diffusely distributed inflammatory infiltrate of mature neutrophils and edema is present in the upper dermis. Endothelial cells may be swollen, small blood vessels may be dilated, and neutrophil nuclei may be fragmented (which is referred to as karyorrhexis or leukocytoclasia). Classically, changes of primary leukocytoclastic vasculitis (such as fibrin deposition or neutrophils within the vessel walls) are absent and the overlying epidermis is normal.

Mature neutrophils are the predominant cells that comprise the infiltrate in the dermis of cutaneous Sweet's syndrome lesions. However, lymphocyte or histiocytes may also occasionally be present in the inflammatory infiltrate. In addition, in the skin lesions of some patients with either the classical or the drug-induced dermatosis, eosinophils have been observed within the dermal infiltrate.

Although the location of the neutrophilic inflammation is typically restricted to within the dermis, neutrophils have been observed within the overlying epidermis (as either neutrophilic spongiotic vesicles or subcorneal pustules) and within the underlying adipose tissue (referred to as subcutaneous Sweet's syndrome). Subcutaneous Sweet's syndrome can involve either the adipose tissue alone or both the dermis and the subcutaneous fat. And, within the subcutaneous fat, the neutrophilic infiltrate is present in the lobules, the septae, or both. Cutaneous lesions of subcutaneous Sweet's syndrome typically present as tender erythematous subepidermal nodules on the extremities, clinically mimicking erythema nodosum. Since Sweet's syndrome can develop concurrently or sequentially with erythema nodosum, a biopsy of one or more new nodules may be necessary to establish the correct diagnosis—even in a patient with histology-confirmed Sweet's syndrome.

Within the dermis, the neutrophils are typically located in the papillary and upper reticular dermis as a dense and diffusely distributed infiltrate. However, some investigators have observed the neutrophils to be perivascular and pathologic changes consistent with leukocytoclastic vasculitis. The vascular changes in these lesions of Sweet's syndrome are considered to be those of a "secondary" leukocytoclastic vasculitis occurring as an epiphenomenon and not representative of a "primary" vasculitis.

In patients with hematological disorders, Sweet's syndrome can occur in one or more of the following forms: a paraneoplastic syndrome, a drug-induced dermatosis (following treatment with either all-trans retinoic acid or GCSF), or a condition whose skin lesions concurrently demonstrate leukemia cutis. In the third form, the dermal infiltrate consists not only of mature polymorphonuclear cells (Sweet's syndrome) but also abnormal neutrophils (leukemia cutis). Only a small number of patients with this unique presentation of Sweet's syndrome have been described; acute leukemia (myelocytic and promyelocytic) are the most frequent hematological malignancy. The other associated hematological disorders were myelodysplastic syndrome and myelogenous leukemia (either chronic or not otherwise specified).

Pathological findings of Sweet's syndrome can also occur in extracutaneous sites. These often present as sterile neutrophilic inflammation in the involved organ. These changes have been described in the bones, intestines, liver, aorta, lungs, and muscles of patients with Sweet's syndrome.

Diagnostic methods

Lesional skin biopsy

A lesional skin biopsy for routine histopathological evaluation is a useful procedure to confirm a clinically suspected diagnosis of Sweet's syndrome. Since the finding of a diffuse inflammatory infiltrate of neutrophils in the dermis, subcutaneous fat, or both can also be observed in cutaneous lesions caused by an infectious agent, it may be prudent to also submit lesional tissue for bacterial, fungal, mycobacterial, and possibly viral cultures.

Laboratory evaluation

The most consistent laboratory abnormalities in patients with Sweet's syndrome are peripheral leukocytosis with neutrophilia and an elevated erythrocyte sedimentation rate. Therefore laboratory evaluation should include a complete blood cell count with leukocyte differential and platelet count. Evaluation of acute phase reactants, such as the erythrocyte sedimentation rate or C-reactive protein, may also be helpful. An elevated white blood cell count is not always observed in all patients with biopsy-confirmed Sweet's syndrome.

Since extracutaneous manifestations of Sweet's syndrome may affect other organs such as the liver or kidneys, serum chemistries (evaluating hepatic function and renal function) and a urinalysis should be considered. Hematuria or proteinuria may be revealed by the latter. And,

since there is possibly a bonafied association between thyroid disease and Sweet's syndrome, it may be reasonable to perform a serological evaluation of thyroid function.

Abnormalities may be found on brain SPECTs, computerized axial tomography, electroencephalograms, magnetic resonance imaging and cerebrospinal fluid analysis in patients with central nervous system involvement. In patients with Sweet's syndrome who have extracutaneous manifestations that involve their lungs, pleural effusions and corticosteroid-responsive culture-negative infiltrates may be present on chest roentgenograms.

In 1993, Cohen and Kurzrock published their recommendations regarding the initial malignancy workup for newly-diagnosed Sweet's syndrome patients without prior cancer. Their recommendations were based upon the neoplasms that had concurrently or subsequently been discovered in previously cancer-free Sweet's syndrome patients and the age-related recommendations by the American Cancer Society for the early detection of cancer in asymptomatic persons.

They recommended:

- (1) a detailed medical history;
- (2) a complete physical examination, including:
 - (a) examination of the thyroid, lymph nodes, oral cavity, and skin;
 - (b) digital rectal examination;
 - (c) breast, ovary, and pelvic examination in women; and
 - (d) prostate and testicle examination in men;
- (3) laboratory evaluation:
 - (a) carcinoembryonic antigen level;
 - (b) complete blood cell count with leukocyte differential and platelet count;
 - (c) pap test in women;
 - (d) serum chemistries;
 - (e) stool guaiac slide test;
 - (f) urinalysis and
 - (g) urine culture; and
- (4) other screening tests:
 - (a) chest roentgenograms;
 - (b) endometrial tissue sampling in either menopausal women or women with a history of abnormal uterine bleeding, estrogen therapy, failure to ovulate, infertility, or obesity; and
 - (c) sigmoidoscopy in patients over 50 years of age.

They commented that it was reasonable to check a complete blood cell count with leukocyte differential and platelet count every 6 to 12 months since the initial appearance of dermatosis-related skin lesions preceded the diagnosis of a Sweet's syndrome-associated

hematological malignancy by as long as 11 years.

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