Case Report

Sweet Syndrome: Etiology and Clinical Associations

Serirat O, MD[1], Ingkaninanda P, MD[1]

[1] Department of Medicine, Rajavithi Hospital, College of Medicine, Rangsit University, Bangkok, Thailand

Background: Sweet syndrome (acute febrile neutrophilic dermatosis) is a distinctive disorder which has four primary features: skin eruption of violaceous tender papules and plaques; biopsy showing dermal nonvasculitis neutrophilic infiltration; fever; and peripheral neutrophilia. Associated factors include infections, malignancies, drug reactions, inflammatory bowel disease and pregnancy.

Objective: To describe the characteristics and underlying causes of Sweet syndrome.

Materials and Methods: The author retrospectively examined the medical records of 9 patients who met the diagnostic criteria for Sweet syndrome in Rajavithi Hospital between 2008 and 2018.

Results: Four patients had a hematologic disorder and solid tumor, while another four had related mycobacterium and atypical mycobacterium infections. One had systemic lupus erythematosus associated with Sweet syndrome. Only one case was the classic type.

Conclusion: Sweet syndrome is diagnosed based on clinical presentation and histopathology showing neutrophilic infiltration without vasculitis. Hematologic conditions are still the main associated causes while infections, especially mycobacterium ones, are being increasingly suspected.

Keywords: Sweet syndrome, Cancer, Mycobacterium tuberculosis, Atypical mycobacterium, Systemic lupus erythematous

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Sweet syndrome is characterized by abrupt onset of fever; peripheral neutrophilia; characteristic skin lesions presenting as tender erythematous papules, nodules, or plaques usually occurring on the face, neck and upper extremities[1]; and skin histopathology showing papillary dermal edema, swollen endothelial cells, and diffuse infiltration of predominantly fragmented neutrophils nuclei with leukocytoclasia or karyorrhexis without evidence of vasculitis.

The exact causes of Sweet syndrome are not fully understood. It may occur as an allergic reaction to unknown agents or when there is a hypersensitive reaction to specific agents such as bacterial or viral infection, cancer, or certain types of drug. In adults, classical Sweet syndrome affects fifteen times more females than males and is generally found in people between the age of 30 and 50 years. In children, there appears to be no gender preference, and this is also true of the paraneoplastic form, which is equally prevalent in the two sexes. In diagnosis of Sweet syndrome, the major criteria are: 1) sudden onset of tender erythematous skin lesions (papules, plaques or nodules); and 2) dense dermal neutrophilic infiltrate in the absence of vasculitis on histopathology. Minor criteria are: 1) fever more than 38°C; 2) ESR >30 mm/h, neutrophil count >70%, positive C-reactive protein; 3) association with underlying infection, pregnancy, inflammatory disease or malignancy; and 4) excellent response to systemic corticosteroids. Two major and two minor criteria are required to confirm diagnosis of Sweet syndrome.

Correspondence to:

Serirat O.

Department of Medicine, Rajavithi Hospital, 2, Phyathai Road, Ratchathewi, Bangkok 10400, Thailand.

Phone: +66-2-3548108 ext. 2107, 2802

E-mail: onsirish@gmail.com

Case Report

After the research proposal was approved by the Institutional Review Board (No. 226/2561), the medical records were reviewed of patients treated at the Dermatology Department over the preceding 10 years (2008 to 2018) who were diagnosed as having Sweet syndrome. The details of the case series are shown in Table 1.

Case 1

A 34-year-old woman treated for pulmonary tuberculosis for 2 months developed a high-grade fever and skin lesions showing as tender erythematous papule-nodule plaques with targetoid lesions on the face and legs spreading to the trunk (Figure 1A, B). Skin biopsy showed marked dermal infiltration of neutrophils without evidence of vasculitis (Figure 1C). Cultures for bacteria, fungus, mycobacterium and atypical mycobacterium were negative. White blood cell count was 34,900 cells//UL, 80% neutrophil, 9% lymphocyte, 4% monocytes, 7% eosinophils, Hb 8.5 g/dL, and platelets 747,000/UL. Anti HIV was non-reactive, bone marrow biopsy showed 100% cellularity with gelatinous

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Table 1. Sweet syndrome presenting symptoms and associated diseases

Cases	Sex	Age	Clinical	Associated disease	Causes	Laboratory
1	Female	34	Tender erythematous papules at face	Pulmonary tuberculosis Cervical cancer	Malignancy Infection	Dermal infiltration of neutrophils Leukocytosis, thrombocytosis
2	Female	52	Fever, diarrhea	Febrile neutropenia Myelodysplastic syndrome	Malignancy	Leukopenia
3	Male	47	Fever, erythematous plaques at trunk, arms		Idiopathic	Dense dermal neutrophils Leukocytosis C-reactive protein positive
4	Female	55	Erythematous papules and pseudovesicles at chest	Scrofuloderma	Infection	Leukocytosis, anemia, thrombocytosis
5	Male	34	Fever erythematous, macules, papulovesicles at trunk	Atypical Mycobacterium infection	Infection	CD4 22% CD8 33%
6	Female	49	Fever, urticarial-like lesions	Acute myelogenous leukemia	Malignancy	Dense dermal neutrophils infiltration Leukocytosis, promyeloblast presenting peripheral blood smear
7	Female	46	Abscess-like lesion at right dorsal hand	Atypical mycobacterium infection	Infection	Dense dermal neutrophils infiltration Leukopenia, anemia, thrombocytosis
8	Female	32	Fever, erythematous plaques, vescicles, pustules at face	Systemic lupus erythematous skin	Autoimmune	Numerous dermal infiltrations
9	Male	67	Multiple pruritic papules, pustules at trunk, extremities	Non-small cell lung cancer	Malignancy	Acute and chronic dermal infiltration, no malignancy or organisms

change, and megakaryocytes were absent. Chromosome study was normal, as was chest roentgenography. She was treated with prednisolone 20 mg/day and had a few repeat episodes of lesion flare-up. Cervical cancer stage IIIB was later diagnosed and treated several years later. At the time of writing, the patient has had no relapse of either cervical cancer or skin symptoms.

Case 2

A 52-year-old female who was diagnosed with Sweet syndrome presented with clinical symptoms of fever, diarrhea, and nausea. Two days later, she was diagnosed with febrile neutropenia. Bone marrow aspiration was non-diagnostic, while bone marrow biopsy showed hypocellular marrow with 10 to 20% cellularity and no apparent malignancy. The patient was treated with systemic steroids and showed a good response.

Case 3

A 47-year-old male was diagnosed Sweet syndrome after presenting with abrupt high-grade fever with multiple erythematous indurated plaques at the trunk and arms. Skin biopsy revealed dense neutrophils while laboratory investigation showed white blood cell count of 11,700 cells/UL, neutrophils 70%, lymphocyte 20%, and Platelets 280,000/UL. Erythrocyte sedimentation rate was 21 mm/h, C-reactive protein was positive, and clinical symptoms were resolved after initiation of systemic prednisolone 30 mg/day.

Case 4

A 55-year-old female with scrofuloderma who had been treated with antituberculosis CAT 1 for 6 months

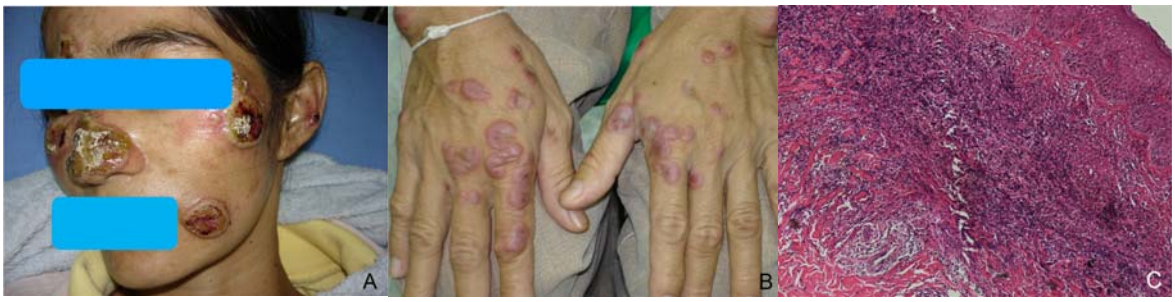

Figure 1. Case 1 showing erythematous plaques and nodules at face and hands (A, B) diffuse dermal neutrophils infiltrate (C).

Figure 2. Case 8 showing vescicles and pustules at face and legs.

presented with erythematous papules and pseudovesicles on her chest. Laboratory findings showed leukocytosis, anemia and thrombocytosis with white blood cell count of 30,000 to 40,000/UL, Hct 25 to 30%, and platelets 500,000 to 700,000/UL. Skin biopsy results were compatible with Sweet Syndrome. CT Abdomen showed lymphadenopathy, gastrohepatic, central mesenteric, bilateral superficial inguinal node. The patient was diagnosed with Sweet Syndrome and treated with colchicine.

Case 5

A 34-year-old male presented with clinical symptoms of Sweet syndrome such as abrupt febrile illness and erythematous macules and papulovesicles at the trunk. He had an underlying mass of diameter 3 cm at the left nipple and was diagnosed with mycobacterium chelonae infection. Bone marrow showed Penicillium Marneffei Immune Deficiency CD4 550 (22%), CD8 826 (33%). Mellioid titer was negative 1: 40, and sputum culture was negative for mycobacterium and atypical mycobacterium infection. The patient was treated with sulperasone, ceftazidine, trimethoprim/sulfamethoxazole and later with itraconazole, doxycycline, amoxicillin-clavulanic acid and amoxicillin.

Case 6

A 49-year-old female presented with fever, seizure and anemia. White blood cell count was 36,000/uL, promyeloblast 641/uL. Bone marrow aspiration showed hypercellular bone marrow with myeloblast, promyelocyte and monoblast 80%. She was diagnosed with AML (M1/M4) and treated with Ara-C. After having a sudden onset of urticarial-like lesions, she underwent skin biopsy which showed dense dermal neutrophilic infiltration, and she was diagnosed as having Sweet's Syndrome.

Case 7

A 46-year-old woman had chronic polyarthritis, proximal muscle weakness, atypical mycobacterium infection and pleural effusion with pelvic mass. Biopsy of cervical lymph node was performed and showed reactive lymph node. She had abscess at right dorsal hand and skin biopsy showed dense neutrophilic infiltration with negative culture for bacteria, fungus and mycobacterium. Laboratory examination showed white blood cell count was 9,200/UL, neutrophil 83%, lymphocyte 15%, monocytes 2%, platelets 699,999/uL and Hct 27.6%. She was diagnosed with Sweet syndrome and treated with prednisolone 20 mg/day for 2 weeks.

Case 8

A 32-year-old woman with underlying SLE had 2 episodes of clinical symptoms. First, she presented with vesicle and erythematous plaque lesions at the face, and on the second occasion, she had multiple pustules, mostly at extremities (Figure 2), concurrent with fever. Skin biopsy revealed numerous neutrophilic infiltrations in dermis, and

she was diagnosed with Sweet syndrome. She was treated with prednisolone and had a good response.

Case 9

A 67-year-old male with underlying non-small cell lung cancer with brain and liver metastasis was treated with gelfitinib and radiation after which he presented with multiple pruritic papules and pustules at the trunk and extremities. Skin biopsy revealed acute and chronic inflammation with no malignancy or organisms. Gram stain showed numerous leukocytes and gram positive cocci (Figure 3) while pus culture showed *Staphylococcus aureus*. The patient was diagnosed as having neutrophilic dermatosis and was treated with prednisolone 10 mg/day for 10 days and topical steroid creams, after which the lesions subsided.

Discussion

Sweet syndrome was initially described in 1964 by Robert Sweet. It was characterized by the abrupt onset of tender, erythematous papules, with nodules usually occurring on the upper extremities, face or neck, accompanied by fever and peripheral neutrophilia. There are 3 main types: classical Sweet syndrome (CSS); idiopathic type, or malignancy-type Sweet syndrome (MASS); and drug-induced Sweet syndrome (DISS). The classic type is often preceded by upper respiratory tract infection, inflammatory bowel disease, or pregnancy[2], and it can be a cutaneous harbinger of undiagnosed visceral malignancy. The onset of malignancy-associated Sweet syndrome might precede, follow or be concurrent with diagnosis of the patient's neoplasm. In hematologic disorders, Sweet syndrome can occur in one or more forms: paraneoplastic syndrome; drug-induced dermatosis sometimes with concurrent leukemia cutis (abnormal neutrophils); and Sweet syndrome (mature polymorphonuclear leukocytes) and acute myelogenous leukemia including the promyelocytic (M3) variant of acute myeloid leukemia which is most common, while others include carcinomas of the genitourinary organs, breast and gastrointestinal tract[3,4]. The classical clinical appearances are tender (painful) red or purple-red papules or nodules asymmetrically on the upper extremities, face and neck while in MASS, many appear as bullous and then become ulcerated and/or mimic morphological features of pyoderma gangrenosum. It can appear as pustular dermatosis, erythematous-based pustules or tiny pustules, neutrophilic dermatosis of the dorsal hands, or pustular vasculitis of the dorsal hand, or subcutaneous forms such as erythematous tender dermal nodule on the extremities. Extra-cutaneous manifestations can involve bone, central nervous system, ears, eyes, kidneys, intestines, liver, lungs, mouth, muscle and spleen. Ocular inflammations, such as conjunctivitis, episcleritis, scleritis, limbal nodules, peripheral ulcerative keratitis, iritis, glaucoma, dacryoadenitis, and choroiditis are common extracutaneous manifestations in around 17 to 72 percent of patients with the CSS variant but are uncommon in MASS and DISS. Oral lesions such as oral ulcers, particularly on the buccal mucosa or tongue, can be more frequently found in hematologic malignancy[5].

Although the etiology of Sweet syndrome remains to be definitely determined, it may be multifactorial. Factors which contribute to the development of this disorder include hypersensitive reactions to bacterial or viral agents, tumors or other antigens, cytokine dysregulation and genetic susceptibility. In CSS, which is the most common presentation type, a bacterial infection may have a causative role, usually presenting with febrile upper respiratory tract infection or tonsillitis preceding skin lesions by 1 to 3 weeks. Some patients clinically improve with systemic antibiotics, especially those with serology-confirmed Yersinia enterolitica intestinal infection[6]. Other bacterial culprits include the Salmonella and Staphylococcus species, *Entamoeba coli*, *Helicobacter pylori*, tuberculous mycobacterium, mycobacterium chelonae[7] and viral conditions such as HIV, cytomegalovirus, hepatitis A and B, and Parvovirus B 19. Potential cytokines are Granulocytecolony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), interferon-gamma, interleukin-1, interleukin-3, interleukin-6 and interleukin-8 in concert with type 1 helper T cells, and these may contribute to the pathogenesis of Sweet syndrome[8]. Antibodies to neutrophilic cytoplasmic antigens do not appear essential to the disease process. In the iatrogenic form, or drug-induced Sweet syndrome, the most common agents are those that increase granulocyte-colony stimulating factor (G-CSF). Others include trimethoprim/sulfamethoxazole, minocycline, levonorgestrel/ethinyl estradiol, and all-trans retinoids acid[9]. Detection of granulocyte-colony stimulating factor in the various malignant tumors of MASS patients also raises the possibility of tumor-associated production of G-CSF capability in the development of symptoms of Sweet syndrome. In hematologic malignancies such as leukemia, where concurrent Sweet syndrome and leukemia cutis exist in the same lesion, circulating immature myeloid precursor cells are thought to be innocent bystanders that have been recruited to the skin as a result of an inflammatory oncotactic phenomenon stimulated by the Sweet syndrome lesions ("secondary" leukemia cutis). Alternatively, the leukemia cells within the skin may constitute the bona fide incipient presence of a specific leukemic infiltrate ("primary" leukemia cutis) and then due to G-CSF therapy, it is possible that sequestered atypical cells of leukemia cutis could develop into mature neutrophils of Sweet syndrome. Finally, the functional properties of neutrophils seem to be more significant than their absolute number because there is evidence that Sweet syndrome can be induced by granulocyte-colony stimulating factor (G-CSF) which suppresses apoptosis and prolongs survival of neutrophils in vivo in a CD34+ cell population, causing the development of lesions as the neutrophil count rapidly increases, despite a decrease in absolute neutrophil count[10-12]. A possible genetic link with HLA-B54 has been observed in a Japanese population[13]. Structural alterations in the long arm of chromosome 3 (3q) affect the regulation of granulopoiesis and neutrophil migration also seen in Sweet syndrome[14].

Of the 9 cases in this study, only one (number 3) was idiopathic or CSS while in the literature, this is the most common type. Infection-related cases in this study accounted for 4 out of 9 incidences and involved tuberculosis mycobacterium and atypical mycobacterium infections. Although an association between Sweet syndrome and infection has been described, respiratory tract infections account for the majority of cases with those of mycobacterium tuberculosis and pulmonary tuberculosis being very rare and usually originating in countries with intermediate and high incidence of tuberculosis. While *Mycobacterium tuberculosis* when present in the body can induce cutaneous reactions of Sweet syndrome,treated Sweet syndrome with corticosteroids should be used cautiously as they can manifest latent tuberculosis or disseminate focal ones.

There were two cases of MASS: acute myelogenous leukemia and myelodysplastic disorder which are hematologic conditions. The remaining two cases involved one patient who was diagnosed with cervical cancer a few years later and another who was found to have concurrent underlying lung cancer. Although MASS can occur anytime there is a potential association with leukopenia, anemia or abnormal thrombocyte count, which should raise suspicion of underlying malignancy (our first case, who had both cervical cancer and pulmonary tuberculosis, showed both anemia and thrombocytosis).Generally Laboratory tests for Sweet syndrome usually show leukocytes with neutrophilia, elevated erythrocytes sedimentation rate (ESR), and/or C-reactive protein (CRP).

Other associated inflammatory-related causes that have been reported with Sweet syndrome are Crohns disease, ulcerative colitis, Sjorgren syndrome, Behcet disease, lupus erythematosus and rare cases have occurred with spinal surgery, sarcoidosis, erythematous nodosum, relapsing polychondritis, thyroiditis, and transplant patients.

Sweet syndrome with systemic lupus erythematosus is exceedingly rare, but we encountered it in case 8 in which it was an underlying disease in a patient who had several attacks of skin lesions with skin biopsy revealing neutrophilic infiltration. She had a good response to systemic corticosteroids. According to cases reported, Sweet syndrome associated with systemic lupus erythematosus is more common in males in their mid-30s. The pathogenesis of Sweet syndrome is uncertain, and there is evidence to point to dysregulation of cytokines, including interleukin-1, interleukin-3, interleukin-6 and interleukin-8 and Granulocyte colony stimulating factor (G-CSF),Granulocyte macrophage colony stimulating factor(GM-CSF) and Interferon gamma, as a cause. Some of these cytokines such as interleukin-6 may also play a role in SLE, including B-cell stimulation and Interferon gamma. It has been suggested that during SLE flare-up in certain patients, some cytokines implicated in eliciting Sweet syndrome are released and show clinical manifestations of Sweet syndrome. Dysregulation of cytokines which share the same pathogenesis of both SLE and Sweet syndrome, raises the hypothesis that Sweet syndrome observed in the setting of lupus may be classified as neutrophilic dermatoses of LE or the first manifestation of SLE[15]. Lastly, whether classical, drug-induced or malignancy-associated, most Sweet syndrome cases show a good response to systemic steroids or potassium iodide. Recurrence mainly occurs in CSS and MASS, and rarely persists for extended periods. Atypical clinical symptoms of MASS presentation with bullous or ulcerative lesions resemble pyoderma gangrenosum and are often recalcitrant to treatment.

What is already known on this topic?

Sweet syndrome is a rare neutrophilic dermatosis which is characterised by sudden onset of fever, leukocytosis, neutrophilia, and tender erythematous plaques infiltrated by neutrophils. Multiple conditions have been associated with this syndrome. In the present study, all patients with Sweet syndrome were carefully investigated for underlying conditions such as hematologic disorder, infection and systemic lupus erythematosus.

What this study adds?

The present study observed data on etiology and clinical signs associated with Sweet syndrome over a period of ten years. The findings revealed that clinical symptoms of Sweet syndrome included sudden febrile illness, characteristic skin lesion treatment response, and neutrophilic infiltration without vasculitis. Hematologic conditions were the most common cause of the disease, while infections, especially mycobacterium infections, are increasingly being suspected. The present study should be considered for counseling and treatment in order to improve patient outcomes.

Potential conflicts of interest

The authors declare no conflicts of interest.

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