Viewpoint

Sweet and Wells syndrome: One disease with different cellular infiltrates?

Ananya Sharma, M. Ramam

Department of Dermatology & Venereology, All India Institute of Medical Sciences (AIIMS), Delhi, India

Dear Editor,

Sweet syndrome and Wells syndrome are both acute, inflammatory conditions with strikingly different infiltrates—neutrophils in Sweet syndrome and eosinophils in Wells syndrome. However, they have several similarities.

Both Sweet syndrome and Wells syndrome occur predominantly in middle-aged (30–60 years) females, although they can occur at any age. [1,2] They are clinically characterized by acute, brightly erythematous, oedematous papules or plaques, with or without pseudo vesicles or frank bullae and pustules. They favour the extremities rather than the trunk. Upper limb involvement is characteristic of Sweet syndrome (71–97%), though involvement of the lower limbs also occurs in 36–55% of cases.[1,3] In a review of 32 cases of Wells syndrome, the upper or lower limbs alone were involved in four (12.5%) cases each, both extremities in six cases (18.8%), and the lower limbs along with the trunk in five cases (15.6%), making lower limb involvement slightly more common overall [Table 1]. Giant or diffuse lesions manifesting as pseudocellulitis and annular lesions occur in both conditions.[4] Tenderness is classical of Sweet syndrome (43%)[5], though pruritus has also been reported in 18% of cases and other symptoms include a burning sensation.[5,6] Pruritus is the primary local symptom of Wells syndrome, though tenderness and burning are seen as well.[2]

Constitutional symptoms are seen in both conditions, though described more frequently in Sweet syndrome (fever in 39–78% of patients, leading to the synonym of "acute febrile neutrophilic dermatoses"). In comparison, Wells syndrome showed constitutional features in 21.9% of patients. Extra-cutaneous involvement is somewhat more common in Sweet syndrome with recent studies reporting musculoskeletal involvement in 18–27% and ocular involvement in 10%.[6–9] Extra-cutaneous involvement in Wells syndrome is only described as case reports, which highlights the overlap of Wells syndrome with the spectrum of hypereosinophilic syndromes having pulmonary and parotid gland involvement.[7] Peripheral blood neutrophilia is seen in 47–80% of patients with Sweet syndrome and peripheral eosinophilia is seen in 67% of patients with Wells syndrome. Both entities have also been associated with haematological malignancies; classically acute myeloid leukaemia is described in Sweet syndrome in 16–35% patients;[6] and chronic lymphocytic leukaemia and non-Hodgkin lymphoma is reported in Wells syndrome (case reports).[10,11]

On histopathology, Sweet syndrome shows intense papillary dermal oedema, and a dense upper dermal diffuse or perivascular infiltrate of neutrophils, with or without secondary vasculitis. The infiltrate may extend into the subcutis and sometimes there is neutrophilic exocytosis into the overlying epidermis. Histiocytoid and predominant lymphocytic variants are described, and eosinophils may be seen in 25.8–77% of cases.[8,9] A very similar pattern of massive papillary dermal oedema and possible sub-epidermal vesiculation (but with eosinophils as the primary cells) is seen in Wells syndrome. Flame figures are often seen in Wells syndrome, as in other diseases with dense eosinophilic infiltrates.[12] It is an extremely rare finding in Sweet syndrome.

Both Sweet syndrome and Wells syndrome resolve spontaneously within 1–3 months but tend to recur in about

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Corresponding author: Dr. M Ramam, Department of Dermatology & Venereology, All India Institute of Medical Sciences (AIIMS), Delhi, India. mramam@hotmail.com

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Table 1: Clinical, epidemiological and histopathological features of Sweet and Wells syndrome

	Sweet syndrome	Wells syndrome
• Pathology	• Unrestricted neutrophil production	• Dysregulated eosinophil production
• Age group	• Mean age: 51 (range 30–75 years)[6] • all ages	• Mean age ± SD 33.6 ± 22.5 years[2] • all ages
• Gender	• Females 44–80%[6]	• Females: 63%[2]
• Triggers/associated diseases	• Classical: 53% • Infections: 24% (90% respiratory tract infections) • Inflammatory bowel disease • Malignancy: 14-35% (of which 78% are haematological malignancies, classically acute myelogenous leukaemia) • Drugs: 12–26% (including antibiotics like minocycline, cotrimoxazole; antiepileptics, oral contraceptive pills, furosemide, azathioprine, colony stimulating factors) • Autoimmune disease: 7% • Pregnancy: 2%[1]	• Idiopathic • Insect bites or stings • Infections (e.g., dermatophytes, viruses, *Toxocara canis*) • Drugs (e.g., tumor necrosis factor alpha inhibitors, antibiotics like penicillin and tetracyclines) • Allergic contact dermatitis • Malignancy: Chronic lymphocytic leukaemia, Hodgkin's lymphoma.
• Clinical features	• Tender (48%), pruritic (18%) or burning erythematous, oedematous plaques, papules, pustules or nodules • Uneven mamillated surface with pseudo vesicular appearance, true vesicles (14%)[6]	• Pruritic, burning or tender erythematous, oedematous nodules and plaques • Vesicles and bullae (50%, 16/32)[2]
• Site	• Upper extremities: 71–97% • Head and neck: 25–63% • Lower limbs: 36–55% • Oral mucosa: 4%[6]	In a review of 32 cases[2]; • Upper limbs alone: 4 (12.5%) • Lower limbs alone: 3 (12.5%). • Trunk alone: 3 (6.3%) • Both extremities: 6 (18.8%). • Lower limbs with trunk: 5 (15.6%) • Multiple sites: 7 (21.9%)
• Systemic complaints	• Fever (39–78%) • Malaise 27% • Musculoskeletal symptoms 18–27%[6,8] • Ocular: 10%[6]	• Fever, malaise and/or arthralgia in 21.9%[2] • Other systems uncommonly involved
• Peripheral blood	• Peripheral blood neutrophilia: 47–80% patients[1]	• Peripheral blood eosinophilia: 67%
• Histopathological examination	• Dense upper dermal diffuse or perivascular infiltrate of neutrophils, with or without secondary vasculitis[19] • Intense papillary dermal oedema (90%), subepidermal vesiculation • Occasionally may extend to subcutis (septal panniculitis) (8%) • Epidermal spongiosis (76%), neutrophilic exocytosis and subcorneal pustules[8] • Histiocytoid, lymphocytic • Eosinophils in 25.8–77%[8,9]	• Dense dermal infiltrate of eosinophils (100%) with flame figures: 96%[2] • Massive papillary dermal oedema to the point of subepidermal bulla formation • Occasional involvement of the subcutaneous fat, fascia, and skeletal muscle • Intra-epidermal vesiculation, with eosinophilic spongiosis
• Cytokines	• Interleukin 1, 3, 6, 8, granulocyte macrophage colony-stimulating factor, Granulocyte colony-stimulating factor, interferon gamma	• Interleukin 5
• Clinical course	• Resolution: 5–12 weeks • Recurrence: 15–23%, within 7 months[8]	• Resolution over 2–8 weeks, with post-inflammatory hyperpigmentation and atrophy • Recurrence: 56% at a mean follow-up time of 11 ± 8 months
• Treatment	• Oral prednisone (0.5–1.0 mg/kg/day) for 2–6 weeks. • Potassium iodide (900 mg/day) • Colchicine (1.5 mg/day) • Dapsone (100–200 mg/day)	• Oral prednisolone 1–2 mg/kg, tapered over 1 month • Cyclosporine (1.25–2.5 mg/kg/day) for 3–4 weeks • Dpsone (100–200 mg/day) • Colchicine (1.5 mg/day) • Antimalarials • Minocycline • Griseofulvin

one-third of patients with Sweet syndrome and in more than half the patients with Wells syndrome.[1,2] The first-line treatment for both Sweet syndrome and Wells syndrome is systemic corticosteroids such as prednisolone 0.5–1 mg/kg/day, with a dramatic response within a few days, so much so that it is included in the diagnostic criteria for Sweet syndrome. A similar response was seen in Wells syndrome in which 12 (92%) of 13 cases went into resolution with systemic corticosteroid therapy.[2] Alternate treatment options are similar in both diseases and include colchicine, dapsone, antimalarials, and immunosuppressives like cyclosporine and methotrexate.

Consigny *et al*.[13] reported a patient of non-Hodgkin lymphoma having successive occurrence of vasculitis, Wells syndrome, and Sweet syndrome and suggested a possible overlap between these diseases. Canine acute eosinophilic dermatitis with oedema is the counterpart of Wells syndrome and sterile neutrophilic dermatosis is the counterpart of Sweet syndrome in canines.[14] They are considered to be significantly overlapping conditions, aside from the type of granulocytic infiltrate and some clinical correlates. It has been hypothesised that variation in individual immune responses leads to these conditions that are arbitrarily categorized into 2 different disorders.

The exact pathogenesis of the conditions is not clear, but both Sweet and Wells syndromes have been described by various authors as hypersensitivities, or 'reactive dermatoses', with an external or internal trigger causing alterations in cell signalling and cytokine production leading to neutrophilic or eosinophilic infiltration of the skin and other tissues.

Classically, Th1-type (T helper type 1) responses mediated by interleukin 1, interferon γ and tumor necrosis factor α tend to result in cellular immunity and neutrophil activation; whereas Th2 responses mediated by interleukins 4 and 5 and 13 result in enhanced eosinophil and basophil functions, humoral immunity and allergy. Cytotoxic CD8+ T cells participate in the Th1 response and enhance neutrophil viability *via* interferon γ, granulocyte macrophage colony-stimulating factor and tumor necrosis factor α. However, the immune system is vastly interconnected, and neutrophil and eosinophil recruitment may not be clearly distinct processes. For example, subsets of $CD8^+$ T cells are now described, including Tc1 and Tc2 (cytotoxic T cells subset 1 and 2), in which the latter is analogous to Th2 and predominantly secretes interleukin 4 and interleukin 5, rather than interferon γ.[15] This might skew the immune response towards Th2 in certain individuals and favour accumulation and activation of eosinophils and/or basophils, relative to neutrophils. Innate lymphoid cells are a recently described innate immunity counterpart of lymphocytes that display functional plasticity amongst their subsets (innate lymphoid cell 1, innate lymphoid cells 2 and lymphoid tissue inducer cells).They function corresponding to Th1, Th2 and Th17 subtypes of adaptive immunity, respectively. Innate lymphoid cells 2 are activated by interleukin 1β and interleukin 18 to produce interleukin 5 and interleukin 13, analogous to the Th2 response, leading to an eosinophilic response.[16] At the same time, interleukin 1β is also a potent stimulator of neutrophils. Stem cell factor is known to augment the colony formation of neutrophils; but has now been shown to stimulate the formation of eosinophil colonies or mixed neutrophil-eosinophil colonies, also.[17]

Both neutrophils and eosinophils are known to release their intra-cellular DNA to form extra-cellular traps (neutrophil extra-cellular traps and eosinophil extra-cellular traps) as an acute response to pathogens, promoting inflammation and tissue damage; while eosinophils also have a role in tissue remodelling. Though the migration from bone marrow is mediated through different chemokines for neutrophils (CXCL12/CXCR4) (chemokine ligand 12/chemokine receptor 4) and eosinophils (CCL11 (eotaxin-1)/CCR3)(chemokine ligand 11/chemokine receptor 3), some local chemo-attractants like leukotriene B cause chemotaxis of both neutrophils and eosinophils, as has been studied in asthma.

This overlap and switching between neutrophils and eosinophils in diseases that typically demonstrate an infiltrate composed of one of these leukocytes, occurs in other conditions, too. Fixed drug eruption and bullous pemphigoid characteristically demonstrate eosinophils in the infiltrate,but may show a predominantly neutrophilic infiltrate. Erythema nodosum leprosum is characteristically associated with a dense neutrophilic infiltrate, but eosinophils are seen in 17.6% (6/34) to 28.1% (9/32) of cases and may be the predominant cell in some biopsies.[18]

The similarities between Sweet and Wells syndromes suggest that they may represent the same disease having different types of leukocyte infiltration.

Declaration of patient consent

Patient consent is not required as there are no patients in this study.

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Conflict of interest

There are no conflicts of interest.

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