Views and Practice

Sweet dreams and nightmares: a case series of Sweet’s syndrome

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Introduction
Sweet’s syndrome (SS) is characterised by tender, erythematous plaques with fever, leukocytosis and neutrophilia. The hallmark histological finding is a neutrophilic infiltrate in the papillary dermis. Due to similarities in clinical features, biochemical markers and lack of awareness, SS is often misdiagnosed as infection. This series aims to illustrate the protean presentations of this syndrome. Twelve patients were identified by the senior author between January 2005 and May 2017 at two major Sydney teaching hospitals in Sydney. In these cases, the diagnosis was made through patient history, clinical findings and compatible histological features.

Case 1
A 39-year-old female presented with acute occipital headache, neck stiffness and photophobia. She was tachycardic, febrile (39°C) and her blood count demonstrated leukocytosis with neutrophilia. The blood culture, cerebrospinal fluid examination, and neuroimaging were all normal. On Day 2, she developed a single erythematous, tender plaque on the left forehead. Skin biopsy revealed granulomatous dermatitis consistent with SS, and the patient was commenced on a course of oral steroids. The prednisone was subsequently weaned over two weeks following resolution of the headache and cutaneous plaque. Ten years later, the patient had a recurrence of SS involving the right foot only, and she required recommencement of prednisone (Figure 1).

Case 2
A 64-year-old male with orthotopic liver transplantation presented with scaly, ulcerated erythematous plaques on his chest and shoulders. He had leukocytosis and neutrophilia. His skin biopsy revealed sub-epidermal blistering with neutrophilic dermatosis (Figure 2). A diagnosis of SS was made, and a short course of prednisone was commenced which led to complete resolution.

Case 3
A 41-year-old female presented with a painful, oedematous right foot. Physical examination found an erythematous patch on the dorsal aspect of the foot with serous discharge. Superficial wound culture was positive for Group A Streptococcus, which led to the patient being commenced on cephalexin. While on treatment, she then developed new blisters on her calf, which was...
managed with escalation to intravenous antibiotics. Despite this, the skin blistering extended onto the medial thigh with purulent discharge and tissue necrosis. The patient was taken to theatre for debridement for presumed necrotising fasciitis. Following debridement, a skin biopsy identified dense dermal neutrophilic infiltrate consistent with SS. Although her cutaneous symptoms resolved with prednisone, the patient unfortunately developed permanent foot deformity from contractures (Figure 3).

Case 4
A 62-year-old male presented to hospital with dyspnoea and fever. Benzylpenicillin was
commenced for the diagnosis of community-acquired pneumonia. On day three, he developed multiple tender, vesiculopapular patches on all four limbs (Figure 4). At the same time, computerised tomography of the abdomen demonstrated aortitis. Following skin biopsy confirmation of SS and subsequent commencement of oral steroids, cutaneous and aortic manifestations were resolved.

**Case 5**
A 44-year-old female with chronic lymphocytic leukaemia was commenced on piperacillin, tazobactam, and gentamicin for presumed febrile neutropenia after presenting with fevers and diarrhoea. She was also given filgrastim. Her septic screen was negative. Two days post presentation, the patient noted multiple tender, erythematous papules on her palms, back and lower limbs. Subsequent skin biopsy showed dense dermal neutrophilic infiltrate. Prednisone was commenced, and filgrastim was ceased. The patient had resolution of all cutaneous symptoms.

**Case 6**
A 53-year-old male presented with bilateral hand eruptions following a burn injury from steel welding. Three days later, similar lesions erupted on the neck, chest and ear. Multiple tender pustular papules with central necrosis were seen on both hands. The face, neck, ears and chest displayed indurated and erythematous pustules. The patient also had associated leukocytosis (15.7x10^9/L), neutrophilia (12.5x10^9/L) and raised CRP (121 mg/L). On the second skin biopsy, there was dense neutrophilic infiltrate throughout the dermis consistent with SS. He was managed with prednisone and betamethasone ointment twice a day with no recurrence.

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**Case 8**
A 61-year-old female presented with a four-day history of a painful, swollen left arm. Her general practitioner had treated her with cephalexin with no improvement. On examination, the left arm was markedly oedematous and circumferentially covered with tender, erythematous macules, nodules and pustules. Her skin biopsy confirmed SS. The lesions resolved with prednisone and topical betamethasone.

**Case 9**
A 78-year-old female presented with a two-week history of tender, erythematous lesions on her hands, elbows, calves and feet. The patient had accompanying leukocytosis, neutrophilia and raised CRP. Her skin biopsy identified a dense infiltrate of neutrophils in the dermis. She was immediately commenced on prednisone. Her malignancy screen revealed high serum paraprotein but her bone marrow biopsy excluded multiple myeloma.

**Case 9**
A 61-year-old female was commenced on antibiotics for infective exacerbation of bronchiectasis. Two days later, she developed
numerous tender, erythematous, ulcerative lesions localised to the dorsum of her left hand (Figure 5). Sweet’s syndrome was confirmed histologically, and the patient was started on prednisone 30 mg for two weeks. Two months later, the patient noted new lesions on her right hand. Her malignancy screen revealed a new diagnosis of monoclonal gammopathy of undetermined significance and she is now regularly reviewed by haematology.

**Case 10**
A 41-year-old female with chronic myeloid leukaemia was admitted with Salmonella enterica positive pleural effusion secondary to dasatinib. She was treated with antibiotics and left lung decortication. Three days post operatively, the patient developed tender, erythematous papules localised to her left forearm. Histology was consistent with SS, and again oral prednisone 25 mg daily and twice daily topical betamethasone was commenced. The patient required maintenance therapy of prednisone 10 mg for four months due to relapse. Currently, her disease is well controlled with topical therapy alone.

**Case 11**
A 50-year-old male presented with a two-year history of multiple violaceous nodules on the dorsum of both hands which would spontaneously resolve after four weeks. His laboratory tests showed leukocytosis and neutrophilia. The skin biopsy found mixed inflammatory infiltrate in the superficial dermis with predominant neutrophils. He was commenced on prednisone 25 mg daily for one week and continued at 12.5 mg daily for another two weeks. Upon review four week later, the patient continued to develop new pustules. Prednisone was then increased back 25 mg. Due to the relapsing nature of his SS, dapsone was added after five weeks of prednisone monotherapy.

**Case 12**
A 51-year-old female was referred by her rheumatologist for a dermatological review of intermittent, painful nodules on her fingers and back for the last 18 months. The rheumatologist had commenced her on doxycycline and nifedipine for chilblains with no obvious improvement. Her skin biopsy demonstrated a neutrophilic dermatosis and the patient was commenced on prednisone for two weeks with resolution of all lesions.

**Discussion**
Sweet’s syndrome was first described by Robert Sweet in 1964.\(^1\) Since then, clinical phenotypes have expanded from the original classic/idiopathic subtype to include drug-related and malignancy-associated SS. There are no reliable epidemiological data for the prevalence of SS. However, this condition is diagnosed worldwide without racial predilection.\(^2\) Classic SS has a female predominance, with 4:1 female to male ratio. The average age of diagnosis is between 30-60 years,\(^3\) although classic SS has been reported in neonates as young as three days old.\(^4\)-\(^6\)

Sweet’s Syndrome is frequently misdiagnosed as an infection. The majority of SS involve skin lesions located on more than one body site, commonly affecting the face, neck and upper extremities.\(^4\),\(^7\)
In classic and drug-induced SS, erythematous papules or nodules may enlarge and coalesce into well-demarcated plaques. Approximately 43% of SS lesions are tender. Uncommon presentations include unilaterally distributed lesions, lesions limited to the dorsum of hands and necrotic lesions.

A striking feature of this series is the large number of patients with SS localised to one body site. Although this is relatively rare in the literature, six patients in our series had asymmetrical and localised skin disease (Table 1). All six patients were diagnosed with idiopathic SS but each case presented with varied lesional morphology and extra-cutaneous clinical features. The SS lesions ranged from macules, papules, plaques to bullous, ulcerated and necrotising lesions. The patient in Case 3 continues to suffer from foot contractures and mobility limitations as a result of delayed diagnosis. This illustrates the importance of being aware of unilateral SS as an important clinical presentation of SS and not diagnosing mistakenly the clinical crisis as protracted cellulitis.

The assessment of suspected SS involves taking a thorough medication history, morphological examination of the lesions, exclusion of infection, and focused search for extra-cutaneous involvements. Laboratory tests should include full blood count with differential, C-reactive protein, erythrocyte sedimentation rate, liver function, renal function, anti-streptolysin O titre, rheumatoid factor, thyroid function tests, and urinalysis (Table 2). A skin biopsy should be sent for histopathology, bacterial, fungal, mycobacterial and viral cultures. A chest X-ray and a computed tomography of visceral organs near the skin lesions is recommended.

Malignancy-associated SS is a polymorphic entity and can occasionally present as bullous, ulcerated papules/plaques similar lesions of pyoderma gangrenosum. In our series, we had three patients (Cases 2, 3 and 6) with bullous SS. Neoh et al, had previously demonstrated that haematological malignancies are not over-represented in bullous SS patients, which is similar to our findings. Interestingly, patient 10 who had underlying chronic lymphocytic leukaemia actually presented with non-bullous skin lesions.

Table 1. Clinical details for the twelve patients with Sweet's syndrome

<table>
<thead>
<tr>
<th>Case</th>
<th>Distribution of the cutaneous lesions</th>
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<tbody>
<tr>
<td>1. 39 F</td>
<td>Originally on left forehead, recurrent disease localised to right foot*</td>
</tr>
<tr>
<td>2. 64M</td>
<td>Chest and shoulders</td>
</tr>
<tr>
<td>3. 41F</td>
<td>Right foot*</td>
</tr>
<tr>
<td>4. 62M</td>
<td>All four limbs</td>
</tr>
<tr>
<td>5. 44F</td>
<td>Palms, back and lower limbs</td>
</tr>
<tr>
<td>6. 53M</td>
<td>Head, neck &amp; chest</td>
</tr>
<tr>
<td>7. 61F</td>
<td>Left arm*</td>
</tr>
<tr>
<td>8. 78F</td>
<td>Hand, both elbows and both feet</td>
</tr>
<tr>
<td>9. 61F</td>
<td>Left hand, recurred on right hand**</td>
</tr>
<tr>
<td>10. 41F</td>
<td>Left forearm, recurrent disease at same site*</td>
</tr>
<tr>
<td>11. 50M</td>
<td>Dorsum of both hands**</td>
</tr>
<tr>
<td>12. 51F</td>
<td>Fingers and back</td>
</tr>
</tbody>
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*Lesions isolated to one body site
**Lesions only on dorsum of hands

Table 2. Key features alerting clinicians to consider Sweet's syndrome as a diagnosis

1. Acute onset of painful, red papules or nodules
2. Fever >38°C
3. Associated diseases: Haematological or visceral malignancy, inflammatory bowels disease, pregnancy; or preceded by upper respiratory tract/gastrointestinal infection
4. Arthralgia, myalgia, malaise & ocular involvement
5. High inflammatory markers: WCC >8x10⁹ with neutrophils >70%, ESR >20 mm/h; high CRP
A recommended malignancy work up involves an examination of the oral cavity, thyroid glands, lymph nodes, breasts, digital rectal examination as well as a prostate exam and pelvic exam. Full blood count, carcinoembryonic antigen, Pap smear, faecal occult blood test, and colonoscopy should be arranged for those over 50 years old. Follow up in six months with repeat baseline blood tests is recommended, as one-third will have a recurrence of SS.

Approximately 20% of all SS diagnoses are malignancy-related, 80% of which are haematological. Acute myeloid leukaemia is the most commonly implicated haematological malignancy. Female gender, older age, anaemia, low platelet count, and high ESR are more common in malignancy-associated SS. In one study involving 83 patients, the mean haemoglobin was 10.6 g/dL in the malignancy group compared to 12.2 g/dL in non-malignancy associated SS. The median age at diagnosis was 59. Commonly reported solid organ tumours were carcinomas of the genitourinary tract (37% of patients), breast (23%) and gastrointestinal tract (17%). Adenocarcinoma was the most common cell type. Associations of SS with pulmonary, head and neck carcinomas and melanomas are also recognised.

Drug induced SS was first reported in 1986 with use of trimethoprim-sulfamethoxazole. The diagnostic criteria requires a temporal relationship between medication administration and clinical symptoms as well as a temporal relationship between drug withdrawal and symptom resolution. Unlike the other variants, abnormal laboratory values such as neutrophilia are not needed for diagnosis. The top five implicated drugs are granulocyte colony-stimulating factor (GCSF) tretinoin, sulfamethoxazole with trimethoprim, bortezomib, and azathioprine. From case report evidence, lesions typically appear seven days post exposure and disappear within two to three days after drug cessation.

Differential diagnoses for SS includes pyoderma gangrenosum and other neutrophilic dermatoses such as neutrophilic eccrine hidradenitis, neutrophilic urticarial dermatosis, palisading neutrophilic granulomatous dermatitis and Behcet's disease.

Systemic corticosteroid therapy is recommended as first line treatment. The usual dosage is prednisone 30-60 mg/day or 0.5-1 mg/kg/day with tapering within four to six weeks. In classic and malignancy associated SS, clinical improvement is expected within days and skin lesions begins to heal within two days. However, some patients require treatment for up to three months. Pulse methylprednisone up to 1000 mg in 5% dextrose for three to five days are useful in severe, refractory and recurrent SS.

Topical corticosteroids may be sufficient as monotherapy in drug induced SS. Intraleisonal corticosteroids is useful for isolated hand lesions. A common regime is 0.75 mL of triamcinolone 3.0 mg/ml in combination with topical 0.05% clobetasol propionate ointment.

If the patient cannot tolerate corticosteroids, colchicine and dapsone are recommended alternatives. Both agents have been used as initial monotherapy or following corticosteroid failure. Colchicine could be commenced at 0.5 mg to 1 mg daily and then titrated as clinically indicated.

**Conclusion**

Sweet's syndrome is a clinically distinctive disorder which can usually be diagnosed without exhaustive investigations. We present a case series of 12 patients with a multitude of unusual presentations of classic and malignancy associated Sweet's syndrome. Drug-induced SS is uncommon although it may be encountered more frequently in the future with rising usage of medications. Early
and correct diagnosis is vital in achieving a favourable outcome as incorrect and delayed diagnosis can lead to unwelcome consequences. With increasing awareness of this syndrome there will hopefully be more sweet dreams than nightmares for the patients and their families in the future.

References