Reminder of important clinical lesson

Sweet's syndrome as the presenting manifestation of gall bladder adenocarcinoma

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Summary

Sweet's syndrome is a neutrophilic inflammatory dermatosis presenting with sudden onset tender red to purple papules and nodules, fever and neutrophilia. Gastrointestinal and urinary tract infections, pregnancy, inflammatory bowel disease, drugs and malignancy are some of the known aetiological factors. Paraneoplastic Sweet's syndrome accounts for 15–20% cases and thus forms an important subset. At times its onset helps in suspecting an underlying malignancy, thus making timely intervention possible. In the present case report Sweet's syndrome was the presenting feature of gall bladder adenocarcinoma; an association that has been rarely reported before.

BACKGROUND

Sweet's syndrome (SS) also termed as acute febrile neutrophilic dermatosis is a reactive process characterised by sudden onset fever, leucocytosis and tender erythematous to violaceous plaque forming papules and nodules. It is an uncommon disease with a reported annual incidence of 2.7–3/10⁶ cases.^{1–2} The disease can present in different clinical settings. Idiopathic or classical SS typically occurs in middle-aged women at times in association with upper respiratory tract or gastrointestinal tract infection, pregnancy or inflammatory bowel disease.³ Drug-induced SS most frequently occurs in patients receiving granulocyte colony stimulating factor (G-CSF). Other causative drugs include antibiotics, antiepileptic drugs, antihypertensive drugs, oral contraceptives and retinoids.⁴ Paraneoplastic SS occurs in patients with underlying malignancy either haematogenous or solid tumours.³ Paraneoplastic SS can be the initial sign of internal malignancy, thus all suspected patients need to be adequately investigated. The present case report also emphasises this fact as the patient had presented with cutaneous lesions suggestive of SS and pain abdomen which on evaluation turned out to be due to underlying gall bladder adenocarcinoma.

CASE PRESENTATION

A 45-year-old lady sought dermatology consultation for severely tender erythematous vesicles and bullae over back, chest and arms. These were sudden in onset associated with fever, nausea and malaise. Along with this she also complained of pain in upper abdomen. There was no history of receiving any drugs prior to the onset of lesions. She did not report any significant weight loss or loss of appetite. On physical examination, her temperature was 38°C, pulse rate was 100/min and blood pressure was 126/72 mm Hg. There were multiple coalescing vesicles and bullae over upper back, chest and arms distributed symmetrically showing areas of pustulation

and necrosis. Surrounding them were multiple pseudovesicular satellite papule (figure 1A,B). On per abdominal examination mild tenderness was present in the right hypochondrium.

INVESTIGATIONS

Patient's initial laboratory investigations showed a total leucocyte count of 12 000 cells/mm³ with 75% neutrophils. The haemoglobin level was 14.3 gm% and erythrocyte sedimentation rate was 30 mm/h. Liver function test, kidney function test and C reactive protein levels were within normal limits. Gram stain from purulent exudates showed only neutrophils without any organisms and culture did not show any growth after 72 h of incubation. A lesional skin biopsy taken from the satellite papule showed neutrophilic infiltration in dermis with papillary dermal oedema and spongiosis (figure 2A,B). Abdominal ultrasonography revealed intraluminal gall bladder mass suggestive of malignancy.

DIAGNOSIS, TREATMENT, OUTCOME AND FOLLOW-UP

On the basis of these findings a final diagnosis of SS associated with gall bladder malignancy was made. She was started on oral prednisolone in dose of 40 mg daily along with symptomatic treatment. Her cutaneous lesions responded dramatically and subsided completely after 1 week of treatment (figure 3A,B). Dose of prednisolone was tapered and an open cholecystectomy was performed. Histopathology of excised tissue confirmed it to be well-differentiated gall bladder adenocarcinoma forming glands and papillae infiltrating the muscularis propria superficially. Cystic duct cut margins were free of tumour (figure 2C,D). Patient's postoperative period was uneventful and she was discharged on tapering doses of prednisolone with advice to follow-up periodically.

Figure 1 (A) Coalescing vesicles and bullae over upper back showing areas of necrosis and ulceration, (B) grouped vesicles surrounded by pseudovesicular satellite papules over arm.

DISCUSSION

Acute febrile neutrophilic dermatosis was described for the first time by Robert Douglas Sweet in 1964 and since then a number of aetiological factors have been reported.⁵ It is classified among the neutrophilic dermatosis; a group of neutrophilic inflammatory skin diseases linked to disorders of internal organs.⁶ Pathogenesis of SS is incompletely understood and various cytokines are thought to play some role. The important cytokines involved include interleukin (IL)-1, IL-6, IL-8, G-CSF and granulocyte monocyte CSF (GM-CSF). Acute myeloblastic leukaemia cells spontaneously produce IL-1 which potentiates synthesis of GM-CSF and G-CSF. In response to GM-CSF;

neutrophils induce the expression of IL-8 gene resulting in IL-8 synthesis. IL-8 acts as a potent neutrophil chemotactic agent and thus the whole inflammatory process is amplified.⁷ In a case report, IL-1 receptor antagonist was found to be effective in a patient with refractory SS; thus supporting the central role of IL-1 in disease pathogenesis.⁸

On the basis of the underlying aetiology, SS is classified into four subgroups: classical/idiopathic, parainflammatory, paraneoplastic and pregnancy induced.⁹ Some authors also include a fifth drug induced variant.¹⁰ Most of the patients fall under classical/idiopathic subgroup (75%), followed by parainflammatory (15–16%), paraneoplastic (10–20%), drug-induced (5%) and pregnancy-associated

Figure 2 (A) Neutrophilic infiltration of dermis with papillary dermal oedema and spongiosis, (B) high-power view showing neutrophilic infiltration, (C) well-differentiated adenocarcinoma forming glands and papillae, (D) high-power view of (C).

Figure 3 (A) and (B) Clearance of lesions with steroid treatment.

(2%) group.¹⁻⁹ According to the diagnostic criteria given by Von den Driesch (table 1) the presence of both major and two of the minor criteria is required for making the diagnosis.⁹

Sudden onset tender erythematous to violaceous papules and nodules which coalesce and form plaques are considered to be the hallmark lesions of SS. Most frequently involved sites are face, neck and upper extremities. Histopathologically, there is an infiltration of superficial dermis with mature neutrophils along with papillary dermal oedema. In addition to skin, there can be aseptic neutrophilic infiltration in organs like lungs, brain, eyes and heart. Systemic symptoms which accompany the cutaneous lesions include fever, arthralgia, malaise and headache. Both systemic and cutaneous lesions respond rapidly to corticosteroids and potassium iodide. Other agents used alone or in combination with steroids include dapsone, cyclosporine, cyclophosphamide and acitretin.³

Malignancy accounts for 10–20% cases of SS. These are either hematological malignancies or solid tumours. Most common hematological malignancies associated are acute myeloid leukaemia and myelodysplastic syndromes. Around 15% cases of paraneoplastic SS are due to solid

tumours involving genitourinary tract, breast and gastrointestinal tract.¹¹ Malignancy-associated SS differs from classical variety in being more persistent, widespread and recalcitrant to treatment. Relapse after treatment is also more frequent.⁹ Paraneoplastic SS differs considerably from classical SS in demographic profile as well as morphology (table 2). Lesions more commonly turn bullous, ulcerative and may mimic pyoderma gangrenosum.¹²⁻¹³ Treatment of underlying malignancy forms the cornerstone of the management of paraneoplastic SS. Recurrence of lesions in such patient's points towards relapse of underlying malignancy.

Onset of paraneoplastic SS can precede, follow or occur concurrent with diagnosis of underlying malignancy. Presence of widespread bullous lesions in our patient pointed towards the possibility of underlying malignancy and further ultrasonography done for pain abdomen helped in making the final diagnosis of paraneoplastic SS. Association of gall bladder adenocarcinoma with SS has been rarely reported before. This case is being reported to sensitise the clinicians and surgeons for need of systemic evaluation in such cases to rule out underlying malignancy.

Table 1 Criteria for diagnosis of Sweet's syndrome

Major criteria	Minor criteria
1. Abrupt onset of painful erythematous plaques or nodules	1. Fever >38°C
2. Histopathological evidence of a dense neutrophilic infiltrate without evidence of leucocytoclastic vasculitis	2. Association with an underlying haematological or visceral malignancy, inflammatory disease or pregnancy, OR preceded by an upper respiratory or gastrointestinal infection or vaccination
	3. Excellent response to treatment with systemic corticosteroids or potassium iodide
	4. Abnormal laboratory values at presentation (three of four): erythrocyte sedimentation rate >20 mm/h; positive C reactive protein; >8000 leucocytes; >70% neutrophils

Table 2 Differences between classical and paraneoplastic Sweet's syndrome (SS)

	Classical SS	Paraneoplastic SS
1. Female : male ratio	3 : 1	1 : 1
2. Clinical feature	Erythematous, tender papules, nodules and plaques	In addition atypical lesions including pustules, blisters, ulcers and purpura
3. Distribution of lesions	Limited; head, neck and upper limbs	Widespread; head, neck, trunk and extremities
4. Extracutaneous manifestations	Less	More
5. Laboratory abnormalities (anaemia and neutrophilia)	More	Less
6. Recurrence	Less	More

Learning points

- ▶ Paraneoplastic Sweet's syndrome is an important disease subset accounting for 15–20% cases of Sweet's syndrome.
- ▶ Presence of atypical lesions including blisters, ulcers and purpura point towards underlying malignancy.
- ▶ Recurrence of lesions after adequate treatment is a marker of relapse of malignancy.

Competing interests None.

Patient consent Obtained.

REFERENCES

1. **Djien V**, Wallach D. Sweet's syndrome: practical conduct. *Ann Dermatol Venereol* 1999;**126**:343–7.
2. **Kemmet D**, Hunter JA. Sweet's syndrome: a clinicopathologic review of twenty nine cases. *J Am Acad Dermatol* 1990;**23**:503–7.
3. **Corazza M**, Lauriola MM, Borghi A, *et al*. Sweet's syndrome: a retrospective clinical, histopathological and immunohistochemical analysis of 11 cases. *Acta Derm Venereol* 2008;**88**:601–6.
4. **Saez M**, Garcia-Bustinduy M, Noda A, *et al*. Drug-induced Sweet's syndrome. *J Eur Acad Dermatol Venereol* 2004;**18**:233.
5. **Sweet RD**. An acute febrile neutrophilic dermatosis. *Br J Dermatol* 1964;**76**:349–56.
6. **Wallach D**. Neutrophilic dermatoses: an overview. *Clin Dermatol* 2000;**18**:229–31.
7. **Fernandez-Fernandez FJ**, Alvarez-Fernandez JC, Romero-Picos E, *et al*. Neutrophilic dermatosis of the dorsal hands associated with a myeloproliferative neoplasm, unclassifiable and a simultaneous cancer of colon. *Acta Medica* 2010;**53**:153–6.
8. **Delluc A**, Limal N, Puechal X, *et al*. Efficacy of anakinra, an IL1 receptor antagonist, in refractory Sweet syndrome. *Ann Rheum Dis* 2008;**67**:278–9.
9. **Von den Driesch P**. Sweet's syndrome (acute febrile neutrophilic dermatosis). *J Am Acad Dermatol* 1994;**31**:535–56.
10. **Prevost-Blank PL**, Shwayder TD. Sweet's syndrome secondary to granulocyte colony stimulating factor. *J Am Acad Dermatol* 1996;**35**:995–7.
11. **Cohen PR**, Holder WR, Tucker SB, *et al*. Sweet syndrome in patients with solid tumors. *Cancer* 1993;**72**:2723–31.
12. **Voelter-Mahlknecht S**, Bauer J, Metzler G, *et al*. Bullous variant of Sweet's syndrome. *Int J Dermatol* 2005;**44**:946–7.
13. **Neoh CY**, Tan AWH, Ng SK. Sweet's syndrome, a spectrum of unusual clinical presentations and associations. *Br J Dermatol* 2007;**156**:480–5.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Jindal R, Jain A, Mittal A, Shirazi N. Sweet's syndrome as the presenting manifestation of gall bladder adenocarcinoma. *BMJ Case Reports* 2012;10.1136/bcr-2012-006869, Published XXX

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