Eponyms in medicine revisited

Summary

Pyoderma gangrenosum and **Sweet's syndrome** are classified as **neutrophilic dermatoses** as they exhibit intense dermal inflammatory infiltrates composed of neutrophils with little evidence of a primary vasculitis. They share several characteristics and respond to immunosuppressives. Aetiology is felt to represent a manifestation of altered immunologic reactivity. Patients with both conditions concurrently have been described. Diagnosis is based on clinical and histopathological findings. However, clinically the typical forms of the two conditions are quite distinct: pyoderma showing cutaneous ulceration with a purple undermined border and Sweet's syndrome having tender, erythematous, nonulcerated plaques and nodules. Approximately 50% of cases of pyoderma are associated with a specific systemic disorder. These include inflammatory bowel disease, rheumatoid arthritis, non-Hodgkin's lymphoma and myeloproliferative disorders. Many associations with Sweet's syndrome have been described, including acute myeloid leukaemia, myeloma and adenocarcinomas, and haematological malignancy. There is overlap between the two conditions with lesions categorised as Sweet's syndrome being clinically more characteristic of atypical pyoderma and vice versa. We believe that pyoderma and Sweet's syndrome represent a continuum of spectrum of disease. The reason for the clinical differences between the conditions is unclear and merits further investigation but may be explained by varying levels of intensity and extent of the inflammatory process. This review will describe the pathogenesis, clinical features, diagnosis, associations and treatment of the two conditions.

Keywords: neutrophilic dermatoses, pyoderma gangrenosum, Sweet's syndrome

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Neutrophilic dermatoses: pyoderma gangrenosum and Sweet's syndrome

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Pyoderma gangrenosum and Sweet's syndrome (acute febrile neutrophilic dermatosis) are clinical conditions sharing several characteristics. They may be classified as neutrophilic dermatoses as they both exhibit intense dermal inflammatory infiltrates composed of neutrophils with little evidence of a primary vasculitis. They respond to immunosuppressives and aetiology is unknown but is felt to be a manifestation of altered immunologic reactivity.¹ Patients with both conditions concurrently have been described^{1,2} and we report another in this article. However, clinically the typical forms of the two conditions are quite distinct and unlikely to be confused: pyoderma gangrenosum showing cutaneous ulceration with a purple undermined border and Sweet's syndrome tender, erythematous, non-ulcerated plaques and nodules.¹

This review will describe the pathogenesis, clinical features, histopathology, diagnosis, differential diagnosis, associations, treatment and prognosis of the two conditions, illustrating their differences and similarities and addressing the notion that they may represent a continuum of spectrum of disease.

Pathogenesis

PYODERMA GANGRENOSUM

The pathogenesis is uncertain but is thought to be related to defective immune responses. Decreased or abnormal immune responses have been described.³ It has also been shown that patients with pyoderma gangrenosum have a failure to induce a contact hypersensitivity response to topically applied dinitrochlorobenzene, suggesting a defect in type 4 immune responses. There are reports of pyoderma gangrenosum in association with monoclonal gammopathies, paraproteins⁴ and HIV,⁵ further supporting the association with decreased immunity. However, pyoderma gangrenosum developing after granulocyte colony stimulating factor administration in patients with solid tumours has been described in the literature.⁶ No clear antigenic trigger has been identified.

SWEET'S SYNDROME

Like pyoderma gangrenosum the pathogenesis is unknown. There can be a preceding infection especially upper respiratory tract or it can occur following vaccination.⁴ Antineutrophil cytoplasmic antibodies can be found but this is probably an epiphenomenon. They may be useful diagnostically in that they appear to be absent in other conditions that may cause clinical or histological confusion.⁷ Some authors have suggested the condition may be an unusual tissue reaction to an unknown allergen.⁷ Neutrophil abnormality studies are conflicting, with some studies showing enhanced chemotaxis⁸ and others reduced.⁹ Interleukin 1 has been postulated as a chemoattractant.¹⁰ Also, as seen in pyoderma gangrenosum, Sweet's syndrome appearing after granulocyte colony stimulating factor administration has been reported, suggesting that granulocyte colony stimulating factor may exacerbate a pre-existing autoimmune inflammatory condition by stimulating neutrophil proliferation and activity at sites of chronic inflammation.⁶ It seems that, like pyoderma gangrenosum, the immune system has a major role in the pathogenesis of Sweet's syndrome.

Clinical features

PYODERMA GANGRENOSUM

Two types of presenting lesions are seen in the typical form (box 1)⁴: a tender, erythematous nodule becoming blue and then ulcerating (figure 1), and vesicopustules which may resemble acne or dermatitis herpetiformis. These lesions usually occur on the legs *de novo* or at sites of minimal trauma (venepuncture, burns, surgery): a pathergic phenomenon. This may explain why some patients get worse with surgical debridement. The lesions can rapidly

Clinical features

Pyoderma gangrenosum

- initial tender nodule or vesicopustules
- ulcerations, particularly lower limbs:
 - elevated purple/blueish border
 - undermined
 - can be rapid and extensive
- healing with atrophic, cribriform scar
- atypical bullous form seen

Sweet's syndrome

- tender nodules and plaques (limbs, trunk, head): red/plum coloured, ulceration uncommon, central clearing
- high fever
- neutrophil polymorphonuclear leucocytosis
- heal with little scarring
- recurrence common

Box 1

Figure 1 Pyoderma gangrenosum: ulceration with purplish, ragged edge

ulcerate and extend to involve large body areas. The edge is purplish in colour, raised and thickened but can be undermined and ragged. On healing often an atrophic, cribriform scar can be seen. Any body area can be affected but there is a predilection for the calves, thighs, buttocks and face.⁴

An atypical form can occur with haemorrhagic bullae and is more superficial than the classical form with a subdued blue-grey halo.¹¹ Other variants include malignant pyoderma which is an aggressive, ulcerative form mainly affecting the head and neck and often associated with neurologic symptoms.¹² Eruptive pustulation can be observed, especially in association with an acute attack of inflammatory bowel disease. Superficial granulomatous pyoderma gangrenosum is characterised by superficial vegetative ulcers with an indolent course.¹²

SWEET'S SYNDROME

An explosive eruption of irregular, tender, dull red or plum-coloured nodules or plaques (figure 2) especially on the forearms or neck with associated fever (50%), raised erythrocyte sedimentation rate and neutrophilia is the classic presentation of Sweet's syndrome (box 1). Not all features are seen in all patients. The skin lesions enlarge and persist for two or more weeks. Later they can become studded with pustules or exhibit central clearing. Conjunctivitis and arthralgia may occur. Unlike pyoderma gangrenosum, lesions tend to heal without scarring.⁴ Incidence is usually in the fourth or fifth decade with a peak in January and February. One study found that Sweet's syndrome accounted for four per thousand new cases in a dermatological unit.¹³ Women are affected five times more commonly than men. Unlike pyoderma gangrenosum, ulceration is rare but can occur, with mouth and genital ulcers being described.⁷ A variant can affect the face with a non-scarring granuloma which runs a recurrent course.¹⁴ Like pyoderma gangrenosum, pathergic phenomena can be seen.¹

Histopathology (box 2)

PYODERMA GANGRENOSUM

Histology varies according to the type of pyoderma gangrenosum, age of lesion and site of biopsy.¹² No appearance is pathognomic. A large sterile abscess with venous and capillary thrombosis, haemorrhage, necrosis and massive cell infiltration are commonly seen. Early lesions may mimic Sweet's syndrome. The advancing border may show features of a leucocytoclastic vasculitis and there is some overlap with this condition.¹⁵ As in Sweet's syndrome, numerous polymorphonuclear cells are seen. Mononuclear cells predominate in the chronic forms. Upper and mid-dermal oedema sometimes amounting to vesiculation is almost invariable. Bullous pyoderma gangrenosum may show spongiosis, intra-epidermal vesiculation and bullae or subcorneal abscess formation.¹²

SWEET'S SYNDROME

An intense, occasionally massive, focal infiltration of mature polymorphonuclear cells in the mid-dermis is typical of Sweet's syndrome. The infiltrate is predominantly peri-vascular with endothelial swelling in some vessels.⁷ There is a varying amount of fragmentation. Lymphocytes and eosinophils may also be present. Vasculitis is not usually a prominent feature.^{4,16}

Diagnosis

There is no specific histologic or serologic marker for pyoderma gangrenosum or Sweet's syndrome. Diagnosis is based on clinical history, morphologic features of cutaneous lesions and histologic examination and microbiologic culture.¹² In Sweet's syndrome, a characteristic cutaneous eruption, complete resolution without scarring and an inflammatory infiltrate in the upper mid dermis are helpful features in diagnosis.¹³ The differential diagnosis is presented in box 3.

Associations

PYODERMA GANGRENOSUM

Approximately 50% of cases are associated with a specific systemic disorder (box 4).^{4,6,12} It is less often reported with Crohn's disease than ulcerative colitis.¹² Approximately 7.2% cases are associated with malignancy, the most common reported malignancy being acute myeloid leukaemia. The presence of pyoderma gangrenosum in leukaemia is a bad prognostic indicator. The bullous

Figure 2 Sweet's syndrome: dull red, indurated nodules

Pyoderma gangrenosum and Sweet's syndrome: histopathology
<i>Pyoderma gangrenosum</i> <ul style="list-style-type: none">sterile abscess with capillary thrombosishaemorrhage, necrosis, neutrophil infiltrationsome overlap with leucocytoclastic vasculitisintraepidermal bullae, spongiosis and vesiculationupper/mid-dermal oedema <i>Sweet's syndrome</i> <ul style="list-style-type: none">intense focal infiltration of mature polymorphonuclear cells in dermisperivascular endothelial swelling and fragmentationlittle evidence of vasculitisupper/mid-dermal oedema

Box 2

Differential diagnosis
<i>Pyoderma gangrenosum</i> <ul style="list-style-type: none">localised gangreneSweet's syndromevasculitis: Wegener's, rheumatoid arthritis, systemic lupus erythematosus, Behcet'sinfections: amoebiasis cutis, cryptococcosis, blastomycosis <i>Sweet's syndrome</i> <ul style="list-style-type: none">cellulitiserythema nodosumallergic vasculitis

Box 3

haemorrhagic form is particularly associated with leukaemia, polycythaemia rubra vera and myelofibrosis. The association with solid tumours is much less frequent than haematological.¹² The IgA form of myeloma is much more common in patients with pyoderma gangrenosum than in those with myeloma alone.¹² The aetiology of this observation is not known.

SWEET'S SYNDROME

Many associations have been described, 10% of which are associated with an underlying haematological malignancy (box 4).^{1,6,7,17-19} Curiously, when not associated with malignancy, Sweet's syndrome affects predominantly females as seen in our patient. Thus the suspicion for malignancy in Sweet's syndrome should be higher in male patients.¹⁷ Atypical pyoderma gangrenosum and Sweet's syndrome in the same patient is especially associated with myeloproliferative disorders.^{16,18} Our patient appears unique in not being associated with a malignancy (box 5).

Treatment

PYODERMA GANGRENOSUM

The mainstay of treatment is high dose corticosteroids 1-3 mg/kg orally daily.³ This may have to be supplemented by cytotoxic therapy such as azathioprine, cyclophosphamide or chlorambucil as seen in our case. Other agents to be used include clofazimine¹² and cyclosporin 5 mg/kg orally daily which can be used on a relatively short term basis.²⁰ Salazopyrine 4-6 g daily has also been used.²¹ This has antibacterial, immunosuppressive and antiprostaglandin properties. Hyperbaric oxygen has been shown to decrease pain and accelerate healing.²² Intralesional triamcinolone²³ and more recently minocycline 100 mg twice daily especially in subacute cases have been shown to be useful.²⁴ Topical therapy should aim at producing a moist, clean wound. Saline soaks, eusol/paraffin dressings, silver sulphadiazine cream (Flamazine) and occlusive dressings may be used. Very potent topical steroids, such as 0.05% clobetasol propionate (Dermovate) can be useful especially if there are contraindications to systemic steroids. Because of pathergy, debridement or grafting should be avoided.¹²

SWEET'S SYNDROME

Sweet's syndrome shows a rapid response to corticosteroids but recurrence is common. Steroids have to be used for a number of weeks and antibiotics have no effect.⁴ Potassium iodide has been used.²⁵ Aspirin, colchicine and indomethacin have been used but have no particular advantage over corticosteroids.⁷ Cyclosporin 4 mg/kg daily initially and then 5 mg/kg daily²⁶ has been useful but the condition recurs on stopping treatment making cyclosporin a longer term therapy. Doxycycline 200 mg daily can be used in chronic Sweet's syndrome.

Prognosis

PYODERMA GANGRENOSUM

The prognosis is usually that of the underlying disease. With Crohn's disease and ulcerative colitis, control of the colitis will usually result in control of the cutaneous lesions.

SWEET'S SYNDROME

There is a marked tendency for the disease to recur. The average duration of the acute illness has been shown to be 3.8 weeks with oral corticosteroids and 4.9 weeks without.¹³

Conclusion

Pyoderma gangrenosum and Sweet's syndrome have many features in common: neutrophilic infiltrate, altered immunologic reactivity, associations with malignancy, particularly haematological, development after granulocyte colony stimulating factor therapy, pathergy, response to immunosuppressives and reports of coexistence in a single patient. They have more common features than differences. There is overlap between the two conditions with lesions categorised as Sweet's syndrome actually being clinically more characteristic of atypical bullous pyoderma gangrenosum and vice versa.²⁷ We believe, as do other authors,^{1,2,18} that pyoderma gangrenosum and Sweet's syndrome represent a continuum of spectrum of disease resulting from a single pathophysiologic phenomenon, the common denominator being an inflamma-

Associations

Pyoderma gangrenosum

- haematological malignancies (lymphoma, myeloma, leukaemia, myelofibrosis, polycythaemia rubra vera)
- inflammatory bowel disease
- rheumatoid arthritis
- ankylosing spondylitis
- Behcet's disease
- diabetes mellitus
- Wegener's granulomatosis
- chronic active hepatitis
- sarcoidosis
- subcorneal pustular dermatosis
- Takayasu's arteritis
- monoclonal gammopathies
- congenital and acquired hypogammaglobulinaemia
- non-Hodgkin's lymphoma
- myeloproliferative disorders
- solid tumours (breast, colon, prostate, bladder and ovary)
- granulocyte colony stimulating factor therapy

Sweet's syndrome

- acute myeloid leukaemia
- myeloma, adenocarcinoma, pelvic carcinoma
- Behcet's disease
- erythema multiforme
- bullous pyoderma gangrenosum
- human immunodeficiency virus
- granulocyte colony stimulating factor therapy

Box 4

Case history: atypical pyoderma gangrenosum in association with Sweet's syndrome without malignancy in a 78-year-old woman

- symptoms: haemorrhagic bullae both lower limbs, increasing in size/number, beginning to ulcerate
- history: angina, congestive cardiac failure, hypertension
- systems enquiry: no symptoms of underlying malignancy
- drug history: frusemide 40 mg od, GTN, flucloxacillin 500 mg qid, isosorbide mononitrate 20 mg bid. No known allergies
- examination: temp 37.5°C; pulse 70 bpm, regular; blood pressure 120/70 mmHg signs of congestive cardiac failure, no abdominal masses or lymphadenopathy, pulse rate normal, multiple punched out ulcers on both lower limbs, undermined, purplish surround
- investigations: haemoglobin, platelets normal, white count $21.6 \times 10^9/l$, 98% neutrophilia, liver, renal thyroid function normal; calcium normal, blood/urine/skin cultures no growth. Chest X-ray, rheumatoid factor, autoantibodies, immunoglobulins, electrophoresis, ANCA, complement, barium enema, sigmoidoscopy, abdominal/pelvic ultrasound, intravenous pyelogram, all unremarkable. Skin biopsy: necrosis, neutrophilic infiltration, intra-epidermal bulla, spongiosis
- diagnosis: compatible with pyoderma gangrenosum
- disease course: one day later, developed scattered, indurated red nodules on face and arms, swinging pyrexia, some central clearing; biopsy compatible with Sweet's syndrome
- treatment: prednisolone 60 mg po daily, minocycline 100 mg bid, azathioprine 50 mg bid
- outcome: unfortunately, she suffered a myocardial infarction, cardiac arrest and died

Box 5

tory process mediated by neutrophils. This spectrum may range from classic to atypical Sweet's syndrome to atypical to classic pyoderma gangrenosum. The reason for the clinical differences between the two conditions is unclear and merits further investigation. However, they may be explained by varying levels of intensity and extent of the inflammatory process.¹

- 1 Caughman W, Stern R, Haynes H. Neutrophilic dermatosis of myeloproliferative disorders. *J Am Acad Dermatol* 1983; 9: 751–8.
- 2 Cooper PF, Innes DJ, Greer KE. Acute febrile neutrophilic dermatosis (Sweet's syndrome) and myeloproliferative disorders. *Cancer* 1983; 51: 1518–26.
- 3 Lazarus GL, Goldsmith LA, Rocklin RE, *et al.* Pyoderma gangrenosum altered delayed hypersensitivity and polyarteritis. *Arch Dermatol* 1972; 105: 46–51.
- 4 Ryan TJ. Cutaneous vasculitis. In: Rook AJ, Wilkinson DS, Ebling FJ, eds. *Textbook of dermatology*, 5th edn, vol 3. Oxford: Blackwell Scientific Publications, 1992; pp 1893–961.
- 5 Casas MAS, Doval JV, Mejuto FC, *et al.* Pyoderma gangrenosum and relapsing polychondritis in a patient with HIV infection. *Eur J Dermatol* 1992; 2: 164–7.
- 6 Johnson MML, Grimwood RE. Leukocyte colony-stimulating factors. *Arch Dermatol* 1994; 130: 77–81.
- 7 Kemmett D, Hunter JAA. Sweet's syndrome: a clinicopathologic review of twenty nine cases. *J Am Acad Dermatol* 1990; 23: 503–7.
- 8 Aram H. Acute febrile neutrophilic dermatosis. *Arch Dermatol* 1984; 120: 245–7.
- 9 Schroeder JM, Szperalski B, Koh CJ, *et al.* IgA associated inhibition of polymorphonuclear leukocyte chemotaxis in neutrophilic dermatoses. *J Invest Dermatol* 1981; 77: 464–8.
- 10 Going JJ. Is the pathogenesis of Sweet's syndrome mediated by interleukin-1? *Br J Dermatol* 1987; 116: 1013–21.
- 11 Perry HO, Winkelmann RK. Bullous pyoderma gangrenosum and leukaemia. *Arch Dermatol* 1972; 106: 901–5.
- 12 Duguid CM, Powell FC. Pyoderma gangrenosum. *Clin Dermatol* 1993; 11: 129–33.
- 13 Gunawardena DA, Gunawardena KA, Ratnayaka RMRS, Vasanathanathan N. The clinical spectrum of Sweet's syndrome- a report of eighteen cases. *Br J Dermatol* 1975; 92: 363–73.
- 14 Whittle CH, Beck GA, Champion RH. Recurrent neutrophilic dermatosis of the face - a variant of Sweet's syndrome. *Br J Dermatol* 1968; 80: 806–10.
- 15 Schroeter AL, Su WPD. The vasculitis of pyoderma gangrenosum. (abstract) *Arch Dermatol* 1980; 116: 13.
- 16 Delaporte E, Gavouau DJ, Piette FA, *et al.* Acute febrile neutrophilic dermatosis. *Arch Dermatol* 1989; 125: 1101–4.
- 17 Berth-Jones J, Hutchinson PE. Sweet's syndrome and malignancy: a case associated with multiple myeloma and a review of the literature. *Br J Dermatol* 1989; 121: 123–7.
- 18 Burton JL. Sweet's syndrome, pyoderma gangrenosum and acute leukaemia. *Br J Dermatol* 1980; 102: 239.
- 19 Heise H. Acute febrile neutrophilic dermatosis oder erythema exsudativum multiforme. *Dermatol Monatssch* 1971; 157: 278–84.
- 20 Curley RK, MacFarlane AW, Vickers CFH. Pyoderma gangrenosum treated with cyclosporin A. *Br J Dermatol* 1985; 113: 601–4.
- 21 Schmutz JL, Bartin RH, Thess F, *et al.* Pyoderma gangrenosum: thérapeutique par la salazosulfapyridine. *Ann Dermatol Vénereol* 1987; 114: 869–70.
- 22 Heng MCY. Hyperbaric oxygen therapy for pyoderma gangrenosum. *Aust NZ J Med* 1984; 14: 618–21.
- 23 Jennings JL. Pyoderma gangrenosum: successful treatment with intralesional steroids. *J Am Acad Dermatol* 1983; 9: 575–80.
- 24 Berth-Jones J, Tan SV, Graham-Brown RAC, *et al.* The successful use of minocycline in pyoderma gangrenosum: a report of seven cases and a review of the literature. *J Dermatol Treat* 1989; 1: 23–5.
- 25 Horio T, Danno K, Okamoto H, *et al.* Potassium iodide in erythema nodosum and other erythematous dermatoses. *J Am Acad Dermatol* 1988; 9: 77–81.
- 26 Bourke JF, Berth-Jones J, Graham-Brown RAC. Sweet's syndrome responding to cyclosporin. *Br J Dermatol* 1992; 127: 36–8.
- 27 Klock JC, Oken RL. Febrile neutrophilic dermatosis in acute myelogenous leukaemia. *Cancer* 1976; 37: 922–7.