Sweet's syndrome: histological and immunohistochemical study of 15 cases

J J Going, S M Going,* M W Myśkow, G W Beveridge*

From the Department of Pathology, Edinburgh University Medical School, Edinburgh, and *University Department of Dermatology, The Royal Infirmary, Edinburgh, Scotland

SUMMARY Conventional histology and immunoperoxidase staining for fibrin, immunoglobulins, and complement components were used to look for evidence of cutaneous vasculitis and immune complex deposition in Sweet's syndrome. These features were not identified in any of the 15 cases studied. The lack of any vasculitis emphasises the distinctive character of Sweet's syndrome when compared with certain spontaneous and experimentally induced inflammatory skin lesions, and may imply a similarly distinctive pathogenesis.

In 1964 RD Sweet described a new syndrome, "acute febrile neutrophilic dermatosis". This disorder (AFND or Sweet's syndrome) has striking clinical and pathological features. The patient, usually female, develops tender, circumscribed, raised erythematos plaques, which most often occur on the face, neck, and arms. Rapid enlargement of these lesions may occur, with fever, neutrophilia, and a raised erythrocyte sedimentation rate. The impression of an acute infective process may be very strong, but no pathogens have ever been isolated, and if spontaneous resolution does not occur there is a rapid response to systemic treatment with steroids. Skin biopsy shows a heavy inflammatory infiltrate, mostly neutrophilic with some mononuclear cells, and pronounced oedema of the papillary dermis. It has been said that vasculitis is not a feature, and tissue necrosis and ulceration are rarely, if ever, seen in true Sweet's syndrome.1,2

The aetiology and pathogenesis of Sweet's syndrome remain unknown, but several cases have been reported in association with other illnesses: most importantly, about 10% of patients either have, or go on to develop, an acute leukaemia, usually of monocytic or myelomonocytic type.3,4 This is of interest in that leukaemic patients may develop pyoderma gangrenosum, a lesion characterised by intense neutrophilic infiltration of the dermis; Sweet's syndrome has been described in a patient with ulcerative colitis and pyoderma gangrenosum.5 Sweet's syndrome also shows histological similarities with erythema nodosum leprosum and, in experimental lesions, with the Schwartzman and Arthus reactions.6,7 As vasculitis and tissue necrosis may be observed in all these conditions it is worth while knowing if vasculitis and necrosis do occur in Sweet's syndrome. In view of its apparent immunological pathogenesis we looked for evidence of immune complex deposition in the skin. Because oedema exclusively affecting the papillary dermis is a feature of some delayed type hypersensitivity reactions, in which basophils may play a part (analogous to the cutaneous basophil hypersensitivity or "Jones-Mote" reaction of guinea pigs),8 stains for basophils and mast cells were performed.

Material and methods

Seventeen skin biopsy specimens from 15 patients with Sweet's syndrome seen in Edinburgh between 1975 and 1984 were examined. The diagnosis was made on combined clinical and histological grounds. The paraffin blocks of all specimens were obtained, recut, and four micron sections stained by the following methods: haematoxylin and eosin, periodic acid Schiff, toluidine blue, Perl's Prussian blue reaction, Masson trichrome, reticulin, Martius scarlet blue, and Alcian blue.

Table 1 Primary antisera and dilutions used for immunostaining

<table>
<thead>
<tr>
<th>Antibody directed against:</th>
<th>Dilution</th>
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<tbody>
<tr>
<td>Fibrin</td>
<td>1/1000</td>
</tr>
<tr>
<td>IgA</td>
<td>1/400</td>
</tr>
<tr>
<td>IgG</td>
<td>1/1000</td>
</tr>
<tr>
<td>IgM</td>
<td>1/400</td>
</tr>
<tr>
<td>x chains</td>
<td>1/1000</td>
</tr>
<tr>
<td>z chains</td>
<td>1/1000</td>
</tr>
<tr>
<td>C3</td>
<td>1/100</td>
</tr>
<tr>
<td>C4</td>
<td>1/100</td>
</tr>
</tbody>
</table>

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Table 2 Clinical data of cases studied

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
<th>Sex</th>
<th>White cell count (10^3/l)</th>
<th>Neutrophils (%)</th>
<th>Distribution of rash</th>
<th>Non-cutaneous manifestations</th>
<th>Other</th>
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<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>F</td>
<td>8</td>
<td></td>
<td>Hand, cheek, neck</td>
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<td></td>
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<tr>
<td>2</td>
<td>56</td>
<td>M</td>
<td>5.2</td>
<td></td>
<td>Arms</td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td>62</td>
<td>F</td>
<td>15.6</td>
<td>68</td>
<td>Arms, face</td>
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<td></td>
</tr>
<tr>
<td>4</td>
<td>73</td>
<td>F</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>M</td>
<td>12.7</td>
<td>80</td>
<td>Hands, arms, face</td>
<td>Conjunctivitis</td>
<td></td>
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<tr>
<td>6</td>
<td>59</td>
<td>F</td>
<td>9.2</td>
<td>82</td>
<td>Arms, legs</td>
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<tr>
<td>7</td>
<td>30</td>
<td>F</td>
<td>10.0</td>
<td></td>
<td>Hands, cheeks</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>64</td>
<td>F</td>
<td>14.3</td>
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<td>9</td>
<td>60</td>
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<td>53</td>
<td>Arms</td>
<td>Night sweats</td>
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<tr>
<td>10</td>
<td>50</td>
<td>M</td>
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<td>80</td>
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<td>Arthralgia</td>
<td></td>
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<tr>
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<td>72</td>
<td>F</td>
<td>9.3</td>
<td>84</td>
<td>Arms</td>
<td>Arthralgia, conjunctivitis</td>
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<tr>
<td>12</td>
<td>76</td>
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<td>70</td>
<td>Arms, face, legs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>34</td>
<td>F</td>
<td>13.1</td>
<td>62</td>
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<td>Periorbital oedema</td>
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<tr>
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<td>F</td>
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<td>83</td>
<td>Arms, legs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>22</td>
<td>F</td>
<td></td>
<td></td>
<td>Face, neck</td>
<td></td>
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</tr>
</tbody>
</table>

and Giemsa. Sections dried at low temperature (56°C) were stained by a three stage peroxidase and immunoperoxidase technique using commercially supplied rabbit polyclonal antibodies (Dako) (table 1). All sections were trypsinised for 15 minutes before staining, using 0.1% trypsin in 0.1% calcium chloride at a pH of 7.6 to 7.8.

Results

Table 2 summarises the clinical details of the 15 cases.

Fig 1 Case 5: pronounced oedema of papillary dermis raises intact epidermis and dense inflammatory infiltrate in deeper layers of the dermis. (Masson trichrome.) × 160.

Fig 2 Case 12: conspicuous neutrophilic dermal infiltrate with leucocytoclasis. (Masson trichrome.) × 500.
patients. The female preponderance (12 of 15) was
typical, as was the often pronounced neutrophilia;
the distribution of the rash, and the arthralgia and
conjunctivitis seen in some cases. Other patients
experienced a range of medical problems, but only
two patients (cases 6 and 12) had new illnesses diag-
nosed at the same time as Sweet's syndrome. One patient (case 6) presented with Sweet's syn-
drome; lymphadenopathy due to a B cell lymphoma
was found and she subsequently developed mesangiocapillary glomerulonephritis. The second
patient (case 12) developed acute pancreatitis, fol-
lowed, after a day or two, by Sweet's syndrome; an-
other patient (case 9) developed acute myeloid leu-
kaemia one year after Sweet's syndrome; and another
(cas e 13) was 16 weeks pregnant.

Body temperature was not consistently recorded
but was raised (38.5–40°C) in those cases where a
record existed.

**HISTOLOGY**

The epidermis showed only minor changes. Mild to
moderate spongiosis was common; spongiotic vesicles
can form. The basement membrane was intact and at
most a very few inflammatory cells had entered the
basal layers. Some flattening of the rete ridges was
seen, and keratinisation was usually unaffected. Epi-
dermal necrosis and ulceration were not seen.

The papillary dermis typically showed a striking
œdema, which may be so severe that the epidermis
seems to be held down by a few attenuated strands of
collagen only (fig 1). A subepidermal bulla may be
simulated, but close inspection will always show some
connective tissue elements spanning the apparent
cleft. A pale homogeneous eosinophilic background
suggests that the fluid is a proteinaceous exudate, in
keeping with the inflammatory nature of the lesion.
The junction with the reticular dermis tends to be
sharply defined, with little œdema in the deeper
levels. Dilated capillaries lined by plump endothelial
cells may be conspicuous at the junction, and some
may run upwards into the oedematous reticular der-
mis. Occasional mitotic figures among the endothelial
cells of these capillaries suggest reparative activity or
new vessel formation.

There was a diffuse, heavy, inflammatory infiltrate
in the reticular dermis; usually neutrophils predom-
inate and nuclear fragments (leucocytoclasis) may be
conspicuous (fig 2). Eosinophils in small numbers are
sometimes seen, and lymphocytes and histiocytes are
always present, sometimes outnumbering the neu-

trophils. Ingestion of nuclear fragments by histiocytes
is conspicuous in some cases (fig 3). The inflammatory
infiltrate is usually heaviest in the mid dermis but may
extend into the subcutaneous fat, although none of
our cases showed conspicuous panniculitis.

Examination of the dermal blood vessels showed
that vasculitic changes (thrombosis, fibrinoid necro-
sis, fibrin deposition, red cell extravasation, inflam-
matory infiltration of vascular walls) were absent in all cases (fig 4).

An attempt to relate the composition of the

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**Fig 3**  Case 2: neutrophil nuclear debris ingested by
macrophages. (Haematoxylin and eosin.) × 500.

**Fig 4**  Case 2: this small dermal vessel shows no evidence of
vasculitis. (Haematoxylin and eosin.) × 320.
absent in all cases (fig 4).

An attempt to relate the composition of the inflammatory infiltrate to the age of the lesion biopsied was unsuccessful because accurate dating of biopsied lesions was not available. Although special fixatives were not used, and we may therefore have underestimated their numbers, basophils and mast cells were inconspicuous and it seems unlikely that they play a part in Sweet's syndrome.

**IMMUNOHISTOCHEMISTRY**

Staining with the antifibrin antibody showed fibrin within vascular lumina and the fluid in the oedematous papillary dermis, in keeping with the fact that this fluid is inflammatory exudate. Fibrin deposits were not present within vessel walls, confirming the absence of a vasculitis (fig 5). A similar pattern of staining occurred for immunoglobulin and complement components, but there was no deposition of reaction product in or around vessel walls.

**Discussion**

The aetiology and pathogenesis of Sweet's syndrome remain unclear. The absence of vasculitis is important in considering similarities with other cutaneous inflammatory syndromes. It has been suggested that Sweet's syndrome, at least when it occurs in association with leukaemia, is closely related to bullous pyoderma gangrenosum, and Caughman et al believe that there is a pathophysiological continuum between classic Sweet's syndrome and classic pyoderma gangrenosum. They state, "clinical differences may be attributed to differences in the intensity and extent of the inflammatory response," and others believe that Sweet's syndrome and pyoderma gangrenosum are closely related. Pyoderma gangrenosum, however, shows some overlap with cutaneous vasculitides, and intravascular thrombosis and haemorrhage are typical. None of the 15 cases of Sweet's syndrome showed these features. Thus, although syndromes intermediate between Sweet's syndrome and pyoderma gangrenosum may exist, we believe that the histological features of these conditions are sufficiently distinct, so that it would be misleading to regard them even as opposed poles of a nosological continuum.

The coexistence of atypical bullous pyoderma gangrenosum and Sweet's syndrome in one reported patient with a myeloproliferative disorder supports this contention, as does the coexistence of atypical pyoderma gangrenosum and typical Sweet's syndrome in a patient with ulcerative colitis.

The lack of evidence of immune complex deposition in the skin of our patients does not prove that deposition does not occur, as immunoperoxidase methods may not be sensitive enough to show minimal deposition, but it does seem unlikely that large complexes formed in conditions of antibody excess are being deposited.

To conclude, we would emphasise that Sweet's syndrome is not a cutaneous vasculitis, and intravascular thrombosis, tissue necrosis, and ulceration are not seen. There is no necessary connection with pyoderma gangrenosum and its variants.

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**References**

6. Stetson CA, Good RA. Studies on the mechanism of the Shwartzman phenomenon. Evidence for the participation of poly-
Sweet's syndrome


Requests for reprints to: Dr JJ Going, Department of Pathology, University Medical School, Teviot Place, Edinburgh EH8 9AG, Scotland.