

## A Case Report of Acute Febrile Neutrophilic Dermatitis (Sweet's Syndrome) and Crohn's Disease

H. BEITNER, T. NAKATANI and H. HAMMAR

Department of Dermatology, Karolinska Hospital, Stockholm, Sweden

**A case of Crohn's disease complicated by Sweet's syndrome is presented. The main ultrastructural findings were the multiplication of basal lamina surrounding the venule, interendothelial gaps and in perivascular locations mixed infiltrates of neutrophils and erythrocytes. The changes indicate that the initial site of the reaction was the walls of the dermal vessels. Key words: Skin disorder; Inflammatory; Ultrastructural; Gastro-intestinal disease.**

(Accepted February 7, 1991.)

Acta Derm Venereol (Stockh) 1991; 71: 360–363.

H. Beitner, Department of Dermatology, Karolinska Hospital, S-104 01 Stockholm, Sweden.

We report on a case of a woman with Crohn's disease complicated by a chronic active hepatitis, who developed a varioliform eruption found to belong to the group of neutrophil dermatoses. The case was interpreted as Sweet's syndrome. This association seems to be very rare and has previously only been reported in a few cases. In the literature, transmission electronmicroscopic studies of Sweet's syndrome are sparse (1–3). In order to find further ultrastructural characteristics of Sweet's syndrome, a transmission electronmicroscopical investigation was performed.

### CASE REPORT

A 33-year-old female with multiple skin lesions and high fever was admitted to the Department of Dermatology, Karolinska hospital. Six months before admittance, a diagnosis of Mb Crohn had been made. Her illness had started two years earlier with symptoms from the gastro-intestinal tract and skin. She had been treated with systemic corticosteroids. During the period following the diagnosis, she suffered from arthritis localised to the joints of the feet, aphthae-like lesions in the mouth, a recto-vaginal fistula, and chronic active hepatitis.

On admittance to the Department of Dermatology she presented multiple varioliform lesions localised to the upper half of the trunk and the face (Fig. 1). She had a temperature of 41°C for several days. Her sedimentation rate was 84 mm/h and total white blood cell count was  $18.5 \times 10^9/L$ , 96 % of which consisted of neutrophils. Only 1 % of the cells were lymphocytes. Autoantibodies against the intercellular substance of skin and basal membrane were

absent, and no deposits of IgA, IgG, IgM or  $C_3$  were detected in the immunofluorescence testing. Isolations of herpes simplex and zoster viruses were negative, as were bacterial cultures from pustules, blood and faeces.

The patient responded to treatment with 100 mg prednisolone/day and became afebrile after 6 days on the systemic corticosteroid treatment. She had two episodes of bloody stools, and Azathioprin was added. However, Azathioprin treatment had to be discontinued due to increased levels of transaminases. The lesions healed slowly, leaving hypertrophic scars, over the following 2 months. During this period the prednisolone dose had been tapered down to 30 mg/day and was kept at that level due to exacerbation of her hepatitis.

### MATERIAL AND METHODS

Biopsies for light microscopy were taken from a papule, a pustule and the border area of a lesion with a central necrosis. Routine hematoxylin-eosin stained sections were prepared.

Two 4-mm punch biopsies were taken from the border area of an erythematous infiltrate with a central necrosis. They were divided and fixed in glutaraldehyde, postfixed in osmium tetroxide and embedded in Spurr, and 50-nm-thick sections were stained with uranyl acetate and lead citrate. The sections mounted on one-hole grids were examined at 80 kV under a JEM-100 S transmission electron microscope.

### RESULTS

#### Light microscopy

The epidermal changes consisted of intra- and extracellular oedema and neutrophilic exocytosis in the

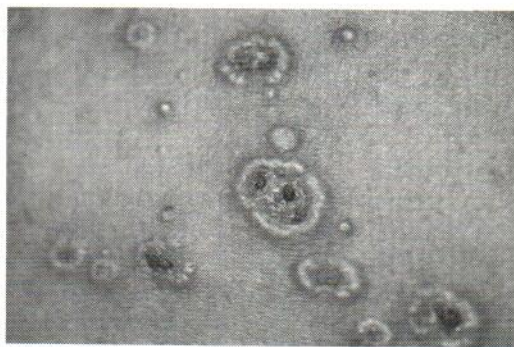


Fig. 1. Varioliform lesions on the back of the patient at admittance. The sizes varied from 1 to 3 cm in diameter.

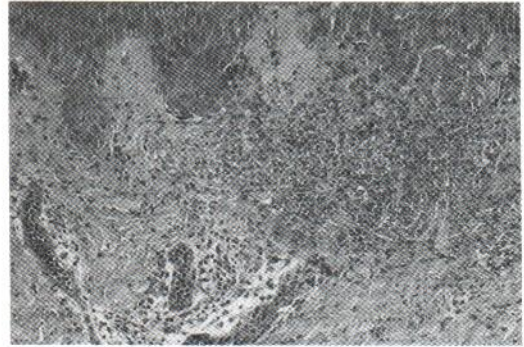
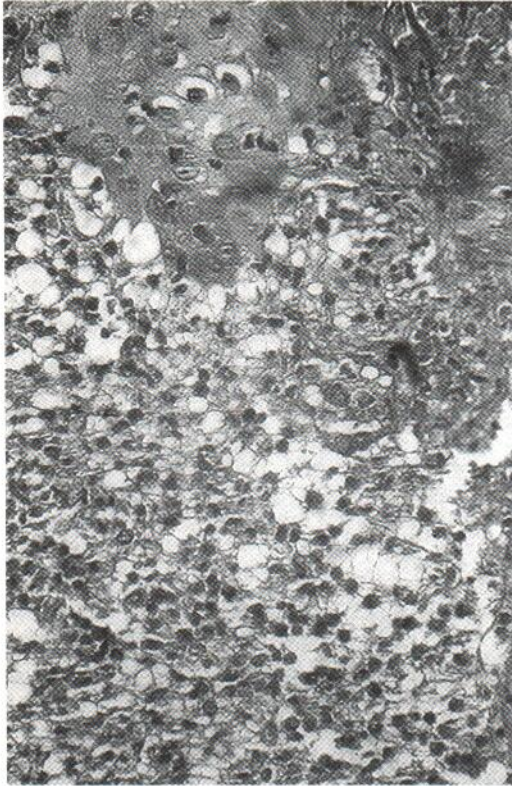


Fig. 2. H&E stained sections of the evolving lesion.

a. Peripheral part of the lesion. Epidermal and dermal oedema. Exocytosis of neutrophils.

b. Central part of the lesion. Leukocyte-rich infiltration in papillary and subpapillary dermis, with extravascular erythrocytes. Perivascular-lymphocyte-dominated infiltration and intravascular neutrophils.

peripheral part of the lesion (Fig. 2a). In the central part, taken from a pustule, partial necrosis of the epidermis was present. In the dermis the superficial vessels were filled with neutrophil leukocytotes. In the more central parts of the lesion, perivascular leukocyte- and erythrocyte-rich infiltrates were seen (Fig. 2b). There was no sign of leukocytolysis, fibrinoid deposition within the walls of the superficial vessels, or necrosis of the walls themselves. The epidermal necrosis was interpreted to be secondary to these dermal changes.

#### *Transmission-electron microscopy*

In perivascular locations, mixed infiltrates of neutrophils and erythrocytes were present. Occasionally, venules showed interendothelial gaps from 0.05  $\mu\text{m}$  to 0.5  $\mu\text{m}$  in width and the presence of fibrin at the site of tight junctions between endothelial cells (Fig. 3). The plasma proteins were deposited in a wave-like pattern around the venules. Multiple concentric bilayered membranes were found surrounding papillary venules (Fig. 4). No fibrinoid degeneration or necrotic changes of endothelial cells were observed in these venules.

#### DISCUSSION

The spectrum of neutrophilic dermatoses has been under discussion in recent literature (4). The relationship between the highly chemotactic activity evoked in neutrophilic dermatoses such as Sweet's syndrome or pyoderma gangrenosum and an immunological vascular reaction has been stressed by Jorizzo et al. (5). Solid evidence for immune complex mechanisms in these disorders is scanty, however.

In addition, overlapping clinical features between the two disorders mentioned may make a precise diagnostic designation less appropriate at least in some instances. Our case may be an example hereof. In summarising the clinical and histological features in this case, the diagnosis of Sweet's syndrome was preferred due to the localisation and multitude of lesions, the absence of vascular necrosis and the aggressive involvement of the epidermis by the inflammatory process.

A few transmission electron microscopic studies of Sweet's syndrome have reported the emigration of neutrophils from venules (1), the multiplication of

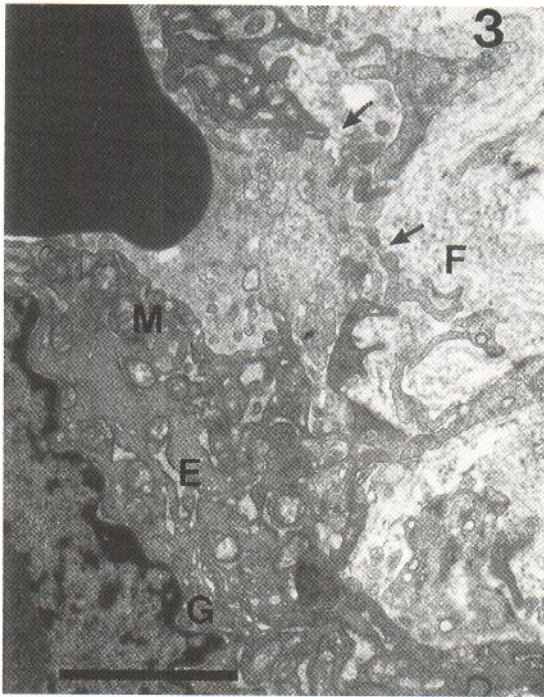


Fig. 3. Endothelial cells with interendothelial gaps (arrows) and fibrin deposits located in the gaps and beneath the cells (F). Endoplasmic reticulum (E). Golgi apparatus (G). Mitochondria (M). Bar = 2  $\mu$ m ( $\times$  11 400).

basal lamina in a concentric shape surrounding venules (2), and focal vascular disruption (3). This inflammatory response was observed in the present case, as well (Figs. 3, 4). The alterations of the vessels were abundant in comparison to those of the epidermis. The multiple membranes around the vessels have been interpreted as duplications of the basal membrane secondary to the inflammatory process. However, a similar alteration have been described in photo-activated porphyria-associated lesions (6).

The interendothelial gaps have not been described in the earlier reports on Sweet's syndrome. These are considered to be of importance in acute inflammation (7). The absence of micromorphological signs of vasculitis suggests that the formation of interendothelial gaps may be induced by toxins or mediators released by an immunological process at the vessel wall. The existence of the gaps can explain the prominent fibrin-containing oedema in the dermis (8), also seen in Fig. 3.

The domination of a process at the site of the vessels indicates that an early event in the course of disease takes place at this level. Markers of the

inflammation such as IgM and C<sub>3</sub> deposits on the vessel walls (9) and the existence of IgM- and IgE-bearing polymorphonuclear leukocytes have been reported (10). In our case immunoglobulin or complement deposits were not revealed by the immunohistological examination.

It is conceivable that other means than an immunological mechanism can mount the inflammatory process, such as toxins from the damaged gastrointestinal canal. An important question remains unanswered, namely the nature of chemotactic factor (s) activating the intense aggregation of neutrophilic granulocytes present in the skin (Fig. 2) in this condition (11).

In this case, the acute febrile neutrophilic dermatosis was combined with Crohn's disease and a chronic active hepatitis. The association with Crohn's disease has previously been reported in 3 cases (12, 13). Sweet's syndrome has also been associated with acute myeloid leukemia, ulcerative colitis, subacute lupus erythematosus and various malignant tumours (4). The link between these different associations and Sweet's syndrome has hitherto not been found. It seems reasonable to conclude that more than one mechanism may trigger the initial reaction at the site of the dermal vessels, initiating a

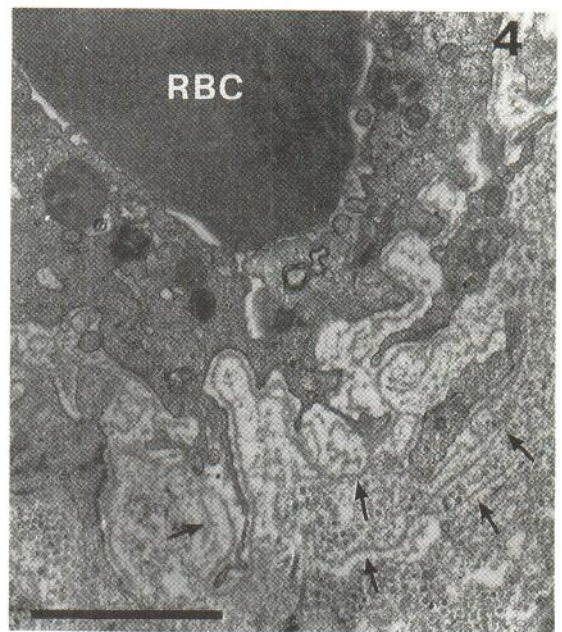


Fig. 4. Multiple basal lamina (arrows) surround a venule. In the endothelial cells abundant dilated endoplasmic reticulum and mitochondria are present. RBC = red blood cell. Bar = 2  $\mu$ m. ( $\times$  13 400).

strong inflammatory reaction, of which the present case is a full example.

#### ACKNOWLEDGEMENTS

This investigation was carried out at the electron microscopical laboratories of the Department of Pathology, Karolinska Hospital, with the valuable support of Associate Professor Romuald Wroblewski. The skilful technical assistance of Barbro Larsson is gratefully acknowledged. The study was supported by grants from the Swedish Medical Research Council (12x-5665), the Foundations of Edvard Welander and the Karolinska Institute.

#### REFERENCES

1. Sweet RD. Acute febrile neutrophilic dermatosis - 1978. *Br J Dermatol* 1979; 100:93-99.
2. Höningsmann H, Kempter R, Wolff K. Akute febrile neutrophile Dermatose. *Wien Klin Wochenschr* 1979; 91: 842-847.
3. Gisser SD. Acute fibrile neutrophilic dermatosis (Sweet's syndrome) in a patient with hairy-cell leukemia. *Am J Dermatopathol* 1983; 5: 283-288.
4. Jorizzo JL. Neutrophilic dermatoses: Sweet's syndrome and pyoderma gangrenosum. In: Gallin JI, Goldstein IM, Snyderman R, eds. *Inflammation: Basic Principles and Clinical Correlates*. New York: Raven Press, Ltd., 1988; 785-802.
5. Jorizzo JL, Solomon AR, Zanolli MD, Leshin B. Neutrophilic vascular reactions. *J Am Acad Dermatol* 1988; 19: 983-1005.
6. Anton-Lamprecht I, Meyer B. Zur Ultrastruktur der Haut bei Protoporphyrinämie. *Dermatol* 1970; 141: 76-83.
7. Hurley JV. Inflammation. In: Andersson JR, ed. *Muir's Textbook of Pathology* 12th ed. London: Edward Arnold Ltd., 1985: 4.1-4.38.
8. Going JJ, Going SM, Mys'kow MW, Beveridge GW. Sweet's syndrome: histological and immunohistological study of 15 cases. *J Clin Pathol* 1987; 40: 175-179.
9. Maekawa Y, Kageshita T, Nagata T. A case of acute febrile neutrophilic dermatosis (Sweet's syndrome) - A demonstration of IgM and C<sub>3</sub> deposits on the vessel walls in involved skin. *J Dermatol (Tokyo)* 1984; 11: 560-564.
10. Nunzi F, Crovato F, Dallegrì F, Patrone F, Cormane RH. Immunopathological studies on a case of Sweet's syndrome. *Dermatologica* 1981; 163: 393-400.
11. Jordaan HF. Acute febrile neutrophilic dermatosis. A histopathological study of 37 patients and a review of the literature. *Am J Dermatopathol* 1989; 11: 99-111.
12. Kemmett D, Gawkrödger DJ, Wilson G, Hunter JAA. Sweet's syndrome in Crohn's disease. *BMJ* 1988; 297: 1513-1514.
13. Becuwe C, Delaporte E, Colombel JF, Piette F, Cortot A, Bergoend H. Sweet's syndrome associated with Crohn's disease. *Acta Derm Venereol (Stockh)* 1989; 69: 444-445.