Acta Derm Venereol (Stockh) 1989; 69: 52–58

Acute Febrile Neutrophilic Dermatosis—A Marker of Malignancy?

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Clemmensen OJ, Menné T, Brandrup F, Thomsen K, Lange Wantzin G. Acute febrile neutrophilic dermatosis—a marker of malignancy? Acta Derm Venereol (Stockh) 1989; 69: 52–58.

A retrospective survey during a 2-year period disclosed 18 patients with acute febrile neutrophilic dermatosis (Sweet's syndrome). An associated lympho- or myeloproliferative malignancy was found in 6 patients. Attacks of Sweet's syndrome preceded the diagnosis of neoplasia in 4 patients (3 months to 6 years). Some differences in symptoms and signs were found in the group of patients with associated malignancy compared with the group without, that is, male predominance, mucosal symptoms, anemia, and frequent recurrence of skin symptoms. The onset of Sweet's syndrome indicates an acute infectious disease, and the patients are frequently referred to departments of internal medicine and infectious diseases. In addition, the skin lesions may mimic those which often accompany a generalized infection (erythema multiforme, erythema nodosum, vasculitis, pustular eruptions and urticaria). Since Sweet's syndrome may precede the possibly associated malignant disease, the initial diagnosis of the syndrome is important and should be made with confidence with increasing awareness of the characteristic symptoms. *Key words: Sweet's syndrome; Neutrophils; Cutaneous paraneoplasia; Leukemia.* (Received May 6, 1988.)

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Acute febrile neutrophilic dermatosis (Sweet's syndrome) was first described by Sweet in 1964 (1). It is characterized clinically by abrupt appearance of erythematous, plum coloured circumscribed, edematous plaques on the skin, fever and neutrophilia in the peripheral blood. Histologically, the dominating characteristic feature is an intense, diffuse dermal infiltration with polymorphonuclear leukocytes. The etiology of the syndrome is unclear but a fair amount of the cases are preceded by various, mostly upper respiratory tract infections (2). Of considerable interest is the association with myelo- and lymphoproliferative disorders (3, 4), and possibly with autoimmune diseases like rheumatoid arthritis, Sjøgren's syndrome and lupus erythematosus (5, 6, 7). Since Sweet's syndrome may precede a later developing (or later recognized) neoplasia (8) it is important to be familiar with the diagnosis. The prevalence of Sweet's syndrome is not known, but probably it is not uncommon (9, 10), and the condition may have been misdiagnosed in the past, for instance as erythema multiforme, which is widely recognized to accompany various infectious diseases.

The purpose of the present retrospective study was to analyse those features in patients with Sweet's syndrome that may indicate an associated (previous, present or future) malignant neoplasia. Our results confirm that such predictive features do exist, and they suggest that the condition has been underreported. However, the important diagnosis of Sweet's syndrome is easy from its clinicopathological correlation, and should be made with confidence with increasing awareness of the disease.

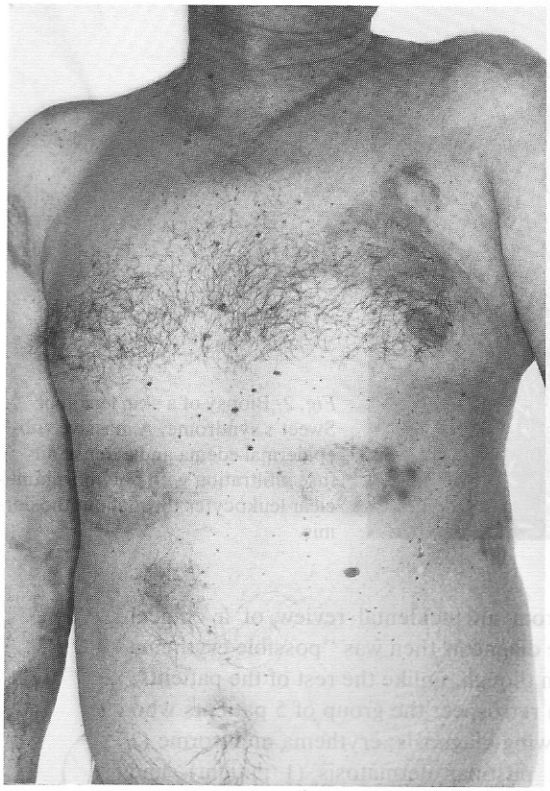

Fig. 1. Erythematous, infiltrated somewhat annular plaques of Sweet's syndrome.

PATIENTS AND METHODS

Patients with a tentative diagnosis of Sweet's syndrome were traced from the files of 4 dermatologic departments through 1985 to 1986 (24 months). Our criteria for the diagnosis were consonant with those of Su & Liu (11). We regard the following features as diagnostic; (*a*) a typical histology (a heavy diffuse polymorphonuclear dermal infiltrate, nuclear dust, edema of the papillary dermis and absence of vasculitis—Fig. 1), and at least 2 typical, discrete skin lesions (circumscribed, infiltrated, red to violaceous dermal plaques, often with vesicles and pustules—Fig. 2), or (*b*) a histology with features of Sweet's syndrome (a diffuse polymorphonuclear dermal infiltrate without vasculitis), at least 2 typical discrete skin lesions, and fever and/or blood neutrophilia.

In order to estimate how often the diagnosis Sweet's syndrome was suggested in our departments a decade before the present study, the files from 1970 through 1975 were screened. The files were not searched for patients, who in retrospect would satisfy the diagnosis Sweet's syndrome, but who were misdiagnosed as erythema multiforme, vasculitis, erythema nodosum, etc.

The clinical and laboratory parameters necessary for the diagnosis of Sweet's syndrome were recorded. The skin biopsies were reviewed without knowledge of the accompanying clinical features. When a diagnosis of Sweet's syndrome was established the relevant clinical, histological and laboratory features were assessed. Possibly provoking factors of Sweet's syndrome were evaluated, and preceding, present or subsequent disorders with special regard to malignant or clinically manifest autoimmune diseases were searched, and the diagnoses (clinically and histologically) were reviewed. Modalities of and responses to treatment were assessed. Recurrences were recorded. Patients were followed until remission and follow-up studies 1 to 2 years later (1987) were conducted. Fisher's exact test was applied with a 5% level of significance.

RESULTS

The tentative diagnosis of Sweet's syndrome, drawn from our files from 1985 through 1986, were reviewed in 23 patients. Eighteen fitted our diagnostic criteria. Among those

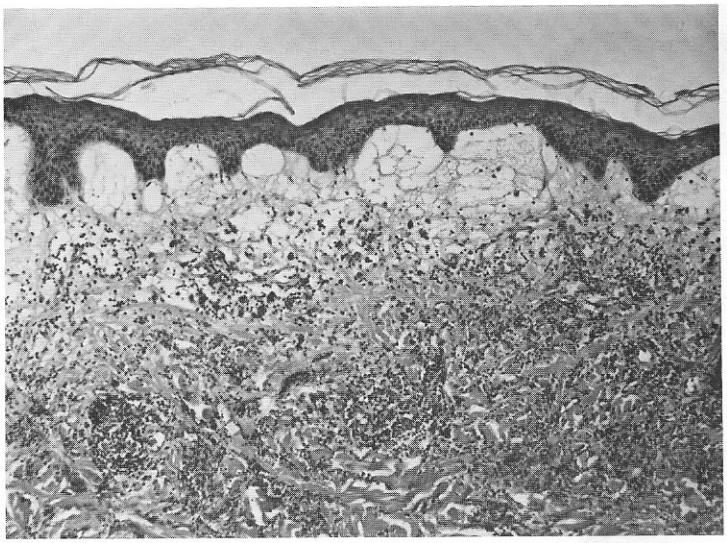

Fig. 2. Biopsy of a skin lesion of Sweet's syndrome. A massive subepidermal edema and a dense diffuse infiltration with polymorphonuclear leukocytes throughout the dermis.

was 1 patient whose diagnosis was suggested from an incidental review of a clinical photograph. Her record dated back to 1972 and the diagnosis then was "possible erythema multiforme". She was included in the material even though, unlike the rest of the patients, she was not traced through our diagnostic files. In retrospect the group of 5 patients who were excluded from the study comprised the following diagnosis; erythema multiforme (2 patients), leukocytoclastic vasculitis (1 patient), pustular dermatosis (1 patient), and possible eosinophilic cellulitis (Well's syndrome) (1 patient). The initial clinical diagnoses of the patients accepted in the study (a definite diagnosis of Sweet's syndrome) were: Sweet's syndrome (9 patients), erythema multiforme (5 patients), Sweet's syndrome alternative to a preferred diagnosis of vasculitis and erythema multiforme respectively (2 patients), urticarial vasculitis and "pustular dermatosis" not otherwise specified (1 patient each).

A concurrent myelo- or lymphoproliferative disease was found in 6 patients, the clinical data of whom are shown in Table I. Three patients had myeloid leukemia, 1 myelodysplastic syndrome, 1 hairy cell leukemia, and 1 Hodgkin's disease, nodular sclerosis. It is seen from Table I that Sweet's syndrome preceded the hematologic symptoms with more than one year in 3 patients, but bone marrow examinations were not performed at the time of the initial skin disease. In one patient, however, the diagnosis of Sweet's syndrome was made at recurrence, and a subsequent bone marrow examination disclosed acute leukemia. Bone marrow examination was performed in 2 of the 12 patients without associated neoplasia due to anemia and a persisting high leukocyte count respectively.

Chromosome abnormalities were found in 3 of 4 patients examined: 1 patient with chronic myelocytic leukemia was Ph 1 positive, and 1 patient with acute myelocytic leukemia had a hyperdiploid clone (+21)—he had no signs of Down's syndrome. In the patient with myelodysplastic syndrome several hypodiploid metaphases (−10, −15) were found, probably representing an abnormal clone. The patient with lymphoma had a normal karyotype. Chromosomal examinations were not performed in the remaining patients with associated neoplasia or in any other patient.

The frequency of the various diagnostic criteria for Sweet's syndrome are seen in Table II. The frequencies of typical histology, typical skin lesions, fever and neutrophilia were in the same range, but fewer typical features were found in the group of patients with

associated malignant neoplasia. The clinical and laboratory differences between the groups with and without associated malignancy are shown in Table III. No feature was specific for one group, but mucosal involvement (oral and conjunctival) was found more often in the neoplastic group. The female/male ratio was reversed, and the patients were generally older. The skin lesions were less often vesicular. None of the features was statistically significantly different between the two groups, but the figures are small. General malaise was found in 15 patients, arthralgia in 9, but with no difference between the two groups. An increased sedimentation rate was found in 16 patients.

Table I. *Patients with Sweet's syndrome and associated malignancy*

CML = chronic myelocytic leukemia, AML = acute myelocytic leukemia, $+Ph^1$ = Philadelphia chromosome positive, +21 = hyperdiploic—extra chromosome 21, n.d. = not done

Patient/ sex	Age (yrs)	Malignant diagnosis	Course	Sweet's syndrome related to neoplasia (+/− yrs)	Number of recurrences	Chromosomal analysis
PV/M	48	CML	Active disease	−6	3–4/6 years	Aneuploid ($+Ph^1$)
MD/M	52	Myelo-dysplasia	Active disease	−3	Several/1 year	Aneuploid (−10, −15)
VEK/M	70	AML	Dead	−1.5	Several/1 year	n.d.
VA/M	79	AML	Dead	−0.25	2/0.25 years	Aneuploid (+21)
EH/F	49	Hairy cell leukemia	Remission	0	5/2 years	n.d.
KH/F	67	Mb. Hodgkin	Remission	+1.5	0/1.5 years	Normal

Table II. *Frequency of diagnostic criteria for Sweet's syndrome in patients with and without associated malignancy*

	Typical histology	Consonant histology	Typical skin lesion	Consonant skin lesion	Fever (≥38°C)	Blood neutrophilia (≥7 mill./ml)
Sweet's syndrome without malignancy (n=12)	10	2	10	2	10	9
Sweet's syndrome with associtated malignancy (n=6)	4	2	3	3	3	2
Total (n=18)	14	4	13	5	13	11

In contrast to the remaining patients, the group with associated neoplasia was characterized by recurrences of the skin lesions (5 of 6 patients), and therapy had to be continued in 2 patients to control recurrences. Anemia was frequently found, and the polymorphonuclear cell count in the peripheral blood covered a wide range with only 1 patient in the interval between 7 to 16×10^9/l typically seen in uncomplicated Sweet's syndrome (Table III).

The detailed clinical records and the clinical follow-up of the patients disclosed no overt autoimmune diseases such as Sjögren's syndrome, systemic lupus erythematosus or rheumatoid arthritis. Serological screening for autoantibodies, however, was not carried out.

In the group without associated neoplasia, a probable eliciting condition to Sweet's syndrome was found in 5 patients (upper respiratory tract infection: 3 patients, labial herpes simplex: 1 patient, yersinia infection: 1 patient).

Therapy was in all cases prednisolone daily in dosages ranging from 15 to 40 mg. The response to treatment was dramatic with normalization of temperature, relief of general symptoms within the first 24 hours, and remission of skin lesions within days. In 2 of the recurrent cases additional therapy with dapsone was necessary.

Analysis of our files from 1970 to 1975 disclosed not a single case diagnosed as Sweet's syndrome.

DISCUSSION

Sweet's syndrome is an entity with characteristic clinical and pathological features (2, 12, 13). The etiology is unknown, but in some cases, e.g. 5 patients in our series, preceding bacterial infections might be the eliciting factor (2, 11). Immunoglobulin and complement C3 has been demonstrated in dermal vessel walls, suggesting an immunological reaction (14), but vasculitis is not a feature of the disease (13). The patients are febrile with general malaise and the polymorphonuclear leukocyte count is raised, suggesting an infectious disease, but specific organisms have never been cultured. Due to the suggestive clinical

Table III. *Clinical and laboratory data on patients with and without associated malignancy*

	Sex M/F	Age mean	Vesicles +/−	Oral erosions +/−	Conjunctivitis +/−	Anemia[a] +/−	Recurrence[b] +/−
Sweet's syndrome without malignancy (n=12)	3/9	51	9/3	2/10	3/9	2/8	3/9
Sweet's syndrome with associated malignancy (n=6)	4/2	61	2/4	4/2	4/2	4/2	5/1

[a] Two patients with iron deficiency anemia responsive to therapy are not counted positive.
[b] "No recurrence" only stated with observation more than 1 year, except for 1 patient followed without recurrence for 10 months.

picture the patients are often admitted to departments of general medicine or infectious diseases, and the relevant differential diagnoses of the associated skin lesion are actually the ones often seen accompanying infections, such as erythema multiforme, vasculitis, erythema nodosum, and urticarial like lesions (11).

We believe that the diagnosis of Sweet's syndrome is underestimated and possibly has been misdiagnosed in the past. In the present study we were unable to trace any patients with Sweet's syndrome in our files from 1970 to 1975. However, incidentally reviewed clinical photographs revealed one patient from 1972 with Sweet's syndrome, and yet another was diagnosed in retrospect as he presented with a recurrence several years later. It is impossible, however, from our retrospective study to state whether the incidence of the disease is increasing or to get an exact idea of its prevalence.

One-third of our patients had associated myelo- or lymphoproliferative diseases. Such associations, including each of the various types of neoplasia in the present series have been described (3, 15, 16), mostly as case reports.

An incidence of associated myelocytic and lymphocytic neoplasia of 10% has been suggested (17), and in a recent series of 15 patients with Sweet's syndrome 1 with acute leukemia and 1 with malignant lymphoma were found (13). The high 33% prevalence of neoplasia in the present series, probably does not reflect the true prevalence, but may reflect the fact that a specific diagnosis of Sweet's syndrome is not made until recurrence of the skin lesions—recurrence by itself being an indicative feature of associated malignancy.

Sweet's syndrome preceded the diagnosis of neoplasia in 4 cases from 3 months to 6 years, but a bone marrow aspiration was not performed at the time of the initial skin disease. In only one patient did the skin symptoms lead to the malignant diagnosis.

Sweet's syndrome has been recorded to occur before, after or at the time of diagnosis of the associated malignancy (3) in agreement with our findings. There are reports of an association between carcinomas and Sweet's syndrome (18, 19). We found no carcinomas among our patients. Chromosomal abnormalities from bone marrow aspiration have been recorded in a patient with Sweet's syndrome and acute myelocytic leukemia (8). Cytogenetic analysis was performed in 4 of our patients (3 abnormal), and shall be considered in a planned prospective study, especially when features indicating a possible association to malignancy are present (vide infra). No specific distinguishing feature was found between patients with Sweet's syndrome alone and those with associated malignancy, however several features differed between the two groups. Those with associated malignancy were older, they were more often males with otherwise unexplained anemia and more frequent oral mucosal lesions. Recurrences of skin lesions were frequent. These features seem to be important in relation to further work-up of the patients and the subsequent control.

The course of a single episode of Sweet's syndrome is variable, but it may clear spontaneously within weeks to months (2). There is prompt response to treatment with prednisolone 20 to 40 mg daily. Most of our patients received 40 mg prednisolone daily for one week with tapering to zero over an additional two weeks. Two patients with associated malignancy needed additional dapsone treatment. We conclude that Sweet's syndrome represents a clinical and histopathological entity, probably underestimated, but important to recognize due to its prompt response to therapy and to its association with myelo- and lymphoproliferative disorders. Distinguishing features between patients with and without malignancy may guide the clinician to the extent of work-up and control.

ACKNOWLEDGEMENTS

The permission to review the relevant histologic slides obtained from Dr N. K. Jensen, Dr J. A. Andersen and Dr N. B. Tinggaard Pedersen, Department of Pathology, Odense University Hospital,

Odense and from Dr H. K. Thomsen, Bispebjerg Hospital, Copenhagen, Denmark, is greatly appreciated.

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