Mod Rheumatol (2004) 14:327–330
DOI 10.1007/s10165-004-0319-0

CASE REPORT

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Sweet's syndrome associated with propylthiouracil-induced antineutrophil cytoplasmic antibody

Received: December 4, 2003 / Accepted: May 18, 2004

Abstract A 44-year-old woman had tender erythematous nodules in both the upper and lower extremities, headache, and fever during the course of propylthiouracil therapy for Graves' disease. Serologic tests showed high titers of antineutrophil cytoplasmic antibody (ANCA) against myeloperoxidase (MPO). A skin biopsy showed neutrophilic dermatitis consistent with Sweet's syndrome. After the cessation of propylthiouracil therapy and the administration of steroids, all her symptoms disappeared and the titer of antineutrophil cytoplasmic antibody against myeloperoxidase decreased. A causal relationship between propylthiouracil (PTU) therapy and Sweet's syndrome is suggested.

Key words Antineutrophil cytoplasmic antibody (ANCA) · Graves' disease · Propylthiouracil (PTU) · Sweet's syndrome · Vasculitis

Introduction

Sweet's syndrome (acute febrile neutrophilic dermatitis) was first described by Sweet in 1964 as including an acute onset of fever, leukocytosis, and erythematous plaques with neutrophil infiltration.[1] Since then, Sweet's syndrome has been reported to develop in association with some systemic inflammatory diseases such as Behçet's disease, rheumatoid arthritis, and ulcerative colitis.[2] Although some studies have detected the presence of antineutrophil cytoplasmic antibody (ANCA) in Sweet's syndrome, the association between this syndrome and ANCA has not yet been completely clarified.[3–5] We treated a patient with Sweet's syndrome who was positive for myeloperoxidase (MPO)-ANCA that developed during the course of propylthiouracil (PTU) therapy for Graves' disease.

Case report

A 44-year-old woman with a 16-year history of Graves' disease was admitted to our hospital in April 2001 with headache, tender erythematous nodules in both the upper and lower extremities, and without any preceding episode (Fig. 1). She had received 400 mg per day of PTU from 1992 for hyperthyroidism, with no other medication.

On admission, physical examination revealed that she had 39°C fever, and tender erythematous nodules on the extensor surfaces of the bilateral forearms and lower extremities. She had struma, exophthalmos, and neck stiffness, with no other neurological findings. She did not have oral aphthae, genital ulcer, arthritis, colitis, or any malignancies.

The results of urinalysis were normal. Hematological examinations revealed a white blood cell count of 9.8×10^9/l (88.9% segmented neutrophils, 6.5% lymphocytes), a hemoglobin level of 11.7 g/dl, and a platelet count of 173×10^9/l. Her serum C-reactive protein level was 8.6 mg/dl and her erythrocyte sedimentation rate was 93 mm/h. Liver enzyme levels and creatinine clearance rate were normal. She was found to be negative for the antistreptokinase O, rheumatoid factor, and antinuclear antibody. The titers of MPO-ANCA and proteinase 3 (PR3)-ANCA determined by enzyme-linked immunosorbent assay (SRL, Japan) were 80 EU (normal range

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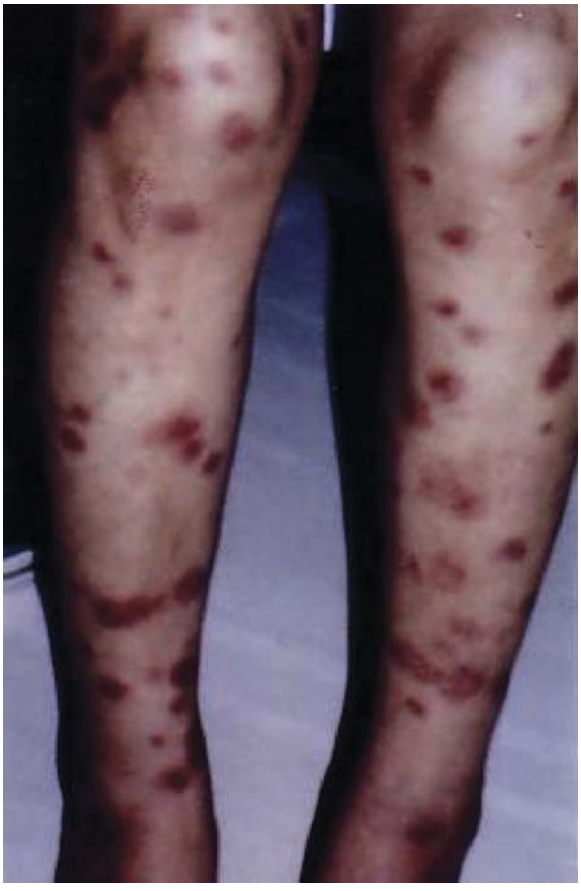

Fig. 1. Nodular erythema on the leg

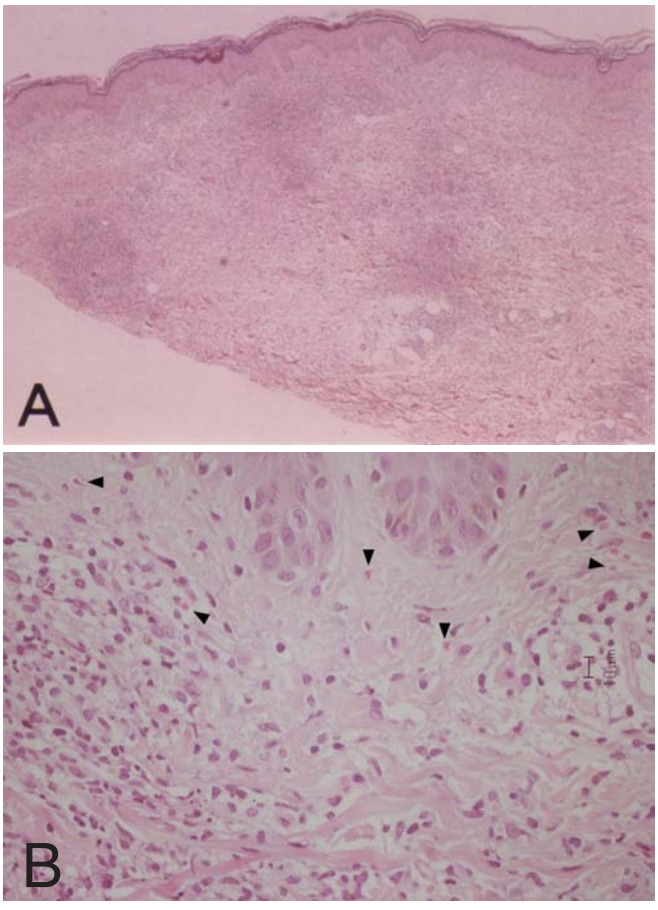

Fig. 2. A A skin biopsy showing scattered nodular lesions on the dermis with a normal epidermis, which is consistent with nodular dermatitis. (Hematoxylin and eosin staining; ×34). **B** Fragmentation of numerous leukocytes without vasculitis and slight erythrocyte extravasation (*arrowheads*) in a nodular lesion. (Hematoxylin and eosin staining; ×400)

10 EU>), and 17 EU (normal range 10 EU>), respectively. She was found to be positive for lupus anticoagulant (LAC). Repeated blood cultures showed the absence of any bacteria. A lumbar puncture yielded a white blood cell count of 71/μl (66 lymphocytes and 5 neutrophils), a protein level of 35 mg/dl, and an IgG index of 0.76 (normal range 0.65>). The staining and culture of cerebrospinal fluid showed the absence of any bacteria. Magnetic resonance imaging of the brain showed no abnormalities. A electroencephalogram showed diffuse slow waves. A chest roentgenograph showed normal findings.

A skin biopsy specimen obtained from the right lower leg showed scattered nodular lesions with a normal epidermis and a mild septal panniculitis (Fig. 2A). The infiltrate consisted of histiocytes, lymphocytes, and neutrophils, with prominent leukocytoclastic debris (Fig. 2B). Although slight erythrocyte extravasation was observed, neither fibrinoid necrosis of vessels nor thrombosis was observed. Sweet's syndrome and aseptic meningitis were the diagnoses. PTU was discontinued, and she was treated with 15 mg prednisolone per day. Her symptoms resolved and the titers of MPO-ANCA and PR3-ANCA returned to the normal range after 2 months. Although the steroid dose was tapered, no relapse in terms of either symptoms or titer of MPO-ANCA was observed.

Discussion

Sweet's syndrome is characterized by multiple, painful, sharply demarcated, raised erythematous plaques on the face, neck, upper chest, back, and extremities. The plaques are usually a few centimeters in diameter, but very occasionally large plaques of up to 10 cm × 20 cm are found. It is not easy to differentiate Sweet's syndrome from erythema nodosum if it occurs on the lower extremities only. Fever occurs in 48%–83% of patients.[6,7] Sweet's syndrome may be a systemic disorder, including arthritis, conjunctivitis, and episcleritis. It sometimes involves the central nervous system, presenting meningitis or encephalitis, and is called "neuro-Sweet."[8] More than 500 cases of Sweet's syndrome have been documented in the literature.[2] These cases are divided into four groups according to the underlying conditions: idiopathic (71%), parainflammatory (16%), paraneoplastic (11%), and pregnancy (2%).[9] Sweet's syndrome may also be a complication of Hashimoto's disease, but is rarely a complication of Graves' disease, and is associated with drug sensitivity.[2] Sweet's syndrome may be

preceded by nonspecific upper respiratory or gastrointestinal infections.[2] The standard therapy for Sweet's syndrome is prednisolone at an initial dose of 0.5–1.5 mg/kg/day. Sweet's syndrome shows an excellent response to prednisolone, and a gradual tapering within 2–4 weeks is recommended, although it may recur frequently.

Our patient had no preceding infection, inflammatory diseases, or malignancy. The titers of MPO-ANCA normalized and her symptoms disappeared at the same time; an association between MPO-ANCA and Sweet's syndrome was suggested.

Idiopathic MPO-ANCA-related vasculitis involves multiple organs, and it is most commonly associated with crescent glomerulonephritis or alveolar hemorrhage. However, there has been no suggestion that Sweet's syndrome may be included in the features of idiopathic MPO-ANCA-related vasculitis, although some recent reported cases showed positivity for ANCA in neutrophilic dermatitis including Sweet's syndrome. Kemmett et al.[3] suggested that ANCA may also be a possible diagnostic marker of Sweet's syndrome, and Bayle et al.[4] suggested that neutrophilic dermatitis may induce ANCA.

It is well known that ANCA-related vasculitis may develop during PTU therapy for Graves' disease, and usually resolves completely with the cessation of the therapy.[10] Miller et al.[11] reported the case of a patient with neutrophilic dermatitis similar to Sweet's syndrome and positive for p-ANCA, which appeared during the course of PTU treatment. They suggested that PTU may induce both p-ANCA and neutrophilic dermatitis including Sweet's syndrome, as was noted in our present patient.

PTU-induced MPO-ANCA with crescent glomerulonephritis or alveolar hemorrhage usually appeared at a high titer. However, MPO-ANCA that appears during the course of PTU therapy does not usually induce ANCA-related vasculitis; in patients without any symptoms or disorders, the titers of MPO-ANCA are usually lower than 50 EU. Table 1 lists 22 cases of MPO-ANCA-related disorders that developed during the course of PTU therapy.[12–22] MPO-ANCA were detected either by enzyme immunoassay (EIA) or enzyme-linked immunosorbent assay (ELISA). Cases with no description of the method for detecting MPO-ANCA were excluded. In many cases, the titers of MPO-ANCA were over 100 EU. However, a few patients whose titers of MPO-ANCA, as detected by either EIA or ELISA, were between 40 and 60 EU also had crescentic glomerulonephritis. Therefore, we suggest that the MPO-ANCA titer of 80 EU in our patient may have had a pathogenetic role, although we could not neglect the possibility that Sweet's syndrome may also induce MPO-ANCA.

The mechanism underlying PTU-induced ANCA-positive vasculitis is still unknown. Jiang et al.[23] proposed that activated neutrophils in the presence of hydrogen peroxidase release MPO from its granules, which converts PTU into cytotoxic products. Von Schmiedeberg et al.[24] speculated that, in the presence of MPO, PTU is converted to PTU sulfonate, which is immunogenic for T cells, and these T cells in turn activate B cells, which mediate the vascular injury. Lee et al.[25] suggested that PTU interacts with MPO to change the heme structure of the enzyme, which may then act as a hapten. In our patient, PR3-ANCA

Table 1. Twenty-two cases of PTU-induced MPO-ANCA-related disorders

	Ref.	Year	Age/sex	MPO-ANCA (EU)	Method	PR3-ANCA (EU)	Disorder
1	12	1994	11/M	141	EIA		GN
2	12	1994	15/F	55	EIA		GN
3	13	1997	36/F	239	EIA		AH, panniculitis
4	14	1997	52/F	60	EIA	50	GN, cutaneous vasculitis
6	15	1995	60/F	437	ELISA		GN
7	15	1995	22/M	502	ELISA		GN
8	15	1995	82/F	120	ELISA		GN
9	16	1995	22/F	107	ELISA		GN, cutaneous vasculitis
10	17	1997	39/F	510	ELISA	52	GN
11	18	1997	44/F	138	ELISA		AH
12	19	1999	30/M	595	ELISA		Wegener's granulomatosis cutaneous vasculitis
13	20	2000	16/M	63	ELISA		
14	21	2001	22/F	204	ELISA		Fever, althralgia
15	22	2002	16/F	298	ELISA		GN
16	22	2002	11/M	859	ELISA		GN
17	22	2002	15/F	441	ELISA		GN
18	22	2002	14/F	42	ELISA		GN, AH, cutaneous vasculitis
19	22	2002	16/F	121	ELISA		GN, AH
20	22	2002	13/F	27	ELISA		GN, AH
21	22	2002	13/F	97	ELISA		GN, cutaneous vasculitis
22	Our case		44/F	80	ELISA	17	Sweet's syndrome

The cases with MPO-ANCA detected by enzyme immunoassay (EIA) or enzyme-linked immunosorbent assay (ELISA) were included, and the cases without the description of methods were excluded

PTU, propylthiouracil; MPO, myeloperoxidase; PR3, proteinase 3; ANCA, antineutrophil cytoplasmic antibody; Ref., reference number; GN, glomerulonephritis; AH, alveolar hemorrhage

and LAC in addition to MPO-ANCA were present, and their titers returned to the normal range after the treatment. These findings suggest that the activation of B cells may be related to the induction of MPO-ANCA in our patient.

The mechanism underlying Sweet's syndrome is yet to be elucidated. Some hypotheses have been proposed, e.g., immunocomplex vasculitis,[26] T-cell activation,[27] and altered functions of neutrophils with abnormal lysosomal enzyme activity.[28] In our patient, PTU-induced MPO-ANCA may possibly have activated the lysosomal enzyme in neutrophils.

If PTU-induced MPO-ANCA plays a pathogenetic role in Sweet's syndrome, can Sweet's syndrome be included in the spectrum of vasculitis? Vasculitis is not usually observed in Sweet's syndrome, and fibrinoid necrosis, thrombosis, and endothelial cell thickening in the vascular walls are not observed histologically.[29] On the other hand, the fragmentation of numerous leukocytes is often seen in Sweet's syndrome.[30] Malone et al.[31] reported that although vasculitis was not the primary process, but occurred secondarily in response to noxious products released from neutrophils, vasculitis was found in 29% of 21 cases of Sweet's syndrome. In our patient, we observed erythrocyte extravasation and septal panniculitis in addition to the fragmentation of numerous leukocytes; these could be presumed to be the features associated with at least some vascular disorders.

Our patient also suffered from headache. A lumbar puncture yielded clear lymphocytosis but without any bacteria, and the diagnosis was aseptic meningitis. In our patient, aseptic meningitis was probably associated with Sweet's syndrome.[8]

In conclusion, we suggest that Sweet's syndrome can be included in the spectrum of PTU-induced MPO-ANCA-related disorders, although this syndrome is not usually complicated by idiopathic MPO-ANCA-related vasculitis.

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