Mod Rheumatol (2004) 14:73–76
DOI 10.1007/s10165-003-0270-5

CASE REPORT

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A case of Weber–Christian disease associated with myelodysplastic syndrome

Received: February 19, 2003 / Accepted: June 19, 2003

Abstract We report the case of a 73-year-old man with myelodysplastic syndrome (MDS) who developed Weber–Christian disease (WCD). Bone marrow aspirates showed refractory anemia with abnormal karyotypes such as trisomy 8, trisomy 8 and 14, and trisomy 8, 9, and 14. The patient had intermittent fever associated with multiple tender erythematous nodules on the skin. A biopsy sample taken from a nodule revealed focal subcutaneous infiltration of neutrophils and necrotizing fat tissue. We diagnosed the patient as having lobular panniculitis associated with myelodysplastic syndrome. The serum levels of soluble interleukin-2 (IL-2) receptor, interferon-γ, IL-1-β, IL-6 and tumor necrosis factor-α were elevated in the active state but returned to normal after prednisolone therapy. This finding appears to implicate a T-cell immune response in the pathogenesis of Weber–Christian disease.

Key words Cytokines · Lobular panniculitis · Myelodysplastic syndrome (MDS) · Trisomy 8 · Weber–Christian disease (WCD)

Introduction

Weber–Christian disease (WCD) is a rare idiopathic lobular panniculitis characterized by fever, arthralgia, and cutaneous lesions.[1] The prognosis is extremely variable. The prognosis is good in patients with cutaneous involvement only, while lobular panniculitis associated with prominent visceral involvement may eventually lead to death. Myelodysplastic syndrome (MDS) is characterized by ineffective hematopoiesis with a normocellular or hypercellular bone marrow, cytopenia, and a possibility of transformation into acute leukemia. In addition, some patients with MDS have been reported to develop immune-mediated complications such as autoimmune thrombocytopenia, Hashimoto's thyroiditis, or rheumatic diseases.[2–7] However, the association of WCD with MDS has been described in only a few reports.[8–10] Here we describe a rare case of WCD associated with MDS and the possible involvement of T-cell immune responses in the pathogenesis of WCD.

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Case report

A 73-year-old man with intermittent fever associated with multiple erythematous tender nodules was admitted to our hospital on November 29, 2000. He was diagnosed as having refractory anemia, a subtype of MDS, in June 2000. Five months before admission, he had undergone a cholecystectomy and choledocholithotomy for cholecystolithiasis. Two months before admission, he had suffered intermittent high fever four times over a period of about 1 week, and developed tender subcutaneous nodules on the limbs and back during an afebrile period of 1–4 weeks.

On admission, his temperature was 39°C. Subcutaneous erythematous tender nodules (5 cm in diameter) were noted on the lower abdomen, thighs, and right side of his back. There was no palpable lymphadenopathy or hepatosplenomegaly. Laboratory tests on admission revealed macrocytic–hyperchromic anemia (red blood count (RBC) 242 × 10^4/μl, hemoglobin (Hb) 6.2 g/dl, Ht 19.1%, MCH 107.9 fl, and mean corpuscular volume (MCV) 35.0 pg) and mild liver and renal dysfunction (Table 1). Low serum iron and high levels of ferritin and C-reactive protein were found. The serum levels of soluble IL-2 receptor (sIL-2R), interferon-γ (IFN-γ), IL-1-β, IL-6, and tumor necrosis factor-α (TNF-α) were increased (Table 2). The test results were negative for rheumatoid factor, antinuclear antibodies, and antineutrophil cytoplasmic antibodies. A bone marrow aspirate showed normocellularity with 3.4% blasts. Several erythroid cells with two nuclei, neutrophils with

Table 1. Laboratory data on admission (November 29, 2000)

ESR	160 mm/h
Hemogram	
RBC	177×10^4/μl
Hb	6.2 g/dl
Ht	19.1%
WBC	8100/μl
Neu	90.0%
Eo	0.0%
Ba	0.0%
Mo	5.5%
Ly	4.5%
Plt	13.4×10^4/μl
Chemistry	
GOT	107 IU/l
GPT	59 IU/l
LDH	284 IU/l
ALP	234 IU/l
γ-GTP	112 IU/l
T. Chol	168 mg/dl
TG	127 mg/dl
HDL-C	28 mg/dl
T. Prot	6.3 g/dl
Alb	3.2 g/dl
Na	135 mEq/l
K	5.5 mEq/l
Cl	107 mEq/l
Urea-N	44 mg/dl
Uric acid	8.8 mg/dl
Cr	2.7 mg/dl
CPK	31 IU/l
Amylase	197 IU/l
Fe	27 μg/ml
Ferritin	1609 ng/ml
Serology	
CRP	32.8 mg/dl
RF	<10 IU/ml
ANA	(−)
MPO-ANCA	(−)
PR3-ANCA	(−)
Bone marrow	
NCC	7.8×10^4/μl
Mgk	75/μl
Myeloid	
Bl	3.4%
Pro	6.4%
My	14.6%
Met	8.8%
St	13.6%
Seg	5.6%
Eo	3.2%
Ba	0.4%
Ly	13.8%
Mo	3.8%
Plasm	1.6%
Ret	9.6%
Erythroid	
Ba	2.6%
Poly	12.6%
Karyogram (20 clones)	
47,XY,+8	2 clones
48,idem,+14	3 clones
49,idem,+9,+14	1 clone

ESR, erythrocyte sediment rate; RBC, red blood count; Hb, hemoglobin; LDH, lactic dehydrogenase; ALP, alkaline leucocyte phosphatase; GTR, guanosine triphosphate; HDL-C, high-density lipoprotein cholesterol; CRP, C-reactive protein; RF, rheumatic factor; ANA, antinuclear antibodies; MPO-ANCA, myeloperoxidase antineutrophic cytoplasmic autoantibodies

Table 2. Serum levels of cytokines and inflammatory markers

	November 29, 2000 (active)	June 7, 2001 (inactive)	Normal serum level
sIL-2R (U/ml)	1340	182	145–519
IFN-γ (IU/ml)	19.5	<0.1	<0.1
TNF-α (pg/ml)	154	24	<40.0
IL-1β (pg/ml)	558	<8.0	<8.0
IL-6 (pg/ml)	83.6	2.4	<4.0
CRP (mg/dl)	32.8	0.03	<0.25

Pelger–Hüet-like nuclei or without granules, and megakaryocytes with multisegmental nuclei or multiple nuclei (which are characteristic of refractory anemia) were present (Fig. 1). A clonal karyotypic abnormality was detected in 2 (trisomy 8), 3 (trisomy 8 and 14), and 1 (trisomy 8, 9, and 14) of the 20 clones analyzed. A skin biopsy sample from a nodule on the right upper arm revealed focal subcutaneous infiltration of neutrophils and necrotizing fat tissue (Fig. 2). We diagnosed the patient as having WCD associated with MDS. Steroid therapy with prednisolone (PSL) at 40 mg/day orally was prescribed, and this resulted in a resolution of the signs and symptoms. After the PSL treatment, the patient's anemia gradually improved (RBC 242×10^4/μl, Hb 8.3 g/dl, and Ht 26.1%). In addition, his mild liver and renal dysfunction disappeared after being afebrile. After the disappearance of the signs and symptoms, his serum levels of soluble IL-2 receptor, IFN-γ, IL-1β, IL-6, and TNF-α returned to normal (see Table 2). PSL was then gradually reduced. The patient's symptoms did not worsen after the start of PSL reduction, and he was transferred to another hospital on June 28, 2001, to continue the reduction of the dose.

Discussion

A description of WCD was published by Christian[11] and Bailey[12] almost 70 years ago, and was based on the signs and symptoms of nodular, relapsing panniculitis lesions, fever, lipoatrophy, and lipophagia. It later became apparent that panniculitis was not restricted to the skin and could present as a systemic illness, and that many diseases could be associated with panniculitis. It has been reported that lobar panniculitis can be associated with acute pancreatitis, acinar cell carcinoma, collagen disease, and hematological diseases.[13]

An association between MDS and rheumatological manifestations has been suggested.[4,7] In a retrospective review covering a 6-month period and including 162 patients with MDS, Castro et al.[7] found 16 patients (10%) with several rheumatological manifestations such as cutaneous vasculitis, lupus-like syndrome, neuropathy, mixed connective tissue disease, Sjögren's syndrome, and rheumatoid arthritis. In a retrospective study of 82 patients with MDS, Billström et al.[4] described ten patients (12%) with immune-mediated complications such as skin vasculitis, temporal arteritis, polymyalgia rheumatica, necrotizing panniculitis,

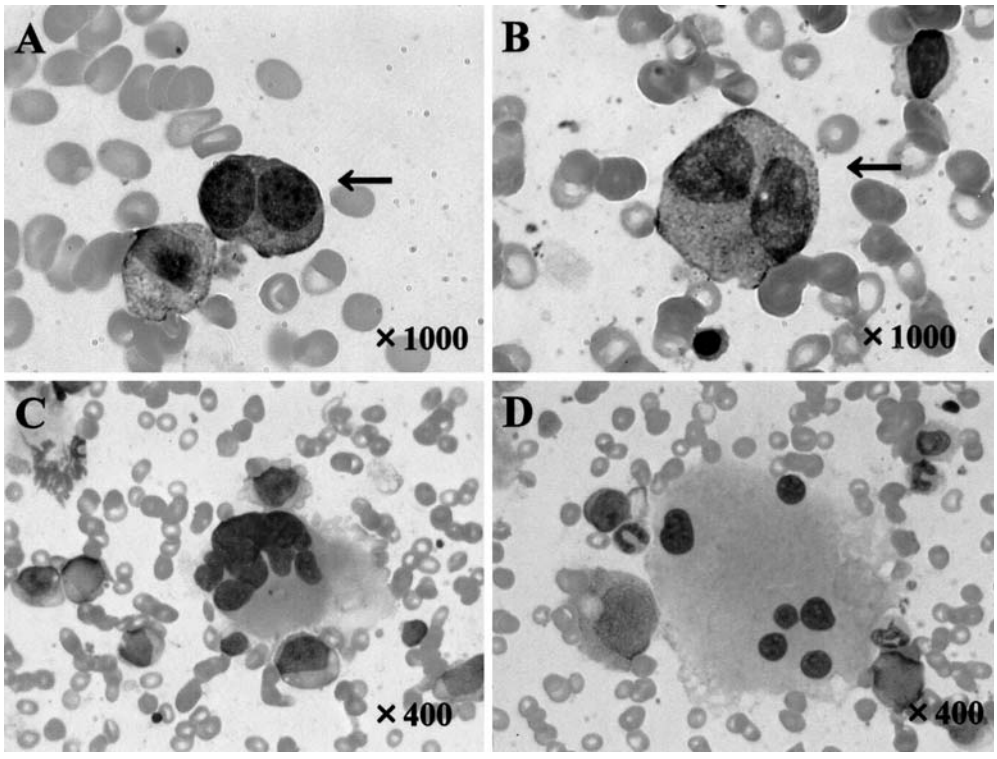

Fig. 1. May–Giemsa-stained photographs of a bone marrow aspiration. **A** Erythroid cell with two nuclei. **B** Neutrophil with Pelger–Hüet-like nuclei. **C, D** Megakaryocytes with multisegmental nuclei or multiple nuclei

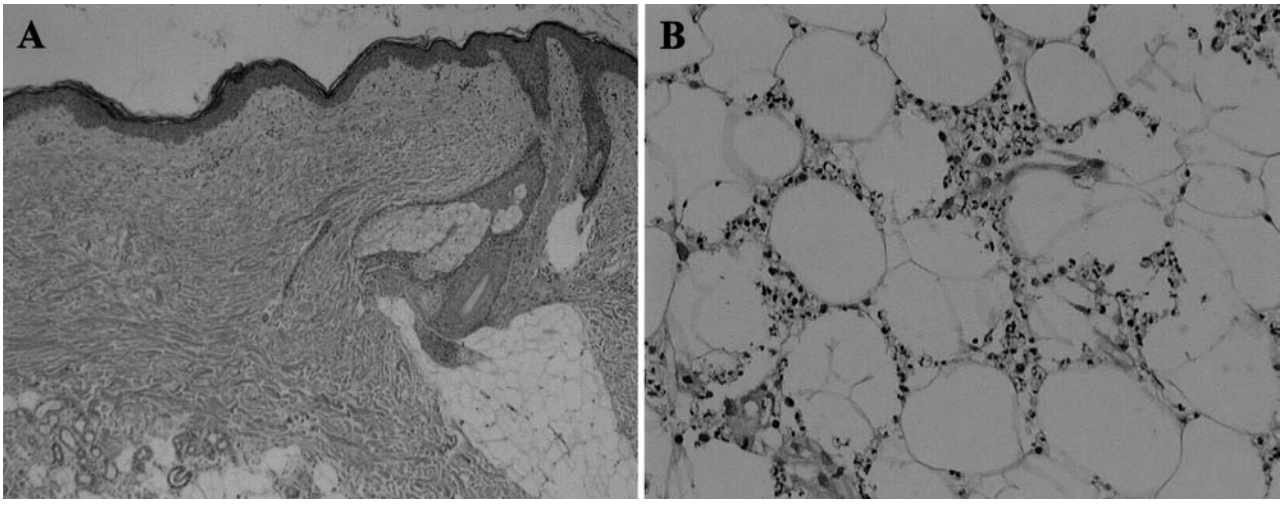

Fig. 2. Photographs of a skin biopsy sample from a nodule on the right upper arm. Focal subcutaneous infiltration of neutrophils and necrotizing fat tissue can be seen. **A** H&E, ×50. **B** H&E, ×200

Hashimoto's thyroiditis, autoimmune thrombocytopenia, and Sweet's syndrome. Compared with the other patients, these patients with immune-mediated complications were more frequently observed to have clonal chromosomal abnormalities and complex karyotypes, such as those in the present case. An association between trisomy 8 and rheumatic diseases has been suggested previously.[14,15] Hasegawa et al. summarized the chromosomal abnormality of Behçet's disease with MDS.[14] Fifteen (75%) of the 21 reported cases had trisomy 8, although trisomy 8 is generally observed in only 10%–20% of patients with MDS. Kimura et al.[15] also described MDS with trisomy 8 as a risk factor for intestinal ulcers and thrombosis with Behçet's disease. The close association of chromosomal abnormalities with rheumatic diseases has only previously been noted in these reports.

Immunological abnormalities are frequent in patients with MDS.[2–4] A number of functional and quantitative abnormalities of monocytes, T-, B-, and NK-lymphocytes have been reported. The abnormal lymphocytes or monocytes in

patients with MDS may act by releasing cytokines that perturb the endothelial cell lining of blood vessels in the skin, synovia, and peripheral nerves or other organs, thus producing the clinical features. In the case reported here, the patient's serum levels of soluble IL-2 receptor, IFN-γ, IL-1β, IL-6 and TNF-α were high, but returned to normal after PSL therapy. An increased concentration of soluble IL-2 receptor indicates the activation of lymphocytes, especially T-cells, and IFN-γ is produced by Th1, CD8+, NK, and monocytes/macrophages. The effector functions of IFN-γ, which induce the production by macrophages of inflammatory mediators such as TNF-α, IL-1β, and IL-6, may contribute to the degeneration and necrosis of adipose tissue. Lesprit et al.[8] reported two patients with MDS associated with WCD, one of whom had a high serum level of TNF-α. Iwasaki et al.[16] reported a patient with WCD with increased serum levels of soluble IL-2 receptor, IFN-γ, IL-6, IL-4, and IL-10, who was treated successfully with cyclosporin A. Cytophagic histiocytic panniculitis (CHP) can be a severe variant of Weber–Christian disease characterized by the histopathological appearance of lobular panniculitis infiltrated by T helper cells, and histiocytes containing blood cell fragments, and by a clinical course with marked systemic features, including multiorgan failure, hypertriglyceridemia, and coagulopathy, which may lead to death.[17–19] However, cyclosporine A is very effective in CHP.[17,19] From these findings and the case study reported here, it is suggested that T-cell immune responses may be involved in the pathogenesis of WCD. We recommend further study on the pathogenesis of WCD.

Acknowledgments The authors thank Dr. Hideki Mori for his support.

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