Successful Treatment of a Patient with Febrile, Lobular Panniculitis (Weber-Christian Disease) with Oral Cyclosporin A: Implications for Pathogenesis and Therapy

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We report a 15-year-old Japanese girl with severe systemic Weber-Christian disease (WCD) who presented with acute onset of high fever associated with tender subcutaneous nodules. Laboratory tests showed an elevated serum concentration of lactate dehydrogenase (LDH), leucopenia, and coagulation abnormalities. The anti-nuclear and anti-DNA antibodies were negative, and the serum pancreatic enzymes and alpha 1-antitrypsin levels were normal. Pulse steroid therapy was not effective, and eventually cerebellar hemorrhage occurred. After initiation of oral cyclosporin A (CyA) therapy, fever came down and her clinical condition improved markedly. Extremely high serum concentrations of interferon-gamma (IFN-γ) and soluble interleukin-2 receptor (sIL-2R) in this patient returned to normal with CyA therapy. These findings suggest that T-cell immune responses are involved in the pathogenesis of WCD, and that CyA is effective against the disease via suppression of T-cell reactions.

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Key words: disseminated intravascular coagulation syndrome (DIC), interferon-gamma (IFN-γ), soluble interleukin-2 receptor (sIL-2R), cerebellar hemorrhage

Introduction

Weber-Christian disease (WCD) is a rare idiopathic lobular panniculitis characterized by fever, arthralgias, and cutaneous lesions (1–3). The etiology of WCD remains unknown, and the prognosis is extremely variable. In patients with only cutaneous involvement, the prognosis is good. On the other hand, lobular panniculitis associated with prominent visceral involvement may eventually lead to death.

We report a case of WCD which became complicated by the disseminated intravascular coagulation syndrome (DIC) and cerebellar hemorrhage before the panniculitis was treated successfully with cyclosporin A (CyA). The serum levels of interferon-gamma (IFN-γ) and soluble interleukin-2 receptor (sIL-2R) in this patient were extremely elevated but returned to normal after CyA therapy. Our findings implicate T-cell immune responses in the pathogenesis of WCD and demonstrate that CyA is effective against the disease due to suppression of T-cell reactions.

Case Report

The patient was a 15-year-old Japanese girl with recurrent episodes of fever associated with tender subcutaneous nodules since 1988. A specimen from a skin biopsy performed shortly after onset showed inflammation of fat lobules, and WCD was diagnosed. She received treatment with corticosteroids for multiple recurrences. In October 1995 she was admitted to our hospital because of high fever and tender subcutaneous nodules over the distal lower limbs. Laboratory studies showed a hemoglobin level of 11.5 g/dl, a white blood cell count of 2,600/μl, and a platelet count of 198,000/μl. Coagulation and liver function tests were normal, but the serum concentration of lactate dehydrogenase (LDH) was elevated to 762 U/l. The serum concentrations of pancreatic enzymes, alpha 1-antitrypsin, and ferritin were within the normal range. Tests for anti-nuclear and anti-DNA antibodies were negative. Extensive microbiological and serological investigations were negative for bacteria, fungi, and parasites, and no significant titers of antiviral antibodies were detected, including antibodies to cytomegalovirus, Epstein-Barr virus, Herpes simplex virus, and human immunodeficiency virus. Bone marrow aspirate showed no hist-
Weber-Christian Disease

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Figure 1. Histological findings in subcutaneous fat (second biopsy specimen). Fat degeneration and necrosis are prominent. An infiltrate of neutrophil and lymphocytes is seen among the fat cells (HE stain, ×400).

We diagnosed a recurrence of WCD, which we treated unsuccessfully with pulse steroid therapy (intravenous methylprednisolone, 1 g/day for 3 days). Gammaglobulin (15 g) then was administered intravenously, also without effect. Fever persisted, and DIC with cerebellar hemorrhage developed. LDH and triglyceride concentrations increased to 7,000 U/l and 700 mg/dl, respectively.

In November 1995 oral administration of CyA was begun, initially at 150 mg/day. In December we increased the dose to 300 mg/day, achieving plasma CyA concentrations of between 50 and 200 ng/ml. Five days after initiation of CyA therapy the fever came down. This change was followed by complete recovery. Abnormal laboratory values returned to normal (Fig. 2). The patient has remained in remission during the 3 years following administration of CyA.

The serum concentration of sIL-2R (normal, 459 ±126.9 U/ml) had been elevated to 3,570 U/ml before treatment but fell to 400 U/ml after CyA. Examination of serum cytokine concentrations revealed an extreme elevation of IFN-γ before CyA; interleukin (IL)-6 and IL-10 were moderately elevated. All of these were normalized with CyA treatment (Table 1).

Discussion

WCD, first described in 1892 by Pfeifer, was delineated further in Weber’s 1925 report of a case of relapsing nonsuppurative nodular panniculitis. After Christian stressed the importance of fever in this syndrome in 1928 it became known as Weber-Christian disease. WCD, as a disease category is not as simple as it was originally described, and the diagnosis of WCD continues to be controversial in dermatopathology literature (1, 2). There has been an attempt to classify the...
panniculitis into lobular and septal types (3), and WCD falls into the lobular type. Since lobular panniculitis may also be seen with infections, alpha 1-antitrypsin deficiency, pancreatitis, systemic lupus erythematosus, malignant diseases, and cytophagic histiocytic panniculitis (CHP), these changes are not diagnostic and the clinicopathological correlation is necessary. Histologic findings include degeneration and necrosis of lipocytes associated with an inflammatory infiltrate composed of polymorphonuclear leukocytes and lymphocytes mainly within lobulated subcutaneous adipose tissue. Classically, the initial mixture of inflammatory cells evolves into a macrophage-predominant stage characterized by many foamy histiocytes. Finally, these foam cells are replaced by fibroblasts as the inflammatory reaction is followed by scarring (4). In the present case, the histological findings of the biopsy specimen were compatible with WCD (Fig. 1). Extensive microbiological and serological investigations and the anti-nuclear and anti-DNA antibodies were negative. The serum pancreatic enzymes and alpha 1-antitrypsin levels were normal. CHP is characterized by the histopathologic appearance of lobular panniculitis with infiltration by histiocytes containing blood cell fragments and by a clinical course with striking systemic features, including multiorgan failure, hypertriglyceremia, and coagulopathy, which may lead to death (5). This entity has been reported with several viral infections. It has also been associated with malignant histiocytosis and both B- and T-cell lymphomas. We did not detect histiocytes in the bone marrow and no significant titers of antiviral antibodies were detected.

The etiology of WCD remains unknown. However, it has been related to an immunologically mediated reaction to diverse antigenic stimuli because of an association in some patients with elevated levels of circulating immune complexes (6). In the present case, we observed a greatly increased serum sIL-2R concentration, which represents T-cell activation. Furthermore, the serum level of IFN-γ was extremely high. Effector functions of IFN-γ which induce production by macrophages of inflammatory mediators such as IL-1, TNF-α, and reactive oxygen or nitrogen species, are likely to contribute to the degeneration and necrosis of adipose tissue.

The present case demonstrates successful treatment of severe steroid-resistant WCD with CyA, an agent which acts primarily on helper T cells and interferes with elaboration of several lymphokines such as IL-2 and IFN-γ (7, 8). In this case, CyA therapy resulted in a dramatic decrease in the serum concentration of IFN-γ followed by rapid clinical improvement. Therefore, it seems reasonable to use CyA for steroid-resistant WCD. Successful treatment of WCD with CyA was described in 1988 (9), and several additional successes have been reported. Recently Ostrov et al have reported a successfully treated case with a review of the literature on CHP and treatment with CyA (10); in instances of severe CHP when CyA was not given, 19 of 27 patients died (70%), but with CyA rapid remission was achieved in 6 of 6 severely ill patients (0% mortality). We consider CyA to be the drug of choice in essentially all severe case of WCD and CHP.

References