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CASE REPORT

Successful Treatment of Cytophagic Histiocytic Panniculitis by Cyclosporin A: A Case Report

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SUMMARY **This is a report of a case, 7 ½ year-old-boy having chronic febrile and recurrent crops of painful subcutaneous nodules on lower extremities, which had previously been diagnosed as Weber-Christian disease, which progressed to have cytophagic histiocytic activity in the skin, bone marrow with abnormal liver function and hemorrhagic diathesis. He was subsequently treated with corticosteroid without good response. After he was diagnosed as having cytophagic histiocytic panniculitis, cyclosporin A was administered intravenously in an initial dosage of 1 mg/kg/day and in oral maintenance dose of 10 mg/kg/day with a successful response and the patient completely recovered within 6 months with mild hypertension as an adverse effect.**

Weber-Christian disease (WCD) is an inflammatory disease of subcutaneous fat first described in 1892. Panush *et al.*[1] analysed the clinical and laboratory features of WCD, including chronic relapsing fever with subcutaneous non-suppurative nodules predominantly on lower extremities, arthralgia or arthritis and myalgia. The laboratory features were elevated erythrocyte sedimentation rate, anemia, leukopenia and hypocomplementemia. Subsequent reports by Winklemann and Bowie[2] in 1980, and by Crotty and Winklemann in 1981[3] found that individual cases of so-called Weber-Christian disease with bleeding diathesis, represented a new and unique syndrome called "cytophagic histiocytic panniculitis" (CHP). CHP was characterized by a clinical course of fever, recurrent nodules of panniculitis, mucous membrane ulcerations, cytopenia, serosal effusion, reticuloendotheliomegaly progressing to liver dysfunction and terminal hemorrhagic diathesis. Pathological features of CHP showed benign histiocytosis, lobular panniculitis, erythrophagocytosis and leukophagocytosis, necrosis of fat with edema and hemorrhage, cytophagic histiocytes in liver, spleen, lymph node, bone marrow, myocardium and lung.

REPORT OF A CASE

A 7½ year-old-boy was admitted to the Department of Pediatrics, Faculty of Medicine Siriraj Hospital for evaluation of chronic, recurrent fever with crops of painful subcutaneous nodules on lower extremities for one month. He was first admitted at the private hospital and treated with antibiotics without benefit. Septic workups showed no evidence of infection. There was no history of previous trauma to the site of the lesion. Prednisolone was given for 3 weeks for suspected diagnosis of erythema nodosum with some clinical response of skin lesions but still sustained high fever; he was referred to Siriraj hospital for further evaluation. There was no history of

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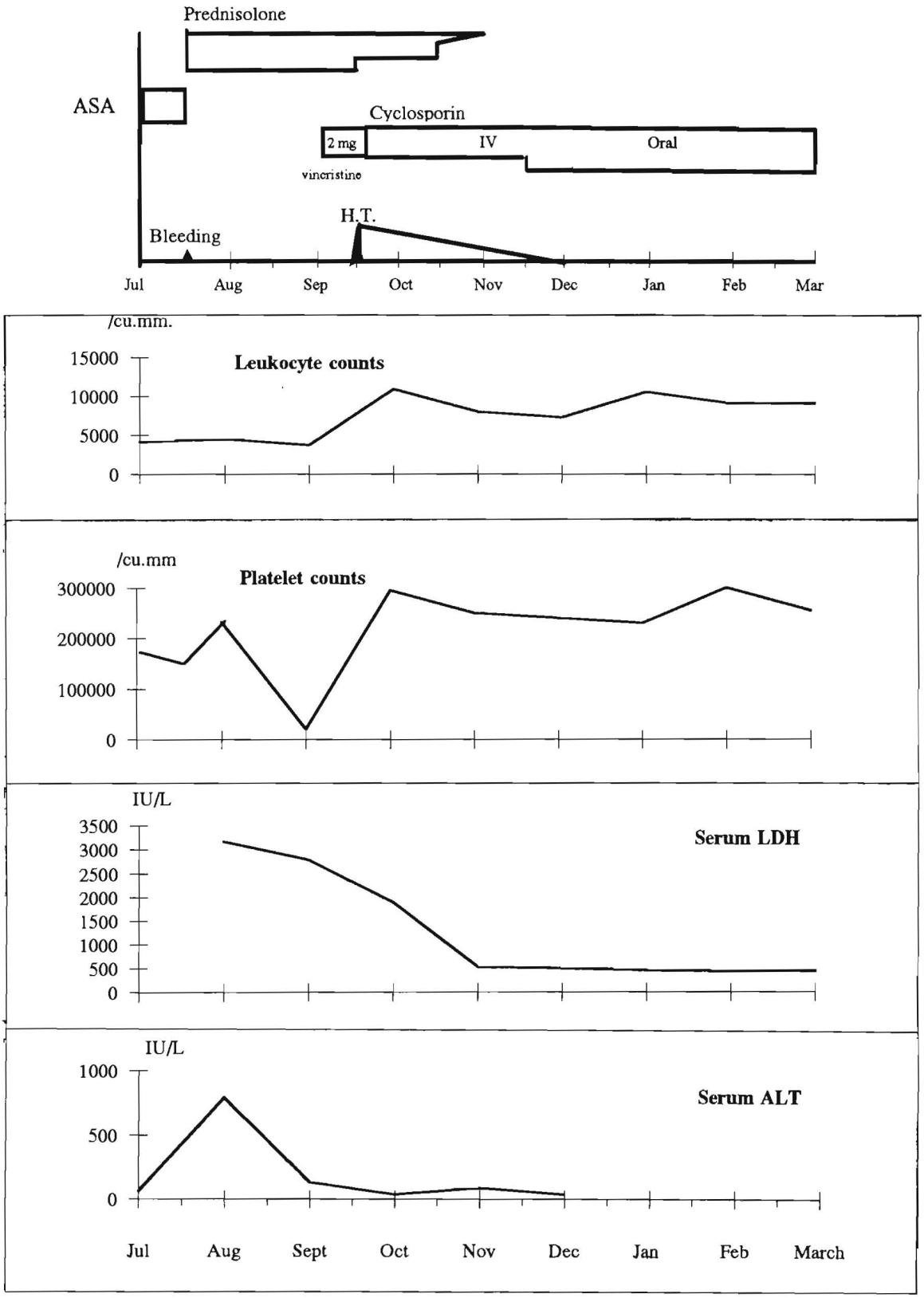

Fig. 1. Laboratory data.

arthritis, arthralgia, viral disease, drug allergy and the family history was unremarkable.

Physical examination revealed a febrile (39°C) boy who appeared to be alert and in no distress. Examination of the skin revealed multiple tender, erythematous nodules, 2 to 6 cm in diameter, distributed on both thighs, the liver was smooth, nontender and palpable at 1 cm below the right costal margin. The spleen was nonpalpable, there was no lymphadenopathy. The other systems were unremarkable.

On admission, laboratory data included a white blood cell count of 4,100/mm^3 (52% polymorphonuclear cells, 46% lymphocytes, 2% monocytes), a hemoglobin level of 10.6 gm/dl, and a platelet count of 120,000 mm^3 Normal levels of liver enzymes and serum lipids (cholesterol and triglyceride). The results of the remainder of the biochemical profile were also within normal limits. The erythrocyte sedimentation rate increased and C-reactive protein was positive, but the remainder of his diagnostic tests were all normal or negative. These included hemoculture, urine culture, gastric wash for acidfast bacilli, PPD skin test, hepatitis B virus profile, HIV antibody, immunoglobulins, C_3 complement, LE test, ANF, anti DNA, rheumatoid factor, anti Sm antigen, anti RNP antigen, and Coombs' test. X-rays of chest, skull, long bones were normal. He was given aspirin in a dosage of 30 mg/kg/day for fever and for suppression of the inflammation during the first two weeks. After skin biopsy revealed lobular panniculitis, with no evidence of vasculitis, prednisolone was given in a dosage of 1.5 mg/kg/day with mild clinical response. The patient developed ecchymosis on the right eyelid with subconjunctival hemorrhage after 2 weeks of hospitalization. Pancytopenia (hemoglobin 9.2 gm/dl, white blood cell count 2,400/mm^3 platelet 95,000/cumm) but normal coagulogram were found. Bone marrow

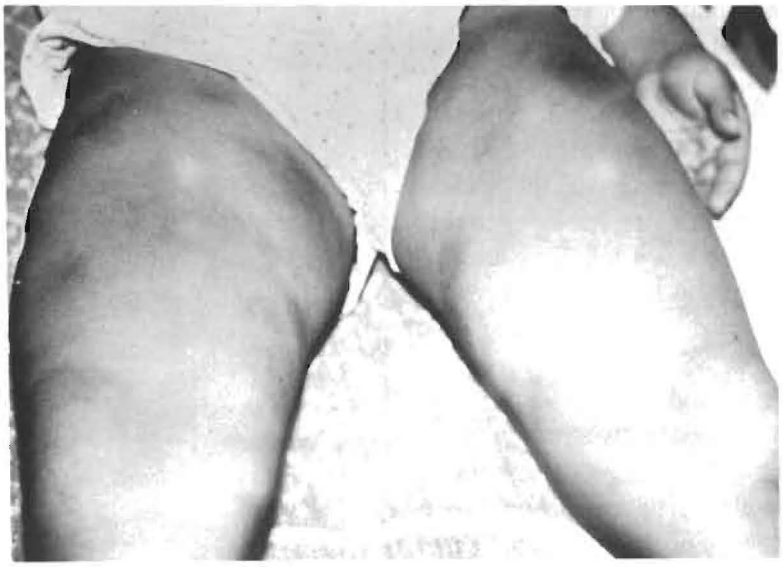

Fig. 2. Erythematous, tender subcutaneous nodules on both thighs (on admission).

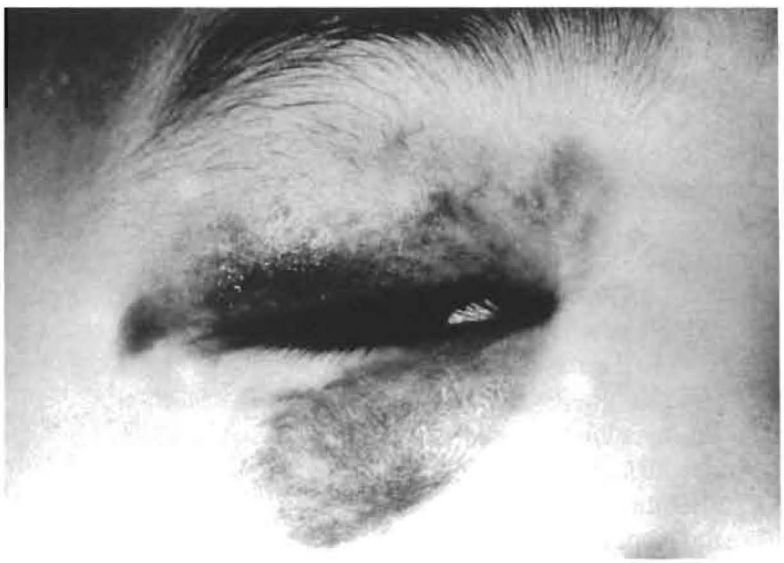

Fig. 3. Ecchymosis and subconjunctival hemorrhage, the right eye.

aspiration was performed, demonstrating benign histiocytes engulfing red and white blood cells, platelets called histiocytic hemocytophagic activity (bean-bag appearance) with normal appearance of other histiocytes, no malignant or metastatic cells. Rebiopsy of the skin also revealed lobular panniculitis with focal fat necrosis, hemorrhage, mixed cell infiltration of mononuclear cells, neutrophils, lymphocytes and some histiocytes which showed active hemophagocytosis. The diagnosis of cytophagic histiocytic panniculitis was confirmed. The study of T-cell subpopulations revealed low numbers of both helper and suppressor T-cells and low ratio of T-helper: T-suppressor cell (241:334 = 0.72). Because of poor response of the disease to corticosteroids, Vincristine was tried (2 mg intravenous route once weekly for two weeks) without clinical improvement. Following marked pancytopenia, marked rise of liver enzymes and serum lipid levels, cyclosporin A was administered 1 mg/kg/day intravenously once daily in light of his impaired liver function. After the initiation of cyclosporin A therapy, mild hypertension was detected (130-140 Torr systolic and 90-120 Torr diastolic levels) and was controlled by adalat and hydralazine. Fever abated by the first week after treatment and by the second week leukocyte and platelet counts increased to normal levels, serum alanine aminotransferase (ALT) returned to normal by the 7th week, serum lactate dehydrogenase gradually decreased to normal level in four months after treatment. After 2 months of intravenous cyclosporin A, a maintenance dose of the oral form was given 10

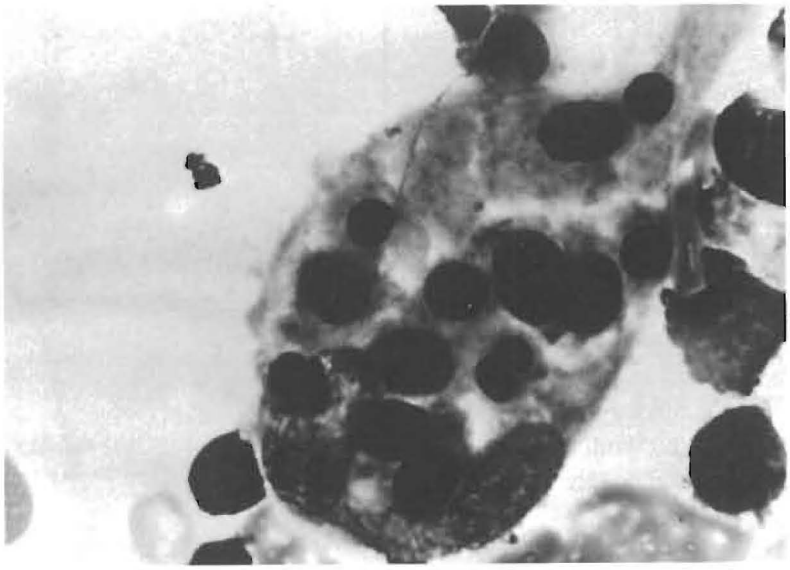

Fig. 4. Bone marrow: Histiocytic hemocytophagosis. Histiocytes stuffed with nucleated red cells, leukocytes and platelets (Bean-bag appearance)

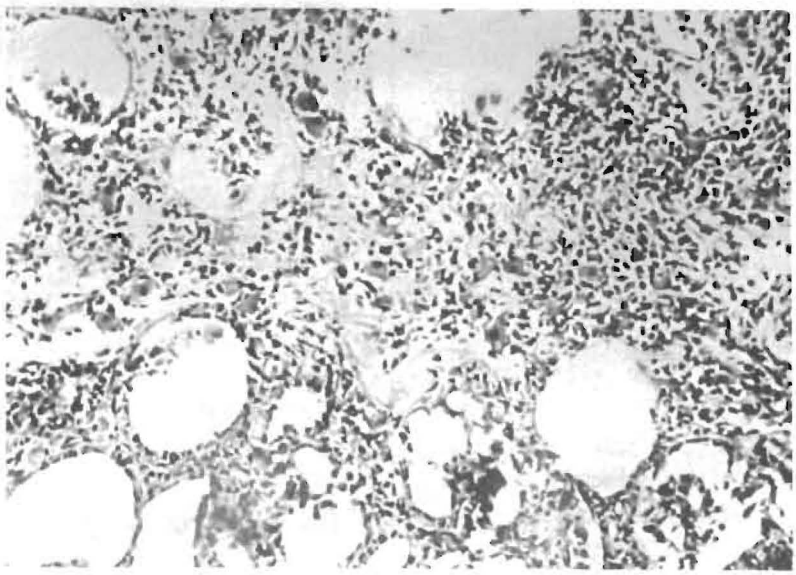

Fig. 5. Skin biopsy: Lobular panniculitis with focal fat necrosis, hemorrhage, mixed cell infiltration (mononuclear, neutrophil, lymphocytes and some histiocytes). Some histiocytes show active hemophagocytosis (erythrocytes and mononuclear cells).

mg/kg/day for 2 months and tapered off in a half dose for another 2 months by which both clinical signs and abnormal laboratory findings became normal. The patient completely recovered leaving depressed skin and some atrophic scars.

DISCUSSION

Cytophagic histiocytic panniculitis was described in 1980 as a chronic histiocytic disease of the subcutaneous fat which manifested with fever, inflammatory panniculitis, serositis and reticuloendotheliomegaly. Winklemann and Bowie[2] described benign histiocytic cytophagic panniculitis with terminal hemorrhagic diathesis in 5 patients. Crotty and Winklemann[3] reported the microscopic and autopsy findings including the presence of "bean-bag" cytophagic cells in the bone morrow, liver, spleen and lymph nodes. Ciclitira *et al.*[4] reported a fatal case of systemic Weber-Christian disease presenting with lobular panniculitis and involvement of internal organs (bone marrow, liver, adipose tissue of small bowel). They found high levels of circulating immune complexes with a Frederickson type I hyperlipidemia suggested that an immune or autoimmune disease of adipose tissue might be the aetiology of the condition. White and Winklemann[5] reported two cases of benign cytophagic histiocytic panniculitis and compared them with fatal cases previously reports. Single report of CHP were published in 1985 by Willis *et al.*,[6] Aronson *et al.*,[7] Peters and Winklemann.[8] The last two reports had the additional features of cutaneous T-cell lymphoma and B-cell lymphoma, respectively. Suster *et al.*[9] reported a case of histiocytic lymphophagocytic panniculitis and massive lymphadenopathy in which the lesions regressed spontaneously without therapy over a period of a few weeks, further supporting the diagnosis of sinus histiocytosis by the immunocytochemical demonstration of S100 protein reactivity within the histiocytic cell. This disease should be considered in differential diagnosis of cutaneous lesions presenting with lobular and septal panniculitis. Willis *et al.*[6] classified the pathology of cytophagocytosis as a primary group of unknown cause (cytophagic panniculitis, sinus histiocytosis, familial hemophagocytic histiocytosis) and a secondary group related to known causes such as infection (viral, bacterial) and hematopoietic diseases.

Our case was originally diagnosed as Weber-Christian disease on the basis of clinical findings, laboratory features and pathological findings which included chronic relapsing fever with crops of painful subcutaneous nodules, leukopenia, mild anemia, no evidence of infection; the pathologic findings revealed lobular panniculitis without evidence of vasculitis. He was previously treated by prednisolone with some clinical response. Later he developed hemorrhagic diathesis, and bone morrow aspiration showed histiocytic hemocytophagocytosis or bean-bag appearance. Rebiopsy of the skin lesion revealed lobular panniculitis with active histiocytic hemocytophagocytosis. Because of liver dysfunction, pancytopenia and hyperlipidemia with the diagnosis of cytophagic histiocytic panniculitis, the same as findings reviewed by Alegre and Winklemann,[10] and the report of successful treatment of a so-called systemic Weber-Christian disease by cyclosporin A by Usuki *et al.*,[11] we made this diagnosis. Our patient experienced poor-responsive treatment to corticosteroid, so he was treated by cyclosporin A with good response with respect to both clinical and laboratory findings within 2 to 7 weeks respectively and completely cured by 6 months. The only adverse effect was mild hypertension which was under controlled by hydralazine. No relapse was detected in either clinical or laboratory findings after treatment during the follow-up period of 5 years.

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