# Successful treatment of reactive hemophagocytic syndrome with cyclosporin A and intravenous immunoglobulin

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Infection-associated hemophagocytic syndrome (IAHS) is a form of the reactive hemophagocytic syndrome. IAHS is associated with viral, bacterial, fungal, mycobacterial, rickettsial and protozoal infections and with various malignant neoplasms. A more accurate designation for this acquired form of the syndrome is reactive hemophagocytic syndrome (HS). Reactive HS is characterized by malaise, fever, hepatosplenomegaly, lymphadenopathy, cytopenia, hypertriglyceridemia, hypofibrinogenemia and hemophagocytosis. Cyclosporin A, VP-16, high-dose steroids, and intravenous immunoglobulin (IVIG) have been used in the treatment of IAHS. Here, a 10-year-old girl with reactive HS due to possible viral infection was treated successfully with cyclosporin A and IVIG. Fever disappeared on the third day, complete blood count reached normal levels on the sixth day and hepatosplenomegaly disappeared on the ninth day after treatment.

We believe cyclosporin A and IVIG may be used in the treatment of reactive HS, at least in selected patients. Further studies are required to confirm its role as first-line therapy for children with IAHS.

*Key words: reactive hemophagocytic syndrome, intravenous immunoglobulin, cyclosporin A.*

Two forms of hemophagocytic syndrome (HS) have been characterized: infection-associated HS (IAHS) and familial erythrophagocytic lymphohistiocytosis (FEL). Because IAHS is not always infection induced, with many cases associated with a variety of malignant neoplasms, a more accurate designation for this acquired form of the syndrome is reactive HS[1].

Common presenting features of this syndrome are fever, malaise, weight loss, hepatosplenomegaly, lymphadenopathy, profound cytopenia involving two or more cell lines, hypertriglyceridemia, hypofibrinogenemia and hemophagocytosis[2]. The clinical course is generally fulminant and may be complicated with hepatic dysfunction and renal failure[2].

Cyclosporin A, high-dose steroids, intravenous immunoglobulin (IVIG), and VP-16 have been used in the treatment of IAHS; however, the treatment of IAHS has still not been standardized[3-6].

Here, we present a case of reactive HS showing a very favorable clinical course following treatment with cyclosporin A and IVIG.

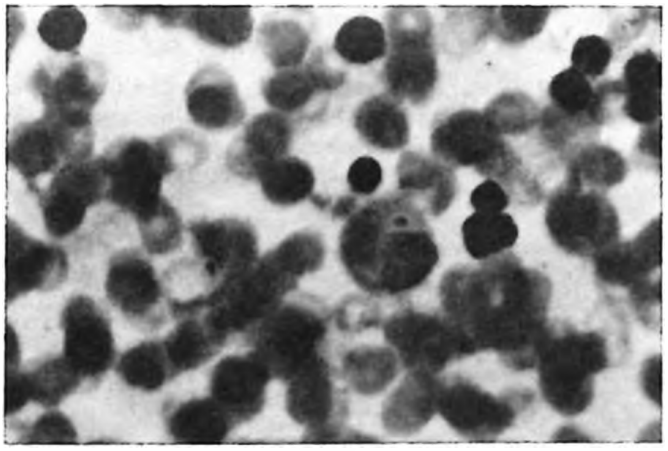
## Case Report

A 10-year-old girl was admitted to our clinic with complaints of fever and weakness for five days. She was the product of a consanguineous marriage and had two healthy siblings. On admission, the patient appeared severely pale and ill with a body temperature of 38.5 °C. Physical examination revealed tonsillopharyngitis, maculopapular eruptions on her trunk and extremities, and cervical, axillary and inguinal microlymphadenopathies. The liver and spleen were palpable 6 and 5 cm below the costal margins, respectively. Clinical findings related to malignant lymphoma and connective tissue disorders such as systemic lupus erythematosus were not determined. The rest of the physical findings were unremarkable.

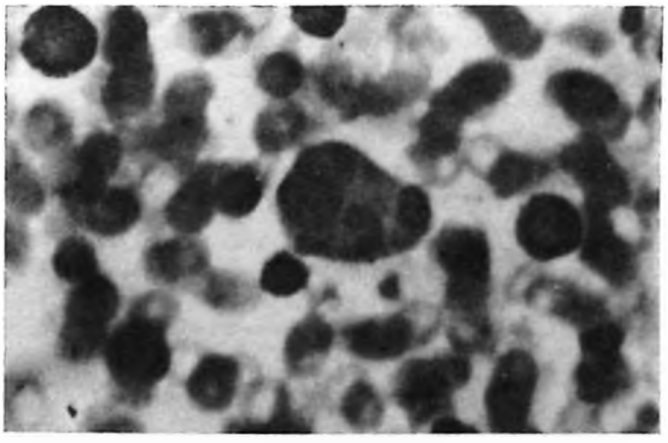
Laboratory tests revealed erythrocyte sedimentation rate (ESR) of 45 mm/h; hemoglobin (Hb) 9.4 g/dl, leukocytes $3.4 \times 10^9$/L with 63% lymphocytes (4% atypical lymphocytes), 34% neutrophils, 3% monocytes and platelets $52 \times 10^9$/L.

The activated partial thromboplastin time (aPTT) was 29.4 seconds, prothrombin time (PT) 12.2 seconds and the plasma fibrinogen levels 220 mg/dl. LDH was 2250 U/L, ALT 91 U/L, AST 164 U/L, GGT 369 U/L, triglyceride 204 mg/dl, cholesterol 104 mg/dl, and ferritin 629 mg/ml. Other biochemical test results were within normal limits. Immunoglobulin levels were IgG 1206 mg/dl, IgA 161.7 mg/dl, and IgM 168 mg/dl. Flow-cytometric analysis of peripheral blood lymphocytes indicated $CD_4$ 34%, $CD_8$ 25% and $CD_4/CD_8$: 1.4. Serology, including Epstein-Barr virus (EBV), parvovirus $B_{19}$ and cytomegalovirus (CMV), was negative. Throat swab and blood cultures were negative. A plain chest radiograph was normal..

Examination of bone marrow aspiration showed an increased number of histiocytes with erythrocytes, thrombocytes, leukocytes and lymphophagocytosis, and no evidence of malignant cells (Fig. 1a, 1b).



(a)



(b)

**Fig. 1.** Photomicrograph of the bone marrow aspirate demonstrating histiocytic phagocytosis of erythrocytes and thromboycles (Fig. 1a), leukocytes and lymphocytes (Fig. 1b).

The patient was treated with IVIG (0.4 g/kg/d) for five days and cyclosporin A (5 mg/kg/d) for 10 days. The patient became afebrile on the third day, blood cell count returned to normal on the sixth day and hepatosplenomegaly disappeared on the ninth day of therapy.

The patient has been in good health for two months.

## Discussion

A diagnosis of reactive HS should be considered if a patient has fever of unknown origin, a variable degree of pancytopenia, the progressive development of multiorgan dysfunction, coagulopathy, and the presence of an increased number of phagocytic histiocytes in bone marrow[1]. Based on these criteria our patient was considered to have reactive HS.

Reactive HS has been known to occur in association with infections by many different microorganisms such as viral, bacterial, fungal, mycobacterial, rickettsial and protozoal, in addition to a wide spectrum of malignant neoplasms[2,7-10]. Therefore, the hemophagocytosis in our patient might have been related to viral infection according to the physical signs and peripheral smear findings, although serology, including EBV, CMV and parvovirus $B_{19}$, was negative.

The mechanism responsible for the hemophagocytic activity of reactive histiocytosis is unclear. Oyama et al.[3] presented data indicating that there is an alteration in T cell function in hemophagocytosis with uncontrolled secretion of T cell producing interferon (IFN)-γ and other lymphokines. Elevated levels of IFN-γ, soluble interleukin (IL)-2 receptor (sIL-2R), soluble $CD_8$, and macrophage colony-stimulating factor (M-CSF) have been found in patients with hemophagocytosis[4,5,11]. Uncontrolled IFN-γ and M-CSF can lead macrophages to a hemophagocytosing and tumor necrosis factor-α (TNF-α) and IL-6 secreting state[3,12].

There is no specific treatment for IAHS. Various drugs such as cyclosporin A, VP-16, high-dose steroids, and IVIG have been used[3-5]. Fort and Buchanan[6] reported a child treated successfully with acyclovir, VP-16 and dmultiple doses of IVIG. Yao et al.[13] described high-dose IVIG plus corticosteroid therapy in two adult patients with hemophagocytic syndrome. The action mechanisms of IVIG are blockage of Fc-receptor-mediated phagocytosis in the mononuclear/

phagocyte system, anti-idiotype effects and possibly down-regulation of immunoglobulin synthesis[14,15]. In addition, IVIG may exert its therapeutic effect by modulating T cell response and associated changes in mediator release[15].

Sixty percent of children with IAHS treated with immunosuppressive drugs, mostly steroids and etoposide or both, showed a response[19]. It was emphasized that only etoposide or immunoglobulin treatment or combination of both led to remarkable improvement in the prognosis of the usually fatal EBV-related HS[17]. In addition, an adolescent patient with IAHS was treated successfully with cyclosporin A[16]. Therefore, we used cyclosporin A in our patient with reactive HS due to possible viral infection although a triggering viral agent could not be determined. The action mechanism of cyclosporin A is suggested to be inhibition of T cell activation due to blockade of IL-2 secretion from $CD_4^+$ lymphocytes[4,17,18]. However, the use of immunosuppressive agents needs special consideration because of their adverse effects in increasing the progression of and mortality rate of IAHS during the acute infection. Here, we report a child with reactive HS due to possible viral infection treated successfully with cyclosporin A and IVIG. Although clinical findings of the patient were not very severe, we decided to use cyclosporin A in addition to IVIG treatment to prevent the progression of the clinical findings. We believe cyclosporin A and IVIG may be used in the treatment of reactive HS. However, further studies are necessary to confirm that this treatment combination is always effective.

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