Hemophagocytic lymphohistiocytosis (HLH) is a clinical entity consisting of high spiking fevers, hepatosplenomegaly, pancytopenia, coagulopathy, and the phagocytosis of hematopoietic cells by activated macrophages. HLH can be the result of a primary genetic defect such as perforin deficiency or be secondary to a number of inflammatory conditions such as systemic juvenile idiopathic arthritis (JIA), viral infections, or malignancy. The fundamental pathologic basis for HLH is thought to be a hypercytokinemia of Th1 cytokines. This results in overexuberant activation of macrophages, leading to fever, hemophagocytosis, and fibrinolysis, which characterizes the disorder. We describe the use of interleukin 1 receptor (IL-1R) blockade in hypercytokineemia in a 14-year-old girl with chronic fever, panniculitis, and severe HLH.

CASE REPORT
A 14-year-old Caucasian girl presented with abdominal pain and hepatomegaly. Her history was remarkable for daily fevers to 104°F since 6 months of age and extensive panniculitis over her entire body resulting in significant lipatrophy. She had been treated over the course of her illness with corticosteroids, cyclosporine, plaquenil, cyclophosphamide, and azathioprine. None of these medications had been able to prevent the fevers, nor allow for growth and development. Treatment with etanercept resulted in a resolution of fevers; however, she developed aphasia and hemiparesis on the medication that took almost 2 years to resolve after discontinuation. At that time magnetic resonance imaging without enhancement revealed diffuse cortical atrophy and ventriculomegaly. For the 2 years prior to presentation, the only treatment had been acupuncture. Physical examination revealed severe growth delay: 50th percentile for a 7-year-old in both height and weight. She had mild hepatomegaly, marked total body lipatrophy, and arthritis of the right thumb and both great toes. Laboratory data revealed white blood cells (WBC) 3.7 × 10^9/l, hemoglobin 9.7 g/dl, platelets 176 × 10^9/l, sedimentation rate (ESR) 6 mm/h, C-reactive protein (CRP) 7.2 mg/dl, ALT 346 U/l, AST 594 U/l, triglycerides 336 mg/dl, and D-dimer 4.23 µg fibrinogen equivalent units/ml. Her baseline ESR was around 80 mm/h.

Bone marrow biopsy revealed hemophagocytosis (Figure 1A). Review of a skin biopsy from age 9 months revealed a mixed lymphocytic and histiocytic panniculitis with cytophagic features (Figure 1B). CD68+ histiocytes could be seen ingesting cellular elements (Figure 1C). Her histological and laboratory findings were consistent with hemophagocytic lymphohistiocytosis (CHP). She was started on cyclosporine, with resolution of fever and abdominal pain. Her D-dimers and cell counts returned to normal. She was discharged, but 2 weeks later she felt ill, and was treated with a 2-week course of prednisone. Her cyclosporine level was 150 ng/ml. One month later, she developed abdominal pain, followed by seizure and decline in mental status requiring endotracheal intubation.

Physical examination at this time revealed massive hepatosplenomegaly and obnubilated mental status with a Glasgow coma scale score of 7. No rash, lymphadenopathy, or fever was present. Cerebrospinal fluid (CSF) studies revealed 3 WBC, 2 red blood cells, normal glucose, and an elevated protein of 102 mg/dl. She had no oligoclonal bands present in her CSF. Head computerized tomographic scan revealed generalized atrophy with non-obstruc-
tive lateral ventriculomegaly. Her D-dimers were elevated along with pancytopenia and hyperferritinemia (Table 1). She was started on pulse intravenous methylprednisolone, 1 g daily. Her cyclosporine dose was titrated to keep levels between 200 and 400 ng/ml. Serum cytokine levels at this time showed an elevated interferon-γ (IFN-γ) and IL-12. Her IL-10 and IL-4 were also elevated. She was given one dose of etoposide; however, her laboratory and clinical picture did not improve significantly.

Three days following the etoposide, anakinra was started 50 mg subcutaneously daily (2 mg/kg). Her methylprednisolone dose was decreased to 25 mg 3 times daily (3 mg/kg total dose). The following day she showed an improvement in her laboratory studies, most notably her D-dimers fell sharply (Table 1). She was able to maintain her hemoglobin without red blood cell transfusion. Her mental status normalized by day 2 of anakinra treatment and she was able to be extubated. Her organomegaly resolved about 1 week after the initiation of anakinra. She was discharged on a regimen of prednisone (25 mg AM, 10 mg PM, PO), cyclosporine (125 mg bid, PO), and anakinra (50 mg daily, SQ). She has remained afebrile for over 6 months on this regimen, her growth has improved, and increased hemoglobin and platelets and normal D-dimer and ESR have been maintained (Table 1). Her prednisone dose has been tapered to 10 mg daily PO. Her weight is now at the 50th percentile for a 9-year-old. She has also begun pubertal changes as she is now a Tanner stage II in breast development.

**DISCUSSION**

CHP is a rare disorder consisting of a lobular panniculitis with infiltration of cytophagic histiocytes. CHP may be associated with fever and organomegaly. In many cases the disease develops into fatal hemophagocytic lymphohistiocytosis².

*Figure 1.* A. Bone marrow. Characteristic hemophagocyte showing ongoing ingestion of hematopoietic cells (H&E, original magnification ×100). B. Subcutaneous adipose tissue. Dense lobular panniculitis consisting of lymphocytes and histiocytes (H&E, original magnification ×20). C. Subcutaneous adipose tissue. CD68+ cells documenting histiocytic infiltrate. Arrow denotes histiocyte with multiple ingested nuclei showing hemophagocytosis in the adipose tissue (CD68 stain, magnification ×100).
Because of its association with T cell lymphomas, many authors feel CHP represents a pre-malignant condition, although there are many cases of long-standing disease, such as our patient’s course of 14 years, without evidence of malignancy. The disease resembles systemic JIA associated with HLH. Both entities may have daily fever, organomegaly, arthritis, and secondary HLH.

Recently there have been reports of successful use of anakinra, an IL-1R antagonist, in the treatment of systemic JIA. Similarly, IL-1ß is associated with the virus-associated secondary hemophagocytic lymphohistiocytosis and hemophagocytosis associated with malignant histiocytosis. For these reasons, and given the refractory features of her disease and the development of HLH while taking cyclosporine, we treated our patient’s CHP with anakinra, which resulted in remarkable improvement. Although we did not obtain IL-1ß levels, she exhibited marked hypercytokinemia including the Th1 cytokines IFN-γ and IL-12, both of which have been associated with HLH. Cytokine blockade of both TNF-α and IL-1ß was effective in our patient, thus suggesting cytokine antagonists can clinically ameliorate hypercytokinemia.

The pathogenesis of HLH is thought to be due to unrestricted stimulation of macrophages by CD8+ T cells and subsequent uncontrolled release of inflammatory cytokines. Since both TNF-α and IL-1ß are the major inflammatory cytokines produced by macrophages, by blocking their function, the downstream effects of this hypercytokinemia can possibly be controlled. Treatment of our patient with prednisone and cyclosporine without cytokine blockade was attempted multiple times and failed to prevent disease flares and promote growth.

Although she received one dose of etoposide, it is unlikely this was the cause of our patient’s improvement. Standard HLH protocols call for at least 8 doses of etoposide. Patients receiving less than 5 doses have poorer outcomes than those receiving the full 8 doses, usually resulting in death. A single dose of etoposide is unlikely to produce the marked and durable response we have seen in our patient. Further, the rapid improvement in our patient was more closely temporally related to initiation of anakinra in contrast to etoposide. While her laboratory values responded slightly to initiation of intravenous methylprednisolone and increasing cyclosporine, suggesting that these measures did contribute to her response, it was not until initiation of anakinra that D-dimer measures fell rapidly and her mental status began to improve, allowing for extubation and recovery. Anakinra clearly improved the longterm course of CHP in our patient, suggesting it might be useful for chronic treatment of this disease.

Lastly, a recent report has suggested that anakinra led to induction of HLH in a patient with systemic JIA. While intriguing, it is difficult to determine whether the medication was the inciting cause or whether other factors may have been involved. Certainly caution must be exercised when generalizing single case reports to entire populations. Although cyclosporine and etoposide remain the standard of care for HLH, given the response in our patient, we believe anakinra might potentially be considered for cases of HLH secondary to autoinflammatory disease refractory to standard therapy.

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REFERENCES


