hyperbilirubinemia and reticulocytosis. The peripheral blood film is usually unremarkable. It is also well known that higher HbF protects against sicklings and that could be an additional factor producing mild clinical picture.

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# Hemophagocytic Syndrome

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Virus-associated hemophagocytic syndrome (VAHS) is characterized by benign hyperplasia of histiocytes showing hemophagocytosis in the reticulo-endothelial system. The patients usually present with high grade fever, failure to thrive, massive hepatosplenomegaly, lymphadenopathy and bleeding tendencies. Since its first report in 1979 by Risdall *et al.*(1), the understanding of this syndrome has improved considerably. We report a similar case, admitted to the pediatric unit of the hospital.

**Case Report**

A 7-year-old boy presented with fever of 7 days duration, headache and blood stained vomiting. He was treated with parenteral chloramphenicol, two days prior to admission, for suspected enteric perforation. On admission the child was toxic but responding to commands and had signs of meningeal irritation. He had scattered ecchymotic spots, bleeding from intravenous sites, subconjunctival and retinal hemorrhages, abdominal distension and bleeding

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from the gastrointestinal tract. The liver was enlarged, with a span of 13 cm. Subsequently, he developed generalized lymphadenopathy, splenomegaly and oral and genital ulceration. He continued to have high spiking fever throughout the hospital stay.

The level of hemoglobin was 13.5 g/dl which dropped to 5.6 g/dl later and was maintained between 10-12 g/dl with repeated blood transfusions. His total leucocyte count of 14,200 also reduced to 2,300. There was neutrophilic predominance throughout. The peripheral smear examination revealed normocytic normochromic anemia with marked leucopenia and thrombocytopenia. The platelet count dropped from an initial 45,000 to 10,000. He had hyponatremia at admission which was corrected in 48 hours. Liver function tests showed marked elevation of SGOT and SGPT which were 4730 IU/L and 1035 IU/L, respectively and a prolonged PT of 37 sec. Serum ammonia was 6 $\mu$g/dl. Serum bilirubin 0.8 mg/dl and total serum protein was 4.7 g/dl with an albumin of 2.3 g/dl and albumin-globulin ratio of 1. The liver function improved subsequently, the SGPT and SGOT dropping to 77 and 155, respectively. The PT became 19 from a peak of 37 sec. The LDH level was 2110 U/L. Random blood sugar was between 73-110 mg/dl and there was no elevation of C-reactive protein. Chest *X*-ray revealed right sided pleural effusion. This was hemorrhagic with leucocytes showing lymphocytic predominance. The serum and ascitic fluid amylase were 200 IU/L and 25 IU/L, respectively, ruling out pancreatic ascites. Ascitic tap also showed hemorrhagic fluid. Aspirates were negative for both Gram negative and acid fast bacilli. Urine contained 1-3 RBCs and 20-25 WBCs per HPF; albumin was 1+. His blood urea and creatinine were normal and blood culture grew *Staphylococcus aureus*. Paul Bunnel test was negative. Abdominal ultrasound suggested acute pancreatitis with ascites.

On the 13th day of admission, child succumbed to the illness. A post mortem examination revealed fatty changes in the liver, and bone marrow showed relative erythroid and myeloid hypoplasia and histiocytic predominance. The histiocytic cells present in aggregates or diffusely, had abundant cytoplasm and oval to elongated nuclei with occasionally prominent nucleolus. Some of the cells showed single to multiple, 2-7 $\mu$/m vacuoles representing hemophagocytosis (*Fig.*). In addition, some of the cells also had ingested lymphocytes and platelets. The megakaryocytes were normal in morphology and number. Numerous plasma cells and plasma cytoid reactive lymphocytes were noted mixed with the histiocytic component suggestive of a host response to viral infection.

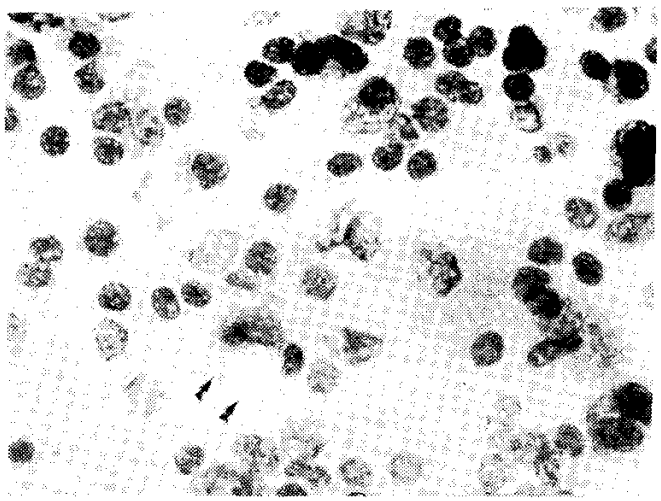

*Fig. Bone marrow aspirate showing mature histiocytes with ingested erythrocytes (arrow head); one histiocyte has phagocytosed a lymphocyte. Giemsa × 450.*

## Discussion

Histiocytic hyperplasia with hemophagocytosis was first described by Scot

and Robb-Smith who coined the term histiocytic medullary reticulosis (HMR) which was considered to be a neoplasia. A familial form of this disorder was later identified in young children designated as familial hemophagocytic reticulosis and familial erythrophagocytic lympho-histiocytosis. The distinction between cytologically benign and malignant histiocytosis was first made by Rappaport in 1966. In 1979, Risdall *et al.*(1) reported the first series of cases of VAHS in children where a viral etiology was attributed for the reactive hyperplasia of histiocytes. He for the first time reported the benign nature and the characteristic clinicopathological features of the syndrome. Subsequently, various other agents like bacterial and protozoal infections, malignancies and even inert substances were attributed to the cause of the syndrome accounting for about 50 reported cases in literature.

Suster(2) coined the term histiocytic hyperplasia with hemophagocytosis (HHH) for a similar state after evaluating 230 consecutive adult autopsies and suggested that it was a common condition in critically ill patients, most often multifactorial than related to a single underlying condition. He found that frequent blood transfusions and bacterial sepsis were the most significant risk factors. Majority of the cases of VAHS were reported in children till then. Suster(2) had excluded pediatric autopsies from this study, and none of them had the clinicopathological syndrome described by Risdall *et al.*(1).

Among 760 consecutive bone marrow smears of patients with unrelated disorders, for a comparative study, Risdal *et al.* observed that 48% showed erythrophagocytosis comparable to Susters observation of 43%. Thus, HHH as described by Suster *et al.*(2) may be representing a secondary phenomenon in critically ill patients undergoing reported transfusions, and having other risk factors. The enhanced hemophagocytic activity is due to an increased state of invasion of tissue macrophages coupled with an increase in surface membrane receptors on RBCs resulting in their premature ingestion(3).

VHS is a clinical syndrome with characteristic clinical, biochemical and hematological manifestations in which a clinical diagnosis is possible and appropriate medical management may arrest the progress of the disease. This disorder could be representing one end of the spectrum of host responses to various immunological insults to the hemopoietic system.

Clinicopathological features of VAHS include fever, constitutional symptoms, hepatomegaly, splenomegaly, lymphadenopathy, abnormal liver function, coagulopathy, peripheral blood cytopenia and histiocytic hyperplasia with hemophagocytosis in bone marrow, liver and lymph nodes. Absent or infrequent erythrophagocytosis and cytological evidence of neoplasia of histiocytes in Langerhans cell histiocytosis differentiates it from VAHS.

A probable underlying immunological derangement in association with HLA predisposition, may explain the pathogenicity of this syndrome. HLA-A 30 B8 and A1/B8 pre-ponderance which is associated with autoimmune phenomena or immuno deficiency states is noticed in most of these patients. The cases reported in literature had an immunosuppressed state like extremes of age, treatment with immunosuppressants, HIV infections, autoimmune disorder, allergy or transient immunological abnormalities as in Ebstein bar virus infection(4,5). Decreased response to mito-

gens, decreased natural killer cell activity and decreased cytotoxic T lymphocytes response to infected cells are also demonstrated in these patients(6). Macrophage activation by the inducing agents and its unlimited proliferations due to the deranged immunogical surveillance system may explain the fever and hemophagocytosis in these patients. Marked increase in the plasma levels of tissue-type plasminogen activator and plasminogen activator inhibitor-1 activity demonstrated in these patients(7), may explain the pathogenesis of the coagulopathy. Fulminant infection and deranged liver functions may also be contributory.

The management of patients with this rapidly fatal illness is by and large ineffective; three-fourth die due to coagulopathy. Promising results were recently obtained by therapy with VP-16 (etoposide). Results of treatment with prednisolone, antiviral and chemotherapeutic agents, splenectomy and exchange transfusions are unsatisfactory. As these patients have high prostaglandin $E_2$, shunting of the synthesis of prostaglandins with indomethacin and decreasing the lipolysis (a factor for liver involvement) by infusing generous amount of glucose along with chemotherapy using VP-16 have given satisfactory results(8).

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