INFECTION-ASSOCIATED HEMOPHAGOCYTIC SYNDROME

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ABSTRACT

An epidemic of an infection associated with circulating hemophagocytes (HP) and activated monocytes (AM) was seen in Bombay. Although certain features overlapped with the well-defined entity of virus-associated hemophagocytic syndrome and familial hemophagocytic lymphohistiocytosis, it was distinct enough to place it in a separate category.

Affected children were predominantly two days to two years of age. They had fever, altered sensorium, neurological symptoms, dyspnea, and/or diarrhea, and significant bleeding. Laboratory tests showed neutrophilia, AM and HP's in every blood smear, coagulopathy, normal cerebrospinal fluid, normal liver transaminases, hypertriglyceridemia, and hypoalbuminemia. Surgical cases were remarkable in that they had small bowel malformations.

These cases were subdivided into four distinct groups based on age of presentation, neonates, infants, children and a surgical group. The clinical differences in each group are described.

Key words: *Circulating monocytes-hemophagocytes.*

An infection-associated hemophagocytic syndrome was encountered in children in Bombay over a period of 8 years. We reported our experience of over 400 cases in 1991(1). In this report we will further define our cases and distinguish them from the other well-described hemophagocytic syndromes of familial hemophagocytic lymphohistiocytosis (FHL) and virus-associated hemophagocytic syndrome (VAHS).

Material and Methods

The cases were detected while doing differential blood counts. If the hematology technician, in blood smears, saw activated monocytes (AM) and hemophagocytes (HP), the detailed clinical and laboratory data on these patients was recorded.

Results

We first noticed the phenomena of AM-HPs in peripheral blood smears in May 1985. The number of patients increased and then decreased after November 1986. In mid 1988 there was a resurgence, and during 1988 we saw 77 patients, in 1989 there were 77 patients and in 1990, 100 patients. In the latter half of 1991, the incidence decreased till September 1993. Whereas in 1986 only 20% of patients were neonates, by 1989,40% cases were from the

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neonatal unit and another 20% from the Pediatric Intensive Care Unit (PICU). In 1990, 84% of positive smears came from the neonatal ward and PICU and none from the surgical wards.

Table I shows the clinical and laboratory features and prognosis of the cases and contrasts them with VAHS and FHL. We previously analysed 66 cases(l); additional cases did not add much to the existing information except that the manifesations were milder to-

TABLE I—*Comparison Between VAHS, FHL and Present Patients*

Parameters	VAHS(1)	FHL(2)	Present patients
Family History	-	+	-
Age at onset below 2 years	?	89	90
Congenital malformations	-	-	Gastrointestinal
Clinical Features			
Fever	+	+	+
Hepatosplenomegaly	+	+	-
Lymphadenopathy	+	+	-
Neurologic signs	+	+	+
Respiratory signs	+	+	+
Diarrhea	-	-	+
Immune dysfunction/suppression	+	-	-
Bone marrow and/or liver failure	+	+	-
Laboratory Signs			
Pancytopenia/hypoplastic bone marrow	+	+	-
Neutrophilia	-	-	+
Lymphopenia	+	?	-
Coagulopathy	+	+	+
Hypertriglyceridemia	+	+	+
Hypoalbuminemia	?	+	+
Hyperbilirubinema (neonates)	+	+	+
Transaminases	elevated	elevated	N
Histologic infiltration with hemophagocytosis in			
Bone marrow and other organs	+	+	-
Circulation	-	-	+
Mortality (%)	85	100	30
Viral etiology	+	-	-

VAHS : Virus associated hemophagocytic syndrome(1).
FHL : Familial hemophagocytic lymphohistiocytosis(2).

wards the end. Ninety five per cent of the patients were under 5 years of age, and further divisions into neonates (age 2-31 days), infants (1 month to 2 years), children (2 to 13 years) and a surgical group (age 2 days to 1 year) showed certain differences.

Clinical symptoms occurred one to 9 days previous to appearance of AM and HP and consisted of fever, neurological and/or respiratory features and later bleeding. Blood counts showed the presence of anemia (2.7-22.0 g/dl) with a neutrophilia (mean WBC 18.4 x 10^{-3}/ml and range 1.0 x 10^{-3}/ml to 61.5 x 10^{-3}/ml) and thrombocytopenia in blood smears. AM and HPs were mainly seen at the edges of the smear. They were much larger than monocytes with 1 or 2 round nuclei, abundant cytoplasm often containing vacuoles and /or pseudopods, and resembled histiocytes (macrophages). In addition, blond smears showed erythrophagocytosis; occasionally polymorphonuclear (PMN) leukocytes and rarely lymphocytes and platelets were engulfed as well. Mitotic figures in peripheral blood were sometimes seen *(Figs. 1-3)*. S-100 proteins, a marker of Langerhans' cells, was negative, non-specific esterase to stain monocytes was weakly positive. Other laboratory findings included increased fibrin split products in 93.7%, an absence of abnormal liver transminases in 84.4%, normal serum creatinine, hypoalbuminemia in 83.3% with levels below 2.9 g/dl post-AM and HP (only 3.8% of asymptomatic children admitted to this hospital have values below 3.0 g/dl), hypertriglyceridemia in 63.3% and a normal CSF. Ante-or post-mortem liver biopsies and bone marrow examination showed none or mild infiltration of histiocytes. Chest X-rays and cranial CT scan were unremarkable.

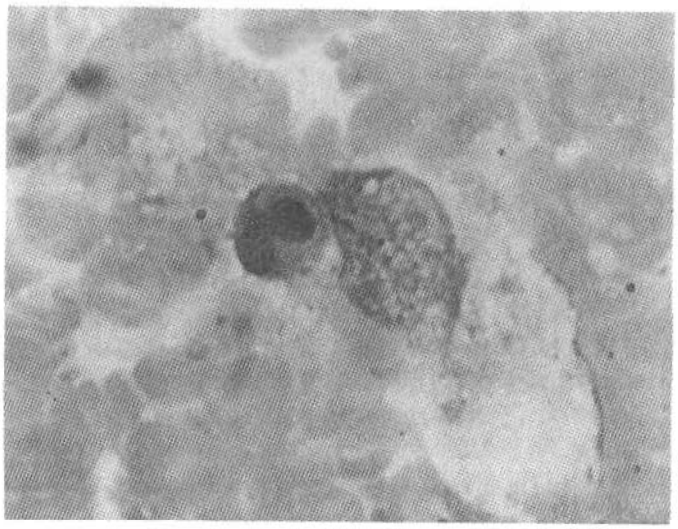


Fig. 1. Binucleated cell ingested in a phagocyte. Note the phagocyte has one nucleus and a large amount of vacuolated cytoplasm.

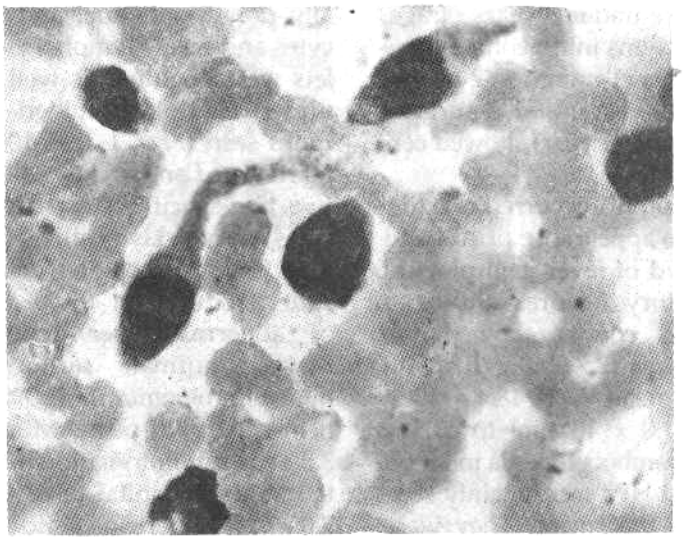
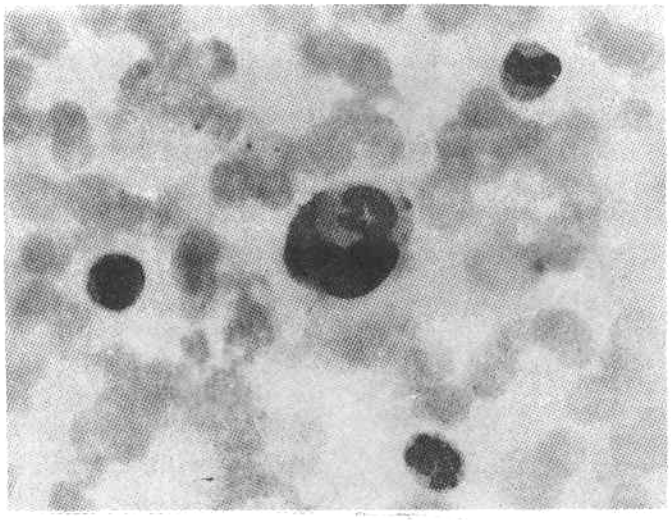


Fig. 2. Two mononuclear cells showing pseudopods.



A comparison among the four subdivisions mentioned above showed certain differences. The neonates showed elevated levels of bilirubin (above 11.73 mg/dl) in 93.7% of medical cases and in 87.5% of surgical cases; infants had

diarrhea in 54.5% of patients; children had concurrent illness *(e.g.,* typhoid, diabetic ketoacidosis, malignancies, HBsAg positive—hepatic encephalopathy) in 80.0% of cases. Neurological features in the form of drowsiness, irritability, altered sensorium, coma, decerebrate rigidity, hemiplegia and hyper or hypotonia were present but not convulsions in children. In neonates and infants, convulsions occurred in 38.1% of cases. The surgical group of infants showed small intestinal pathology including atresia, stenosis, malrotation, volvulus or perforation. They also had fever, neonatal jaundice (as mentioned), neurological signs in 64.3% (including convulsions in 50.0%), periods of apnea, sclerema and impressive bleeding within 1 to 2 days of AM and HP.

The course of the illness was brief and in those that recovered it resolved without residua within 2 weeks. However, mortality was significant; 35.0% in neonates, 22.7% in infants, 40.0% in children, and 71.4% in surgical patients. Death was due to uncontrolled bleeding, respiratory or cardiorespiratory failure or secondary sepsis, usually from Gram negative bacilli or *Staphylococcus aureus.*

Discussion

The temporal and local coincidence of this outbreak is suggestive of a viral etiology and because these patients subsequently were from the neonatal ward and PICU, we assumed it was due to a nosocomial infection. Attempts to isolate a specific pathogen from stools or serum or blood were unsuccessful.

The clinical and laboratory criteria for VAHS include fever, hepatosplenomegaly, liver dysfunction, neurologic signs, coagulation abnormalities, pancytopenia, generalized histiocytic proliferation with benign cytologic features and marked hemophagocytosis(2,3). An allied but perhaps distinct syndrome is FHL(4). The illness in our patients is probably a part of the spectrum that includes both these entities. In common with VAHS and FHL, our patients showed fever, neurologic and/or respiratory features, exaggerated hyperbilirubinemia in newborns, a bleeding diathesis associated with anemia, thrombocytopenia, coagulopathy and hypertriglyceridemia. In patients with FHL and in our patients, most had onset of the illness during infancy but without a positive family history or consanguinity; they had hypbalbuminemia and hypertri-glyceridemia. At variance with VAHS and FHL, our patients had no hepatosplenomegaly or lymphadenopathy, no abnormal transaminases, no pancytopenia with bone marrow failure; they had neutrophilia and a normal cerebrospinal fluid. All surgical cases had a gastrointestinal malformation or perforation. The course of the illness was dissimilar; 65-75% of our medical patients below 2 years of age recovered in 2 weeks while in VAHS most patients die rapidly with organ failure or sepsis. The diagnosis of VAHS is documented at autopsy and by viral isolation(2,4). There is evidence of infiltration of mature erythrophagocytic histiocytes in several organs but not in blood(2,4). Our cases, however, showed AM and HPs on peripheral blood smears for about a week in those that survived, and there was slight or no infiltration in bone marrow, lungs, liver, spleen or brain.

The illness in our patients affected

the monocytes-macrophage in the brain, lungs and bone marrow. Neurological symptoms and fever preceded AM and HPs by a mean of 7 days, and bleeding occurred within 1 to 2 days of demonstration of AM and HPs on the smear. Elevated levels of monocyte cytokines may have reduced the bone marrow transit time of the maturing monocyte precursors from the normal of 6 days(5) to one day (as evidenced by the presence of AM and HPs in a 2-day-old neonate) and amplified divisions (as evidenced by the presence of mitosis on peripheral blood smear examination).

In active FHL(6) and VAHS(7) increased levels of T-cell and monocyte-macrophage cytokines have been recorded. The clinical features in our patients are compatible with the known effects of monocyte-macrophage cytokines: Interleukin-1 and tumor necrosis factor act singly or synergistically and induce many effects including fever, neutrophilia, procoagulant activity, vascular leak, hypoalbuminemia, hyperlipidemia(8,9), shock(9), pulmonary hemorrhage(8) and erythro-phagocytosis(lO). Interleukin-6 induces fever and increases hematopoiesis. Our findings suggest that elevated levels of these cytokines may have resulted following a possible viral infection, which activated monocytes to secrete its cytokines and induce hemophagocytosis. An over-production of these cytokines or an inability to modulate them could conceivably have led to the observed harmful and lethal effects.

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