Two Types of Histiocytic Syndromes in One Infant

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Histiocytic syndromes in children are divided into 3 classes: (i) Langerhans-cell histiocytosis (LCH) or Histiocytosis-X (H-X), *(ii)* Hemophagocytic syndromes—Familial erythrophagocytic lymphohistiocytosis (FEL) and infection-associated hemophagocytic syndrome (IAHS) due to viruses (VAHS), and occasionally bacterial, fungal or parasitic, and *(iii)* Malignant histiocytic disorders(l). The lesional histiocytic cell in LCH/H-X is a dendritic cell, in IAHS an ordinary histiocyte (macrophage) as in pulmonary alveoli or Kupffer cells in the liver. Both cells arise from the mono-histiocytic lineage in the bone marrow and enter circulation till they reach tissues(2). We saw an interesting case in an infant who had both H-X and in IAHS.

Case Report

An 11-month-old male infant was admitted for fever, cough and dyspnea in June 1987. Physical examination revealed an uncomfortable little boy, afebrile, with a respiratory rate of 70/minute. He had fine bilateral rales, the liver was 3 cm palpable and the spleen was not felt. Chest X-rays showed a miliary nodular pattern, the grandmother had tuberculosis, and a diagnosis of miliary TB was entertained. He was treated accordingly, including prednisone; and discharged 6 days later.

Past history revealed that he had a similar episode of dyspnea one month ago. He also had 2 episodes of afebrile generalized convulsions, 15 days apart, in late April and early May 1987. He had no physical findings; the CSF was normal.

Three weeks after admission, he had diarrhea. A day later, he had a slight drop in Hb/Hct, and monocytosis, histiocytes and hemophagocytcs (26-6-87) (HPs) were noticed on his blood smear *(Fig.* 7). A blood count done 2 days earlier and 2 days later were normal. Bone marrow examination was unremarkable.

He was admitted several times for periodic attacks of fever and dyspnea from June 1987 to September 1988. Chest X-rays taken on 5 occasions during this period showed a progression of the bilateral interstitial infiltrate. Chest X-rays in 1990 showed improvement. Arterial blood gases revealed a compromized lung function, pO_2 varying between 40 and 55 mm of mercury and 60 mm of Hg in October 1989. Lung biopsy in July 1988 showed histiocytes and eosinophils, compatible with a diagnosis of H-X (No EM for Birbeck granules or T_6 antigen surface marker or antibody against S-100 protein studies were done).

Liver function studies showed normal bilirubin and transaminases that were normal. A temporary low albumin of 2.6 g/dl was noted post-HP in June 1987, otherwise,

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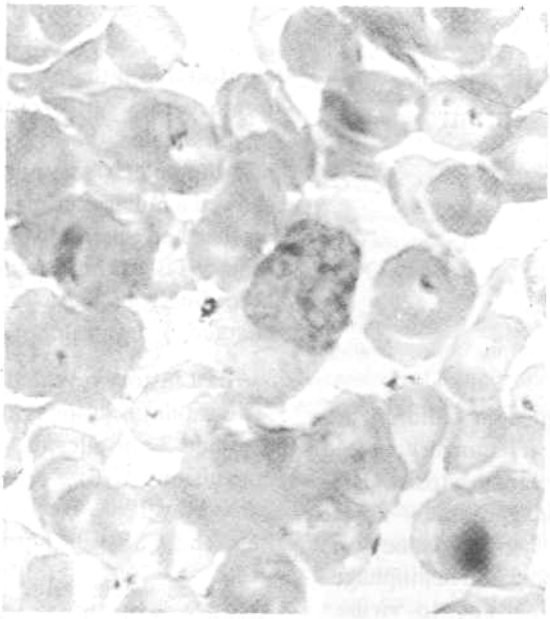

Fig. 1. Hemophagocytosis in peripheral circulation as seen on blood smear.

it was over 3.5 g/dl. A liver biopsy done in June 1987 was unremarkable.

In June 1987 his immunoglobulins and C_3 were normal. In September 1988, IgG was normal (980 mg/dl), IgM and IgA were elevated (286 mg/dl and 170 mg/dl, respectively). The per cent of B, T cells and CD 4:8 cells were normal, and blast transformation with PHA was normal.

In August 1987, he developed diabetes insipidus.(DI). Skull X-rays and CT Scan of the brain were normal. He was placed on diabinase. In October 1988, he had a hypoglycemic convulsion due to diabinase and his medication was changed to DDAVP.

Since September 1989 he has been asymptomatic, apart from DI (although under control with DDAVP).

Discussion

Our patient, an infant, had an illness that consisted of seizures (CNS), respiratory distress (pulmonary) and polyuriapolydypsia (hypothalamus-postcrior pituitary). LCH/H-X is diagnosed by biopsy of the tissues or organs involved by Langerhans histiocytes. A lung biopsy was compatible with LCH/H-X. These cells show Birbeck granules, S-100 neuroprotein, Mannosidase, CD 1 (T6) positivity, and halo dot with peanut lectin(2). Signs and symptoms are directly related to the sites of infiltration with the dendritic cells or their cytokines. The main target in our patient was the lungs. Primary pulmonary H-X is rare and serious diseases in children, but 11 cases have been reported, including infants. However, 2 children additionally had hepatomegaly and one had skeletal lesions, but none had DI (10% of adults with primary pulmonary H-X develop DI). Six of the 11 children died within one year of diagnosis(3).

IAHS is due to several micro-organisms and parasites. Children who have fever, hepatosplenomegaly, bone marrow and/or liver failure, coagulopathy, hypertriglyceridemia, and on biopsy, histiocytosis with

hemophagocytosis in bone marrows, lymph nodes, liver, spleen, CNS fit into the category of FEL or VAHS. In the majority of cases, the Epstein-Barr Virus (EBV) is the culprit, although cytomegalovirus and adenovirus may be combined with EBV or be the sole virus(4). The illness is often rapidly fatal. In 1991, we described an IAHS, probably viral (VAHS) in etiology(5). Unlike the previously described VAHS, monocytes, histiocytes (S-100 neuroprotein negative) and hemophagocytes (HPs) were visible in blood smears, for 1-10 days, in our patients, and without bone marrow and/or liver failure. Ninety per cent of our cases occurred below 2 years of age (as in FEL) with fever, CNS, respiratory, and/or gastrointestinal symptoms, and no diabetes insipidus. Within 9 days, monocytes, histiocytes and HPs were noted in blood smears, and coagulopathy (bleeding and gangraneous lesions), triglyceridemia and hypoalbuminemia developed. As in VAHS and FEL, these signs and symptoms are in common with our cases. Unlike other VAHSs, 75% of our infants got completely well in 2 weeks; the rest 25% died of bleeding, cardiorespiratory failure, or secondary sepsis.

The patient described had a mild attack of IAHS/VAHS. He had diarrhea and histiocytes, HPs in his circulation for less than 2 days. Seizures and respiratory signs and fever occurred 1-2 months before HPs were seen, and his VAHS course was not complicated by massive bleeding or serious CNS signs (altered consciousness, palsies or paralysis) that we saw in most cases.

The pertinent question is that, if a patient has both dendritic (LCH/H-X) and ordinary (IAHS) histiocytosis, do these cells or their cytokine products influence one another in a positive or negative fashion, or do they interact at all? Our case cannot answer this, but because of the comparatively mild course of both H-X and VAHS, they either acted independently or synergistically modifying the severe course he might have otherwise had.

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