To the Editor:

Hemophagocytic lymphohistiocytosis (HLH) was first described as a familial disease by Farquhar and Claireaux, but it is now known to be a syndrome consequent to a poorly controlled activation of the cellular immune system. HLH includes the frequently indistinguishable conditions familial hemophagocytic lymphohistiocytosis (FHL) and virus-associated hemophagocytic syndrome (VAHS). Diagnostic guidelines for both HLH subtypes, partly in contrast to previous recommendations, have been recently established by the FHL Study Group of the Histiocyte Society. The morphologic hallmark of HHL is the demonstration of nonmalignant histiocytes-macrophages phagocytizing, most particularly, red blood cells. This "critical feature" has been said to be best appreciated in Romanowsky-stained smears of aspirated bone marrow, which is a less hazardous procedure than splenic aspiration, especially if performed in severely thrombocytopenic and hemostatically impaired patients. However, it must be pointed out that in the stained myeloaspirates "the histiocytes may not be numerous... and are easily damaged so that their morphology may not be distinct". In addition, the phagocytosed erythrocytes are most generally hemolyzed, so that only nondiagnostic postphagocytic vacuoles are discernible. The purpose of this letter is to emphasize the much greater validity of the microscopic examination of fresh, supravitally stained marrow preparations.

The patient was a 18-year-old Caucasian male who presented with a hemorrhagic syndrome (epistaxis, retinal hemorrhages) after a flu-like episode in March 1993. He was pancytopenic, and was referred to the S Martino's Hospital on April 3, 1993. On admission, he was found to be confused and to have a high fever and a conspicuously enlarged and painful spleen. Severe pancytopenia was present (hemoglobin, 8 g/dL; white blood cell count, 0.8 × 10^9/L; platelet count, 8 × 10^9/L). Profound coagulation disorders were also present. The myeloaspirate showed erythroblastic and megakaryocytic hyperplasia. A few vacuolated histiocytes were reported. CD4+ lymphocytes were reduced, and CD8+ lymphocytes were enhanced. Eight days after admission, spontaneous rupture of the spleen occurred; after splenectomy, it was found to weigh 2,985 g, with 3 L of blood in the abdomen. The patient was appropriately transfused, but deteriorated steadily, developed profound hepatic and renal insufficiency that required dialysis, and died after a series of epileptic seizures that were negative on a CAT scan. Autopsy was not performed for technical reasons.

A second myeloaspirate was performed 3 days after splenectomy, and was examined in the fresh state both by phase and after supravitally staining with brilliant kresyl blue. Erythrophagocytosis was conspicuous (Fig 1), whereas at the same time only a few vacuolated histiocytes could be seen on the fixed and Romanowsky-stained preparations. Sections of the spleen also showed impressive erythrophagocytosis by morphologically benign histiocytes (Fig 2).

The HLH syndrome, especially in the VAHS subtype, can be an extremely severe disorder. The clinical course has already been described as fulminant in some cases, with coagulation abnormalities, hepatic dysfunction, and renal failure. Chemotherapy and eventually allogeneic bone marrow transplantation have been used with some success, and it has been shown recently that the presence of a small proportion of cells of donor origin, which is what happens in cases with partial engraftment, can prevent FHL-related lymphocyte and macrophage activation. Of course, FHL allows some time for programming. But even for the sporadic VAHS patient, an early diagnosis is a prerequisite for a hopefully successful treatment plan. We submit that the examination of fresh, supravitally stained and/or phase contrast myeloaspirates may be more helpful for establishing the correct diagnosis than the usual fixed and stained procedures that are, at least in our experience, equivocal and much less informative.

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Fig 1. Myeloaspirate observed in the fresh state after supravital staining with brilliant kresyl blue. Three macrophages phagocytizing a great number of red blood cells are seen in the same microscopic field.

Fig 2. Spleen section stained with a Romanowskian method (Giemsa). Eleven discrete erythrocytes are phagocytized by a morphologically benign histiocyte.
REFERENCES


Virus-associated hemophagocytic syndrome: interest of examination of fresh myeloaspirates [letter]

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