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### Fulminant hemophagocytic syndrome as presenting feature of T-cell lymphoma and Epstein-Barr virus infection

We describe a patient who presented with a fulminant hemophagocytic syndrome. Morphologic and immunohistochemical studies showed infiltration of the marrow and tonsil by neoplastic T-cells. A genomic amplification by means of polymerase chain reaction revealed the presence of EBV DNA in the serum. In spite of aggressive immunosuppression and multiagent chemotherapy this patient died of disseminated intravascular coagulation-induced multiorgan failure.

Sir,

Hemophagocytic syndrome (HPS) is a clinicopathologic entity characterized by systemic proliferation of hemophagocytic histiocytes, fever, cytopenia, deranged liver function, and frequently, coagulopathy and hepatosplenomegaly.<sup>1,2</sup> There are two major clinical subsets of HPS: the aggressive disease known as malignancy-associated HPS and the more benign, reactive hemophagocytic syndromes such as virus-associated HPS.<sup>3</sup> In a few cases HPS presents at the time of initial diagnosis of lymphoma in the absence of any pre-existing disease or immunosuppressive therapy.<sup>4,5</sup> We describe a case of fulminant HPS as the presenting feature of a recent Epstein-Barr virus (EBV) infection and disseminated T-cell lymphoma.

A 50-year old woman was admitted to our hospital with fever, rapid deterioration of her general condition and marked weight loss. Physical examination revealed an ulcerative lesion in the right tonsil, slightly enlarged cervical and axillary lymph nodes, and hepatosplenomegaly. Complete blood count included hemoglobin level of 9.3 g/dL, platelet count of  $92 \times 10^9/L$ , and white blood count of  $2.2 \times 10^9/L$ . Laboratory studies also disclosed the following values: fibrinogen 130 mg/dL, D-dimer 4  $\mu\text{g/mL}$ , alkaline phosphatase 222 U/L, aspartate aminotransferase 83 U/L, alanine aminotransferase 45 U/L, and lactate dehydrogenase 826 U/L. A genomic amplification by means of polymerase chain reaction (PCR) showed a single 54 bp band indicating the presence of EBV DNA in the serum. Bone marrow aspiration and biopsy revealed an increase of reticulin fibers and histiocytic hyperplasia showing fresh, conspicuous hemophagocytosis (Figure 1). Bone marrow biopsy also demon-

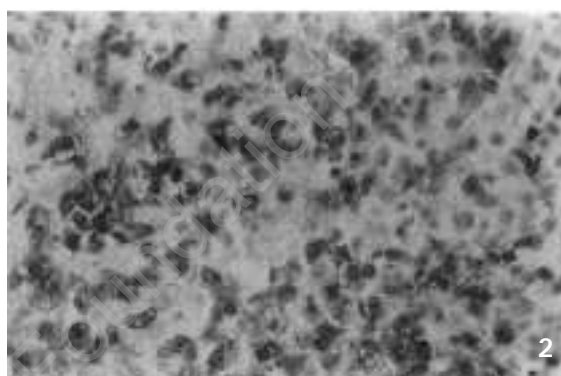
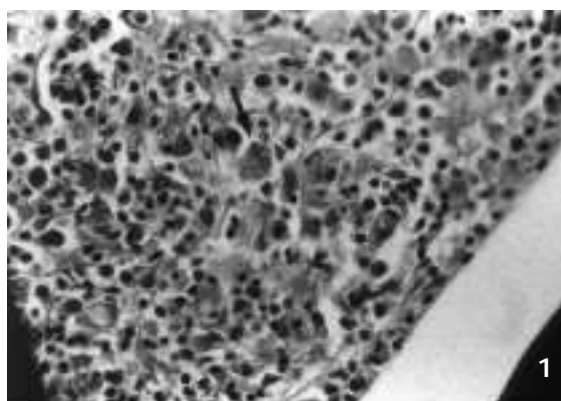


Figure 1. Small and medium sized irregular lymphocytes infiltrating bone marrow and a histiocyte with marked hemophagocytosis (arrow) (x750).

Figure 2. Bone marrow biopsy showing intense membranous CD3 staining in abnormal lymphocyte cells (x500).

strated clusters of abnormal lymphocytes. These abnormal cells were small to medium sized lymphoid cells and had a high nuclear to cytoplasmic ratio and irregular hyperchromatic nuclei (Figure 1). Immunohistochemistry showed staining of the abnormal lymphocytes with primary antibodies directed against CD3 and CD45RO but not CD20, CD74 and MB2 (Figure 2). Incisional tonsillar biopsy revealed a diffuse atypical lymphocytic infiltrate underlying the ulcerated and inflamed mucosal lining. Tonsillar lymphoid cells showed similar morphologic and immunophenotypic patterns as the bone marrow lymphoid cells. We evaluated PCR amplification of the rearranged  $\gamma$  T-cell receptor (TCR) from bone marrow samples. Clonal rearrangement for the TCR  $\gamma$ -chain gene was not detected. The patient was first treated with high doses of steroids and when results were consistent with T-cell lymphoma, she was treated with combination chemotherapy that contained adriamycin, cyclophosphamide, vincristine, and prednisolone. However, this patient's HPS was refractory to the chemotherapy, and she died of disseminated intravascular coagulation-induced multiorgan failure on her 20<sup>th</sup> day in hospital.

HPS has been reported in patients with non-Hodgkin's lymphoma, usually as a terminal compli-

cation. In contrast, a few cases have been reported of HPS as an early and prominent manifestation of an underlying cell lymphoma.<sup>4,5</sup> Differentiation from other causes of HPS is difficult and lack of histologic proof of malignancy in the initial stage often delays definitive diagnosis and treatment. Demonstration of clonal TCR gene rearrangements has been useful for the diagnosis of clonality in peripheral T-cell lymphomas.<sup>6</sup> However, monoclonality can be demonstrated using PCR in only 50-73% of peripheral T-cell lymphomas.<sup>7</sup> For the present, there are no reliable treatment strategies for malignancy-associated HPS. When HPS occurs at the time of initial diagnosis of a malignancy, patients should receive aggressive therapy including chemotherapy and supportive care. Furthermore, initial therapy with steroids and etoposide for rapidly progressing HPS has been suggested to control the cytokine storm during the acute phase of the disease preventing acute death.<sup>3</sup>

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### Key words

Hemophagocytic syndrome, Epstein-Barr virus, T-cell lymphoma

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## Splenectomy in patients with refractory or relapsing thrombotic thrombocytopenic purpura

Thrombotic thrombocytopenic purpura (TTP) is managed with plasma exchange. Rarely, patients do not respond or develop refractory disease. In these cases, treatment options are limited. Splenectomy has been associated with achievement of complete remission. We present the case histories of four patients undergoing splenectomy for refractory or relapsing TTP, three of whom achieved complete remission.

Sir,

Thrombotic thrombocytopenic purpura (TTP) is a syndrome characterized by thrombocytopenia, microangiopathic hemolytic anemia and, less commonly, neurologic and renal impairment and fever.<sup>1,2</sup> Currently, the use of plasma exchange, alone or combined with other agents, has resulted in a survival rate of over 80%.<sup>2,3</sup> However, 20-40% of patients undergo recurrent episodes of TTP, with an estimated 10-year risk of relapse of 36% in some series.<sup>4</sup> Splenectomy has been occasionally reported to achieve permanent control of the disease in this setting, although its definitive role is still unknown.<sup>5-7</sup> We describe the results of splenectomy in four patients with refractory or relapsing TTP.

From 1995, splenectomy has been performed at our institution in four patients with refractory (2 cases) or relapsing TTP (2 cases). Refractory patients had not responded to first-line therapy with a combination of daily plasma exchange (PE) and 200 mg/day of prednisone (or an equivalent dose of intravenous prednisolone).<sup>8</sup> Splenectomy was performed in one case after 20 PE and in the other case after 28 PE. The remaining two patients initially responded to PE and steroids. One of them relapsed 45 months after diagnosis. No response was obtained after 28 rounds of PE. It was considered a refractory relapse and splenectomy was subsequently performed. Finally, the remaining patient had five relapses at 8, 14, 36, 47, and 57 months after the initial diagnosis. In every case, he responded to PE and steroids. However, laparoscopic splenectomy was indicated after the fifth relapse while in remission. The patient's main characteristics are summarized in Table 1.

There were no major surgical complications or post-operative deaths. One patient required additional treatment with PE after splenectomy (four rounds), but no therapy was administered following surgery in the remaining cases. Patients were discharged a median of 14 days (range, 2-17) after surgery with normal platelet counts and LDH values. Three out of the four patients are still in remission at 11, 24 and 27 months after splenectomy. The patient who underwent splenectomy in refractory relapse suffered a new relapse five weeks later. He was then treated with cyclosporin A, and is currently alive and in remission.

Despite considerable controversy, splenectomy remains an important part of TTP treatment. Some groups have reported high mortality in patients not responding to medical therapy.<sup>1</sup> However, our results