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CASE REPORT

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Haemophagocytic syndrome after liver transplantation in adults

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Abstract The haemophagocytic syndrome is defined as a proliferation of phagocytic macrophages in the bone marrow, lymph nodes and spleen. Clinically, it is characterised by fever and pancytopenia. We present here a case of haemophagocytic syndrome after liver transplantation in a 63-year-old man who had undergone transplantation for autoimmune hepatitis. One month after liver transplantation, he developed ascites, fever and progressive pancytopenia. Bone marrow biopsy showed proliferation of non-neoplastic histiocytes, demonstrating phagocytosis of haemopoietic cells. No infectious or neoplasm-associated disease was found. Several kinds of treatment were attempted, but the course was fatal. The haemophagocytic syndrome is uncommon after liver transplantation, but this diagnosis has to be kept in mind in cases of pancytopenia of unknown origin.

Keywords Haemophagocytic syndrome · Liver transplantation

Introduction

Haemophagocytic syndrome (HPS) is a haematological disorder that is not yet fully understood. The main laboratory finding is pancytopenia, but some hepatic dysfunction features, such as low factor V and hypertriglyceridaemia, can also commonly be found. Bone marrow biopsy is frequently required to establish the diagnosis of HPS; haemophagocytosis features can also be found in the spleen, lymph nodes and liver, but not consistently, and they have not yet been fully characterised. Haemophagocytosis is defined as a proliferation of non-neoplastic histiocytes, demonstrating phagocytosis of haemopoietic cells [1].

This syndrome has been described in association with many diseases, mainly conditions where immunity is affected. Besides some neoplastic and lymphoproliferative disorders [2, 3], other cases have been related to viral [4] and bacterial infection [5], systemic lupus erythematous disease [6] and immunosuppressive therapy [7]. Few cases of HPS have been described after liver transplantation (LT) [8, 9, 10]. Here, we report a case of HPS after liver transplantation in an adult.

Case report

A 63-year-old diabetic man was diagnosed as suffering from autoimmune hepatitis. Hepatitis C and B sero-

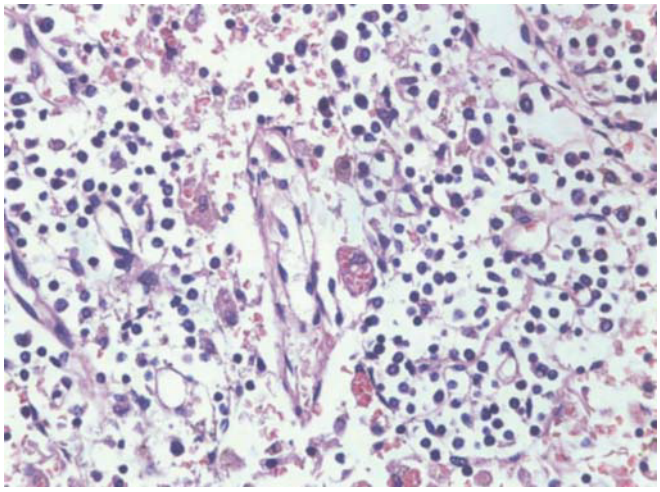

Fig. 1 Proliferation of activated macrophages with haemophagocytosis

logical tests were negative, while antinuclear antibodies (ANA) and smooth muscle antibodies (SMA) were positive (1/160). Before LT the patient had had several episodes of upper gastrointestinal bleeding that finally required a transjugular porto-systemic shunt (TIPS). He underwent transplantation in March 2002, and postoperative evolution was uneventful. Immunosuppression was attained with basiliximab (Simulect, Novartis Pharma AG, Basel, Switzerland), two doses of 20 mg on days 0 and 4, and cyclosporine (Sandimmun, Novartis Pharma) in monotherapy, 10 mg/kg per day from day 1, to reach the target C2 levels of 1,000 ng/ml.

The patient came back to the hospital 1 month after LT with symptoms of ascites and vomiting. The episode resolved spontaneously, but the patient presented again 1 month later with the same symptoms. An upper gastrointestinal study and computed tomography revealed no pathological finding.

During the admission period, ascites increased, and renal function worsened. The patient developed fever, jaundice and fatigue. Laboratory findings showed evidence of pancytopenia and progressive deterioration of clotting parameters (white blood count 1,700/mm^3; blood haemoglobin 8.5 g/l; platelet count 25,000 mm^3; prothrombin ratio 2.2; factor V 30%). Liver function tests showed only an increased level of bilirubin, with neither cholestasis nor cytolysis (total bilirubin 134 μmol/l; alkaline phosphatase 186 U/l; gammaglutamyl transferase 102 U/l; aspartate aminotransferase36 U/l; alanine aminotransferase 30 U/l).

Although the patient had a continuous body temperature of 39°C for more than 15 days, all bacteriological, viral, fungal, leishmania and mycobacterium cultures of blood, urine and ascites were negative. A liver biopsy was obtained; the only findings were lymphocytic lobular infiltrate and Kupffer cell hyperplasia. Cultures of liver biopsy were also negative.

Bone marrow biopsy demonstrated proliferation of non-neoplastic histiocytes, demonstrating phagocytosis of haemopoietic cells (Fig. 1).

With the diagnosis of HPS, the patient was initially treated with intravenous ganciclovir and tuberculostatic therapy (ethambutol and isoniazid) for some undetected infection. Finally, he was treated with steroids and intravenous immunoglobulins. There was no response to any of the attempted treatments, and, eventually, the patient died from diffuse upper gastrointestinal tract bleeding.

Post-mortem study revealed a liver with hepatocellular necrosis without signs of granulomatosis, siderosis or steatosis. Haemophagocytosis was found in the spleen, lymph nodes and bone marrow, and, to a low degree, in the liver. The central nervous system study was normal. All post-mortem specimens were cultured without any pathological finding.

Discussion

The pathogenic mechanism of HPS is uncontrolled T-cell proliferation, secretion of various cytokines, and stimulation of macrophage activity. The activated macrophages have increased phagocytic activity, while the cytokines are involved in the systemic manifestations of HPS [11]. Many causes have been associated with HPS, the best known being several types of infections (mainly viral [4]), and lymphoproliferative diseases [2, 3]. Nevertheless, other diseases that lead to disorders of the immune system have been associated with HPS. Indeed, a familiar type of HPS has been described [12].

In the clinical setting of LT, few cases of HPS have been described [8, 9, 10]. As far as we know, HPS after LT has been reported in five cases. Three of them were paediatric patients [9, 10]; the cause of HPS was unknown in one patient, while in the other two patients it was associated with Epstein–Barr virus infection in one case, and with herpes virus-6 infection in the other case. The only two adult patients with HPS after LT, described in a recent review [8], were in the setting of recurrent hepatitis C and cytomegalovirus hepatitis, respectively.

The patient in this report did not have any of the known causes of HPS. All studies performed to exclude some type of infection were negative, and no evidence of haematological or solid neoplasm was found. The diagnosis of HPS was made on clinical symptoms (fever, fatigue, jaundice) and biochemical data (pancytopenia, hyperbilirubinaemia and coagulation disorders); these data were coupled with the previously described hallmarks of HPS [8, 13].

Early recognition of HPS is essential to avoid the fatal course of these patients [13]. Nevertheless, the prognosis can only be improved if an underlying disease is diagnosed. Liver biopsy has proven to be useful in such cases. Other common manifestations that were also found in the present case are Kupffer cell hyperplasia and sinusoidal dilatation [8]. It is important to note that in the present case the liver biopsy did not show proliferation of activated macrophages with haemophagocytosis; the diagnosis was made on the basis of a bone marrow biopsy. Thus, if HPS is suspected, it is very important to perform a bone marrow biopsy promptly, to establish the diagnosis early. All other clinical data are non-specific.

Several treatment approaches have been described for HPS, which reflects the difficulty in finding the ultimate solution. In cases of an underlying disease, it is clear that the treatment will focus on that disease, be it either infectious or neoplastic. However, in cases without an underlying disease, various methods of treatment have been tried, such as immunosuppression [14] (cyclosporin, immunoglobulin, steroids), chemotherapy [13], plasmapheresis [15], and chloroquine [16]. In the present case, the patient was already under immunosuppression when he developed the clinical symptoms, and although various empiric treatments were tried, none was effective.

In summary, we describe a new case of HPS after LT that had a fatal outcome. This syndrome has to be suspected in immunosuppressed patients with pancytopenia of unknown origin, and a prompt bone marrow biopsy has to be carried out to allow prompt diagnosis and treatment. Further studies are needed to clarify the best treatment for this syndrome.

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