CASE REPORT

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Severe aplastic anemia following liver transplantation in a patient with non-A-E fulminant hepatitis

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Aplastic anemia is a rare complication after liver transplantation. Its incidence has been estimated to be 0.007%. Aplastic anemia was observed in 23.2 - 33% of patients who underwent liver transplantation for fulminant non-A-E viral hepatitis. In this paper, we describe a child suffering from aplastic anemia who eventually died from sepsis after liver transplantation for non-A-E fulminant hepatic failure.

Key words: Liver transplantation, aplastic anemia, fulminant hepatitis

Non A-E fulminan hepatitli bir hastada karaciğer nakli sonrası gelişen ciddi aplastik anemi

Karaciğer nakli sonrası aplastik anemi nadir bir komplikasyondur. Aplastik anemi insidansı yaklaşık %0.007'dir. Fulminan non A-E viral hepatit nedeniyle karaciğer nakli yapılan olgularda ise aplastik anemi %23.2-33 olarak gözlenmektedir. Bu yazıda non A-E fulminan hepatit nedeniyle karaciğer nakli yapılan ve sonrasında aplastik anemi gelişen ve sepsis nedeniyle kaybedilen bir olgu sunulmuştur.

Anahtar kelimeler: Karaciğer nakli, aplastik anemi, fulminan hepatit

INTRODUCTION

Aplastic anemia (AA) is a rare complication after liver transplantation. Its incidence has been estimated to be 0.007% (1). AA was observed in 23.2 - 33% of patients who underwent liver transplantation for fulminant non-A, non-B and non-C viral hepatitis (1,2). Occurrence of AA after liver transplantation performed for non-A, non-B and non-C fulminant hepatic failure is more frequent in children than in adults (33% vs. 5%) (1). The mortality rate was 39%. Systemic infections and bleeding were the most frequent causes of death, occurring in 67% and 25%, respectively (2).

In this paper, we describe a child suffering from AA who eventually died from sepsis after liver transplantation for non-A-E fulminant hepatic failure.

CASE REPORT

A 10-year-old girl with non A-E fulminant hepatitis stage III encephalopathy was intubated by giving mannitol and furosemide for brain edema and within 24 hours underwent hepatic transplantation using the left lobe of the liver of her mother.

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Whole blood count and biochemical values during and after transplantation are shown in Tables 1 and 2. The transplantation was uneventful. The patient was extubated just 3 days after transplantation. After transplantation, tacrolimus and prednisolone were initiated according to our center's hepatic transplantation protocol. While prednisolone was reduced step by step, tacrolimus was regulated to maintain the blood level between 12-16 ng/ml. After extubation, the patient's general condition was good and her vital signs were normal. While the parameters of the whole blood count of the patient before transplantation were in normal ranges, pancytopenia developed on the 3rd day of transplantation and gradually deepened to absolute neutrophil count (ANC) of 0.1 x 10^9/L, platelets of 22 x 10^9/L and reticulocyte of 0.5% on the 12th day.

At that time, bone marrow aspiration showed decreased cellularity. There was no infiltration or dysplasia and all three lineages were present in the bone marrow. Febrile neutropenia occurred on the post-transplant 12th day. Empiric therapy including meropenem and amikacin was initiated following blood, urine, throat, and stool cultures. Granulocyte colony-stimulating factor (G-CSF) at the dose of 7.5 µg/kg/day was also started. For the aim of supportive treatment, irradiated and leucoreduced erythrocyte and platelet suspensions were given. She also received irradiated granulocyte infusions taken from donors prepared by using G-CSF treatment. On the 19th day of transplantation, a second bone marrow aspiration was performed with biopsy since severe pancytopenia persisted. Cellularity of bone marrow biopsy was defined as 5%. Vancomycin and amphotericin B were added to the treatment because of insufficiency in controlling fever, although a positive culture result could not be obtained. The prophylactic doses of acyclovir and trimethoprim-sulfamethoxazole (TMP-SMX) were increased to treatment doses. Serological evaluation revealed Epstein-Barr virus (EBV) VCA IgM (-) and polymerase chain reaction (PCR) for EBV and B19 DNA (-). Serologic evaluation for hepatitis A, B, C, D and E did not show a current infection. IFAT and ELISA tests for toxoplasmosis IgM and IgG were found to be negative. Cytomegalovirus (CMV) antigen and CMV DNA PCR were found to be negative. The patient was transferred to the intensive care unit and mechanical ventilation support was started on the 31st day of transplantation and on the 19th day of febrile neutropenia, with the findings of acute respiratory distress (ARD) and septic shock. The findings of the bone marrow biopsy repeated

Table 1. Hematologic laboratory values

	During Tx	3rd day after Tx	12th day after Tx	1st month after Tx
Hemoglobin (g/dl)	10.8	8.3	7.6	7.1
Mean corpuscular volume (µm^3)	75	75	85	85
White cell count (per mm^3)	12100	2900	700	470
Differential count (%)				
Neutrophils	64	56	14	10
Lymphocytes	28	38	82	90
Monocytes	6	6	4	
Eosinophils	2			
Platelet (per /mm^3)	104000	67000	25000	11000

Tx: Transplantation.

Table 2. Blood chemical values

	During Tx	3rd day after Tx	12th day after Tx	1st month after Tx
SGOT (IU)	369	166	208	97
SGPT (IU)	494	456	463	95
Alkaline phosphatase (IU/L)	338	241	273	458
GGT (IU)	30	64	67	96
Total bilirubin (g/dl)	17.9	8	96	8.6
Prothrombin time (second)	21	15	13	12

Tx: Transplantation. SGOT: Aspartate aminotransferase. SGPT: Alanine aminotransferase. GGT: Gamma glutamyl transpeptidase.

six weeks after the onset of pancytopenia confirmed the diagnosis of AA. On the postoperative 54th day, the patient died in the intensive care unit because of uncontrolled sepsis and septic shock despite intense antibiotherapy with granulocyte infusions and supportive treatment.

DISCUSSION

Complication of AA following hepatic transplantation was first defined by Stock (3) in a 7-year-old child with non-A, non-B fulminant hepatitis. It is rare among all hepatic transplantation complications. The etiology is not completely understood. According to one hypothesis, AA develops with immunopathogenic mechanisms triggered by viral agents (4). Another hypothesis is that AA can develop as a result of an increase in T cell activation, especially the increase in serum levels of active CD8+ cells (5). Improving the patient's response to treatment by increasing immunosuppression supports these hypotheses. Furthermore, as this has been seen at an average age of 10 years and much more rarely in adults, it has been thought that the agent could be a virus against which adults have already acquired immunity before exposure (2).

The whole blood count of our patient before transplantation was normal. Pancytopenia developed on the 3rd day of transplantation. Investigation directed to the etiology could not reveal any viral agent (especially CMV and parvovirus B19 frequently causing pancytopenia). There were no findings of graft versus host disease, including no skin rash, fever or gastrointestinal system findings. Prophylactic treatments started after hepatic transplantation were discontinued, since it was considered that the drugs may have triggered the pancytopenia. We could not identify the etiology of the fulminant hepatitis.

The main immunosuppressive agents used in AA are antithymocyte globulin (ATG)/ antilymphocyte globulin (ALG) and cyclosporine. In the literature, in patients who developed AA following hepatic transplantation, G-CSF, granulocyte/macrophage colony-stimulating factor (GM-CSF), rhEPO, and immunosuppressive agents like ATG, ALG and OKT-3 have been used, and bone marrow transplantation has been performed if an HLA-compatible donor is available (6). It has been reported that ATG, used frequently among these treatments, shows delayed effect and has a 50% success rate (2). There are also several reports showing the success of bone marrow transplantation in these cases (7).

Granulocyte colony-stimulating factor (G-CSF) was given to this case, and although the dose was increased to 15 µg/kg/day, the leukocyte count did not elevate. ATG, ALG and OKT-3, which are used for AA, were not given to our patient as she was in neutropenic sepsis and ARDS. Tissue types between the patient and her healthy brother were not compatible; immunosuppressive treatment was not applied to avoid causing secondary deterioration in our patient with severe infection/sepsis.

The clinical benefit of granulocyte transfusions is controversial. In 1995, Strauss (8) evaluated the results of 32 studies in which granulocyte transfusion treatment was applied for severe infections to serious neutropenic patients. Although most of these studies were uncontrolled small studies, successful treatment results were reported as 75% in patients having non-specific fever, and as 64% in pneumonia cases in which the organism could not be isolated. In our patient, with the existence of neutropenia showing long-term continuity, radiated granulocyte infusions taken from donors prepared by using G-CSF treatment were used. Hypotension, increase in respiratory distress (especially in patients treated with amphotericin B, like our patient) and acute lung damage associated with transfusion-like problems are reported as being likely to develop during granulocyte infusion, but they were not observed in this patient.

Occurrence of AA after hepatic transplantation in cases with non A-E fulminant hepatitis is frequent. In these cases, sepsis and hemorrhage-like complications can develop rapidly. Appropriate immunosuppressive treatment should be started and rapid bone marrow transplantation should be performed in the early stages in these cases before the development of infections.

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