Case report of two haematopoietic stem cell transplanted patients with chronic graft-versus-host disease resembling acute viral hepatitis

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ABSTRACT

Chronic graft-versus-host disease (GVHD) of the liver usually presents as an indolent cholestatic syndrome associated with abnormalities in the skin, oral mucosa, and lacrimal glands observed beyond day 100 after allogeneic bone marrow transplantation. Because of its cholestatic nature, chronic liver GVHD is not generally considered in the differential diagnosis of markedly elevated serum transaminases and jaundice. However, sudden rise in serum transaminase levels after day 70 posttranplant should always raise the question of chronic liver GVHD. We report here two cases, in whom the presentation of chronic graft-versus-host disease of the liver strongly resembled acute viral hepatitis. Chronic GVHD of the liver should also be taken into account in the differential diagnosis of marked elevations of liver enzymes in allogeneic stem cell transplant recipients and appropriate diagnostic and therapeutic measures should be applied.

Key Words: Graft-versus-host disease, Haematopoietic stem cell transplantation, Hepatitis.

ÖZET

Akut viral hepatiti taklit eden ve kronik greft versus host hastalığı olan iki hematopoietik kök hücre nakli olgusu

Karaciğerde kronik graft-versus-host hastalığı (GVHH) genellikle allogeneik kemik iliği transplantasyonunu izleyen 100. günden sonra ortaya çıkan kolestatik karaciğer fonksiyon bozukluğu, cilt ve oral mukoza lezyonları ile karakterize bir tablodur. Kolestatik komponentin ön planda olması sebebiyle, akut gelişen sarılık ve artmış transaminaz düzeyleri söz konusu olduğunda ayırıcı tanıda kronik GVHH öncelikli olarak yer almaz. Ancak bazen posttransplant geç dönemde gelişen akut hepatit kronik GVHH'nin ilk bulgusu olabilir. Bu yazıda, kronik GVHH'nin akut viral hepatit benzeri bir tablo ile ortaya çıktığı iki olgumuzu sunuyoruz.

Anahtar Kelimeler: Graft versus host hastalığı, Hematopoietik kök hücre nakli, Hepatit.

INTRODUCTION

Markedly elevated serum aminotransferases in allogeneic haematopoietic cell transplant recipients does not always indicate acute liver failure. There are multiple potential causes of such a clinical presentation, such as veno-occlusive disease, viral disease, drug toxicity, the likelihood of which varies depending on the time interval since transplantation[1,2].

In a retrospective analysis we came across to two cases of chronic GVHD resembling acute viral hepatitis among a total of 60 bone marrow transplantations carried out in the Adult Haematology Department of Cerrahpasa Medical Faculty of Istanbul University between 1993-2003.

CASE REPORTS

Case 1

A 33-years-old female patient with a diagnosis of chronic myeloid leukemia (CML) in first chronic phase received an allogeneic bone marrow transplant from her HLA identical brother in October 1995. Busulfan and cyclophosphamide were used as the conditioning regimen. Prophylaxis of acute GVHD consisted of cyclosporine and a short course of methotrexate. Engraftment of leukocytes and thrombocytes occurred on days 20 and 22 posttransplant, respectively. The patient was discharged without any complication on day 87. No evidence of chronic GVHD was apparent around day 100 posttransplant. Upon reoccurrence of bcr/abl positivity fifty six months after transplantation, the patient was begun interferon-α 3 million U/day, s.c.. Following 3 months of interferon therapy she received two donor buffy coat perfusions 37 days apart to induce a graft-versus-leukemia effect. One month after the second perfusion the patient was complaining of generalized itching that worsened at night when she was seen in the outpatient clinic. There was no obvious drug history. She appeared to be in good general condition with a performance score of 100 (Karnofsky). Her physical examination was unremarkable except for mild xerosis on distal extremities and a morbiliform rash on her back. Oropharyngeal examination revealed a whitish film on the tongue, white plaques on right buccal mucosa and hyperemia on the left . The patient was in haematological remission though eosinophilia (900/mm^3) in the peripheral blood was noted. Blood chemistries were normal except for alkaline phosphatase (ALP): 445 U/L (N: 64-306), alanine aminotransferase (ALT): 1034 U/L (N: 5-37) , aspartate aminotransferase (AST): 828 U/L (N: 5-37), lactate dehydrogenase (LDH): 634 U/L (N: 160-480) and total bilirubin level was 0.73 mg/dL. Serologic markers for hepatitis viruses (A, B and C) were found to be negative. The Schirmer test revealed no pathology. Pulmonary function tests were normal. Ultrasonographic study showed a normal-size liver with an increased echogenicity. Microscopical examination of the biopsy specimen of the morbiliform rash was consistent with acute GVHD (grade II). Oral mucosal biopsy revealed lichenoid dermatitis. Liver biopsy showed bile duct destruction, minimal endothelitis with portal inflammatory changes and periportal parenchymal cell necrosis. These findings were accepted to be consistent with GVHD. Oral cyclosporine A (CsA) was initiated at a dose of 6.25 mg/kg bid. Pruritus subsided after a while. Blood chemical findings done after 40 days of CsA were as follows: AST: 73 U/L, ALT: 65 U/L, ALP: 225 U/L, total bilirubin: 1.8 mg/dL. Since this was a case of relapsed CML and cytogenetic remission was achieved with donor buffy coat infusions to some extent, GVHD was treated with a single agent instead of a combination.

Case 2

A 23-years-old male patient underwent peripheral blood stem cell transplantation for acute lymphocytic leukemia [FAB L1, CALLA (-), pre-B cell, bcr/abl (+)], in first complete remission from his ABO-mismatched, HLA-identical sister in June 1997. His conditioning regimen consisted of cyclophosphamide and

total body irradiation. As prophylaxis against GVHD, he received a short course of methotrexate and CsA. The patient had both leukocyte and thrombocyte engraftments on day 17 and was discharged without any complication on day 40 posttransplant. The GVHD screening on day 100 was negative. CsA was tapered and stopped at 180 days after transplant. The patient was readmitted to the hospital on day 210 posttransplant because of fatigue, loss of apetite, scleral icterus and pruritus of two weeks duration. He was in good general condition. Physical examination was unremarkable except for abrasions on the skin caused by scratching and reticular white plaques on buccal mucosa accompanied by vesicular lesions on hard palate. Blood analysis revealed haematologic remission with apparent eosinophilia (774/mm^3). Blood chemical findings on admission were as follows: ALP: 1237 U/L (N: 64-306), AST: 500 U/L (N: 5-37), ALT: 710 U/L (N: 5-37), gamma-glutamyl transpeptidase (GGT): 342 U/L (N: 7-49), total bilirubin: 6.71 mg/dL (N: 0-1.2), direct bilirubin: 6.39 mg/dL (N: 0-0.35), LDH: 629 U/L (N: 240-480). The clinical presentation was interpreted as cholestatic type acute viral hepatitis and prednisolone 1 mg/kg/day was begun. The liver and bile ducts appeared normal on ultrasonographic examination. Serologic markers for HAV, HBV, HCV were negative as was the CMV DNA antigen. IgG type antibodies to HSV, VZV and EBV were positive denoting prior infection. The Schirmer test was negative and pulmonary function tests showed no abnormality. Microscopical study of the buccal biopsy specimen revealed periductal and periacinar lymphoplasmacyctic infiltration and mild fibrosis which were consistent with chronic GVHD. Thirteen days after initiation of steroid therapy a liver biopsy was performed. Examination of the specimen showed marked bile duct damage with bile stasis and prominent inflammatory reaction of portal spaces indicating GVHD. Consequently, the steroid dose was doubled and IV CsA at a dose of 1.5 mg/kg twice a day was added. As bilirubin levels continued to rise in spite of this treatment a magnetic resonance cholangiography was performed which revealed no pathologic finding. On the 40th day of immunosupressive therapy, total bilirubin level peaked to 20.1 mg/dL. Antithymocyte globulin at a dose of 10 mg/kg (every other day for six times) was added to the treatment as the third immunosuppressant. Only half of the planned first two doses could be administered to the patient due to complicating hypotension, bradycardia and fever. On the day following the second antithymocyte globulin dose a meningoencephalitis-like picture developed and progressed rapidly so that the patient died before any diagnostic procedure could be performed.

DISCUSSION

Chronic GVHD is the principal cause of transplant-related morbidity in long-term survivors of allogeneic haematopoietic stem cell transplantation.

Chronic GVHD affects 33% to 64% of long-term survivors of allogeneic bone marrow transplantation[3]. Main characteristics of the disease are: dry eyes, oral mucositis with salivary gland damage, a scleroderma-like skin disease, polyserositis, immunodeficiency, autoimmune disorders affecting other organs and chronic liver disease. Chronic GVHD-induced liver disease is primarily cholestatic, ie it is associated with elevations in serum alkaline phosphatase levels and varying degrees of jaundice[1]. Liver involvement is observed in 73% to 86% of patients with GVHD. It usually responds more slowly than do abnormalities in other organs[4]. Chronic GVHD develops beyond 2 to 3 months after transplantation. There is often evidence of multiorgan involvement with skin, exocrine glands, squamous epithelium, and lungs being involved. However, limited disease with only skin and liver involvement is also seen, and extensive multisystem involvement is not necessary for the diagnosis of chronic GVHD[1].

We have reported here two allogeneic stem cell transplant recipients in whom the clinical presentation suggested acute hepatitis but which turned out to be unusual examples of GVHD of the liver.

Both patients were off immunosupressive therapy. Since there is no standart approach for patients who are refractory to initial therapy we added ATG to treat the GVHD in the second patient but he died before effective dosage of ATG could be delivered[5]. Strasser et al indicate in their article that combination immunosuppressive therapy should be initiated to avoid progressive cholestasis and ductopenia[2]. Exceptional to this comment our first patient showed a rapid response to CsA monotherapy, while the second patient died in spite of combined immunosupressive treatment.

Cases of GVHD resembling acute hepatitis have been described previously[2,5]. The majority of the reported patients responded promptly to treatment with high-dose steroids with or without CsA as was the case with our first patient who showed a rapid response to CsA.

We conclude that chronic GVHD of the liver should also be taken into account in the differential diagnosis of marked elevations of liver enzymes in allogeneic stem cell transplant recipients and appropriate diagnostic and therapeutic measures should be applied.

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