CASE REPORT

TJG
The Turkish Journal of Gastroenterology

Vanishing bile duct syndrome after allogeneic bone marrow transplantation: Is it the end of the road?

Şule Mine BAKANAY[1], Aynur UĞUR BİLGİN[1], Mehmet BEKTAŞ[2], Ramazan İDİLMAN[2], Esra ERDEN[3], Mutlu ARAT[1], Önder ARSLAN[1]

Departments of [1]Hematology, [2]Gastroenterology and [3]Pathology, Ankara University, Medical School, Ankara

In this paper, we report the case of a 19-year-old male patient who presented with lymphoblastic phase of chronic myeloid leukemia and received an allogeneic bone marrow transplant from his cousin. The patient experienced severe, steroid-refractory acute graft-versus-host disease of skin, gastrointestinal tract and liver that required further immunosuppression. However, hepatic graft-versus-host disease was complicated with vanishing bile duct syndrome, characterized by progressive destruction of small intrahepatic bile ducts, which was refractory to all available therapies and eventually led to end-stage liver disease. The pathogenesis and treatment of graft-versus-host disease after allogeneic hematopoietic cell transplantation is discussed with an emphasis on liver transplantation for intractable hepatic graft-versus-host disease.

Key words: Hematopoietic cell transplantation, hepatic GVHD, vanishing bile duct syndrome

Allojeneik kemik iliği nakli sonrası gelişen "kaybolan safra kanalı sendromu": Yolun sonu mu demektir?

Kronik miyelositer löseminin lenfoblastik fazında tanı alan ve kuzeninden allojeneik kemik iliği nakli yapılan 19 yaşında bir erkek olgu bildirilmektedir. Hastada, nakil sonrası cilt, gastrointestinal sistem ve karaciğerin etkilendiği ağır ve steroide dirençli akut graft-versus-host hastalığı gelişmiş, çok sayıda immünsupresif tedavi verilmek zorunda kalınmıştır. Ancak, karaciğer graft-versus-host hastalığının, küçük intrahepatik safra kanallarının ilerleyici yıkımı ile karakterize 'kaybolan safra kanalı sendromu' ile komplike olduğu saptanmış, bu durum verilen tedavilerin hiçbirine yanıt vermemiş ve son dönem karaciğer yetmezliği gelişmiştir. Bu olgu raporunda, allojeneik hematopoietik hücre nakli sonrası graft-versus-host hastalığı patogenezi ve tedavisi anlatılmakla birlikte dirençli karaciğer graft-versus-host hastalığında karaciğer naklinin gerekli olabileceğine de işaret edilmektedir.

Anahtar kelimeler: Hematopoietik hücre nakli, karaciğer graft-versus-host hastalığı, kaybolan safra kanalı sendromu

INTRODUCTION

Allogeneic hematopoietic cell transplantation (AHCT) is the only curative approach for many hematologic malignancies. However, development of graft-versus-host disease (GVHD) is an important cause of morbidity and mortality after AHCT. Although novel agents have been introduced for the treatment of acute and chronic GVHD, treatment of corticosteroid-resistant GVHD is still controversial, and the results are disappointing especially in a group of patients with advanced-stage GVHD. It has been reported that initial liver involvement in acute GVHD and persistent jaundice is predictive for overall non-relapse mortality. Chronic hepatic GVHD may rarely be associated with prog-

Address for correspondence: Şule Mine BAKANAY
Ankara University Medical School, Department of Hematology, Ankara, Turkey
E-mail: sulemine@yahoo.com

Manuscript received: 09.06.2012 **Accepted:** 12.08.2012

Turk J Gastroenterol 2013; 24 (4): 359-362
doi: 10.4318/tjg.2013.0604

ressive destruction and disappearance of intrahepatic bile ducts, so called the vanishing bile duct syndrome (VBDS) (1, 2).

CASE REPORT

A 19-year-old male patient was diagnosed at the acute lymphoblastic phase of chronic myeloid leukemia. After a remission induction chemotherapy which was followed with imatinib mesylate, the patient attained hematologic remission without a molecular response. Four months after diagnosis, he received an allogeneic bone marrow transplant from his human leukocyte antigen (HLA)-compatible, 11-year-old male cousin. The conditioning regimen consisted of cyclophosphamide (120 mg/kg) and total body irradiation (1200cGy); GVHD prophylaxis was done with cyclosporine and short-term methotrexate. A successful engraftment was achieved with simultaneous development of a skin eruption, colicky diarrhea, and a mild jaundice. The skin and colonic biopsies revealed a grade II skin and grade III-IV gastrointestinal (GI) tract GVHD, respectively. The patient was immediately started on 2 mg/kg/d methylprednisolone. Ursodeoxycholic acid (UDCA) was also added for mild increase in cholestatic parameters. The patient had complete resolution of skin GVHD. However, his diarrhea progressed to daily 1.5 liter. Although the patient was administered anti-thymocyte globulin (ATG) 10 mg/kg/day for 5 days followed by 2 g/day oral mycophenolate mofetil, his diarrhea showed no signs of improvement. Moreover, severe electrolyte imbalance and malnutrition developed. On day +76, he received a single dose of 1 mg/kg methylprednisolone into the mesenteric artery which resulted in a 25% reduction in the volume of diarrhea. Starting from day +109, the patient received 10 mg/kg weekly anti-tumor necrosis factor-α (TNF-α) for 4 weeks and was discharged with a complete improvement in GI symptoms and a better nutritional status.

The patient remained in complete remission with full donor type chimerism during the out-patient follow-up. However, he was admitted again on day +198 with a progressive increase in total bilirubin up to 20 mg/dL and conjugated bilirubin up to 17 mg/dL along with elevated alkaline phosphatase, gamma-glutamyl transferase, and transaminases. The viral etiology was ruled out, the autoimmune panel did not reveal any abnormality, but serum ferritin was increased to 3261 ng/dL. The magnetic resonance cholangiopancreaticography revealed sludge inside the gallbladder and collapsed intrahepatic bile ducts. Minimal sphincterotomy through endoscopic retrograde cholangiopancreaticography was performed without any improvement in cholestasis. Since the total bilirubin level reached 40 mg/dL, intermittent therapeutic plasma exchange was started. Cyclosporine was tapered and stopped while rapamycin 2 mg/day was started, but this approach could stabilize the total bilirubin levels at 10-15 mg/dL only for a few weeks. The liver biopsy was performed and microscopic examination of the liver showed that none of the portal areas contained interlobular bile ducts and only a few of them had minimal inflammatory cell infiltration. Bile infarcts, cholestatic plugs, and rosette formation at the centrilobular areas were also observed. Reactive changes in the hepatocytes and iron deposition mainly at the periportal areas were noted. These changes were consistent with VBDS and grade 3 hemosiderosis (Figure 1,2).

Consent for a liver transplantation from the same bone marrow donor could not be obtained from the donor's family. Unfortunately, there was a gradual loss of response to therapeutic plasma exchange with rebound increase in bilirubin levels and prolonged prothrombin time. The process was further complicated with a *Staphylococcus aureus pneumonia,* and the patient died with hepatic coma on day +268.

DISCUSSION

Cholestasis after AHCT is not rare, and GVHD is one of the various causes which include hepatoto-

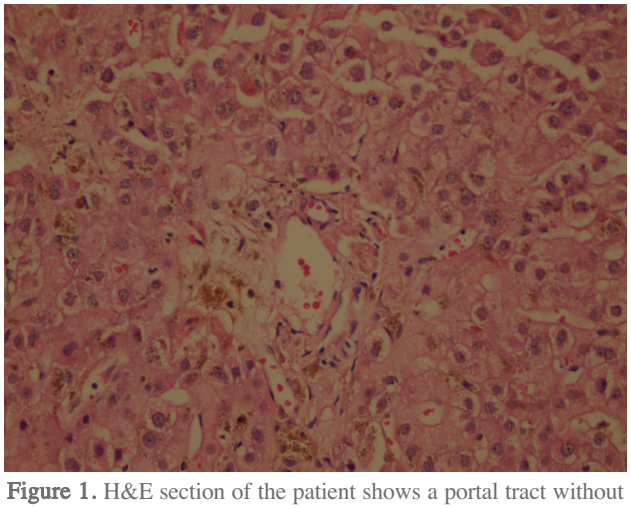

Figure 1. H&E section of the patient shows a portal tract without interlobular bile duct and prominent yellow-brown pigment deposition in hepatocytes.

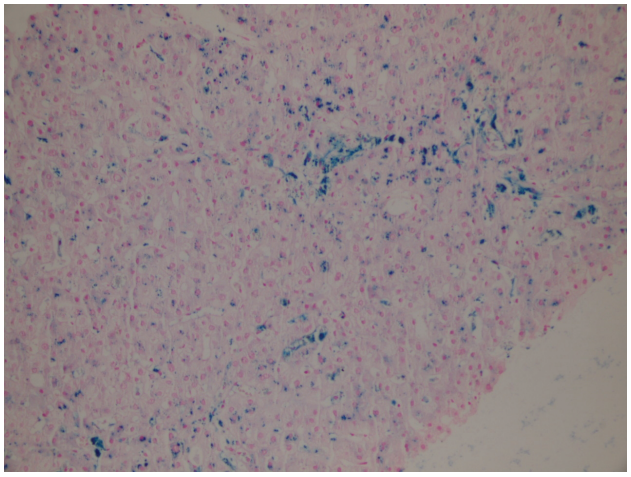

Figure 2. Iron stain (Prussian blue) shows iron deposition in Kupffer cells and hepatocytes consistent with the yellow-brown pigment in the H&E section.

xicity of drugs, venoocclusive disease, total parenteral nutrition, viral hepatitis, sepsis, and opportunistic infections (3, 4). Since the liver is rarely biopsied because of thrombocytopenia early after transplantation, diagnosis is usually made by clinical exclusion. Acute GVHD after AHCT develops when donor T lymphocytes respond to genetically defined proteins on host tissues. Besides HLA, it has been revealed that non-HLA antigens also contribute to the development of GVHD. Bile duct epithelial cells present foreign antigens that are recognized by donor T lymphocytes, ultimately resulting in immune cell infiltration into the intraepithelial layer of the bile ducts, T cell cytotoxicity leading to bile duct apoptosis, injury, and loss. Chronic hepatic GVHD with ductopenia is potentially reversible if ongoing immunologic destruction of epithelium ceases. However, progressive destruction of small intrahepatic bile ducts causes VBDS leading to end-stage liver disease (1, 5).

Our patient had a very severe and intractable form of progressive chronic GVHD, which means that an acute GVHD started and merged to a chronic form. It should be noted that acute GVHD involved three organs: skin responded to the first-step therapy with steroids; GVHD involving the GI tract responded to anti-TNF-α. However, liver was the only organ involved in the chronic form of the disease. This can be partly explained by particular susceptibility of the GI tract to damage from TNF-α, because cytotoxic T lymphocytes that use the perforin/granzyme pathways are more important in the GI tract and skin. On the other hand, cytotoxic T lymphocytes that appear to predominate in GVHD liver damage preferentially use Fas/Fas-L pathway (6, 7). The liver was only mildly affected early after transplantation. However, a severe chronic GVHD resulted in isolated liver damage.

Pretransplant iron overload has been associated with adverse posttransplant events. However, whether excess iron contributes to the development of GVHD is not clear. It is well-known that elevated serum ferritin level particularly in patients with chronic GVHD, chronic viral hepatitis, and other liver diseases may not accurately reflect the tissue iron stores. Our patient did not have a high pretransplant transfusion burden, but he still had iron accumulation in the liver biopsy specimen after the transplantation. It has been suggested that the development of GVHD is one of the factors contributing to hepatic iron overload via dysregulation of hepcidin iron homeostasis through hepatic and intestinal injury. Fas/Fas-L mediated signals from alloreactive T lymphocytes leading to hepatocyte apoptosis have been associated with iron deposition (8,9). So, it is possible that our patient had an exaggerated iron accumulation during the process of acute and chronic GVHD.

Steroids with potent antilymphocyte and antiinflammatory activity are the gold standard first-line treatment for both acute and chronic GVHD. However, steroid-resistant GVHD is difficult to treat. None of the salvage regimens so far have been shown to improve the overall survival rates in severe forms of GVHD. Treatment with UDCA is a frequent approach in allogeneic transplant setting and has been demonstrated to decrease the GVHD-related cholestasis and improve the outcomes (9-11). T lymphocyte depletion by addition of ATG in patients who show early signs of steroid resistance have been shown beneficial in some but not all studies (12, 13). Based on the case reports supporting the efficacy and safety in steroid-resistant GI tract GVHD, we employed intra-mesenteric arterial steroid administration. However, a minor response was observed, which is consistent with the results of studies reporting poor response to intra-arterial corticosteroid therapy when combined liver and GI tract GVHD is encountered (14, 15). In fact, our patient's GI symptoms were controlled mainly by the administration of anti-TNF-α agent. Besides the persistence of donor derived alloreactive T cells and uncontrolled autoreactive T cells, there is increasing role of antibody producing B cells in the pathogenesis of chronic GVHD.

However, our patient was still refractory to rapamycin, an inhibitor of mammalian target of rapamycin kinase, which prevents both T and B lymphocyte activation by cytokines (16).

Currently available therapeutic agents may be insufficient in preventing the progression from ductopenia to VBDS and eventually to end-stage liver disease. Unfortunately, at this stage, there is no established therapy other than liver transplantation. Some studies have reported successful liver transplantation from alive or deceased donors for intractable hepatic GVHD after HCT (17-19). Increased risk of relapse as a result of life-long immunosuppression after solid organ transplantation might be a major concern especially in high-risk patients. Liver transplantation from the same hematopoietic cell donor may be preferred because in presence of full donor chimerism, tolerance to the transplanted organ is expected and this does not require any further immunosuppressive therapy (20).

REFERENCES

1. Reau NS, Jensen DM. Vanishing bile duct syndrome. Clin Liver Dis 2008; 12:203-17.
2. Robin M, Porcher R, de Castro R, et al. Initial liver involvement in acute GVHD is predictive for nonrelapse mortality. Transplantation 2009; 88:1131-6.
3. Akpek G. Graft-versus-host disease: An evidence-based management guideline. Turk J Hematol 2003; 20:123.
4. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. Lancet 2009; 373:1550-61.
5. Lee SJ, Vogelsang G, Flowers ME. Chronic graft-versus-host disease. Biol Blood Marrow Transplant 2003; 9:215-33.
6. Welniak LA, Blazar BR, Murphy WJ. Immunobiology of allogeneic hematopoietic stem cell transplantation. Annu Rev Immunol 2007; 25:139-70.
7. van den Brink MR, Burakoff SJ. Cytolytic pathways in hematopoietic stem-cell transplantation. Nat Rev Immunol 2002; 2:273-81.
8. Deeg HJ, Spaulding E, Shulman HM. Iron overload, hematopoietic cell transplantation, and graft-versus-host disease. Leuk Lymphoma 2009; 50:1566-72.
9. McDonald GB. Hepatobiliary complications of hematopoietic cell transplantation, 40 years on. Hepatology 2010; 1: 1450-60.
10. Ruutu T, Eriksson B, Remes K, et al. Nordic Bone Marrow Transplantation Group. Ursodeoxycholic acid for the prevention of hepatic complications in allogeneic stem cell transplantation. Blood 2002; 100:1977-83.
11. Arat M, Idilman R, Soydan EA, et al. Ursodeoxycholic acid treatment in isolated chronic graft-vs.-host disease of the liver. Clin Transplant 2005; 19:798-803.
12. MacMillan ML, Weisdorf DJ, Davies SM, et al. Early antithymocyte globulin therapy improves survival in patients with steroid-resistant acute graft-versus-host disease. Biol Blood Marrow Transplant 2002; 8:40-6.
13. Arai S, Margolis J, Zahurak M, et al. Poor outcome in steroid-refractory graft-versus-host disease with antithymocyte globulin treatment. Biol Blood Marrow Transplant 2002; 8:155-60.
14. Shapira MY, Bloom AI, Or R, et al. Intra-arterial catheter directed therapy for severe graft-versus-host disease. Br J Haematol 2002; 119:760-4.
15. Tfayli A, Selby G, Maqbool F, et al. Role of intra-arterial steroid administration in the management of steroid-refractory acute gastrointestinal graft-versus-host disease. Am J Hematol 2006; 81:959-62.
16. Martínez C, Urbano-Ispízua A. Graft-versus-host disease therapy: something else beyond glucocorticoids? Haematologica 2011; 96:1249-51.
17. Barshes NR, Myers GD, Lee D, et al. Liver transplantation for severe hepatic graft-versus-host disease: an analysis of aggregate survival data. Liver Transpl 2005; 11:525-31.
18. Teisseyre M, Teisseyre J, Kalicinski P, et al. Liver transplantation for severe hepatic graft-versus-host disease in two children after hematopoietic stem cell transplantation. Transplant Proc 2010; 42:4608-10.
19. Koenecke C, Hertenstein B, Schetelig J, et al. Solid organ transplantation after allogeneic hematopoietic stem cell transplantation: a retrospective, multicenter study of the EBMT. Am J Transplant 2010; 10:1897-906.
20. Shimizu T, Kasahara M, Tanaka K. Living-donor liver transplantation for chronic hepatic graft-versus-host disease. N Engl J Med 2006; 354:1536-7.