Cirrhosis as a Consequence of Graft-Versus-Host Disease

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A 28-yr-old woman with severe idiopathic aplastic anemia received an HLA-identical mixed lymphocyte culture nonreactive bone marrow transplant from her brother. In the months after successful engraftment, she developed cutaneous and hepatic graft-versus-host disease, associated with marked cholestatic jaundice. Despite a series of therapeutic maneuvers, cholestasis persisted but remained relatively stable over the ensuing 10 yr. However, serial liver biopsies revealed progressive biliary-type fibrosis culminating in cirrhosis. Subsequently, her clinical course deteriorated and she developed signs of hepatic failure, and ultimately died 10.5 yr after bone marrow transplantation. The evolution of chronic graft-versus-host disease to cirrhosis may be a limiting factor in the long-term survival of this group of bone marrow transplant recipients. The lack of correlation between the stable clinical or biochemical indices and the progressive hepatic disease underscores the need for sequential liver biopsies in patients with sustained liver function abnormalities after bone marrow transplantation.

The success of bone marrow transplantation in recent years has created new challenges in the care of long-term survivors. A particularly troublesome complication is graft-versus-host disease (GVHD), which occurs in upwards of 45%-70% of allogeneic bone marrow transplant recipients (1). Chronic GVHD is characteristically a multiorgan disease, and liver involvement is common, as reflected by mildly abnormal but nonspecific elevations in liver function tests (2). The long-term hepatic complications associated with GVHD are inadequately defined, and only recently has their life-threatening potential been appreciated (3).

A unique opportunity to document the clinical and histologic progression of chronic hepatic GVHD occurred in a bone marrow transplant recipient who eventually died of hepatic failure from cirrhosis, 10.5 yr after transplantation. The lack of correlation between routine biochemical indices of hepatic function and hepatic pathology was striking, and raises important issues with regard to the evaluation and treatment of long-term bone marrow transplant survivors with abnormal liver function.

Case Report

Our patient (UPN#024) was first seen in 1974 at the age of 28 yr for increasing fatigue and shortness of breath. Evaluation revealed profound pancytopenia with accluarity of all marrow elements on bone marrow biopsy. No history of drug or toxin ingestion, industrial exposure, or known blood dyscrasia was elicited. A diagnosis of severe idiopathic aplastic anemia was made, and supportive transfusion therapy was begun. She was unresponsive to androgen administration and was transferred to this institution for allogeneic bone marrow transplantation. Liver function tests were normal at this time. Following a previously described ablative chemotherapeutic regimen of cyclophosphamide, procarbazine, and antithymocyte serum (4), transplantation of $1.9 \times 10^8$ cells/kg of marrow from her HLA-identical mixed lymphocyte culture nonreactive brother was performed on May 1, 1974. Engraftment
was rapid and complete for all cell lines, as documented by chromosomal analysis.

Twenty-one days after transplantation she developed severe diarrhea, pneumonitis, a diffuse macular violaceous rash over her face and chest, and abnormal liver function tests, including a serum total bilirubin of 1.7 mg/dl (normal <1.0 mg/dl), alkaline phosphatase of 143 IU/L (normal <95 IU/L), and serum glutamic oxaloacetic transaminase (aspartate transaminase) of 105 IU/L (normal <47 IU/L; see Figure 1 for a detailed summary of liver function tests over the entire course of the disease). Both the clinical features and skin biopsies were consistent with acute GVHD, and her posttransplant methotrexate dosage was increased, with mild but transient symptomatic improvement.

By posttransplant day 40 she became jaundiced and complained of diffuse pruritus, associated with nontender hepatomegaly. Serum hepatitis B surface antigen and antibody were negative. Prednisone was then added to her immunosuppressive regimen with abatement in symptoms and a decrease in liver size. Liver function remained markedly abnormal, however, exhibiting a cholestatic profile with a serum total bilirubin of 19 mg/dl (direct reacting, 18.5 mg/dl), alkaline phosphatase of 817 IU/L, and serum glutamic oxaloacetic transaminase (aspartate transaminase) of 134 IU/L. Sustained biochemical abnormalities in liver function prompted a liver biopsy in March 1975, 10 mo after transplantation (see above). Endoscopic retrograde cholangiopancreatography documented patent common bile, cystic, and pancreatic ducts, and no gallstones or masses were visualized.

Digital clubbing and splenomegaly were first detected at this time, with no other signs of chronic liver disease or portal hypertension evident on physical or radiographic examination. Despite the institution of azathioprine, the spleen continued to enlarge and progressive pancytopenia developed as a result of hypersplenism. Splenectomy and an intraoperative wedge biopsy of the liver were performed in June 1976, with resultant normalization of all hematologic parameters. No extrahepatic biliary obstruction was found at the time of laparotomy.

Her jaundice was unremitting, with an average serum total bilirubin of 10–13 mg/dl, of which 8–11 mg/dl was direct reacting (a decrease from pretransplant values). Serologic markers for hepatitis A and B viruses, cytomega-
antibody were all consistently negative. Pruritus remained unrelieved by alovirus, Epstein-Barr virus, and serum antimitochondrial antibody were all consistently negative. Pruritus remained unrelieved by antihistamines, antiviral agents, and plasmapheresis was initiated on a one to two weekly basis in an attempt to relieve the intense pruritus and to control the markedly elevated serum cholesterol (470 mg/dL, normal 130–260 mg/dL), both with considerable success. Liver function tests also improved after initiation of plasmapheresis (Figure 1).

From 1980 to 1983, her course was characterized by increasing bouts of diarrhea and colicky abdominal pain, in addition to sustained biochemical cholestasis with pruritus. Evaluation in June 1983 revealed a fecal fat content of 14.6 g/day (normal 5 g/day), with normal d-xylene excretion and Schilling tests. An upper gastrointestinal/small bowel follow-through radiographic examination showed prominent esophageal varices. No additional treatment was instituted, apart from restriction of dietary fat intake. A third liver biopsy was performed in June 1983.

In March 1984, 10 yr posttransplant, she presented with new onset of shortness of breath, orthopnea, and bilateral pectus excavatum, and was noted to be mildly irritable and forgetful. Ascites and encephalopathy were documented, and treatment was commenced with diuretics and lactulose. After a period of amelioration of her fluid overload and encephalopathy, her condition suddenly deteriorated in August 1984, and she developed acute pulmonary edema, bilateral pleural effusions, and pronounced ascites. Abdominal ultrasound demonstrated a patent inferior vena cava and hepatic veins, massive ascites, and a nondilated biliary tree. Serum ammonia was 550 μmol/L (normal 4–31 μmol/L). The ascites and pleural effusions again improved gradually with high-dose diuretic therapy.

In October 1984, she was readmitted for renewed shortness of breath, abdominal distention, and fever. She was confused and combative. Absent breath sounds at the lung bases, tense ascites, telangiectasias on her face and chest, a reducible umbilical hernia, and marked asterixis were noted on physical examination. Blood and pleural fluid cultures grew out Escherichia coli and Clostridia perfringens, respectively, and appropriate antibiotic therapy was instituted. Ascitic fluid exhibited a pH of 7.4 with 7000 white blood cells/mm³, of which 83% were neutrophils, but multiple anaerobic and aerobic cultures were negative. She developed a progressive, severe metabolic acidosis with serum pH values of 7.2–7.3, responsive only to bicarbonate infusion. Signs of her hepatic failure worsened, with deepening coma, unresponsive to lactulose or neomycin. She suffered a respiratory arrest on November 2, 1984, 126 mo after transplantation. Attempts at resuscitation were unsuccessful.

Pathology

Pathology specimens obtained antemortem included four bone marrow biopsy specimens documenting her initial acellular marrow and its repopulation after bone marrow transplantation, eight skin biopsy specimens, and four liver biopsy specimens. Skin biopsy specimens of the diffuse erythematous rash on her face and torso obtained 29 days after transplantation revealed features of acute GVHD, with epidermal necrosis and dyskeratosis, scattered lymphocytic infiltrates of the rete ridges and basal layers of the epidermis, and a perivascular upper dermal lymphocytic infiltrate. Progression to the pattern of chronic cutaneous GVHD was documented over 2 yr, with more severe epidermal degeneration, vacuolization, and necrosis associated with dermal sclerosis. At autopsy, hypopigmented skin areas on the torso exhibited epidermal atrophy and increased dermal collagen.

Hepatic histology examined between 1975 and 1984 displayed a progressive biliary-type fibrosis culminating in cirrhosis. Initially in 1975, 10 mo after transplantation, there was marked parenchymal cholestasis (Figure 2A), associated with a notable decrease in interlobular bile ducts (0.18 ± 0.04, mean ± SD, interlobular bile ducts per portal tract, 42 portal tracts counted at three levels). Identifiable bile ducts exhibited nuclear irregularity, thinning of the epithelium, and disruption of the basement membrane, and were surrounded by a sparse mononuclear infiltrate (Figure 2B). There was mild bile ductular proliferation along the margin of the portal limiting plates, as well as mild perportal stellate fibrosis with focal portal-portal bridging. The hepatic parenchyma not directly adjacent to portal areas was free of hepatocellular acidophilic bodies and mononuclear cells. The wedge biopsy obtained in 1976 at the time of splenectomy showed similar changes, with mild progression of the perportal fibrotic pattern and comparable paucity of interlobular bile ducts (0.18 ± 0.05 per portal tract, 66 portal tracts counted at three levels). Viral inclusions, granulomas, and fatty change were not present in any of the biopsy specimens, and central vein was unremarkable. Neutrophilic infiltrates were generally absent.

By 1983 the percutaneous needle biopsy was cirrhotic, with broad bands of mature connective tissue separating regenerating nodules and areas of parenchymal collapse. Interlobular bile ducts within the fibrotic bands remained scarce (0.40 ± 0.08 per fibrotic band, 36 bands counted at four levels). At autopsy a cholestatic biliary-type cirrhosis was well established (Figure 3A), associated with cholestasis, edema, and generalized absence of septal bile ducts (Figure 3B).

A small bowel biopsy specimen obtained 2 wk before death showed mild regenerative changes and a pericryptal lymphoid infiltrate, but no typical crypt lesions of GVHD. At postmortem examination, the duodenum was focally congested with superficial hemorrhage, but was otherwise unremarkable. The lungs exhibited mild interstitial fibrosis, mild emphysema, and pulmonary edema.

Discussion

With long-term survival of bone marrow transplant recipients, the potentially life-threatening nature of hepatic complications has become increasingly apparent. The patient described in this report...
Figure 2. Liver biopsy 10 mo after transplantation. The liver parenchyma shows marked canalicular cholestasis (A) associated with a substantial loss of interlobular bile ducts (see text). Identifiable bile ducts exhibited nuclear irregularity, thinning of the epithelium, and disruption of the basement membrane, and were surrounded by a sparse mononuclear infiltrate (B). H&E-stained paraffin sections. A. Magnification ×800. B. Magnification ×800.
Figure 3. Liver specimen obtained at autopsy. Biliary-pattern cirrhotic liver with broad fibrous bands (A) demonstrating cholestasis, edema, and a generalized absence of septal bile ducts (B). A. Magnification ×40. B. Magnification ×120.
developed cutaneous and visceral GVHD in the months after bone marrow transplantation, with slowly progressive hepatic disease characterized clinically by severe cholestasis and debilitating pruritus. Hepatic histology early in her course exhibited extensive bile duct damage and loss associated with marked cholestasis. Over the ensuing years her liver became progressively fibrotic, culminating in cirrhosis and leading to her demise as a result of hepatic failure. The evolution of hepatic GVHD to frank cirrhosis with development of hepatic failure in a long-term survivor of bone marrow transplantation has not previously been described. Progression to hepatic bridging fibrosis has been observed on several occasions (3,5), with mention of 1 patient with “early” cirrhosis (5). In these reports, however, it is not possible to correlate the clinical and biochemical course of the disease with the development of hepatic fibrosis and its consequences. The unique aspect of this case is the clear documentation of the histologic evolution of the pathology and natural history of chronic hepatic GVHD.

Of particular note is the incipient development of cirrhosis in the interval between the patient’s second and third liver biopsies, 2 and 3 yr after transplantation, respectively. During this period, the patient had stable indices of hepatic function, with a normal serum albumin and coagulation times. Serum bilirubin and alkaline phosphatase levels remained elevated, as shown in Figure 1, but did not deteriorate with time. In fact, both clinical and biochemical improvement were evident after the institution of plasmapheresis, 5 yr after transplantation; however, this improvement most likely represented simple extraction of bile acids, bilirubin glucuronides, and other compounds in cholestatic serum (6), rather than improved hepatic function. Although the development of cirrhosis in the setting of cholestasis with paucity of bile ducts is reminiscent of the pathologic progression of primary biliary cirrhosis (7), patients with this disorder characteristically have low serum bilirubin levels until late in their course, when the onset of jaundice heralds clinical and histologic deterioration (8). Although the endpoint is similar, this patient’s hepatic function appeared clinically stable despite 10 yr of relentless hyperbilirubinemia.

The unexpected and sudden deterioration 10 yr after transplantation and her ultimate demise as a result of hepatic failure, therefore, reflect the failure of the clinical and biochemical features to predict the progression and severity of the hepatic pathology.

The histologic features of hepatic GVHD characteristically include extensive bile duct damage and atypia with mild inflammatory change, associated with luminal endothelialitis of portal or central veins and marked cholestasis (5,9). Patients with acute GVHD appear to have more extensive parenchymal necrosis and endothelialitis, whereas those with chronic GVHD have a greater degree of bile duct damage and loss; however, the distinctions between the two entities are somewhat imprecise (9–11). Other causes of posttransplantation hepatic dysfunction such as venocclusive disease, viral or fungal infection, and metabolic or drug-related toxicity may cause diagnostic difficulties (5,12). In this patient, extrahepatic biliary obstruction was effectively ruled out by the normal endoscopic retrograde cholangiopancreatography at the time of her first biopsy, as was venocclusive disease histologically. Biochemical screening and precirrhotic biopsies were not characteristic of either hemochromatosis (13), Wilson’s disease (14), or α1-antitrypsin deficiency (15). There was no history of exposure to potential hepatotoxins or ethanol use before bone marrow transplantation. Methotrexate may induce hepatic fibrosis and, in rare cases, cirrhosis (16), although the duration of exposure to high blood levels appears to be the critical factor in liver injury (17). The low doses of methotrexate given this patient (18), as well as the fact that severe cholestasis and periportal inflammation do not develop until cirrhosis is advanced, virtually rule out the possibility of methotrexate toxicity. Although azathioprine can produce jaundice associated with hepatocyte necrosis and cholestasis (19), this drug was introduced into this patient’s regimen 17 mo after transplantation and thus cannot explain the patient’s preexisting cholestatic liver disease.

Despite consistently negative serologic markers for viral infection, the numerous blood products administered in the months before and immediately after transplantation raise the possibility of non-A, non-B viral hepatitis. The hepatic pathology associated with chronic non-A, non-B viral infection generally reflects hepatocellular involvement with loss of parenchymal cells (20), a feature that was absent in this case. Moreover, in non-A, non-B hepatitis with cholestatic features, the bile ducts characteristically have a multilayered, piled-up epithelium with intact basement membranes, and are not decreased in number (19). In contrast, the thin, irregular bile duct epithelium and striking loss of bile ducts observed in the present case are typical of hepatic GVHD (19). Finally, although the effect of immunosuppression on the evolution of chronic non-A, non-B viral hepatitis has not been described, it is unlikely that this would produce the biliary cirrhotic features that were so evident in this patient.

The insidious development of cirrhosis in this patient underscores the value of sequential liver biopsy in patients with sustained liver function abnormalities after bone marrow transplantation.
Indeed, this report provides an objective basis for recommending routine evaluation of hepatic histology in long-term survivors of bone marrow transplantation, particularly those with abnormal liver function. Precise evaluation of the incidence and natural history of hepatic fibrosis in chronic hepatic GVHD, however, must await prospective clinical studies. Hepatic failure secondary to cirrhosis may, in fact, represent a future frontier for improving the survival of bone marrow transplant recipients. Only with improved treatment modalities of GVHD will this ominous long-term complication of bone marrow transplantation be averted.

References