Jaundice in a Leukemia Patient Status-Post Allogeneic Stem Cell Transplantation

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Case Presentation
A 61 year-old Caucasian female with a past medical history significant for chronic lymphocytic leukemia (CLL) presented with dark amber-colored urine, jaundice, and nausea for three days. She reported increased fatigue and poor appetite but denied fever, chills, shortness of breath, chest pain, vomiting, abdominal pain, diarrhea, constipation, or bleeding. She denied any change in her medications or recent travel history.

She was diagnosed with CLL two years ago and had undergone a matched unrelated allogeneic stem cell transplant three months ago. Her post transplant course was complicated by viremia with cytomegalovirus (CMV) and Epstein-Barr virus (EBV), which were successfully treated with foscarinet and rituximab, respectively.

Other past medical history included hypertension and basal cell carcinoma of the face. Past surgeries included a cholecystectomy, a hysterectomy, and bilateral knee replacements. She denied alcohol use, smoking, or drug abuse. Medications on admission included atenolol, a multivitamin, trimethoprim/ sulfamethaxazole, voriconazole, and valacyclovir. She was allergic to codeine and lorazepam.

Vital signs on admission were stable. Physical exam was significant for icteric sclera, jaundice, and mild abdominal discomfort on palpation of the right upper quadrant. Admission labs were notable for total bilirubin 14.9 mg/dL, direct bilirubin 7.2 mg/dL, alkaline phosphatase (AP) 421 IU/L, aspartate transaminase (AST) 558 IU/L, and alanine amino transferase (ALT) 738 IU/L. White blood cell count was 3 B/L with 75% neutrophils, hemoglobin was 9.5 g/dL, and platelet count was 124 B/L. Her basic metabolic panel was within normal limits. Her urinalysis was significant for 1+ bilirubin.

Jaundice and abnormal hepatic function tests in this patient with the history of CLL and allogeneic stem cell transplant raised concerns for active hepatitis, graft-versus-host disease (GVHD) of the liver, drug toxicity, hepatic veno-occlusive disease, and obstructive cholestasis.

Hospital Course
The patient underwent an abdominal ultrasonography with dopplers that showed a normal liver status-post cholecystectomy with no intrahepatic or extrahepatic ductal dilatation and normal hepatic vasculature, ruling out obstructive cholestasis and hepatic veno-occlusive disease. With her history of CMV and EBV viremia, it was crucial to rule out residual or recurrence of either infection. Her CMV viral load was less than 100 copies/ml (reference range <100 copies/ml), and EBV viral load was less than 350 copies/ml (reference range <350 copies/ml). Further laboratory studies for Hepatitis A, Hepatitis B, and Hepatitis C were all negative. Adenovirus, which has been increasingly known to cause disease in post transplant patients, was also negative. A transjugular liver biopsy was done since there was no obvious cause of elevated liver function tests from the available laboratory studies. The liver biopsy revealed mild portal inflammation and bile duct injury characteristic of GVHD with moderate cholestasis.

With the diagnosis of GVHD of the liver, the patient was immediately started on immunosuppressive therapy which included high-dose methylprednisolone, tacrolimus, and micophenolate mofetil. Although she continued to have minimal clinical symptoms other than jaundice, she failed to show significant improvement in her hepatic function tests. By hospital day 15, the laboratory results were as follows: total bilirubin 39.1 mg/dL, direct bilirubin 17.8 mg/dL, AP 557 IU/L, AST 151 IU/L, and ALT 355 IU/L. While her transaminases were trending down, total bilirubin, direct bilirubin, and AP were worsening. Without much improvement with the conventional immunosuppressive therapy, a monoclonal antibody called muromonab or OKT3 was added. Muromonab, which is a monoclonal antibody directed against the CD3 antigen closely associated with the T-cell receptor, has been used as a second line therapy in patients who did not respond to steroids for GVHD. Even after the treatment with muromonab for 10 days, her hepatic function tests did not improve significantly: total bilirubin 30.3 mg/dL, direct bilirubin 12.7 mg/dL, AP 436 IU/L, AST 78 IU/L, and ALT 104 IU/L. She was discharged with oral corticosteroids for continued treatment of her GVHD of the liver. At this time, it is difficult to predict whether she will recover completely from the GVHD. Of note, the treatment of her GVHD was complicated by a rise in her CMV viral load on day 24 of her hospital stay to 375 copies/mL and clostridium difficile enterocolitis.

Discussion
Hematopoetic stem-cell transplantation is an important and common treatment in malignancies and multiple hematologic disorders. In the early 1960s, allogeneic transplantation became feasible after the identification and typing of HLA, the major histocompatibility complex. In the 1970s, Thomas and colleagues conducted successful allogeneic stem cell transplants in end-stage leukemic patients and achieved first remissions in more than half of their patients, thus laying a foundation for use of this treatment in conjunction with conventional chemotheraphy and radiation.

When allogeneic stem cell transplantation takes place, unsuppressed donor T-cells can recognize either major histocompatibility or minor histocompatibility antigens of a recipient, which leads to the activation of the donor T-cells against the recipient’s organs. This phenomenon is also known as graft-versus-host disease (GVHD).
GVHD that occurs within 100 days after transplantation is considered acute GVHD, as was the case for this patient. GVHD that occurs after 100 days is considered chronic. Both types of GVHD occur more frequently with cases involving older patients, unrelated donors, older donors, CMV-positive donors, female donors, and donors with previous pregnancies or transfusion sensitization. Clinically significant GVHD happens in 30% to 50% of recipients of allogeneic hematopoietic transplants.

The primary target organs in GVHD are the skin, liver, gastrointestinal tract, and the hematopoietic system. The liver is the second most commonly involved organ in acute GVHD, and manifests with abnormal liver function tests. The earliest and most common finding is the rise in direct bilirubin and alkaline phosphatase, which is explained by the fact that GVHD causes damage to bile canaliculi and results in cholestasis.

The rise in direct bilirubin and alkaline phosphatase is nonspecific, however, so other causes of hepatic damage require evaluation. Hepatic infections, primarily viral hepatitis, must be ruled out since many of these patients are immunocompromised and are at an increased risk of infection. Another important diagnosis to consider is hepatic veno-occlusive disease, which is characterized by obstruction in the hepatic circulation as result of damaged sinusoidal endothelium. Total-body irradiation and chemotherapy that are used as preparative agents for stem cell transplant are the cause of this relatively common complication. Patients with hepatic veno-occlusive disease present with painful hepatomegaly, jaundice, and retain fluid. Another diagnosis to consider is drug toxicity from chemotherapeutic drugs, corticosteroids, antibiotics, antifungal agents, and anti-GVHD drugs. Biopsy is the definitive method to diagnose GVHD of the liver, and transjugular liver biopsy may be preferable over percutaneous liver biopsy due to the high bleeding risk since many of these patients are thrombocytopenic. Transjugular biopsy may be also helpful in assessing the hepatic venous pressure gradient to identify hepatic veno-occlusive disease.

The first and most effective treatment of GVHD is the use of glucocorticoids. Research suggests that starting with low dose steroids (2mg/kg per day) is appropriate; randomized studies showed no difference in mean response rates or actual survival rates between different dosages of steroids. If glucocorticoids are not successful, other immunosuppressive drugs such as cyclosporine, tacrolimus, antithymocyte globulin, or mycophenolate mofetil may be considered. If these treatment strategies fail, then a more aggressive approach such as using extracorporeal photophoresis and monoclonal antibodies directed against CD 25, TNF-alpha, T-cell receptor, and IL-2 receptor may be considered.

In summary, this is a case of a 61 year-old female with a history of CLL status-post allogeneic stem cell transplant who presented with jaundice and a rise in bilirubin and alkaline phosphatase on laboratory testing, which raised concerns for possible GVHD of the liver. However, it was very important to consider all other disease possibilities. Especially in this case, a distinction between an active infection versus graft-versus-host disease was crucial as immunosuppressive therapy would have worsened the patient’s condition if the cause had been an active infection. The patient underwent a transjugular liver biopsy that was consistent with the GVHD of the liver, and she has been on different regimens of immunosuppressive drugs. The immunosuppressive therapy for the GVHD led to the complications of elevation of the CMV viral load and clostridium difficile infection, which highlights the fact that sometimes medicines intended for treatment can in effect cause harm. This reinforces the lesson to always weigh the benefits against the risks when choosing to implement a therapy.

References