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Benign Transient Hyperphosphatasemia Associated With Epstein-Barr Virus Enteritis in a Pediatric Liver Transplant Patient: A Case Report

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Abstract

Transient hyperphosphatasemia was found in a 3-year-old male liver transplant recipient. The condition was associated with diarrheal disease due to the Epstein-Barr virus (EBV). Immunosuppression was tapered and valganciclovir prescribed for 3 months, after which the diarrhea resolved and the EBV polymerase chain reaction assays became negative. After 6 months, alkaline phosphatase levels normalized. Isolated elevation of alkaline phosphatase in conjunction with enteric infection is a rare condition. No further diagnostic or therapeutic interventions except treatment of the underlying infection are needed, as this has been shown to be a benign, transient condition.

In 1977, Posen et al published the first record of transient hyperphosphatasemia (TH) in the pediatric population.¹ Although the nature of this condition has since been considered benign, the etiology has remained uncertain. Proposed etiologies include infectious disease, celiac disease, drug toxicity, and idiopathic mechanisms yet to be elucidated.^{2–7} TH in pediatric patients of age less than 5 years is characterized by variable symptoms including a transient increase in serum alkaline phosphatase (AP) activity predominantly of bone and liver isoforms, with no identifiable liver or bone diseases, which return to normal levels within 4 months.⁵ Diarrheal disease is one of the most commonly described triggers. A multitude of infectious agents may cause diarrhea in transplant recipients including rotavirus *Clostridium difficile*, Epstein-Barr virus (EBV), and cytomegalovirus (CMV).^{8–11} Since 1998, several reports have recorded a rise in AP to extreme levels even in transplanted patients. Gennery et al published two case reports showing that elevated AP in cardiac transplant patients is a benign finding.¹² In 2006, Arikan et al reported two liver transplant (OLT) patients with greatly elevated AP after enteric infections.¹³ The obscure condition may cause problems in differential diagnosis, as elevated AP is a key feature of graft associated complications following OLT. Furthermore, additional data involving hyperphosphatasemia in this patient population is limited at present. TH is a diagnosis of exclusion. Knowledge of this condition should avoid unnecessary, invasive tests including liver biopsies or percutaneous transhepatic cholangiography.

CASE REPORT

This 3-year-old white boy underwent living-related OLT in May 2007 for complications of Alagille syndrome. The child was born to a 25-year-old woman at 37 weeks gestation after a healthy pregnancy. Shortly after birth, his total bilirubin was elevated at 10 to 15 mg/dL with the conjugated bilirubin of 6 to 7 mg/dL despite treatment with ultraviolet light and ursodeoxycholic acid. A hepatobiliary iminodiacetic acid scan showed no bile excretion into the small bowel. An operative cholangiogram showed a hypoplastic biliary tree with common bile duct patency. Liver biopsy revealed cannicular cholestasis with bile duct paucity, leading to the diagnosis of Alagille syndrome. Persistent jaundice despite treatment with ursodeoxycholic acid, incessant pruritus treated with naltrexone, a palpable spleen, and a plateauing of growth as well as evidence of portal hypertension were the indications for OLT in February 2006. Initial immunosuppression consisted of tacrolimus (TAC; trough levels 8 to 12 ng/mL), mycophenolate mofetil (250 mg daily), and a steroid taper. The early posttransplant course was uneventful without surgical, immunological, or infectious complications. The patient was initially EBV negative; however, the EBV polymerase chain reaction (PCR) assay became positive with 1500 copies/mL after 3.5 months. Two weeks later the patient presented with severe diarrhea, namely, up to 20 bowel movements per day and an isolated elevation of alkaline phosphatase to 1782 U/L. The remainder of the liver function tests, including *AST*, *ALT*, *INR* and bilirubin, were all within normal limits. A Doppler ultrasound was performed with normal vascular elements and no evidence of cholestasis. The patient's immunosuppression was maintained within adequate TAC levels and without evidence of liver dysfunction. A liver biopsy was not performed. Parainfectious benign transient hyperphosphatasemia associated with EBV enteritis was suspected; therefore, steroids were immediately discontinued. Following the decrease in immunosuppression, the EBV PCR assay became negative but the diarrhea only marginally improved. One month later, EBV PCR assay became again positive with 2500 copies/mL and mycophenolate mofetil was discontinued. TAC levels were maintained at 8 ng/dL. One month later, AP peaked at 10,099 U/L with heated AP of 1613 U/L (ie, 16% fig 1). Over the next 3 weeks, AP descended to 4000 U/L, normalizing after 5 months (8 months post-OLT). Transaminases and gamma glutamyl-transferase (γ GT) were never elevated. However, 5' nucleotidase was 15-fold elevated (162.7 U/L), but normalized within a few months. Intermittent diarrhea improved with cholestyramine therapy. Stool cultures for *C difficile*, *Cryptosporidium*, and rotavirus antigen remained negative on several occasions. CMV assays remained negative. TAC was tapered to trough levels of 4 to 6 ng/mL and valganciclovir was prescribed for 3 months. Finally, the diarrhea completely resolved; EBV PCR assays became negative. The patient is currently in excellent condition without any complications, receiving TAC monotherapy with stable graft function.

DISCUSSION

Complications that cause elevation of the AP following OLT can be technical, immunologic, toxic, or infectious.¹⁴ The evaluation may require invasive procedures such as liver biopsies. Recently the incidence of acute cellular rejection has decreased as a result of administration of more potent immunosuppressive agents, but this has been paralleled by an increased incidence of some opportunistic infections. Pediatric OLT recipients are at increased risk for these infectious complications, because they are often immunologically naive to CMV and EBV infections, as was the patient in our case. EBV infection following OLT can result in a spectrum of diseases from benign asymptomatic viremia to infectious mononucleosis or clonal proliferation of lymphocytes. These diseases are called posttransplant lymphoproliferative disorders. Frequent lab monitoring as well as screening for EBV and CMV are imperative in the pediatric transplant population especially for an EBV-negative

patient who received a graft from an EBV-positive donor. TH has thus far not been reported as a complication of EBV infection.

Liver function tests, which are routinely monitored post-OLT, include serum aminotransferases, AP, γ GT, international normalized ratio, and bilirubin. Elevation of these parameters after OLT may result from technical, immunologic, or infectious complications.^{15,16} The consequence of an abnormal spectrum of laboratory values often necessitates excluding graft dysfunction and injury from a variety of potential insults, including vascular and biliary causes, graft rejection, infection, or rare causes such as drug toxicity. To definitively rule out acute cellular rejection, patients will undergo a liver biopsy. However this procedure carries a significant risk for complications, such as hemorrhage, pain, bile peritonitis, sepsis, colon perforation, pneumothorax, intrahepatic arteriovenous fistulas, and even mortality.¹⁷ Pediatric patients also require sedation and/or anesthesia, which add to the morbidity of a biopsy.

The incidence of TH in young children who have under-gone OLT has been reported to be as high as 2.8%.⁹ Several authors have emphasized that this condition is benign and usually occurs secondary to an infectious cause. The hyper-phosphatasemia is also transient, developing in the absence of other liver function abnormalities which was again confirmed by our case. It has been reported in other solid organs as well as stem cell transplantations, and the mechanism has been well defined, with adults being rarely affected by the condition.^{18–25} Patients who have been identified with benign TH should be monitored with no further interventions or procedures to avoid unnecessary complications. In the case of diarrhea, testing for multiple pathogens should be performed. In our case, diarrhea was caused by EBV. EBV infection following OLT frequently responds to reduction in immunosuppression, but antiviral therapy may be required in high-risk patients. Evaluation for other complications of EBV should be performed. Physicians must be aware of the possibility of benign TH among pediatric OLT recipients with enteric infections.

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Fig 1. Clinical events and course of alkaline phosphatase posttransplant. LT, liver transplant; EBV PCR; Epstein; Barr virus polymerase chain reaction; MMF, mycophenolate mofetil; TAC; tacrolimus; ValGCV; valganciclovir.