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Transient hyperphosphatasemia following pediatric liver transplantation in a patient with hepatic and skeletal abnormalities

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Abstract

Background: We report a unique case of transient hyperphosphatasemia in a pediatric patient with a history of hepatic and skeletal abnormalities.

Patient and Methods: A 2-month old male was diagnosed with progressive familial intrahepatic cholestasis type-2 and osteoporosis after marked increases in liver function tests were noted at 1 month of age. He underwent a second liver transplantation at 1 y. The increased liver function test trend resolved a few weeks post-transplantation. Four months after successful liver transplantation, unexplained significant increases in alkaline phosphatase (ALP) were observed, and they persisted for almost 9 months. Among the etiologies under consideration for the isolated increased ALP activity were viral infections and macro-ALP.

Results: A persistent trend in abnormally increased ALP for 9 months was investigated leading to a confirmed diagnosis of transient hyperphosphatasemia (TH).

Conclusion: Pediatric post-liver transplant patients with skeletal and hepatic abnormalities including isolated markedly increased ALP activities represent a previously undescribed TH patient population. The 4.3% prevalence of TH in pediatric liver transplant recipients within our healthcare system is considerably higher than the previously reported prevalence of 2.1% for patients within the United States.

Keywords

Transient hyperphosphatasemia; Alkaline phosphatase; Pediatric liver transplant; Alkaline phosphatase isoenzyme

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1. Introduction

The post-liver transplantation standard of care includes conducting liver function tests (especially serum alkaline phosphatase (ALP) and gamma glutamyl transferase (GGT)) to monitor allograft rejection or biliary obstruction. However, there are reports of isolated post-liver transplant cases with transient marked increase of serum ALP (transient hyperphosphatasemia; TH) after liver transplantation (3.5–14 months) in the absence of biliary obstruction or transplant rejection. The prevalence of such cases of TH among the pediatric patient population is reported to be 2.1% [1] in the U.S. and 4.3% in the U.K. [2].

TH by definition is increase of serum ALP 5-times the upper limit of the adult reference range in a child < 5 y with no evidence of underlying disease to explain the biochemical abnormality [3]. This phenomenon is often misdiagnosed warranting particular attention when caring for pediatric liver transplantation patients. This case report presents a unique characteristic feature of TH that has not been previously considered in the commonly-accepted clinical presentation of TH.

2. Case presentation

A 2-month-old male diagnosed with progressive jaundice and heterozygous *ABCB11* mutations (E297G and D482G), which are pathogenic for ABCB11-related progressive familial intrahepatic cholestasis type 2 (PFIC 2), at age 9 months presented to the pediatric gastroenterology service for jaundice and liver transplant evaluation. His case was complicated by osteoporosis secondary to vitamin D deficiency (25-hydroxy Vitamin D < 11 μg/l, reference range 20 – 75 μg/l) with rib and compression fractures, chronic malnutrition and failure to thrive. The patient had mild pruritus (no sleep disturbances), without fever, chills, cholangitis, heart or lung abnormalities, or other major medical problems. Past medical history included hyperbilirubinemia secondary to PFIC 2, and surgical history included percutaneous liver biopsy. Family history was negative for liver disease.

The patient was confirmed to have end-stage liver disease due to PFIC 2 with a calculated pediatric end-stage liver disease (PELD) score of 12 and was considered a good candidate for liver transplantation, which occurred at 1 y (Fig. 1a). Three days post-liver transplant, the patient experienced early hepatic artery thrombosis. In the following three days he had an emergent second liver transplantation without any immediate complications. The patient and donor were positive for cytomegalovirus (CMV) and both were negative for Epstein-Barr virus (EBV). In addition to immunosuppressive medications (prednisone, tacrolimus and mycophenolate mofetil) the patient was placed on long-term prophylactic anticoagulation with aspirin and Lovenox. Liver function tests (LFTs) were serially monitored (Fig. 1b). Concerns of rejection developed due to a history of increased aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Following a treatment course of methyl-prednisone, the patient was placed on daily prednisolone and his LFTs normalized within the respective reference ranges within one month after his second transplantation. However, 4 months after the second liver transplant, a marked increase in ALP was observed (820 U/l; Reference range: 110 – 320 U/l). Within the next week an abrupt increase in ALP to > 2330 U/l was noted and the chemistry service was contacted to aid in the investigation

of prolonged isolated increase of ALP activities. Viral infection and macro-ALP were among the considered differential diagnoses. The increased ALP activities persisted for 9 months before a trend in decreasing activity was noted (Fig. 1b) and a diagnosis of TH was confirmed based on ALP isoenzyme analysis (Fig. 1c).

3. Discussion

During the investigative work-up of the prolonged isolated ALP increase, TH was included in the differential, but the patient's presentation was not completely congruent with the clinical features commonly associated with this benign disorder. TH is characterized by ALP increase > 5-times the upper limit of the adult reference range in a child < 5 y without any evidence of bone, gastrointestinal or liver disease. The upper limit of the adult ALP reference range within our healthcare system is 150 U/l. The patient partly met these criteria, but he also had a history of increased ALT and osteoporosis secondary to vitamin D deficiency. However, owing to multiple sources of ALP in tissues including liver, bone, intestine, and placenta, a confirmed diagnosis of TH warranted additional scrutiny. Increased serum ALP is of interest in the diagnosis of hepatobiliary disease (cholestasis, particularly with obstructive jaundice) and bone disease associated with increased osteoblastic activity. Moderate increase of ALP may occur in other disorders such as Hodgkin disease, congestive heart failure, ul-cerative colitis, regional enteritis, and intra-abdominal bacterial infections.

To meet the diagnostic criteria of TH we sought to confidently rule out other potentially contributory sources of the isolated increased ALP activities. Macro-ALP was ruled out by performing polyethylene glycol precipitation. The mean percent precipitable activity (%PPA) of ALP from three samples collected over a period of one month was 2.48% (proposed ALP% PPA reference range: 0–36%) [4].

To differentiate between liver and bone sources of increased ALP activity, gel electrophoresis analysis of ALP isoenzymes was conducted at a reference laboratory. Serum samples were electrophoresed using differences between liver and bone isoenzyme sialylation to achieve mobility separation. The sample was applied to the agarose gel in duplicate; one aliquot was passed through wheat germ lectin [wheat germ agglutinin (WGA)] and deposited anodally from the sample application point. The bone ALP isoenzyme, which is rich in sialic acids, reacts with WGA and precipitates adjacent to the lectin application point [5]. The results from analysis of the patient's serum confirmed an atypical isoenzyme pattern suggestive of TH and established the liver as the source of the increased ALP activities (Fig. 1c). The patient's ALP actvities were monitored approximately weekly thereafter until his activities returned to within the reference range 12 months after his second liver transplant.

This was the first case of TH that came to the attention of the chemistry service within the past 10 y. Accordingly, this prompted us to investigate the prevalence of TH within our healthcare system and also the number of pediatric liver transplant patients in whom this diagnosis was potentially missed. We conducted a large-scale chart review of all pediatric patients within our healthcare system who had a liver transplant between January 1, 2010 - December 31, 2018. A total of 92 pediatric patients met the inclusion criteria. Including

the patient who is the focus of this case report, 4 patients (4.3%) were discovered to have undiagnosed TH. The 4.3% prevalence of TH in our patient population is higher than the 2.1% prevalence in the United States reported 30 y ago; however, a report from the United Kingdom in 2002 indicated a TH prevalence of 4.3%. In a healthy population the prevalence of TH is reported at 1.5–2.8% [6–8].

Other characteristic features of TH include an average time interval between liver transplantation and increased ALP activities of 3.5–14 months [1], and increased ALP activities that typically return to normal within 12 weeks, with some patients requiring up to 80 weeks [9–13]. All 4 pediatric patients with potentially undiagnosed TH identified from our 10-y chart review met these reported characteristics, further confirming their missed TH diagnoses. Immunosuppressive medications such as cyclosporine and FK506 (tacrolimus) prescribed for liver transplant recipients as well as healthy and non-transplant recipients have been implicated as plausible contributory factors for isolated increased ALP activities [1,3,6,14]. Two patients in our cohort were prescribed tacrolimus and two other patients were prescribed a combination of prednisolone, basiliximab and mycophenolate. In agreement with other reports [1,3,6,14], a causative relationship between the use of immunosuppressive medication and TH cannot be established.

4. Conclusion

Although TH is mostly a benign condition in young children, the timely recognition of this phenomenon avoids unnecessary invasive investigative procedures and treatment. Here, we report a unique case of TH that was diagnosed in a patient with underlying hepatic and skeletal abnormalities. Therefore, it is important to increase the awareness of TH as a potential underlying etiology for isolated, prolonged increases in ALP activity, particularly in pediatric patients post-liver transplantation.

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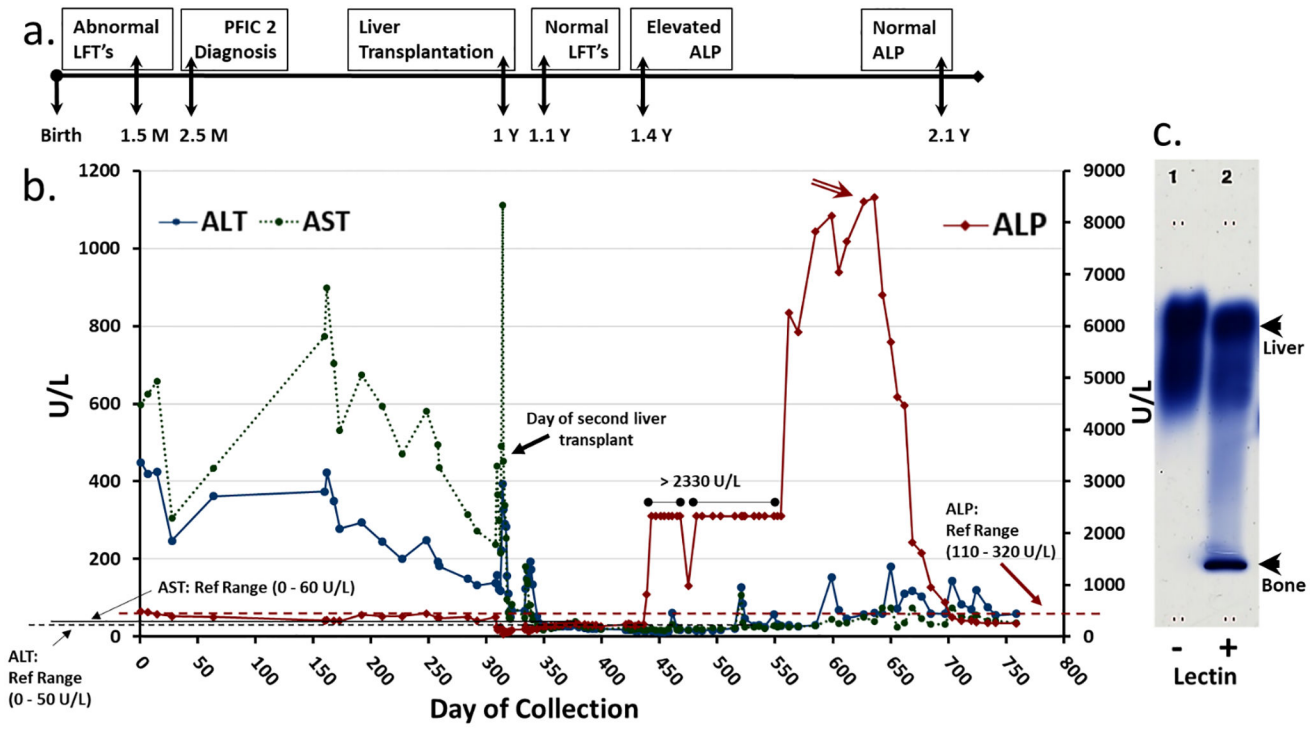

Fig. 1.

Trend of AST, ALT, and ALP activities in relation to liver transplantation. a) Timeline of events including increased and resolved activities of ALT, AST, and ALP in relation to liver transplantation. M, month; Y, year. b) Serial enzymatic colorimetric-based ALT, AST, and ALP measurements conducted prior to and post-liver transplantation. Day 0 corresponds to the first report of abnormal liver function tests (LFT's) at 1 month of age (45 days after birth). The patient's first liver transplantation occurred at age 363 days. Due to hepatic artery thrombosis, the patient had a second transplantation at age 369 days. LFT's normalized within their respective reference ranges at age 390 days. At age 484 days (124 days after second liver transplantation) the patient's first reported increase of ALP occurred. ALP measurements were performed using an enzymatic colorimetric assay. The transient increase of ALP persisted on serial investigations. In TH, the ALP values typically range from 4000 to 27,000 U/l, which exceeds the analytical measurement range of most enzymatic colorimetric ALP assays. The upper limit of the reportable range for the ALP assay used in our acute care clinical laboratory is 2330 U/l. The values > 2330 U/l shown in the graph were obtained using manual dilutions. The double-lined arrow indicates the date of the specimen collection used for gel electrophoresis-based ALP isoenzyme analysis. c) Separation of ALP isoenzymes using the Sebia® Hydragel system. Lectin binds bone ALP preventing its co-migration with the liver ALP isoenzymes. An atypical isoenzyme pattern suggestive of TH is observed in lane 2 (+Lectin) which established the liver as the source of the increased ALP activity in the patient.