

Unexplained Hepatic Cirrhosis in A 7-Year-Old Girl: Rare Case With a Review of Literature

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ABSTRACT

Chronic liver disease (CLD) presents as jaundice and abdominal distention. It has significant morbidity and mortality. CLD is often associated with cirrhosis of the liver and causes of CLD vary from infection to metabolic diseases. Here we present a case of a 7-year-old female who presented with abdominal distention and shortness of breath. Her liver function tests were not normal. An enlarged liver was found on ultrasound and computed tomography scan showed moderate ascites with heterogeneous nodular enhancement on the liver surface. Workup for Wilson disease, viral infections, and autoimmune causes was found to be negative. There was no evidence of metabolic diseases. Biopsy of the liver showed evidence of cirrhosis. No evidence of esophageal varices was found. Supportive management for CLD was started. The case highlights the importance of detailed workup for identification of the cause which can be difficult in a resource-limited setting.

Keywords: Liver cirrhosis, chronic liver disease, CLD, idiopathic, pediatrics, degenerative changes.

INTRODUCTION

In the pediatric population injury to the liver typically manifests itself as jaundice, deranged liver function test, and hepatomegaly. It could be due to various etiologies; infective, metabolic or neoplastic. Biliary atresia and neonatal hepatitis can also occur [1]. Disorders of liver particularly chronic liver diseases (CLDs) represent a major public health concern in low to high-income countries [2]. Chronic liver failure is most often associated with cirrhosis, a condition manifested by a diffuse transformation of the entire liver into regenerative parenchymal nodules surrounded by fibrous bands and variable degrees of vascular shunting. In association with modifiable and non-modifiable risk factors, the prevalence of clinically significant liver fibrosis differs between 0.7% and 25.7% among the general population [3]. Although more prevalent among adults, chronic liver disease is a common cause of morbidity and mortality in children. The etiological profile of chronic liver disease varies with geographical location. Hepatitis virus is a leading cause of chronic liver disease in South East Asia, the Middle East, and some other Asian countries [4]. The major presenting complaints of chronic liver disease are jaundice and abdominal distension. However, in the pediatric population, poor weight gain is often the primary sign of cirrhosis. Due to late presentation and concomitant complications at the time of diagnosis, it is typically associated with poor prognosis. In infants, cirrhosis is generally caused by metabolic and genetic diseases and biliary atresia while in older children, it can

be a consequence of chronic viral hepatitis, autoimmune hepatitis, alpha-1 antitrypsin deficiency, Wilson disease or primary sclerosing cholangitis. Other less common causes include drug toxicity, Allagile syndrome, Wolman disease, hemochromatosis, and other inherited disorders [5]. The analysis of CLD cases in the pediatric population reported from tertiary care hospitals in Rawalpindi and Islamabad, Pakistan demonstrated that 31.6% of the patients had hepatitis C and 5% had hepatitis B. Glycogen storage diseases were seen in 8.3% cases while biliary atresia and Wilson disease constituted about 8% each. Autoimmune hepatitis, drug-induced hepatitis, TORCH infections, and hepatoma were seen as less common cases accounting for about 1.7% each [6]. The complications of pediatric cirrhosis are identical to those observed in adult patients. Gastrointestinal bleeding due to esophageal varices or congestive gastropathy, ascites and spontaneous bacterial peritonitis are major complications of chronic liver disease. The present case emphasizes the unusual presentation of pediatric chronic liver disease and its diagnostic evaluation. Further, we have also highlighted supportive treatment protocol followed leading to better outcomes.

CASE PRESENTATION

An Afghan origin seven-year-old girl, unvaccinated, without any premorbidity presented to the emergency department of Abbasi Shaheed Hospital with a history of gradual distension of abdomen for two months and difficulty breathing for a day.

The child was in her usual state of health two years back when she developed pain in the right hypochondrium. The pain was mild, dull, and non-radiating. It was not associated with vomiting, food intake, movement, fever or cough. The pain was relieved by taking analgesics.

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An abdominal exam by a local doctor revealed that the child had an enlarged liver and further workup was advised. Her abdominal distension gradually increased in the last two months to such an extent that she had difficulty breathing and passing urine. There was no history of jaundice, bleeding, itching, melena, abnormal movements, altered behavior or headache. No history of blood transfusion and medication was present. Birth history was insignificant. There was no history of prolonged jaundice in infancy. Family history of tuberculosis or bleeding disorder was insignificant.

Physical examination showed that the child was pale with gross abdominal distension. Swelling of lower limbs up to the level of the sacrum was noted. She was tachypneic and tachycardic but afebrile. Her anthropometric measurements were below the 10th centile. No evidence of hepatic encephalopathy was present. Other systemic examinations were normal.

A complete blood picture showed leukocytosis. Kidney functions were normal. Liver function tests were deranged (Table 1).

Table 1: Values of different parameters.

| Parameters | Values |
|------------------|------------|
| Total bilirubin | 0.6 mg/dl |
| Direct bilirubin | 0.3 mg/dl |
| Albumin | 3.0 gm/dl |
| AST | 437 IU |
| ALT | 43 IU |
| ALP | 161 IU |
| Prothrombin Time | 20 seconds |
| INR | 1.14 |

AST-aspartate aminotransferase, ALT-alanine aminotransferase, ALP-alkaline phosphate, INR- International Normalized Ratio.

Ultrasound abdomen with Doppler studies showed enlarged liver span (12.5 cm) with coarse echotexture and splenomegaly (9.3 cm) with gross ascites but no dilated vessels/portal vein. Computed tomography (CT) scan abdomen showed moderate ascites, heterogeneous nodular enhancement of liver but there was no evidence of duct dilation. Echocardiography was normal. The differential diagnosis of viral hepatitis, autoimmune hepatitis, Wilson disease, hemochromatosis, tyrosinemia, metabolic disorders were considered. The child was worked up for various etiologies of chronic liver disease. Viral markers (A, B, C, D and E) were normal and workup for Wilson's disease was negative. Markers for autoimmune hepatitis (anti-LKM 1 antibody and anti-smooth muscle antibody), tyrosinemia (alpha-fetoprotein) and inborn errors of metabolism (arterial blood gases, serum lactate, serum ammonia, blood sugar) were within normal limits. However, due to financial constraints, the workup for glycogen storage diseases and lysosomal storage disorders was not done. Stool for occult blood was positive. All cultures (blood, urine, and ascitic fluid) were negative.

The child was started on supportive management for chronic liver disease and was managed in line with a deranged coagulation profile and received fresh frozen plasma (FFP) and packed cells during the admission. Further treatment included fat-soluble vitamins in recommended doses according to age, intravenous antibiotic, lactulose, and ascitic paracentesis. Her endoscopy was done on the 10th day of admission which showed no esophageal varices but congestive gastropathy was seen.

Liver biopsy was done which revealed a single linear core of liver parenchyma showing mild periportal inflammation as well as septal fibrosis with architectural distortion and nodule formation. No significant increase in plasma cells was seen in inflammatory infiltrate. Special stain for iron (Perl) was negative. Hence, according to Batt's and Ludwig's grading and staging system of chronic hepatitis, it was mildly active (grade II) with septal fibrosis and nodule formation (cirrhosis, stage IV fibrosis).

The child clinically improved on the 20th day of admission. Her parents were counseled regarding liver transplant and frequent follow-up.

DISCUSSION

There is a vast array of clinical findings associated with hepatic cirrhosis in the pediatric population. The typical manifestations of hepatic cirrhosis are jaundice, abdominal distension, hepatomegaly, splenomegaly, edema, and anemia [7]. However, when associated with complications, the patient can present with ascites, coagulopathy from decreased hepatic synthetic function, variceal bleeding and congestive gastropathy due to portal hypertension, spontaneous bacterial peritonitis, and hepatic encephalopathy which are indicators of decompensated disease [8]. In our case, the patient presented with anemia, moderate abdominal pain and progressive distension causing difficulty in breathing and urination and edema of lower limbs. This is an atypical presentation as it is not associated with jaundice, the major presenting complaint of liver diseases. Further even manifested with moderate hepatosplenomegaly and leukocytosis, no association with fever, cough, rash, melena, dermatitis or altered neurological activity was present. However, the loss of caloric intake was noticed.

Hepatic disorders are usually marked by deranged liver function tests, coagulation profiles and blood picture [9]. Identical to typical cases of chronic liver disease, the diagnostic laboratory findings of this patient were found to be altered *i.e.* abnormal bilirubin, total protein, albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphate (ALP). Albeit different radiologic modalities may demonstrate the classic signs of cirrhosis, no test is considered to be standard [10]. Ascites, hepatosplenomegaly and hepatic or portal vein thrombosis can be easily detected by various radiologic studies. The degree

of hepatic fibrosis depicted by texture and increased echogenicity, splenic enlargement and degree of ascites are some of the findings that can be detected non-invasively through abdominal ultrasonography [11-13]. The ultrasonographic evaluation of this patient showed hepatomegaly with a coarse texture, splenomegaly, and ascites. However, there was no dilation of the portal vein or other hepatic vessels observed on Doppler ultrasound which seems to be inconsistent with US findings of portal hypertension [11, 14]. Similarly, Computerized tomography scanning can help in categorizing chronic liver disease through differences in the degree of ascites, morphological differences in nodular fibrosis and associated extrahepatic manifestations [15]. The underlying pathophysiology of ascites is increased sinusoidal pressure due to hepatic fibrosis leading to the accumulation of excess fluid in the peritoneal cavity [16]. A moderate degree of ascites with heterogeneous nodular enlargement of the liver was noticed in the CT abdomen of this patient. Nevertheless, liver biopsy is considered as a gold standard in the evaluation of liver disease but is now needed less for diagnosis than for grading and staging of disease.

A number of studies demonstrate the variations in the etiological profile of hepatic cirrhosis in the pediatric population. Viral hepatitis, biliary diseases, autoimmune hepatitis, metabolic or genetic disorders like glycogen storage disorders, Wilson disease, hemochromatosis, cryptogenic and tyrosinemia are some of the prevalent causes of chronic liver disease in the pediatric population in different geographical locations [9, 17, 18].

In Pakistan, viral infections especially hepatitis B and C were observed to be the prime cause of deteriorating liver functions in the pediatric population [6, 19]. Surprisingly, despite the mother being diagnosed positive for hepatitis B, there were no diagnostic markers of hepatitis or any other viral infection in this patient. Similarly, the liver biopsy did not show the ground-glass appearance of hepatocytes and lymphoid follicles or fatty changes in scattered hepatocytes, the diagnostic hallmarks of hepatitis B and C respectively. Hence HBV and HCV as a cause of cirrhosis in this patient were excluded.

Autoimmune hepatitis, a chronic and progressive form of liver disorder in which the body's immune system attacks its own hepatocytes can also lead to scarring and consequently to liver failure. The presence of diagnostic autoantibodies especially anti-LKM1 is considered as a main serologic marker of autoimmune hepatitis type 2 [20]. Although more prevalent in female teenagers and children the serological test of this patient did not show any presence of autoantibodies or increased immunoglobulin G. Further there were no signs of interface hepatitis on histological examination or family history of recurrent infections so autoimmune hepatitis was excluded.

Clinical signs and symptoms suggested that in our patient cirrhosis might have developed due to tyrosinemia, a genetic disorder characterized by disruptions in the breakdown of tyrosine. Type 1 tyrosinemia is usually seen in infants with failure to thrive, enlarged liver and spleen, jaundice, distended abdomen, increased tendency to bleed particularly nose bleeds and swelling of legs. While type 2 tyrosinemia is often presented in early childhood with painful red eyes, intellectual disabilities and skin manifestations. However, in chronic or complicated cases, tyrosinemia is often associated with hepatic cirrhosis [21]. In this case, the tyrosine and alpha-fetoprotein levels were not found to be elevated and there were no extrahepatic manifestations suggesting that the patient was not suffering from tyrosinemia.

In the differentials of this case, inborn errors of metabolism possess importance and clinical features suggest that patients might have glycogen storage disorders (GSDs) or lysosomal storage diseases (LSDs) [22, 23]. Although arterial blood gases, serum lactate, ammonia, and blood sugar were in their normal limits, we could not evaluate the characteristic enzyme levels specific for GSDs and LSDs due to financial constraints. Similarly, the liver biopsy did not show glycogen deposition or fat vacuoles and pathognomic abnormal cell accumulation. Furthermore, there were no bruising, neurological complications, involuntary muscle spasms, hypotonia or feeding problems in this child despite hepatosplenomegaly and anthropometric measurements below 10th centile which may exclude some common inborn errors of metabolism like Gauchers disease and GSD type Ia, Ib and III.

Biliary diseases either congenital or autoimmune are usually marked by jaundice, dark urine, gray or white stools, slow weight gain, abdominal pain, nausea, vomiting, itching, and fever. As the child has not developed any of these symptoms despite abdominal pain, we suggested that our patient was not suffering from any biliary disease. Similarly, laboratory workup and abdominal ultrasonography did not show autoimmune markers of primary sclerosing cholangitis and specific signs of biliary atresia or gallbladder abnormalities related to Allagile syndrome or choledochal cysts respectively [20, 24].

Among rare causes of hepatic cirrhosis, Wilson disease, hemochromatosis and alpha 1 antitrypsin deficiency have been associated with altered liver metabolism progressing gradually to liver failure in children. Wilson disease is an autosomal recessive disorder with impaired copper excretion in bile and a failure to incorporate copper in ceruloplasmin due to mutations in the ATP7B gene. This leads to the accumulation of toxic levels of copper in different organs of the body principally liver, brain, and eye. In this case, the child neither developed neurological or psychiatric signs and characteristic eye lesions of Wilson disease nor the clinical investigations and biopsy of liver demonstrated apparent signs of Wilson

disease *i.e.* lobular inflammation, ballooning, rosetting and Mallory hyaline [25]. Primary hemochromatosis is an inherited disorder with excessive iron absorption and deposition in parenchymal organs of the body. As Perl stain for iron was negative, hemochromatosis was also excluded [26]. Similarly, as there was no previous history of blood disorder requiring transfusions, it was suggested that our patient was not suffering from secondary hemochromatosis. Alpha 1 antitrypsin deficiency is also an important cause of cirrhosis in the pediatric population presenting as abdominal distension, ascites and gastrointestinal bleeding from esophageal varices and congestive gastropathy. Some of these children have a prior history of neonatal jaundice and transient elevation of aminotransferases in early childhood [27]. For diagnosis of alpha 1 antitrypsin deficiency (AATD), serum alpha 1 antitrypsin should be low and in this case, it was found to be negative.

Xenobiotic-induced liver damage poses a major concern for health care as it is associated with significant morbidity and mortality. Xenobiotics include a variety of agents, *e.g.* pesticides, aflatoxin (mycotoxin), and compounds like N-nitrosodimethylamine, hydrazine, and carbon disulfide. They can be generated through food processing. Metabolism of xenobiotics in the liver produces free radicals, electrophiles and highly reactive and unstable chemical species. These unstable molecules damage DNA enzymes, and organelles in hepatocyte. They alter the structure and function of the liver and can cause acute liver failure, liver cirrhosis, and even carcinoma of the liver. Xenobiotic induced liver damage manifests in a variety of ways and can be a diagnostic challenge for the physicians [28, 29]. In our case, the patient had no history of exposure to possibly harmful chemicals but the probability of xenobiotic induced liver damage cannot be ruled out.

As the underlying cause of cirrhosis remains unclear after extensive clinical, serologic and pathologic evaluation, this patient is labeled as a case of cryptogenic cirrhosis. Patients with indeterminate acute liver failure have higher rates of death and liver transplantation as compared to those with known causes. The research workshop sponsored by the National Institute of Diabetes and Digestive and Kidney diseases highlighted that the emerging treatment practices for indeterminate pediatric liver failure are not evidence-based. Specifically, the role of suppressing the immune response in pediatric patients with indeterminate liver failure through steroid therapy has not been tested adequately [30]. Since Pakistan is a third world country with an underdeveloped health care system and limited resources, the majority of rare cases remain undiagnosed and inadequately treated leading to an inclination of people towards spiritual and non-medicinal treatments. The improvement of this child with supportive management for unexplained CLD highlights the necessary consideration of evaluation and treatment protocol followed in cases of pediatric end-

stage liver disease despite knowing the definite etiology [31]. Hence it is elucidated that unexplained causes of cirrhosis do exist in some settings and can be treated adequately with better outcomes. Regardless of the cause, liver transplantation is the standard treatment for patients with chronic liver disease [32]. Consequently, the patient was advised for frequent follow-ups and liver transplantation.

CONCLUSION

Despite being a common disorder in the pediatric population, the etiology of chronic liver disease still remains a quandary in some settings as depicted by this case. This leads to a delay in appropriate management and eventual morbidity and mortality of children. In a resource-limited setting, making a diagnosis can be a challenge and all available resources need to be availed before drawing a conclusion.

ABBREVIATIONS

Chronic liver disease (CLD); Computed tomography (CT); fresh frozen plasma (FFP); aspartate aminotransferase (AST); alanine aminotransferase (ALT); alkaline phosphate (ALP); glycogen storage disorders (GSDs); lysosomal storage diseases (LSDs); alpha 1 antitrypsin deficiency (AATD).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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