Case Report

Living with cholesterol ester storage disease: A case study

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ABSTRACT

Lysosomal storage diseases are metabolic disorders caused by dysfunctional lysosomal enzymes, resulting in the build-up of excess substrates in organ cells. Lysosomal acid lipase (LAL) deficiency is a rare genetic disorder caused by the absence of the LAL enzyme. The disease encompasses infantile-onset (Wolman disease) and later-onset forms of cholesteryl ester storage disease (CESD). A 16-month-old female with upper abdominal distension was admitted without significant comorbidities. She had elevated triglycerides, transaminitis, and a homozygous missense variant in the *LIPA* gene, indicating CESD. Live donor liver transplantation was chosen, with the father as the donor. The procedure was uneventful, and post-operative recovery was smooth. Immunosuppression was provided post-transplant and tapered upon discharge. She received prophylactic medications and was monitored for 3 months, tolerating the treatment well.

Key words: Cholesteryl ester storage disease, Lysosomal acid lipase, Rare genetic disorder, Sebelipase alfa

Lysosomal storage diseases are metabolic disorders caused by the accumulation of excess substrates in various cell types, including hepatocytes, splenocytes, and endothelial cells of blood vessels, due to lysosomal enzyme dysfunction [1]. One such condition is lysosomal acid lipase (LAL) deficiency, a rare genetic disorder caused by the lack of the LAL enzyme. The phenotypic spectrum of LAL deficiency ranges from the infantile-onset form (Wolman disease) to later-onset forms, collectively known as cholesteryl ester storage disease (CESD). The LAL enzyme is essential for the breakdown of triglycerides and cholesteryl esters in lysosomes. When LAL is deficient, specific fatty compounds such as cholesteryl esters and triglycerides accumulate in cells in various tissues [2]. CESD results from mutations in the *LIPA* gene, leading to LAL deficiency or dysfunction. This enzyme is essential for the breakdown of cholesteryl esters and triglycerides within lysosomes, a process critical for lipid metabolism. When LAL is deficient, cholesteryl esters and triglycerides accumulate in lysosomes in various cells, particularly in the liver, spleen, and blood vessels. This build-up disrupts normal cellular function, leading to tissue damage and systemic effects.

CASE REPORT

A 16-month-old girl who was apparently ill was admitted to the hospital with complaints of insidious onset, progressive upper abdominal distension. There was no history of jaundice, altered sensorium, or upper gastrointestinal bleeding. The child was alive, alert, and afebrile on admission. She was the third-born daughter of third-degree consanguineous parents and was delivered by lower segment cesarean section due to breech presentation. The birth weight was 3 kg. She had achieved all her developmental milestones and had been vaccinated until 9 months of age. The elder sibling died at 9 months of age, probably due to a similar condition.

She was evaluated for elevated triglyceride levels, probably due to a storage disease. During the evaluation, the patient had transaminitis and elevated cholesterol and triglyceride levels. Abdominal ultrasonography revealed hepatosplenomegaly with massive ascites and increased liver parenchyma texture. Acid lipase activity was significantly lower (0.02 nmol/punch/h) (reference range: 0.37–2.30 nmol/punch/h). Exome sequencing revealed a homozygous missense variant in the *LIPA* gene, LIPA NM_000235.4:c.266T>C (p.Leu89Pro), suggestive of CESD.

The options of sebelipase alfa, hematopoietic stem cell transplantation, and living donor liver transplantation were discussed with the patient's family. They opted for living donor liver transplantation because the father was a match. Given the patient's advanced hepatic involvement, living-donor liver transplantation was chosen after discussing the available treatment options. Although sebelipase alfa requires lifelong intravenous administration at regular intervals, the

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associated long-term financial burden was a significant consideration for the family. As the patient's father was a suitable donor, transplantation offered a sustainable treatment option for her severe hepatic disease without dependence on repeated enzyme replacement therapy.

Live donor liver transplantation with left lateral segmentectomy was performed under general anesthesia. The child's liver was enlarged and fatty, and moderate splenomegaly was noted. Explant hepatectomy was performed as a standard procedure and was uneventful in the patient. Implantation and anastomosis were uneventful, and intraoperative Doppler was within normal limits, ensuring proper blood flow. She was then transferred to the intensive care unit and sedated with fentanyl and propofol infusions. Overnight, the serum lactate levels gradually normalized, and the patient was extubated on the 1st post-operative day.

Postoperatively, there was a declining trend of transaminases, total and direct bilirubin levels, and C-reactive protein levels. Immunosuppression was provided by intravenous methylprednisolone (90 mg), which was then tapered to an equivalent dose of oral prednisolone (20 mg) upon discharge, and tacrolimus (0.5 mg), which was adjusted according to the serum trough levels and continued after discharge. She was treated with valganciclovir (150 mg), fluconazole (50 mg), and piperacillin–tazobactam (900 mg) as post-transplant prophylaxis, and the former two were continued after discharge. Injection dalteparin was administered during hospitalization and discontinued at discharge. Aspirin (30 mg) was added on the third post-operative day and continued after discharge. In addition, mycophenolate mofetil (75 mg) was administered upon discharge. Cefixime (40 mg) was prescribed for 5 days after discharge. She was reviewed after 3 months and tolerated the immunosuppression well.

DISCUSSION

CESD affects males and females at the same rate. Although approximately 50 cases have been documented in the medical literature, numerous patients with CESD have probably been misdiagnosed with other illnesses. CESD is a challenging clinical diagnosis since multiple other disorders, such as Wolman disease, Niemann–Pick disease, and Canary–Dorfman syndrome, have identical clinical, imaging, and laboratory findings, which further emphasizes the importance of accurate diagnosis [3,4].

The key processes involved in the pathophysiology of CESD are as follows: Cholesteryl esters and triglycerides that are not broken down accumulate in the lysosomes, resulting in engorged cells, particularly affecting hepatocytes and macrophages. Since the primary storage sites of lipids include the liver and spleen, accumulation of these substrates causes hepatosplenomegaly. In severe cases, this can progress to cirrhosis and liver failure. Due to hyperlipidemia, the risk of developing atherosclerosis and other cardiovascular diseases increases. In addition to other systemic symptoms, including fatty liver disease, the deficiency causes aberrant lipid levels in the blood (often low high-density lipoprotein cholesterol and high low-density lipoprotein cholesterol) by interfering with normal lipid recycling and distribution in the body. Cellular lipid accumulation can trigger inflammatory cascades, exacerbating disease development and causing tissue injury [3].

The U.S. Food and Drug Administration has approved Kanuma (sebelipase alfa) as a first-line treatment for CESD. Additional therapeutic strategies include implementing a hypolipidemic diet and using statins and fibrates. Individualized treatment approaches are tailored to address the specific symptoms of each patient. Some individuals have benefited from a hypolipidemic diet and statin therapy to significantly lower their blood cholesterol levels [5,6].

Liver transplantation has been performed with positive outcomes in individuals with CESD who develop chronic liver disease. The consideration of specific therapeutic interventions, such as liver transplantation, is contingent on various factors, including disease severity, age, overall health, and other pertinent considerations. Genetic counseling is recommended for affected individuals and their families. Supportive and symptomatic treatments remain integral to the comprehensive management of CESD [7,8]. The disease can also present in unusual ways, such as ptosis and external ophthalmoplegia, which have not been reported in patients with CESD [9-11].

As the child presented at the hospital with manifestations of end-stage liver disease and the father was a suitable donor for living donor liver transplantation, the parents chose this option for treatment. The patient has since shown positive progress and has not experienced any instance of transplant rejection.

CONCLUSION

The appropriate diagnosis and treatment of CESD require an organized approach. To identify the specific cause, a comprehensive history and physical examination should be performed. In conclusion, ancillary testing, including imaging and genetic testing, plays a crucial role in confirming the diagnosis of CESD. Given the nature of the treatment provided, evaluation of graft rejection should be a priority during the initial assessment and subsequent follow-up visits. Treatment decisions should be guided by the pathophysiology of CESD and the clinical presentations of individual patients.

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