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Case Report

Refractory Infantyl Chylous Ascites Treatment by Everolimus

Everolimus ile Refrakter İnfantil Şiloz Asit Tedavisi

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ABSTRACT

The accumulation of lymphatic fluid in the abdomen is defined as chylous ascites. Different causes play a role in the etiology of the disease. Congenital anomalies are the most common cause in pediatric patients. A high protein, low fat diet rich in medium-chain fatty acids should be planned. The first-line treatment is dietary management and is total parenteral nutrition, and the first preferred medical agent is somatostatin. In patients who do not respond to standard treatments, surgical treatment or new limited alternative medical agents are applied. A six-month-old girl presented with a complaint of abdominal swelling was diagnosed with chylous acid. The patient was put on the standard nutritional therapy and somatostatin treatment but did not respond to these treatments. The chylous ascites was controlled with everolimus treatment.

Keywords: Infantile chylous ascites, everolimus, medical treatment

ÖZ

Karında lenfatik sıvı birikimi şilöz asit olarak tanımlanır. Etiyolojide farklı nedenler rol oynamaktadır. Konjenital anomaliler pediyatrik hastalarda en sık neden olan etiyolojidir. Yüksek proteinli, düşük yağlı ve orta zincirli yağ asitlerinden zengin bir diyet planlanmalıdır. İlk basamak tedavi diyet yönetimi ve toplam parenteral beslenme olup, ilk tercih edilen medikal ajan somatostatindir. Standart tedavilere cevap vermeyen hastalarda cerrahi tedavi veya yeni sınırlı alternatif medikal ajanlar tedavi için uygulanmaktadır. Altı aylık kız hasta karında şişlik şikayeti ile başvurdu ve şilöz asit tanısı konuldu. Hastaya standart beslenme tedavisi ve somatostatin tedavisi başlandı, ancak bu tedavilere yanıt vermedi. Şilöz asit everolimus tedavisi ile kontrol altına alındı.

Anahtar kelimeler: İnfantil şilöz assit, everolimus, tedavi

INTRODUCTION

Ascites is the collection of fluids in the abdominal cavity. It can occur in the intrauterine period and postnatally during childhood. There are many causes of chylous ascites. Chronic liver disease and cirrhosis are known to be the primary causes of liver-related health issues in children[1]. Chylous ascites is a rare type of ascites. Its reported incidence at a large university-based hospital over a 20 year period is approximately 1 in 20,000 admissions[2]. It may develop due to congenital malformations, lymphangiomatosis (LAM), peritoneal bands, tumors, and chronic inflammatory processes in the intestines. Changes in nutritional management, total parenteral nutrition (TPN), and somatostatin therapy are preferred as first-line treatment. In patients refractory to these treatments, surgical treatments and new medical agents are considered. In this case report, the diagnosis and treatment with everolimus of a six-month-old girl with refractory chylous ascites is presented.

CASE REPORT

The parents of patient have signed consent to publication form and the form is held by our institution.

A six month old baby girl was brought in with abdominal swelling for one month. At the time of

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her admission, she had a sickly appearance. In the physical examination, her abdomen was observed to be distended. Her body weight was 7,600g (50-75 p); her height was 60 cm (<3 p). Her vital signs were compatible with her age, and she was hemodynamically stable. Her laboratory findings were shown in Table 1. Free fluid was observed in abdominal ultrasonography. No pathology was seen in portal Doppler ultrasonography, abdominal magnetic resonance imaging (MRI), and MRI angiography, except diffuse intraabdominal fluid. After diagnostic paracentesis, the triglyceride level in the fluid was found to be 1.274 mg/dL. Chylous ascites was thus defined. In etiology, conditions such as trauma, surgical conditions, malignancy, infections, and heart diseases were excluded. For etiological investigation, lymphoscintigraphy was performed. With the patient's clinical, laboratory, and paracentesis findings, the intra-abdominal fluid detected was evaluated as chylous by the medical team. However, due to the young age of the patient and technical conditions in lymphoscintigraphy, the focus of lymphatic leakage could not be clearly demonstrated (Figure 1). Malrotation was also not detected in the small intestine passage radiography. The patient's oral nutrition was discontinued and TPN was started. Somatostatin analogs were added to the treatment at 1 mcg/kg/hour intravenously. In the follow-up, nutrition was started with a formula rich in medium-chain fatty acids. As the abdominal distension increased and tachypnea developed in the follow-up period, the chylous fluid was drained with several paracenteses. The chylous acid increase continued intermittently, and the patient developed hypoalbuminemia. Because of acid refractoriness, somatostatin analog therapy was gradually increased to 7 mcg/kg/hour. Intermittently, on the basis of case monitoring, the peritoneal fluid was drained through a catheter, albumin support was provided, and the patient's daily weight and waist circumference were monitored. The TPN support was continued, but the oral nutrition was partially replaced with a special lipid-free formula supported by medium-chain triglyceride oil. As the patient's acid regressed in the 6th week, her oral nutrition was increased and the somatostatin dose was gradually decreased to 4 mcg/kg/h. After the somatostatin dose reduction, the fluid around the abdomen was observed to have increased. Upon re-evaluation through lymphoscintigraphy, the site of lymph leakage into the abdomen was not detected. The patient was thus evaluated as needing pediatric surgery due to the treatment-resistant prognosis and the discovery of the lymph leakage focus. However, surgical intervention was not considered due to surgical difficulties owing to the persistence of intraabdominal diffuse ascites. The somatostatin treatment was increased again, and oral nutrition had to be discontinued intermittently. Since the desired improvement was not achieved with the standard treatments, everolimus was started at week 12. TPN was eventually stopped due to the reduction of the patient's ascites, and the somatostatin infusion was tapared for four weeks following everolimus administration. After the first month of everolimus treatment, the somatostatin dose was reduced to 1 mcg/kg/day, and subcutaneous treatment was started. In the 16th week, the patient was followed up as an outpatient, and ultrasonography was conducted. The somatostatin

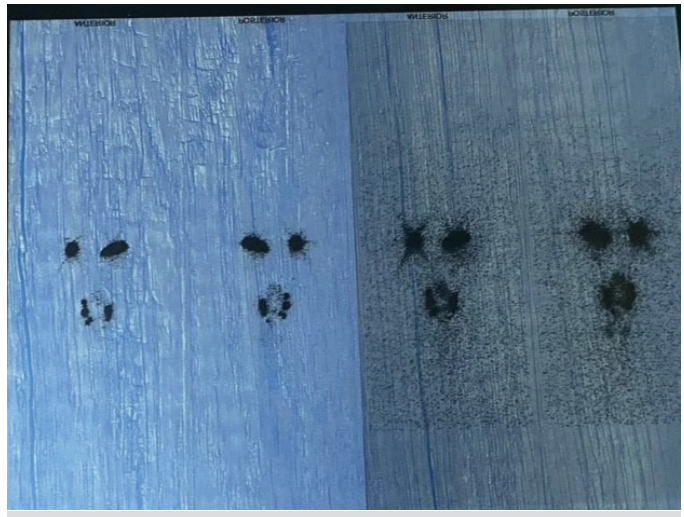

Figure 1. Normal findings in lymphoscintigraphy image of the patient.

Table 1. Laboratory findings of patient.

Hemoglobin	**11.4 gr/dL**	**Triglyceride**	**327 mg/dL**	**GGT**	**24 U/L**	**Creatinine**	**0.4 mg/dL**
Leukocyte	5300/mm^3	**Albumin**	4.1 g/dL	**ALP**	180 U/L	**Sedimentation**	11 mm/h
Platelets	391,000/mm^3	**LDH**	475 U/L	**Total bilirubin**	0.75 mg/dL	**IgG**	0.72 g/L
C-reactive protein	2.8 mg/L	**Sodium**	133 mmol/L	**Direct bilirubin**	0.06 mg/dL	**IgM**	0.33g/L
ALT	57 U/L	**Potassium**	4.6 mmol/L	**EBV**	Negative	**IgE**	111 IU/mL
AST	141 U/L	**Magnesium**	2.6 mg/dL	**CMV**	Negative	**IgA**	0.26 g/L

ALT: Alanine aminotransferase, AST: Aspartate transferase, LDH: Lactate dehydrogenase, GGT: Gamma-glutamyl transferase, ALP: Alkaline phosphatase, EBV: Epstein-Barr virus, CMV: Cytomegalovirus, Ig: Immunoglobulin

treatment was discontinued in the 20th week. Treatment with everolimus was continued for twenty-four-months. No recurrence of acid was observed in the patient. No drug-related adverse events were observed during follow-up. The patient is now 6-years-old, and no recurrence was found (the parents of patient have signed consent to publication form and the form is held by our institution).

DISCUSSION

Chylous ascites, which commonly occurs during the neonatal period but can also be seen in infancy, has many possible etiologies. Congenital etiologies, including lymphatic hypoplasia or dysplasia, such as LAM and intestinal lymphangiectasia, are the most common causes of chylous ascites in the paediatric population[1]. In children, chylous ascites can also be secondary to an operation, blunt trauma, a traffic accident, or child abuse[1]. The etiology, however, is not always evident. Diagnostic paracentesis is essential in identifying the etiology. The presence of a milky, creamy ascitic fluid with a triglyceride content of 200 mg/dL establishes the diagnosis of chylous ascites, although some authors use a threshold of 110 mg/dL[3]. Lymphoscintigraphy, lymphangiogram, or surgical laparotomy can be used as diagnostic methods. The nutritional approach should be the primary agent in chylous ascites management. A high-protein/low fat diet rich in medium-chain fatty acids is essential. In cases where there is no response to enteral feeding, however, feeding with TPN should be started. In the treatment of chylous ascites in children and adults, octreotide, a somatostatin analogue, has been used as an adjunct to TPN. The mechanism of action in chylous acid is not clearly known. Somatostatin reduces fat absorption from the intestine, lowers triglycerides in the thoracic duct, reduces lymph flow in the main ducts, and also decreases gastrointestinal secretions and motor activity[3]. The success rates of nutritional therapy and somatostatin treatment can be found in the literature, mostly in cases of chylothorax and chylous ascites[2,4].

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase regulated by phosphoinositide-3-kinase, and is involved in a number of cellular processes, including cellular catabolism and anabolism, cell motility, angiogenesis, and cell growth. Sirolimus was recently reported to reduce refractory chylothorax and chylous ascites in patients with LAM. This effusion was ameliorated by the administration of octreotide, a somatostatin analog peptide, in addition to sirolimus. Some reports have shown that chylous effusion was ameliorated by sirolimus[5]. Everolimus is also an mTOR inhibitor and is a sirolimus derivative, but has fewer side effects. Its bioavailability is higher than that of sirolimus, and its half life is short. In cases where the focus of lymph leakage had been identified, surgical repair with glubran or cautery was successfully performed. In our patient, the location of the lymph leakage could not be determined by lymphoscintigraphy and no lymphangioma was found but the lymph leakage with lymphatic ascites responded to everolimus treatment. Therefore, we recommend the use of alternative and successful treatments such as everolimus and sirolimus before the surgical approach considering the possible surgical complications in the concerned childhood age group, and particularly in the patient group whose lymph leakage focus has not been found, we recommend the use of alternative and successful treatments such as everolimus and sirolimus before the surgical approach. Cases of chylous ascites and lymphedema due to sirolimus treatment after organ transplantation have been reported in literature[6]. It is remarkable that these side effects related to treatment, are observed especially in patients who underwent surgeries such as organ transplantation. The mechanism of sirolimus action is unclear, but it may be related to the disruption of the proliferative signals that are necessary for sealing the perivascular lymphatics and for promoting wound healing[7]. Its treatment effects are thought to be due to the angiogenic properties of both agents. This treatment was found to be appropriate in our patient with congenital chylous ascites without any previous surgery. After the treatment, the patient was closely monitored for side effects. No drug-related adverse events were observed during follow-up. Somatostatin treatment was stopped after two months of everolimus treatment. The patient's clinical and laboratory parameters were followed up using imaging methods, and no recurrence of the ascites occurred during the twenty-four-month follow-up after the discontinuation of everolimus. The use of everolimus for the treatment of congenital lymphatic disorders such as chylous ascites, which is resistant to diet and somatostatin treatment, should therefore be considered[8].

CONCLUSION

Although dietary management and TPN are the first-line treatments for chylous ascites, there are cases that benefit from somatostatin treatment. In cases of refractory chylous ascites, as in our patient, alternative treatment is needed. Among these treatments, sirolimus has been shown in the literature to be effective. This case has shown, that Everolimus would also be an alternative treatment method in refractory chylous ascites.

Ethics

Informed Consent: The parents of patient have signed consent to publication form and the form is held by our institution.

Footnotes

Author Contributions

Surgical and Medical Practices: M.B., G.K., Concept: S.K., G.D., Design: B.A., Data Collection and/or Processing: M.B., H.O.H., Analysis and/or Interpretation: Y.C.A., Literature Search: S.K., Writing: M.B., S.K.

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