CASE REPORT

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Hepatic hydrothorax in the absence of ascites in a child with autoimmune hepatitis: Successful management with octreotide and pleurodesis

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Hepatic hydrothorax is a rare complication of liver cirrhosis and portal hypertension. It carries a diagnostic and therapeutic difficulty especially if occurring in the absence of ascites. We report a nine-year-old child with autoimmune hepatitis type 1, who presented with a right-sided hepatic hydrothorax in the absence of ascites. The patient was treated successfully with diuretics, octreotide and pleurodesis together with immunosuppressive therapy for autoimmune hepatitis. There was no recurrence of effusion after a long follow-up duration. In conclusion, hepatic hydrothorax should be considered in the differential diagnosis of pleural effusion occurring in children with cirrhotic liver, whether associated with ascites or not. Octreotide as a splanchnic vasoconstrictor can be used in establishing the diagnosis and in the treatment of hepatic hydrothorax. The need for liver transplantation in such patients may be avoided when the liver disease can be treated specifically.

Key words: Hydrothorax, octreotide, pleural effusion, pleurodesis

Otoimmun hepatitli çocuk hastada assit olmadan gelişen hepatik hidrotoraksın oktreotid ve plörodez ile başarılı tedavisi

Hepatik hidrotoraks, sirozun ve portal hipertansiyonun nadir bir komplikasyonudur. Assit olmaksızın gelişmesi halinde tanıda ve tedavide zorluklar ile karşılaşılmaktadır. Burada tip 1 otoimmun hepatiti olan 9 yaşında; assit olmadan sağ taraflı hepatik hidrotoraks ile başvuran çocuk hasta sunulmuştur. Hasta immun supresif tedaviye ek olarak diüretikler, oktreotid ve plörodez ile başarılı bir şekilde tedavi edilmiştir. Uzun süreli takip sonunda plevral effüzyon tekrar etmemiştir. Sonuç olarak, sirozlu çocuklarda hepatik hidrotoraks; beraberinde assit olsun olmasın, plevral effüzyonun ayrıcı tanısında akılda tutulmalıdır. Splanknik vazokonstriktör olan oktreotid hepatik hidrotoraksın tanısında ve tedavisinde kullanılabilir. Karaciğer hastalığı özgül olarak tedavi edilebilir ise bu hastalarda karaciğer nakline gerek duyulmayabilir.

Anahtar kelimeler: Hidrotoraks, ocreotide, pevral effüzyon, plörodez

INTRODUCTION

Hepatic hydrothorax is a pleural effusion occurring in patients with liver cirrhosis and portal hypertension without cardiopulmonary disease. It is relatively uncommon (1). In the majority of cases, hepatic hydrothorax is associated with ascites. However, it has been reported in adults to occur, rarely, in the absence of ascites. In these cases, extensive diagnostic evaluation may be undertaken, as liver cirrhosis is not commonly considered a distinct cause of pleural effusion (2). The pleural space is limited, and modest accumulation of fluid may lead to dyspnea. In such cases, it is

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considered one of the emergency complications of cirrhosis. Usually, patients with hepatic hydrothorax have end-stage liver disease and are considered potential candidates for liver transplantation (3).

CASE REPORT

In January 2008, a nine-year-old male child was admitted to the Pediatric Hepatology Department because of easy fatigability and remittent jaundice of one-year duration. At that time, he had a trace of jaundice, pallor and his body weight was 30 kg. Abdominal examination revealed shrunken liver, splenomegaly, and no ascites. Abdominal ultrasonography confirmed the clinical data. Laboratory investigations were as shown in Table 1. (first column). A diagnostic workup was performed. Upper gastrointestinal endoscopy revealed three cords of esophageal varices grades I-II. The child was then discharged on propranolol (1 mg/kg/day) and supportive treatment awaiting the laboratory results.

One month later, in February 2008, the child presented to the Pediatric Hepatology Department with respiratory distress of insidious onset and progressive course developing over one week. On admission, he was conscious with a respiratory rate of 44/min, blood pressure of 110/70 mmHg, heart rate of 84/min, and body temperature of 37.2 °C. Clinical examination revealed a trace of jaundice, dullness and diminished air entry over the right side of the chest, shrunken liver, splenomegaly, and no ascites. Chest x-ray (CXR) showed massive right-sided pleural effusion (Figure 1A). Laboratory investigations at that time were as shown in Table 1 (second column). Insertion of an intercostal tube (ICT) to alleviate the respiratory distress was performed with drainage of about 1.5 L/day (Figure 2). Pathological analysis of the drained fluid showed an exudate, negative for malignant cells. The chemical analysis revealed total proteins of 6.1 g/dl, albumin of 2.9 g/dl, glucose of 94 mg/dl, lactate dehydrogenase of 394 IU/L, and leukocytic count of $11.9x10^3/mm^3$, mainly lymphocytes. Bacteriology revealed gram-negative bacilli, negative Ziehl-Nelsen stain for *Mycobacterium tuberculosis* (TB), and negative polymerase chain reaction (PCR) for TB-DNA. Adenosine deaminase was 44 IU/L (upper limit of normal: 40 IU/L). The child received culture-guided antibiotics, diuretics (furosemide at 1 mg/kg/d, spironolactone at 2 mg/kg/d) and 20% human albumin.

The results of the diagnostic workup made on first admission were checked, and showed the presence

Table 1. Laboratory investigations

	1st admission to NLI (05/01/08)	Admission with dyspnea (04/02/08)	One month after immuno-suppressives (29/03/08)	Last follow- up (10/10/11)
Total bilirubin (mg/dl)	1.4	2	1.3	0.9
Direct bilirubin (mg/dl)	0.5	1.2	0.5	0.15
Total protein (g/dl)	7.6	6.7	6.1	6.5
Albumin (g/dl)	3.1	2.7	3.6	3.7
AST (U/L)	347	428	52	34
ALT (U/L)	340	436	46	29
ALP (U/L)	233	207	132	119
GGT (U/L)	35	56	14	12
Prothrombin time (sec)	20	20.5	16.4	14.2
INR	1.62	1.66	1.33	1.15
Hemoglobin (g/dl)	10.6	12.6	12.5	12.8
TLC (x $10^3/\mu l$)	3.2	4.8	8.3	5.6
Platelets (x $10^3/\mu l$)	79	112	131	211
Urea (mg/dl)	21	17	--	--
Creatinine (mg/dl)	0.33	0.4	--	--
Na (mEq/L)	138	136	--	--
K (mEq/L)	3.6	4.2	--	--
ESR		15/30		

NLI: National Liver Institute. AST: Aspartate transaminase. ALT: Alanine transaminase. ALP: Alkaline phosphatase. GGT: Gamma glutamyl transpeptidase. INR: International normalized ratio. TLC: Total leukocytic count. ESR: Erythrocyte sedimentation rate. Transaminases upper limit of normal = 40 U/L.

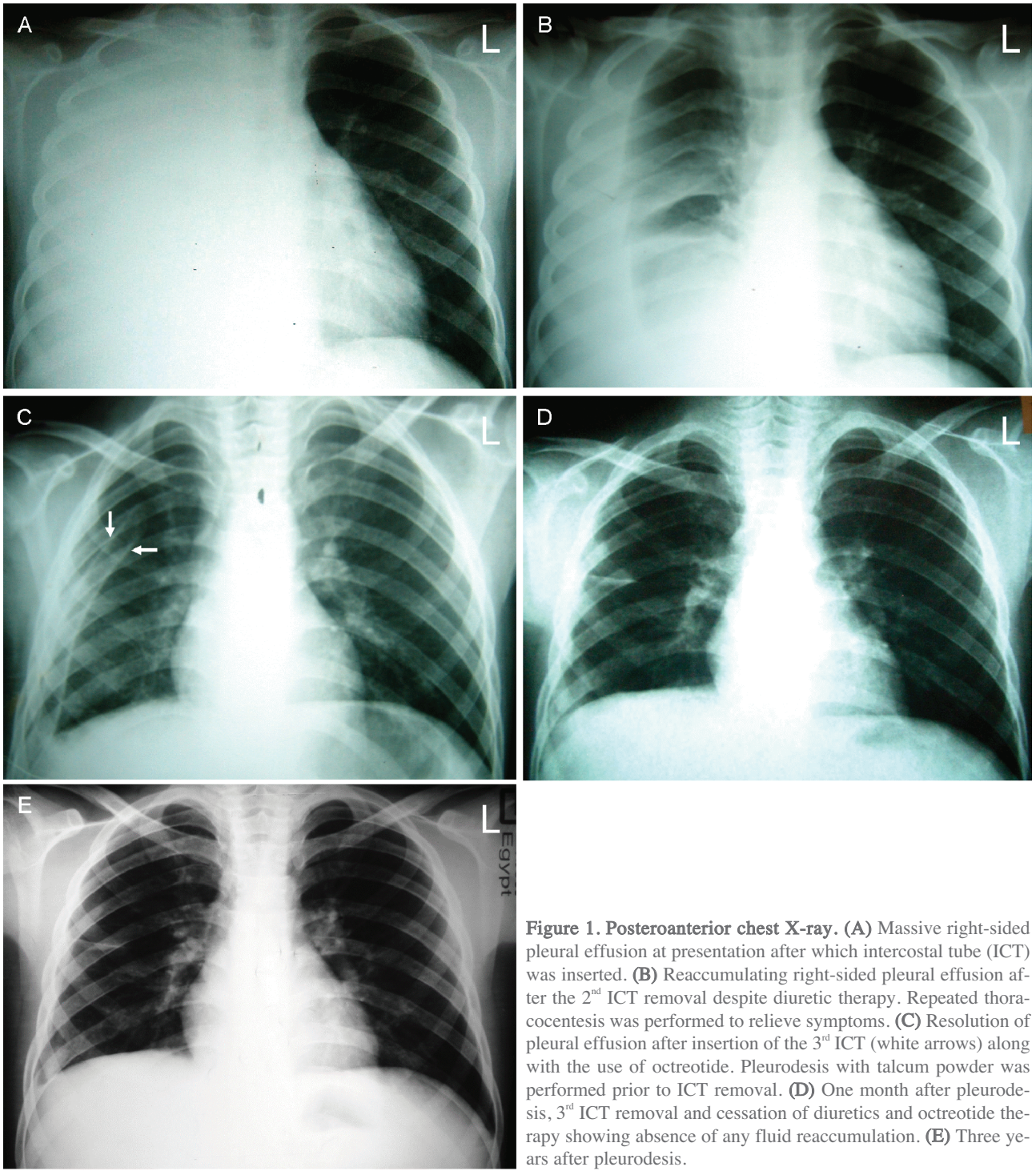

Figure 1. Posteroanterior chest X-ray. (A) Massive right-sided pleural effusion at presentation after which intercostal tube (ICT) was inserted. **(B)** Reaccumulating right-sided pleural effusion after the 2nd ICT removal despite diuretic therapy. Repeated thoracocentesis was performed to relieve symptoms. **(C)** Resolution of pleural effusion after insertion of the 3rd ICT (white arrows) along with the use of octreotide. Pleurodesis with talcum powder was performed prior to ICT removal. **(D)** One month after pleurodesis, 3rd ICT removal and cessation of diuretics and octreotide therapy showing absence of any fluid reaccumulation. **(E)** Three years after pleurodesis.

of hypergammaglobulinemia and positive anti-smooth muscle antibody together with negative hepatitis viral markers. Liver biopsy showed a fibrosis stage of 5/6 and an activity grade of 15/18 according to Ishak scoring system (4). Based on these results, the child was diagnosed as autoimmune hepatitis (AIH) type 1 with an AIH score of 13 (5).

During this admission for dyspnea, chest computed tomography revealed right-sided pleural effusion with collapsed lower lobe of the right lung, normal vascular and bronchial distribution and normal lung architecture. Echocardiography, urine analysis, 24-hour urinary proteins, and creatinine clearance were normal. Tuberculin test was

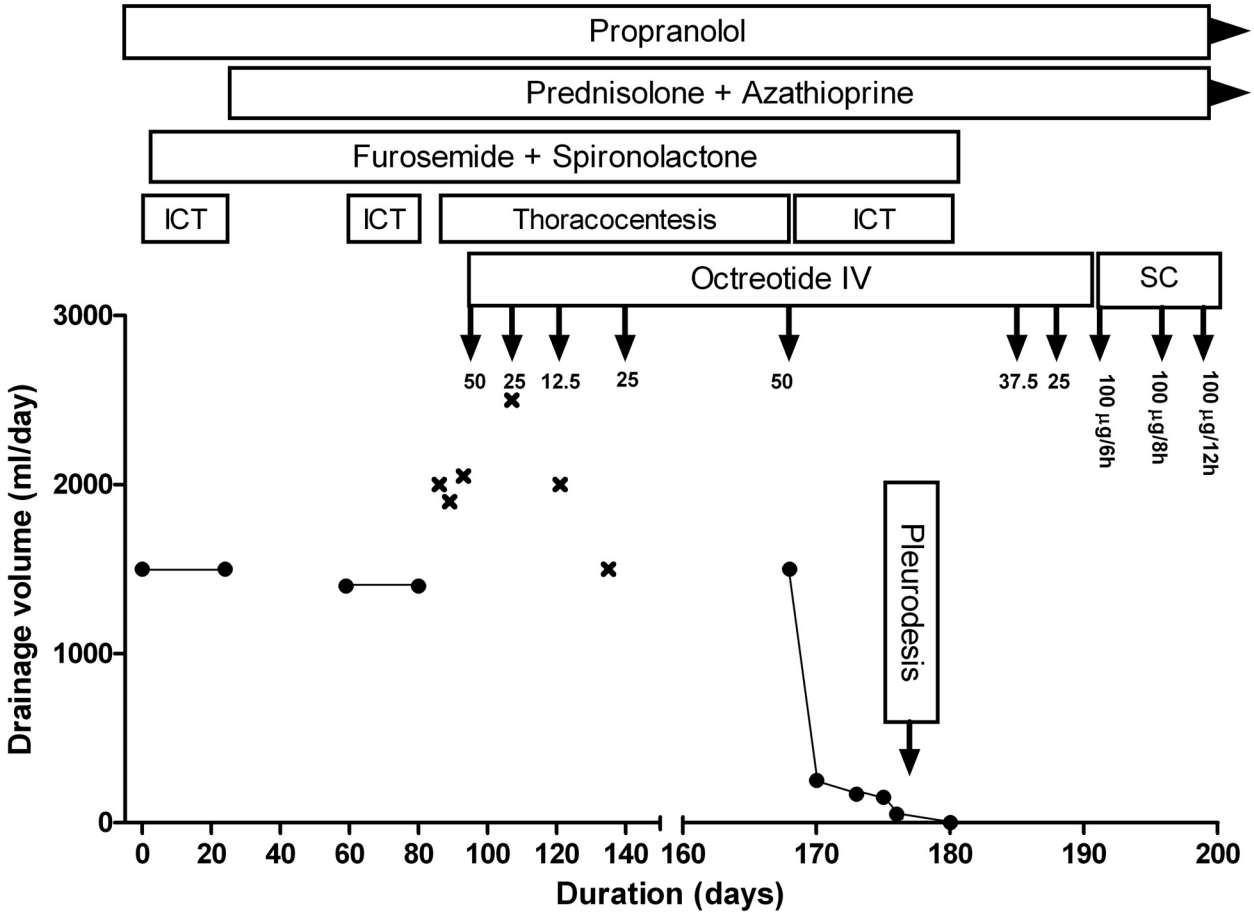

Figure 2. Time-course management of the hepatic hydrothorax. Drainage volume of intercostal tube (ICT; •, solid line) and thoracocentesis (x). s of medications and interventions are indicated by the boxes. Box with right-sided arrowhead indicates drug continuity. Timing and dosage (μg/kg/h) of intravenous (IV) octreotide is indicated by downward arrows and numbers. Increasing octreotide dose markedly diminished the drainage just before pleurodesis.

negative. Serum anti-double-stranded DNA (anti-dsDNA) was positive and complement 3 (C3) was 40 mg/dl (normal: 90- 180 mg/dl). Follow-up pleural fluid analysis showed a transudate with no culture growth and leukocytic count of 400/mm^3, mainly lymphocytes. The ICT was removed after 24 days (Figure 2) while the patient was on diuretic therapy. He was then started on immunosuppressive therapy (prednisolone 30 mg/day plus azathioprine 25 mg/day) with near normalization of transaminases after one month (Table 1). A gradual decrease of prednisolone to 5 mg/day was then achieved. Due to reaccumulation of pleural effusion, a second ICT was inserted five weeks after removal of the first. The ICT drained about 1.4 L/day of a transudate and it was removed after three weeks (Figure 2). A pleural biopsy taken at this time showed pleurisy with lymphocytic infiltration and mesothelial irritation with no evidence of TB or malignancy.

With the absence of local or systemic causes of pleural effusion, the possibility of hepatic hydrothorax was then raised. Due to recurrence of respiratory distress, repeated thoracocentesis was performed to relieve symptoms with tapping of about 2 liters every three days (Figure 1B). Octreotide was then introduced in an attempt to establish the diagnosis of hepatic hydrothorax and to reduce the rate of reaccumulation. After starting intravenous infusion of octreotide at a dose of 50 µg/h, the rate of reaccumulation decreased to the extent that there was a need to tap only 2.5 liters in over a two-week period to relieve distress. Decreasing the dose to 25 µg/h did not change the rate of reaccumulation in the next two weeks, as a tap of only 2 liters was needed for distress relief. On the other hand, decreasing the dose to 12.5 µg/h was associated with an increased rate of reaccumulation radiologically. Therefore, the dose was reverted to 25 µg/h. For the following two weeks, drainage of

only 1.5 liters was needed to relieve symptoms.

On 23 July 2008, a third insertion of an ICT was decided in an attempt to prepare the patient for pleurodesis. At that time, octreotide was increased to 50 µg/h. There was a stepwise decrease in the daily drainage from the ICT; 1.5 liters immediate after insertion, then 250 ml, 170 ml, and 150 ml in the following days, and finally 50 ml just before pleurodesis (Figure 2). Pleurodesis was performed using talcum powder together with maintaining diuretics and octreotide. The ICT was removed three days after pleurodesis, at which time there was no drainage from the tube, and CXR showed no evidence of pleural fluid (Figure 1C). Diuretics were stopped the day after tube removal, while octreotide at 50 µg/h was maintained for five days. The dose of octreotide was reduced to 37.5 µg/h for three days, then to 25 µg/h for another three days before shifting to subcutaneous (SC) administration. SC injection of octreotide was given at a dose of 100 µg/6 h for five days, then every eight hours for a further three days, and finally, after every 12 hours for another 3 days, it was stopped. CXR was performed after removal of the ICT, and revealed complete resolution of the effusion. A follow-up CXR was performed weekly for one month without any evidence of reaccumulation (Figure 1D). The child was maintained on prednisolone 5 mg/day, azathioprine 25 mg/day and propranolol 60 mg/day with regular follow-up. He maintained normal liver function (Table 1) with occasional relapse and flare of enzymes because of non-compliance. All through the follow-up duration up to October 2011, there was no reappearance of pleural effusion (Figure 1E) or development of ascites.

DISCUSSION

Hepatic hydrothorax is an infrequent complication of liver cirrhosis. It is usually right-sided, and is associated with ascites in most of the cases. In spite of being reported without ascites in adults (2,6), there are no previous reports of similar cases in pediatrics. Regarding our experience in pediatric hepatology, it is the first case confronted in which hepatic hydrothorax occurred in the absence of ascites. However, it was essential to exclude other causes of pleural effusion, particularly since there was no ascites, clinically or radiologically.

Computed tomography of the chest showed free underlying lung parenchyma. Pleural fluid showed negative Ziehl-Nielsen stain for TB, negative PCR for TB-DNA and near-normal adenosine deaminase. Tuberculin test was negative with no significant elevation of erythrocyte sedimentation rate (ESR). Pleural biopsy was negative for TB and malignancy. All of these investigations made the possibility of a pulmonary etiology of hydrothorax unlikely. In addition, echocardiography, urine analysis, urea, creatinine, creatinine clearance, and 24-hour urinary protein were normal, ruling out cardiac and renal causes. Positive anti-dsDNA and low C3 were found, which may suggest collagen disorder; however, both can be explained by the AIH etiology (7,8).

The absence of other causes of hydrothorax raised the possibility of hepatic hydrothorax. Pleural fluid in hepatic hydrothorax is considered an ascitic fluid, which was transferred to the pleural cavity through diaphragmatic defects. The negative intrapleural pressure compared to that of the peritoneal cavity facilitates the one-way transfer of fluid and its subsequent trapping in the pleural space. Hepatic hydrothorax occurs when the accumulation of fluid exceeds the absorptive capacity of the pleura, and ascites seems to occur only if the collection rate in the abdomen exceeds the pleural space capacity to maintain a pressure gradient sufficient to drain the peritoneal cavity. Thus, pleural effusion meets the criteria of a transudate (3). On this basis, octreotide was attempted, as a splanchnic vasoconstrictor, to establish the possible diagnosis of hepatic hydrothorax. Reduction in the fluid reaccumulation after octreotide introduction highlights its possible role in the diagnosis of hepatic hydrothorax, especially when ascites is absent.

In our case report, pleural fluid aspirate was consistent initially with exudate. This can be explained by the presence of superadded infection, a picture which has been recorded in other case reports (9). Moreover, the change in the pleural fluid character to a transudate after treating the infection is supportive of its original transudate nature.

Hepatic hydrothorax is managed as if treating for ascites. In refractory cases necessitating frequent thoracocentesis, liver transplantation is considered the ultimate goal. However, measures like transjugular intrahepatic portosystemic shunt (TIPS) are undertaken as a bridge until the liver transplantation is available (3). Patients with severe dyspnea often require ICT placement, as was performed in our case. This procedure has many complications such as excessive protein and electrolyte depletion. ICT removal is sometimes im-

possible due to the high-volume drainage. This has led many authors to contraindicate ICT placement (1,10).

In our experience (11) and others (12), children with AIH who are responsive to immunosuppressive therapy have a good outcome with regression of the liver fibrosis. This led us to search for the least invasive palliative measure to control the hydrothorax in hope of gradual improvement in the liver disease stage with the given specific therapy, and ultimately, avoidance of liver transplantation.

Although TIPS was shown to be an effective palliative treatment for hepatic hydrothorax, serious side effects can occur (6). Octreotide is used to reduce the portal pressure and has been reported to reduce hepatic hydrothorax in adults (9,13,14). The use of octreotide had an evident effect on reducing the drainage volume and it was dose-related. Pleurodesis for the treatment of hepatic hydrothorax in adults was reported to be unsuccessful due to the continuous fluid drainage (6,10). In our case, reducing the rate of fluid drainage by octreotide helped in proceeding to a successful pleurodesis.

In conclusion, hepatic hydrothorax should be considered in the etiology of pleural effusion in cirrhotic children with or without ascites after exclusion of other causes. Octreotide can be a helpful tool in establishing the diagnosis. Moreover, its usage together with pleurodesis is an effective treatment of hepatic hydrothorax in children, especially if the primary liver disease can be specifically treated and controlled.

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