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A Multifaceted Disease of Problematic Diagnosis in Childhood; Hereditary Hemorrhagic Telangiectasia: A Case Report

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Abstract

Hereditary hemorrhagic telangiectasia (HHT) is a vascular dysplasia inherited in an autosomal dominant manner and may involve skin, mucosa, and internal organs. HHT may cause arteriovenous, arterioportal, and portovenous shunts in the liver, resulting in cirrhosis and portal hypertension. An eight-year-old male patient with a diagnosis of myelodysplastic syndrome for two years was admitted with melena. Portal doppler ultrasonography showed a heterogeneous appearance of the liver parenchyma and splenomegaly (spleen size of 14 cm) with no portal hypertension. An extended etiological investigation for chronic liver disease was conducted. Afterliver biopsy, the patient's general condition deteriorated, with abdominal distension and reduced hematocrit. The Doppler and hepatic angiography results together with a history of recurrent episodes of epistaxis led to the diagnosis of HHT. The patient was referred to the transplant center for liver transplantation due to the irreversible bleeding from the liver. Hepatic telangiectasias may be present in patients without hematologic disorders who have uncontrollable bleeding after liver biopsy.

***Key Words*:** Children, Hereditary hemorrhagic telangiectasia, Lıver transplantation.

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1- INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant genetic disorder characterized by recurrent epistaxis, mucocutaneous telangiectasias, and arteriovenous malformations (AVM) in visceral organs (1). Although telangiectasia is commonly prominent in the lips, tongue, buccal mucosa, face, chest, and fingers, large arteriovenous malformations may develop in the lungs, liver, pancreas, and brain (2). HHT can also cause arteriovenous, arterioportal, and portovenous shunting in the liver, leading to cirrhosis and portal hypertension. In a case series of three patients, both liver transplantation and treatment with bevacizumab were effective in reducing symptoms of liver AVMs (3). Liver transplantation in HHT patients with liver AVMs has in the past been the treatment of choice for patients with severe symptoms despite serious adverse effects and complications (4). Here, a case of HHT is studied that was incidentally detected following a detailed etiological investigation of chronic liver disease in a patient diagnosed with myelodysplastic syndrome who was referred to our Pediatric Oncology clinic due to symptoms of hepatosplenomegaly and pancytopenia.

2- CASE PRESENTATION

An eight-year-old male patient with a diagnosis of myelodysplastic syndrome has been followed at our Pediatric Oncology outpatient clinic for the previous two years. First, hepatosplenomegaly and pancytopenia were detected during a respiratory infection. Myelodysplastic syndrome was diagnosed through bone marrow aspiration and biopsy. The patient was not under any treatment during the follow-up. At the time of his last hospitalization, the clinic was consulted for a new onset of melena. Detailed history of the patient revealed recurrent heavy epistaxis together with frequent need for blood transfusions irrespective of myelodysplastic syndrome since the age of six. On physical examination, he appeared severely pale, lethargic, and weak. No sign of petechiae, purpura, ecchymosis, and telangiectasia was present. The patient palpable hepatomegaly (3 cm in size) and splenomegaly (6 cm). Laboratory workup revealed a hemoglobin level of 7 g/dl, WBC count of 1600/mm^3, and a platelet count of 25.000/m^3 (**Table.1**). Doppler ultrasound of the portal vein showed a heterogeneous appearance of the liver parenchyma and 14 cm splenomegaly without portal hypertension. As myelodysplastic syndrome was excluded with a repeat bone marrow biopsy, an extensive etiological investigation was conducted for chronic liver disease, and infectious agents were ruled out with serological tests. Blood and urine tests and enzyme assays for inborn errors of metabolism gave completely normal results. Autoimmune pathologies were excluded on the basis of normal serum immunoglobulin levels and negative antibody results. Echocardiography showed moderate left ventricular hypertrophy and dysfunction.

A liver biopsy was obtained to reach a definitive diagnosis. However, the patient's condition began to deteriorate severely due to intra-abdominal bleeding which required immediate hepatic angiography. Markedly tortuous and dysplastic intraparenchymal branches of the hepatic artery and extravasation from the hepatic segment VI were observed during this invasive procedure and a coil embolization was performed (**Figure.1**). Three additional urgent laparotomies were carried out within one week due to massive hemorrhagic drainage and a significant drop in hematocrit levels. Large volumes of hemorrhagic fluid and hematoma were intraoperatively detected in the abdomen. Pathological examination of the liver biopsy specimen demonstrated non-specific changes, with some regenerative nodules, which were not consistent with overt cirrhosis. Proliferation of the vessel lined with thin, flattened endothelium was also present (**Figure.2**).

Repeat portal Doppler ultrasonography (USG) showed several peripheral arteriovenous shunts between hepatic artery branches and hepatic veins in the right and left hepatic lobes. Doppler USG and hepatic angiography findings together with the history of recurrent epistaxi led to the diagnosis of HHT. An initial dose of bevacizumab was administered for the treatment of uncontrolled bleeding from the liver before transferring the patient to the liver transplantation center.

Table-1: Laboratory values of the patient.

Parameters	First presentation (at the age of 6)	Hospitalization (at the age of 8)	After liver biopsy	Before liver transplantation
Hemoglobin (g/dL)	6.9	7	4.2	7.4
WBC count (mm^3)	1750	1600	1600	1700
Platelet count (mm^3)	51000	25000	25000	17000
Absolute neutrophil count (mm^3)	800	800	800	300
Total protein (g/dL)	6.1	4.7	4.2	5.3
Albumin (g/dL)	3.4	2.6	2.2	2.7
Aspartate Aminotransferase (U/L)	102	931	93	97
Alanine Aminotransferase (U/L)	55	23	23	37
Alkaline Phosphatase (U/L)	255	318	539	316
Gamma-Glutamyl Transpeptidase (U/L)	92	17	20	17
Total bilirubin	3.9	2.48	2.6	5.5
Direct bilirubin	1.7	0.6	0.4	0.7
Prothrombin Time (sec)	16.1	15.2	16.8	15.2
International Normalized Ratio	1.35	1.3	1.45	1.3
Activated partial thromboplastin time	37.4	35.8	39.6	35.8
Total cholesterol (mg/dl)		180		
Triglyceride (mg/dl)		126		
High-density lipoprotein (mg/dl)		14		
Low-density lipoprotein (mg/dl)		140		
Ferritin		240		
Anti-nuclear antibody		Negative		
Anti-mitochondrial antibody		Negative		
Anti-smooth muscle antibody		Negative		
LKM-1		Negative		
Immunoglobulin A		0.9		
Immunoglobulin G		5		
Immunoglobulin M		0.53		
Alpha 1 antitrypsin (mg/gl)		30		
Ceruloplasmin (mg/dl)		40		
24-hour urinary copper excretion		25		

LKM-1: anti-liver kidney microsomal antibody type 1.

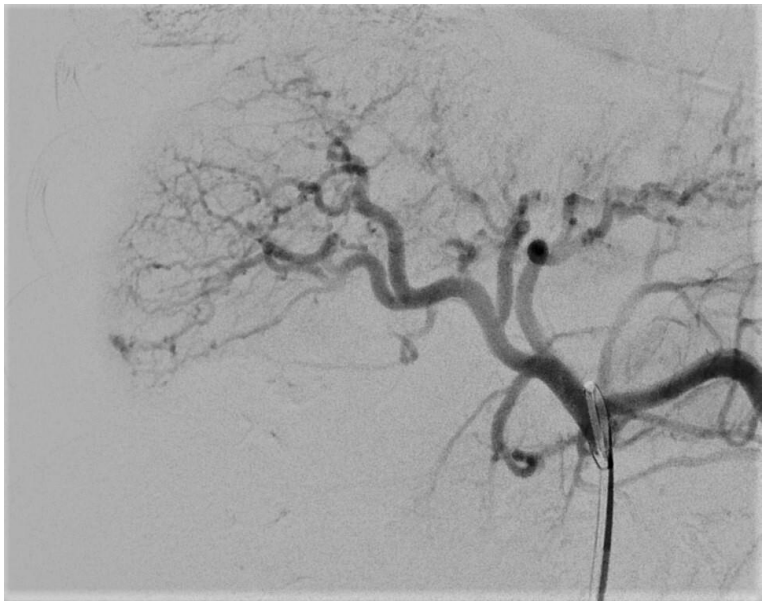

Fig.1: Hepatic angiogram showing dysplastic, tortuous vessels and subcapsular small AV shunts.

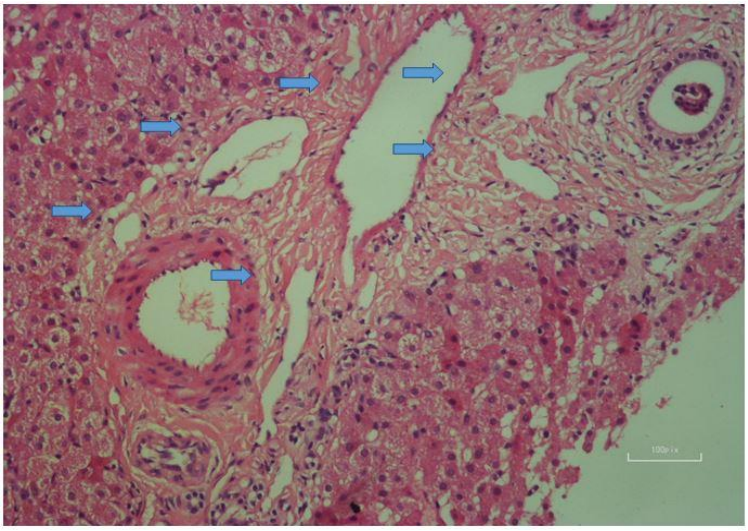

Fig.2: Proliferation of the vessel lined with thin flattened endothelium (H&E X200).

3- DISCUSSION

Hereditary hemorrhagic telangiectasia (HHT) is a vascular dysplasia which is inherited in an autosomal dominant manner and may involve skin, mucosa, and visceral organs (5). HHT occurs with an equal frequency in both sexes and has an incidence of 1-2 per 100,000. Excessive angiogenesis caused by stimulation of endothelial cell proliferation and migration as a result of an increase in the vascular endothelial growth factor has been implicated in its pathogenesis (6). Mutations have been identified in three different genes in families with a history of HHT. These include the Endoglin (ENG) gene on chromosome 9, Activin A receptor type II-like-1 (ACVRL-1) on chromosome 12, and SMAD4 (7). Twenty percent of the patients have a negative family history. Recurrent, spontaneous nose bleeding is the most common symptom of HHT and occurs in 60-98% of the patients. Telangiectasias may develop at any age, but usually appears during adolescence

and later. Patients are often diagnosed under the age of 30 (6). Cutaneous symptoms of the disease include telangiectasia in the lips, tongue, and nasal mucosa, palms of the hands, and soles of the feet (8). Isolated involvement of the liver is a rare manifestation of HHT, which is dependent on the genotype. Angiodysplasias, fibrosis, cirrhosis, and portosystemic shunts are common hepatic manifestations of HHT (9). Right-to-left shunts in hepatic fistulas may cause increased cardiac preload, congestive heart failure, hepatomegaly, pulmonary hypertension, mesenteric ischemia, and biliary disease. In rare cases, portal hypertension and hepatic encephalopathy may develop as a result of shunts between hepatic artery and portal vein (10).

These arterioportal shunts occur rarely and are associated with ascites and massive gastrointestinal bleeding due to portal hypertension. Unfortunately, the patient's diffuse arteriovenous shunts could only be seen later during liver biopsy and in urgent laparotomies. The diagnosis of HHT was further supported by a repeat Doppler ultrasound of the portal vein, which showed a thousands of peripheral arteriovenous shunts. Additionally, and consistent with the literature, hepatic angiography of the patient revealed markedly tortuous and dysplastic intraparenchymal branches of the hepatic artery. Selective angiography of the hepatic artery is the gold standard of imaging in HHT (9).

However, since it is an invasive procedure, Doppler ultrasonography is recommended for the diagnosis and follow-up of HHT, especially in children (9, 11). On hepatic Doppler ultrasonography, characteristic appearance of HHT includes dilated common hepatic artery, tortuous tubular structures with marked pulsation, and increased intrahepatic vascularization as is the case in the studied patient (9). Computed tomography (CT) scanning or MR imaging is used only in the differential diagnosis in the case of hepatic nodules. In the studied patient, the appearance of liver nodules reported intraoperatively by the pediatric surgeons were not suggestive of cirrhosis and the liver biopsy result indicating non-specific changes supported the diagnosis of HHT. Myelodysplastic syndrome was the initial probable diagnosis for the patient by pediatric oncologists due to massive hepatosplenomegaly and pancytopenia. However, anemia was the result of his chronic condition and frequent epistaxis and GI hemorrhage from the age of two, which eventually led to pancytopenia due to hypersplenism with the contributing factor of arteriovenous shunts.

Bevacizumab, when administered by intravenous route, was reported to reduce cardiac output and symptoms of heart failure in patients with hepatic involvement secondary to hepatic AVMs of HHT (12). Liver transplantation is a therapeutic option for patients with hepatic involvement whose massive bleeding cannot be managed with other supportive measures (13). The patient was given an initial dose of bevacizumab for the treatment of uncontrolled bleeding from the liver before his referral to the liver transplantation center.

4- CONCLUSION

HHT can mimic myelodysplastic syndrome with hepatosplenomegaly, pancytopenia, and myelodysplastic changes in the bone marrow aspiration due to a chronic process of the disorder. Also, hepatic telangiectasia should be considered in patients with uncontrolled bleeding after liver biopsy without a known hematologic problem, and diffuse hepatic nodules detected by abdominal radiographic examinations may not necessarily indicate cirrhosis and may be the initial symptom of HHT.

5- CONFLICT OF INTEREST: None.

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