

Ganglioneuroma in a child with hereditary spherocytosis

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Hereditary spherocytosis (HS) is the most frequent cause of congenital hemolytic anemia. Extramedullary hematopoiesis (EMH) mimicking a mass may develop in the lymph nodes, kidneys, pleura, mediastinum, adrenal gland, and in particular the spleen and liver. Other than EMH, B-cell lymphoma, acute lymphoblastic leukemia, and pancreatic schwannoma cases were reported in patients with HS. We present a 13-year-old female patient with HS and ganglioneuroma in the adrenal gland. This association is probably coincidental; however, with increasing cancer cases in HS and the genetic studies being made, this association will be clarified.

Key words: hereditary spherocytosis, child, ganglioneuroma, adrenal gland, cytogenetics, extramedullary hematopoiesis.

Hereditary spherocytosis (HS) is the most frequent cause of congenital hemolytic anemia and occurs at a frequency of 1/5,000¹. Affected individuals are almost asymptomatic; however, they may present with severe hemolysis. Extramedullary hematopoiesis (EMH) mimicking a mass may develop in the lymph nodes, kidneys, pleura, mediastinum, adrenal gland, and in particular the spleen and liver²⁻⁵. Other than EMH, B-cell lymphoma⁶, follicular mixed type lymphoma⁷, acute lymphoblastic leukemia^{8,9}, and pancreatic schwannoma¹⁰ cases were reported in patients with HS. Furthermore, in the literature, adenomatous polyposis coli¹¹ and juvenile polyposis coli^{12,13} were reported in patients with HS. We present the first case of ganglioneuroma in the adrenal gland in patients with HS.

Case Report

A 13-year-old female patient with a four-year history of HS was admitted to our center with abdominal pain for one month. The physical examination was normal. Splenectomy had been performed two years ago. Her laboratory studies at the time of the diagnosis of HS had revealed hemoglobin 4.2 g/dl, hematocrit 12.3%, leukocyte count 8900/mm³, and reticulocyte count 4.6%. Her peripheral

smear had shown spherocytes, anisocytosis and polychromasia. Her total bilirubin was 4.3 mg/dl, indirect bilirubin 4.1 mg/dl, and lactate dehydrogenase (LDH) 739 IU/L. Her osmotic fragility test was increased. Abdominal ultrasonography showed a heterogeneous, hypochoic 5 cm mass in the right suprarenal gland. Abdominal computed tomography revealed a hypodense mass measuring 66x54x23 mm, which contained small calcifications. Abdominal magnetic resonance imaging (MRI) was performed to further characterize the mass. The mass stemmed from the adrenal gland and showed heterogeneous hypointensity in T1- and hyperintensity in T2-weighted images (Fig. 1).

Urine vanillylmandelic acid (VMA), plasma homovanillic acid (HVA), and neuron-specific enolase levels were normal. Plasma rennin, cortisol and adrenocorticotrophic hormone (ACTH) were within normal limits. There was no rosette formation in bone marrow smears. Tru-cut biopsy was performed. Histopathology was consistent with ganglioneuroma. A complete tumor resection was performed. The mass was 7x5.5x4 cm and encapsulated. In sectioning, it appeared diffuse, creamy and solid. Microscopically, the tumor consisted of scattered mature ganglion cells embedded in

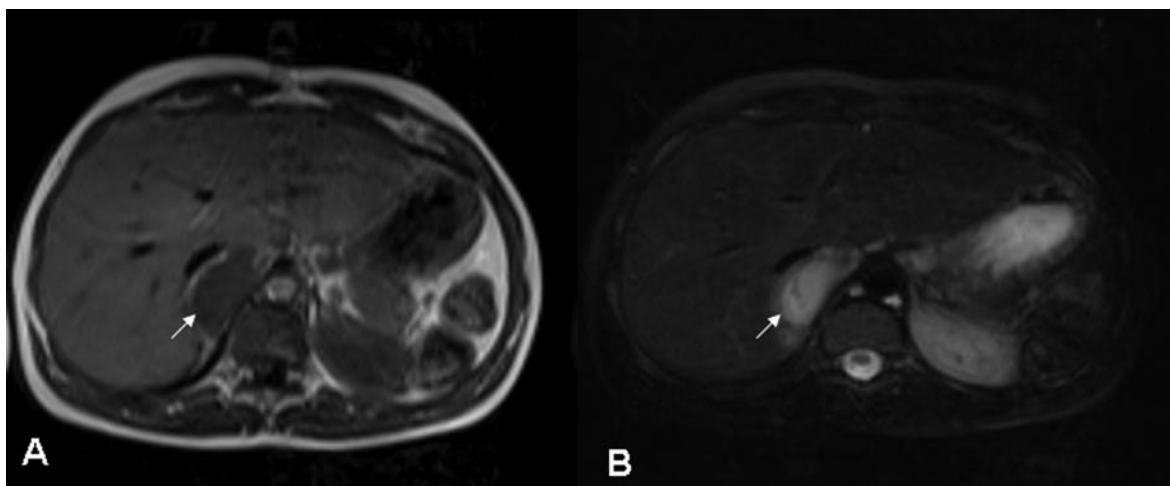


Fig. 1. Right adrenal gland mass showing hypointensity in T1- (A) and hyperintensity in T2-weighted images, arrows (B).

a schwannomatous stroma. It also contained scattered lymphoid aggregates and dystrophic calcification fields and infiltrated the surrounding fat focally (Fig. 2). Cytogenetic analysis was normal. MYCN amplification in tumor tissue was not detected. The patient is under follow-up without disease.

Discussion

Hereditary spherocytosis (HS) is a disease included in the congenital hemolytic anemia group, which occurs due to the deficiency of proteins in the erythrocyte membrane, and it presents autosomal dominant inheritance³. However, 25% of the cases are found to be sporadic¹⁴. It has been reported that HS is caused by a defect in the vertical relationship between membrane carcass and lipid bilayer, which arises as a result of the deficiencies mostly in ankyrin, spectrin and band 3 proteins¹⁵. As a result, icterus, splenomegaly, cholecystolithiasis, and hemolytic and megaloblastic crises may develop in patients with HS due to hemolysis^{2,3}.

Extramedullary hematopoiesis (EMH) may develop in such patients and mimic a solid tumor due to the medullary hematopoiesis deficiency arising as a result of chronic anemia in children with HS^{1-4,16}. To the best of our knowledge, EMH has been reported mostly in adults^{2-5,16} and in only one child. This situation may be explained by the fact that the bone marrow production capacity in children is higher than in adults.

Since EMH is rarely seen in children with HS, we first considered a solid tumor originating from the adrenal gland based on the radiological findings in our patient. Considering the location of the mass, we performed a Trucut biopsy for a neuroblastic tumor. Primary surgical resection was performed for both treatment and eliminating neuroblastoma and ganglioneuroblastoma since its pathology was consistent with ganglioneuroma. As the mass was entirely ganglioneuroma, the patient was taken under follow-up without applying any treatment. No neuroblastic tumors have been reported in patients with HS in the literature. However, in patients with HS, malignant diseases, such as lymphoma^{6,7}, leukemia^{8,9} and pancreatic schwannoma¹⁰, have been reported. No explicit relation has been determined between malignant diseases and HS; possible genetic relations may be conceived as the number of cases increases and by means of cytogenetic studies. In our case, we performed cytogenetic analysis but did not find any anomalies. On the other hand, Hayama et al.⁶ reported chromosomal translocation of t(6;14) in a patient with diffuse large B-cell lymphoma and reported that studies on the mechanism of lymphomagenesis are needed. In another splenic lymphoma case, it was speculated that splenomegaly and lymphoma may develop due to chronic stimulation as a result of hemolysis⁷.

It has been reported that, among the genes that cause deficiency in membrane proteins in

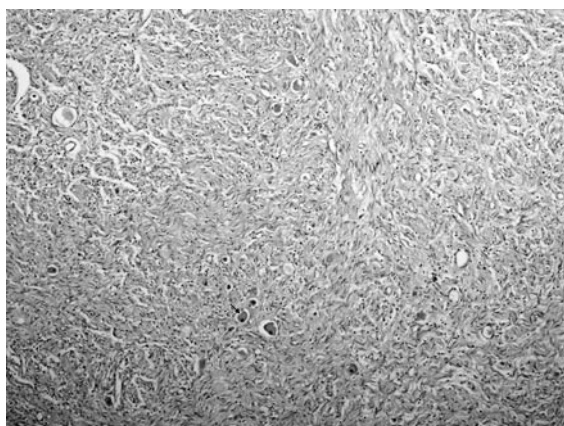


Fig. 2. Mature ganglion cells (arrows) in schwannomatous stroma (hematoxylin & eosin [HE]x100).

HS, band 3 locates on chromosome 17q12-q21, ankyrin 1 on 8p21.1-p11.2, alpha-spectrin on 1q21, band 4.2 on 15q15-q21, and beta-spectrin on 14q23-q24.2^{11,17}. On the other hand, neuroblastic tumors consist of neuroblastoma, ganglioneuroblastoma and ganglioneuroma, and their clinical behavior may present different courses, from spontaneous regression to aggressive progression^{18,19}. In the studies made on neuroblastomas, it has been reported that some alterations occurred in the 1p36, 1q, 2p13-p14, 3p21, 3p26, 3q24-p26, 4q33-q35, 6p11-p22, 11q23, 12q, 14q32, 17q, and 19q related genes¹⁹. Furthermore, there is no detailed study on ganglioneuromas and these genes. The possible relationship between 1q, 14q32 and 17q from the genes responsible for HS and 1q21, 14q23-q24.2 and 17q12-q21 in neuroblastomas may be responsible for the development of this tumor. However, since the gene studies on ganglioneuromas are restricted, it is difficult to assert such a claim.

Although the relationship has not been proven and is rare, certain cases of leukemia, lymphoma and solid tumor have been reported in patients with HS. No case of ganglioneuroma in patients with HS has been reported in the literature. This association is probably coincidental. However, with increasing cancer cases in HS and the genetic studies being made, this association will be clarified.

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