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Is the Coexistence of Hereditary Elliptocytosis with Osler-Weber-Rendu Syndrome Coincidental?

Kalıtsal Eliptositoz ve Osler Weber Rendu Birlikteliği Rastlantısal mı?

CASE REPORT
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ABSTRACT
ÖZET

Hereditary haemorrhagic telangiectasia (HHT) and hereditary elliptocytosis (HE) are genetic diseases that may cause anaemia and show hereditary inheritance. Several mutations have been defined which may cause the occurrence of both diseases. However, there is no study that shows if there is or is not a common mutation for these two diseases. In this article, a case in which recurrent spontaneous epistaxis, mucocutaneous telangiectasia and elliptocytosis in the peripheral smear were determined during an evaluation for anaemia. Some family members of this case were found to be positive for elliptocytosis and haemorrhagic telangiectasia. No similar reports have been published in the literature.

Key words: Elliptocytosis, hereditary, hereditary haemorrhagic, telangiectasia

Hemorajik herediter telenjektazi (HHT) ve herediter eliptositoz (HE) kalıtsal geçiş gösteren ve anemiye neden olabilen genetik hastalıklardır. Her iki hastalığa neden olabilecek çeşitli mutasyonlar tanımlanmıştır. Ancak iki genetik hastalıkta ortak bir mutasyon olup olmadığı konusunda yayın bulunmamaktadır. Makalede anemi nedeni ile yapılan incelemede, tekralayan spontan epistaksis, mukokutanöz telanjiektaziler ve periferik yaymasında eliptozitoz tespit edilen ve yapılan aile taramasında diğer aile bireylerinde eliptositoz ve hemorajik telenjatazi saptanan bir vaka daha önce literartürde yayınlanmaması nedeni ile sunulmuştur.

Anahtar kelimeler: Eliptositoz, herediter hemorajik, kalıtsal, telenjiektazi,

Introduction

Epistaxis, which is the earliest symptom of hereditary haemorrhagic telangiectasia (HHT), appears at the beginning of the third decade in approximately half of patients. It is more prevalent in males during childhood and in the newborn period. However, it is more prevalent in females in the third and fourth decades (1, 2). Telangiectasia typically appears after the appearance of epistaxis. It progresses with recurrent multiple dermal, mucosal and visceral telangiectasias. In approximately half of patients, internal organ involvement is seen in subsequent years after the appearance of these findings. In 15% of patients, pulmonary arteriovenous malformations may develop (3). These malformations are dangerous and may cause paradox embolism, sometimes septic embolism and rarely haemoptysis and haemothorax (4).

Hereditary elliptocytosis, which has a prevalence of 1:3000, is a morphological disorder in which more than 15% of erythrocytes are ellipsoid. There are four different clinical phenotypes of hereditary elliptocytosis according to the different molecular defects. These are hereditary elliptocytosis, mild hereditary elliptocytosis, hereditary pyropoikilocytosis and spherotic hereditary elliptocytosis.

The clinical presentation of HE is heterogeneous, ranging from asymptomatic carriers to patients with severe, life-threatening anaemia. Most patients with "typical" HE are asymptomatic and are diagnosed incidentally during testing for unrelated conditions. However, symptoms may vary between members of the same family and symptoms may vary in the same individual over time. These normochromic, normocytic elliptocytes may number from a few to 100%; the degree of haemolysis does not correlate with the number of elliptocytes present.

Case Report

A 54-year-old female patient with symptoms of frequent nosebleeds, fatigue, weakness and palpitations consulted at our clinic. Symptoms had been present for 15 years; she was hospitalised on several occasions and received iron replacement treatment and blood transfusions. It was underlined in her history that the patient had been treated for diabetes mellitus, hypertension, coronary artery disease and she had been operated on with a diagnosis of cholelithiasis. It was determined that frequent nosebleeds were also present in her grandfather, father, sister and grandchildren, and her sisters and grandchildren had been treated for anaemia. The arterial blood pressure was 110/70, pulse was 112/min and the conjunctiva were pale.

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The ocular examination was normal; telangiectasias were present at the larynx, oral mucosa, nasal mucosa and lips (Figure 1).

In the cardiovascular examination, the heart beat was rhythmic, tachycardic, and a 2/6 systolic murmur was present at the apex. Splenomegaly and hepatomegaly were determined upon abdominal examination. The other systemic examinations were normal. Laboratory examination of the patient provided the following: white cells 2800/mm^3, thrombocytes 69000/mm^3, Hb 5.8 mg/dL, Hct 19.2%, MCV 59 fl, RDW 19.2%, sedimentation rate 8 mm/min; hepatic function tests, thyroid function tests and renal function tests were normal. Prothrombin time was 15.8 s, aPTT 39 s, INR 1.2, iron 16 µg/dL, total iron binding capacity 299, ferritin 12.5 ng/mg, vit-B12 234 pg/mg, folate 10.9 ng/mg, CRP 3.2 and reticulocytes 1.17%. Hepatosplenomegaly was determined by abdominal ultrasonography and the gall bladder could not be seen due to prior removal.

Erythrocytes were hypochromic and microcytic on the peripheral smear, and anisocytosis, poikilocytosis, target cells and elliptocytes were identified (Figure 2). Thrombocytes were seen as decreased in number. A slight increase in osmotic resistance was determined by the osmotic fragility test. The sickling test and haemoglobin electrophoresis were normal. There was no malignant infiltration and no space-occupying lesions were found upon bone marrow aspiration and biopsy. Iron storage was assessed and found to be decreased.

The iron deficiency of the patient was thought to be a result of telangiectasia of the gastrointestinal system because of the presence of telangiectasias in the oral mucosa and lips, and a few telangiectasic lesions at the corpus and bulbus were seen by endoscopy of the upper gastrointestinal system. Family scanning was performed because it was thought that the elliptocytosis and telangiectasic lesions of the patient could be the result of hereditary transmission.

In the peripheral smears of three children and two brothers of the patient, elliptocytes were determined and an increase in osmotic resistance of erythrocytes was determined by osmotic fragility tests. Telangiectasic lesions were found in two children and two sisters in the family scanning. A diagnosis of hereditary elliptosis and hereditary haemorrhagic telangiectasia was considered in this patient. Intravenous iron replacement therapy was started and it was supported with 1 mg/day of folate. The laboratory examination two months later found white cell 5100/mm^3, thrombocytes 104000/mm^3, Hb 10.2 mg/dL and Hct 31.2%.

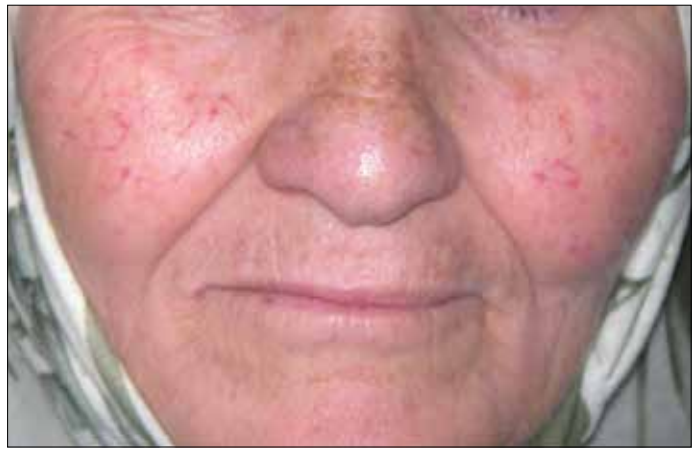

Figure 1. Telangiectasias on the cheeks and lips

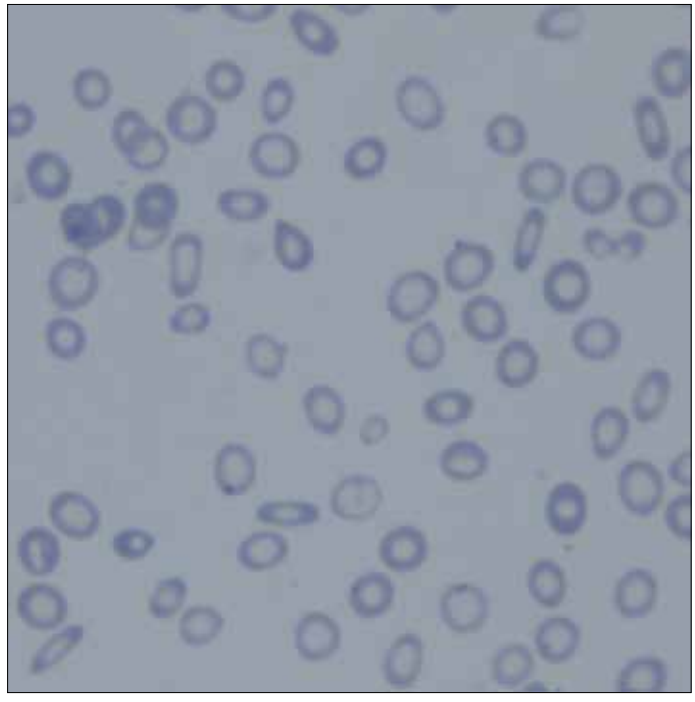

Figure 2. Erythrocytes were hypochromic and microcytic in the peripheral smear and anisocytosis, poikilocytosis, target cells and elliptocytes were identified

Discussion

The fragility of abnormal vessels is thought to be responsible for recurrent bleeding in patients with HHT (5). Thrombocyte functions, bleeding time, clotting time and prothrombin time are generally normal (2-6). The recurrent complications can be listed as severe anaemia, portal hypertension, pulmonary hypertension and stroke. The characteristic finding of this disease is the presence of diffuse arteriovenous malformations which are localised, abnormal arteriovenous connections that affect both microvascular structures and large vessels (7).

In HHT, which is known to be genetically transmitted, two loci related to this disease have been identified: the ACVRL1 gene and the ENG gene. HHT1 and HHT2 are the two major types of this disease and are related to these two genes. Another type of HHT is HHT3, and the gene related to this type is linked to chromosome 5 (8).

HE is transmitted as an autosomal dominant trait and at least four genetic loci are implicated in the pathogenesis of HE. The elliptical shape of erythrocytes is found only in the circulation which explains why reticulocytes and bone marrow red blood precursors are normal in shape. Morbidity ranges from asymptomatic cases most of the time to severe transfusion-dependent disease, and rare fatalities have been documented. While HE has no sex predilection, it is more common in African and Mediterranean regions (9). The most common complications in patients with HE are gallstones and haemolytic crises, and more rarely chronic leg ulcers and/or dermatitis may be seen (10, 11). The association between hereditary elliptocytosis and several other diseases has been reported as

case reports. Some of these are chronic leg ulcers or dermatitis (10, 11), MDS (12), Chédiak-Higashi syndrome (13) and beta thalassemia. In this study, heterozygous family members with either the beta-thalassaemia trait or HE were asymptomatic, whereas the two with both beta-thalassaemia and HE had marked red blood cell deformities and haemolysis. Red blood cell abnormalities in patients with the beta-thalassaemia trait might be enhanced by an association with HE owing to a protein 4.1 deficiency (14). The human anion exchanger 1 (AE1 or SLC4A1) gene encodes the anion exchanger 1 (or band 3) protein in erythrocytes and in the alpha-intercalated cells of the kidney.

Elliptocytes may be seen in association with several disorders such as megaloblastic anaemia, hypochromic microcytic anaemia, myleodysplastic syndrome and myelofibrosis. History and additional laboratory testing usually clarify the diagnosis of these disorders. Osmotic fragility is abnormal in severe HE and HPP. Other laboratory findings in HE are similar to those found in other haemolytic anaemias and are non-specific markers of increased erythrocyte production and destruction. In difficult cases or cases desiring a molecular diagnosis, specialised testing such as erythrocyte membrane protein quantfication and genetic testing are available (15).

In the peripheral smears of patients with iron deficiency anaemia, a partial increase in elliptocytes may present. For this reason, it has to be shown that the elliptocytosis is not a result of iron deficiency anaemia. In our patient, hereditary haemorrhagic telangiectasia, which causes both elliptocytosis and iron deficiency anaemia, was present.

However, the history of splenomegaly and cholelithiasis in the patient and the determination of telangiectasia and more than 15% ellipsoid erythrocytes in the peripheral smear make us think that elliptocytosis is hereditary. It is obvious that iron deficiency anaemia contributes to elliptocytosis. We thought that these diseases may be asymptomatic if they occur alone; however, the presence of erythrocyte membrane defects make the anaemia evident. We thought that the anaemia in the patient and in the family members was related to iron deficiency and erythrocyte membrane defects. However, other diagnoses have to be considered and hereditary conditions that rarely cause anaemia have to be considered after excluding the possible diagnosis. The diagnosis has to be verified by scanning the family members of patients in whom hereditary transmission is considered.

Conclusion

As a result, it was kept in mind that, HHT and HE are genetic diseases that may cause anaemia andshow hereditary inheritance. This report attempts unusual combination of HHT and HE which is not yet been discussed in the literature.

Conflict of interest
No conflict of interest was declared by the authors.

Authors' contributions: Conceived and designed the study: ÖA, EA, FG. Examination and follow-up of the patient: MÖ, MA. Wrote the paper: ÖA, NA. All authors read and approved the fi nal manuscript.

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