CASE REPORT

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Two juvenile polyps, hereditary hemorrhagic telangiectasia and SMAD4 mutation

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An adolescent girl with recurrent iron deficiency anemia, epistaxis, cyanosis, hypoxemia, clubbing, two juvenile polyps in the colon, oro-naso-pharyngeal telangiectasias, multiple arterio-venous malformations of the lungs, and a new homozygous mutation in SMAD4 gene is reported. Patients with juvenile polyps should be examined carefully for mucocutaneus findings and digital clubbing. When a combination of these signs is noted, a genetic testing is warranted inspite of low polyp count in order to prevent potential risk of malignancy and other complications.

Key words: SMAD4 mutation, child, juvenile polyp, arteriovenous malformations

İki jüvenil polip, herediter hemorajik telenjiektazi ve SMAD4 mutasyonu

Tekrarlayan demir eksikliği anemisi olan adolesan kız hastada, burun kanaması, siyanoz, hipoksemi, çomak parmak, kolonda iki adet juvenil polip, oronazofagiyal telenjiyektaziler, akciğerlerde çok sayıda arteriyovenöz malformasyonlar ve SMAD4 geninde yeni bir homozigot mutasyon bildirilmiştir. Kolonda juvenil polipi olan hastalar mukokütanöz bulguları ve çomak parmak açısından dikkatle incelenmelidir. Bu belirtiler bir arada belirlendiğinde, kolonda az sayıda polip olsa bile genetik test yapılması malignite ve diğer potansiyel tehlikeleri önlemek için önemlidir.

Anahtar kelimeler: SMAD4 mutasyonu, çocuk, jüvenil polip, arteriyovenöz malformasyon

INTRODUCTION

Sporadic colonic juvenile polyps may be single or multiple, and are considered to be benign solitary lesions. They usually present with rectal bleeding, and occur in up to 2% of the pediatric population (1). Juvenile polyposis syndrome (JPS) is characterized by multiple juvenile polyps, usually in the colon, however may also be found in the stomach as well as the small intestine. SMAD4 (18q21.1) is a tumor-suppressor gene (2), and its involvement has been described in patients with JPS (3-5).

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder leading to vascular dysplasia. Common symptoms include skin and mucosal telangiectasias, pulmonary, cerebral and hepatic arteriovenous malformations, and hemorrhage associated with these vascular lesions. There are many reports in patients with JPS that display symptoms of HHT (6-8), and these disorders overlap clinically as well as genetically (9).

There are four genes (SMAD4; endoglin (ENG); activin A receptor type II-like 1 (ACVRL1); and type I receptor for bone morphogenetic protein (BMPR1A) involved in the pathogenesis of both JPS and HHT disorders, and they encode members of the TGF-beta signaling pathway (3). TGF is involved in many biological processes including cell-cycle control, embryogenesis, growth, development, and differentiation of several cell types (10).

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SMAD4 protein is an integral downstream effector of the TGF signal transduction pathway. SMAD4 mutations in endothelial cells may contribute to vascular dysplasia, whereas the same mutation in colonic mesenchymal or epithelial cells may lead to polyp formation.

Here we report a child with a SMAD4 mutation of c.1608delA having typical clinical findings of HHT, but clinical symptoms not typical of JPS in terms of polyp count.

CASE REPORT

A 12 year-old female was admitted to a referring hospital with weakness, paleness, and recurrent iron deficiency anemia. She had received previous oral iron treatment several times and she experienced recurrent nose bleedings for eight years, but she did not have any melena or hemotochesia episodes. Her parents were not consanguineous. Physical examination showed growth retardation. She was 33 kg in weight and 144 cm tall. She had cyanosis, as well as clubbing of the fingers and toes. She had red tiny nodular spots on her tongue and lips (Figure 1,2). Colonic polyps were found during colonoscopy, and she was subsequently referred to our pediatric gastroenterology unit for polypectomy.

Her complete blood count showed a hemoglobin of 6.35 gr/dl, hematocrit of 24.8%, MCV of 55.4 fl, RDW of 17, and thrombocytes of $2.9x10^5/mm^3$. Coagulation parameters were normal. Anti tissue transglutaminase antibodies were negative.

While hospitalized at our center, we observed severe nose bleeding in this patient. We referred her to our ear-nose and throat clinic. Fiber optic endoscopy showed multiple telangiectasias on her tongue, epiglottis, posterior pharynx, nasopharynx, nasal septum, and adenoids. Upper endoscopy showed millimeter size lesions red lesions on her gastric corpus and antrum mucosa. No polyps were detected. Colonoscopy showed two very large polyps in the transverse colon and the hepatic flexure (Figure 3). The terminal ileum was normal. Polypectomy was performed, and histological examination showed mucin-filled multiple dilated crypts consistent with juvenile polyps (Figure 4). Crypts showed dysplastic and non-dysplastic epithelium. Small bowel contrast radiography was normal. The patient was cyanotic. Oxygen saturation via pulse oximetry was noted to be 80%. Arterial blood gas analysis showed pH

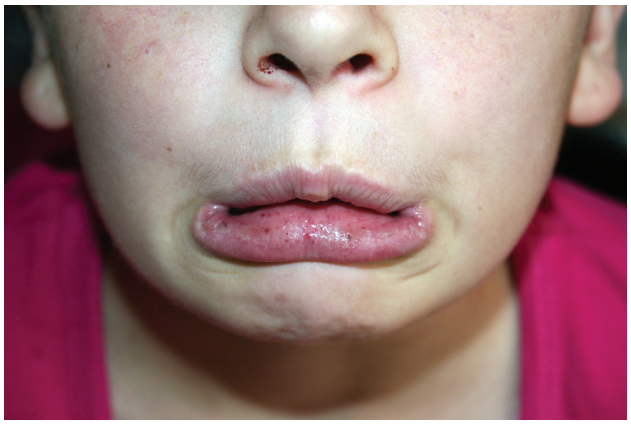

Figure 1. Mucosal red spots (lips)

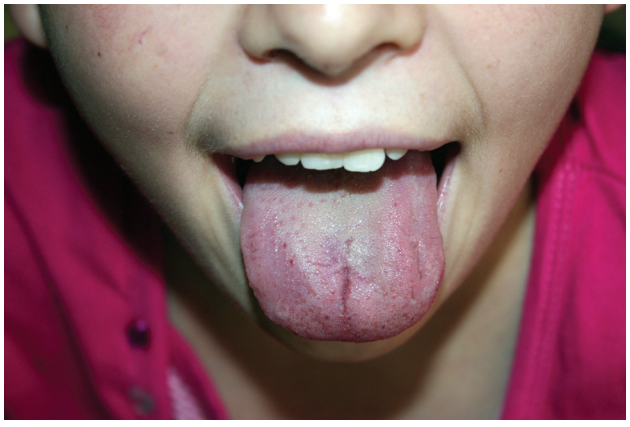

Figure 2. Mucosal red spots (tongue)

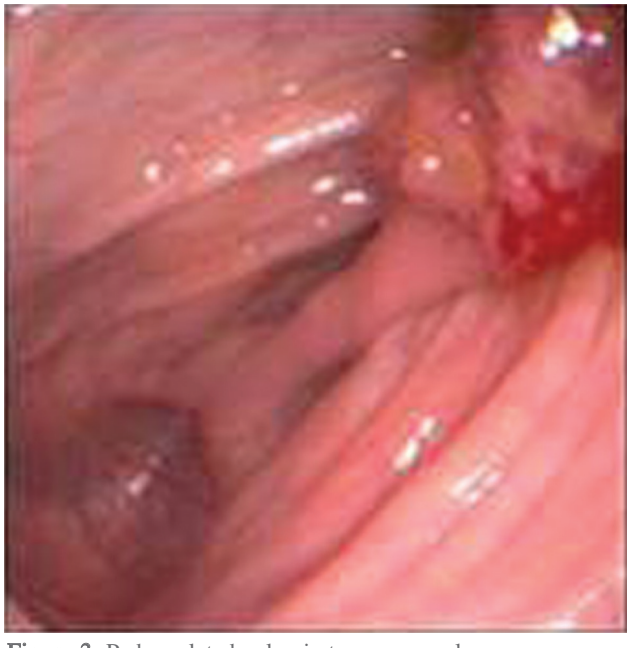

Figure 3. Pedunculated polyp in transverse colon

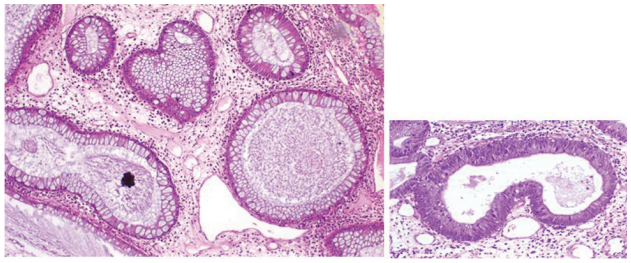

Figure 4. Juvenil polyp which contains dilated crypts. Crypt shows dysplastic and nondysplastic epithelium (Haemotoxylin–Eosin x10 x20 original magnification)

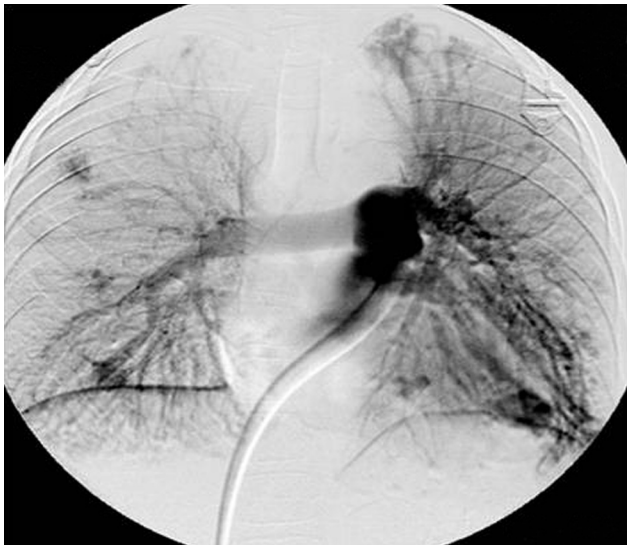

Figure 5. Bilateral pulmonary arteriovenous malformations and coil embolization of the left lung

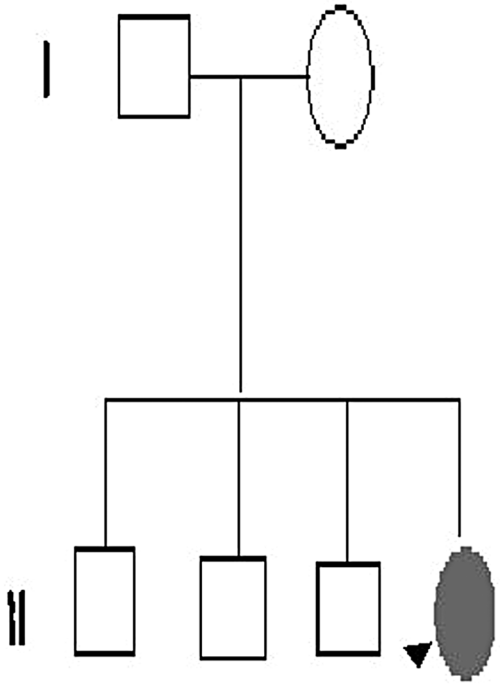

Figure 6. Pedigree

of 7.48, PaO_2 of 56 mmHg, $PaCO_2$ of 24 mmHg, and alveoli-arterial gradient of 72 mmHg (N:< 20), while the patient was sitting. Contrast echocardiography demonstrated pulmonary arterio-venous shunts. Pulmonary arteriography showed bilateral arteriovenous shunts, and three of these noted to be in the left lung were obstructed with coil embolization (Figure 5). One month later, the patient underwent pulmonary angiography again for the right lung showing diffuse shunts, and despite coil embolization, no significant rises in arterial blood oxygenation could be obtained. She has been using an oxygen concentrator for oxygen support since this procedure. Cerebral MR angiography and abdominal ultrasonography did not indicate an arteriovenous malformation.

In our patient with juvenile polyps, diffuse telangiectasis, and arteriovenous malformations in the lungs, we diagnosed her condition as a combined syndrome of juvenile polyposis and hereditary hemorrhagic telangiectasis with SMAD4 mutations. Genetic testing (11) confirmed a SMAD4 mutation in exon 11 (c.1608delA; amino acid consequence of p.Asp537ThrfsX15). It is a true deleterious mutation with a frame shift due to deletion of one nucleotide within the coding sequence. The consequence of this frame shift deletion is the synthesis of a shortened protein, lacking the C-terminus, and lacking the corresponding functional domains (Direct sequencing DNA genomic –ABI PRISM 3130, 3500).

DISCUSSION

Juvenile polyposis is based on diagnostic criteria of the presence of any one of the following: three (five) or more colorectal juvenile polyps, juvenile polyps throughout the gastrointestinal tract, or any juvenile polyps in a patient with a family history of JPS (12). Although our patient had diagnostic criteria of HHT, she did not fulfill JPS criteria, as the patient had only two juvenile polyps. Although both JPS and HHT are inherited in an autosomal dominant fashion, there was no family history, indicating a possible de-novo mutation of the pro-band. SMAD4 mutation in exon 11 (c.1608delA; p.Asp537ThrfsX15) has not been described before. Her mother and three siblings were tested for the SMAD4 mutation although they were asymptomatic (Figure 6). The mother of the pro-band rejected gastrointestinal examination of her other children. Initial clinical signs of HHT may be subtle, as disease expression is age-rela-

ted. For this reason, genetic analysis was offered to them. Her father was not alive, therefore we could not know precisely whether the father transmitted the mutation, or whether this was a de-novo mutation.

An aggressive screening protocol for visceral arteriovenous malformations is warranted for individuals with SMAD4 mutations. The patient we report had pulmonary AV malformations leading to severe hypoxemia. Unfortunately, an aggressive endovascular treatment intervention was not successful.

Iron deficiency anemia in a patient with known hereditary HHT may be attributed to the presence of mucosal telangiectasias causing epistaxis, and occult or overt gastrointestinal bleeding. These patients with HHT who have recurrent iron deficiency anemia, gastrointestinal bleeding, or digital clubbing should be examined for juvenile polyposis to ensure proper clinical management. Genetic testing of patients presenting with either JPS or HHT phenotypes will reveal those at risk of this combined syndrome due to SMAD4 mutations.

Gallione et al. (13) reported on fourteen patients with both JPS and HHT phenotypes. They demonstrated de-novo SMAD4 mutations in three family members. Seven of twelve patients with reported polyps were diagnosed within the first decade of life, and five others by age fifteen. One patient had only a single tubular adenoma in the cecum.

In conclusion, JPS patients with SMAD4 mutations should be screened for clinically silent vascular lesions. These patients are at increased risk of HHT. HHT patients with SMAD4 mutations are at increased risk of colorectal cancer. Possibility of a combined syndrome should be considered. The definition of "Three (Five) or more colonic polyps" may cause underestimation of JPS.

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