Gastric angiodysplasia in a hereditary hemorrhagic telangiectasia type 2 patient

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Abstract

Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal-dominantly inherited disease that occurs in approximately one in 5000 to 8000 people. Clinical diagnosis of HHT is made when a person presents three of the following four criteria: family history, recurrent nosebleeds, mucocutaneous telangiectasis, and arteriovenous malformations (AVM) in the brain, lung, liver and gastrointestinal (GI) tract. Although epistaxis is the most common presenting symptom, AVMs affecting the lungs, brain and GI tract provoke a more serious outcome. Heterozygous mutations in endoglin, activin receptor-like kinase 1 (ACVRL1; ALK1), and SMAD4, the genes involved in the transforming growth factor-β family signaling cascade, cause HHT. We report here the case of a 63 year-old male patient who presented melena and GI bleeding episodes, proven to be caused by bleeding from multiple gastric angiodysplasia. Esophagogastroduodenoscopy revealed multiple angiodysplasia throughout the stomach. Endoscopic argon plasma coagulation was performed to control bleeding from a gastric angiodysplasia. The patient has been admitted several times with episodes of hemoptysis and hematochezia. One year ago, the patient was hospitalized due to right-sided weakness, which was caused by left basal ganglia hemorrhage as the part of HHT presentation. In family history, the patient’s mother and elder sister had died, due to intracranial hemorrhage, and his eldest son has been suffered from recurrent epistaxis for 20 years. A genetic study revealed a mutation in exon 3 of ALK1 (c.199C > T; p.Arg67Trp) in the proband and his eldest son presenting epistaxis.

Key words: Hereditary hemorrhagic telangiectasia; Angiodysplasia; Intracranial hemorrhage; Epistaxis; Activin receptor-like kinase 1

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INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), also called Osler-Weber-Rendu syndrome, is a rare autosomal dominant genetic disorder occurring in about one in 5000 to 8000 people worldwide. HHT is characterized by family history, recurrent nosebleeds, mucocutaneous telangiectasia, and arteriovenous malformations (AVMs) in the brain, lung, liver and gastrointestinal (GI) tract. Clinical diagnosis of HHT is made when a person presents with three of these four symptoms. However, due to the highly variable onset and penetrance of these clinical symptoms, HHT is often misdiagnosed. Epistaxis and skin telangiectasia are the most common presenting symptoms that appear in over 90% of HHT patients aged over 60 years. Cerebral and pulmonary AVMs occur in around 10%-20% and 50% of HHT patients, respectively, and are associated with high mortality and morbidity due to stroke or brain abscess. AVMs in the GI tract can lead to melena, brisk GI bleeding, and hematochezia. Most elderly HHT patients suffer from anemia due to epistaxis and GI bleeding.

Genetic studies have shown that heterozygous mutations in endoglin (ENG) or activin receptor-like kinase 1 (ALK1; ACVR1L1) cause HHT. HHT by ENG or ALK1 mutations is designated as HHT1 or HHT2, respectively, although they are clinically indistinguishable. Some juvenile polyposis (JP) patients with SMAD4 heterozygous mutations have shown HHT symptoms and are designated as JP-HHT. Two additional genetic loci in chromosomes 5 (HHT3) and 7 (HHT4) have been identified. HHT1 and HHT2 account for over 80% of HHT worldwide.

In this report, we describe a case of a patient presenting with multiple gastric angiodysplastic lesions, intracranial hemorrhage (ICH), and a family history of ICH and epistaxis. Through genetic testing, we found a known mutation in ALK1 (c.199 C > T; p.Arg67Trp), resulting in loss of function. Additionally, the patient’s son had been suffering from epistaxis. To our knowledge, this is the first case in Korea of genetic confirmation of HHT2 with multiple gastric angiodysplasia.

CASE REPORT

A 63-year-old male was admitted due to melena. Examination revealed stable vital signs with normal blood pressure and heart rate, but routine laboratory tests revealed mild anemia with a hemoglobin level of 9.6 g/dL. Esophagogastroduodenoscopy (EGD) revealed multiple angiodysplastic lesions throughout the stomach (Figure 1A and B). Conservative treatment, including proton pump inhibitors, led to a stable clinical condition. The patient was subsequently hospitalized again due to hemoptysis, and then once more due to hematochezia; all were managed by conservative treatment regimens. We carefully investigated the patient’s medical and family history. The patient’s mother and older sister died from ICH. His eldest son had been suffering from recurrent epistaxis for 20 years (Figure 2A). Therefore, due to the presumptive diagnosis of HHT, we carried out genetic screening for the ENG and ALK1 genes. A heterozygous mutation in ALK1 was detected from the proband of both the patient and his eldest son, but not from a daughter who did not show any apparent HHT-related symptoms (Figure 2B). A single nucleotide substitution from “C” to “T” at the 199th coding nucleotide (c.199 C > T) in exon 5 changed the 67th amino acid, arginine, to tryptophan (p.Arg67Trp), resulting in loss of ALK1 function (Figure 2B). Abdomino-pelvic computed tomography (CT) scan of the proband, performed for evaluation of a gallbladder stone, revealed multiple intrahepatic AV shunts (Figure 3A). Later, the proband received peritoneoscopic cholecystectomy, and then the patient was hospitalized again due to the sudden onset of right-sided weakness. Brain CT revealed ICH at the left basal ganglion, and he was transferred to a local rehabilitation facility (Figure 3B). The patient was recently admitted for percutaneous endoscopic gastrostomy insertion.

DISCUSSION

In the present case, we report a patient with multiple angioplastic lesions in the stomach, chronic hemorrhages in the GI tract, and stroke by ICH. Presence of ICH and epistaxis in his immediate family members (mother, sister and son) led us to diagnose HHT. Genetic screen-
The substitution mutation at the 199th coding nucleotide of the ALK1 gene, specifically in the proband and the son presenting as epistaxis, but not in the daughter who had no apparent symptoms [18-23]. These data confirmed the clinical diagnosis and showed that the patient carries the HHT2 subtype. HHT1 and HHT2 are clinically similar in presentation, but genotype-phenotype correlation studies have shown that occurrence of pulmonary AVMs is significantly higher in HHT1, whereas liver AVM tend to be more common in HHT2 [20,21,24-28]. Cerebral involvement and spinal AVMs are reported in 10%-20% and 1%-2% of HHT1 and HHT2 cases, respectively [8,27]. Whether genetic or environmental factors contributed to this observation in this family or the wider Korean HHT population remains to be determined. The mutation found in this family (c.199 C > T; p.Arg67Trp) has previously been reported by five other groups [18-23]. The 67th amino acid is located in the ligand binding domain of ALK1. Previous biochemical analysis of the Arg67Gln substitution resulted in a deficiency in signal transduction, suggesting a null mutation [29]. Life-threatening cerebral and pulmonary AVMs that form during development and the neonatal period are often asymptomatic for a prolonged period. Manifestations of epistaxis, skin telangiectasis, and GI AVMs are generally absent at birth, but develop over puberty and progressively worsen with age [7,30,31]. Genetic screening of asymptomatic family members would allow detection of deadly forms of vascular lesions in advance, before complications arise. GI bleeding associated with HHT occurs in about 15%-30% of patients, and GI telangiectasia, including angiodysplasia, is a relatively common manifestation of HHT [17,23]. However, reports of this syndrome in the form of angiodysplasia on EGD in the GI tract, including the stomach, are rare. 

Figure 2 Pedigree and genetic analysis of an hereditary hemorrhagic telangiectasia family. A: Pedigree of a family with genetic mutations and/or symptoms of hereditary hemorrhagic telangiectasia (HHT) and intracranial hemorrhage (ICH). The proband is indicated by an arrow. A divided symbol represents the individual with ICH. Deceased individuals are indicated by a slash; B: Genetic studies of unaffected and affected family members. The affected member had a heterozygous activin receptor-like kinase 1 (ALK1) mutation (c.199C > T; p.Arg67Trp). The amino acid translation is shown above each codon. The mutation was found in exon 3, indicated by an asterisk; 3. Protein domains of ALK1 are indicated under the exons: extracellular domain (ECD), transmembrane domain (TM), and kinase domain (KD). 

Figure 3 Hepatic arterio-venous shunt and cerebral hemorrhage. A: Abdominal computed tomography (CT) showing an intra-hepatic arterio-venous shunt; B: Cerebral hemorrhage was noted in the left basal ganglia on brain CT.
Together with epistaxis, GI bleeding is a serious issue for elderly HHT patients. Recent studies indicate that environmental factors such as injury and inflammation, in addition to genetic predisposition (ALK1 or ENG mutations), are critical for development of AVMs in adults. Multiple anti-inflammatory, anti-angiogenic, and anti-oxidants drugs such as thalidomide, bevacizumab and N-acetyl-cysteine have been tested as potential therapies for ameliorating epistaxis and GI bleeding. We report here that the proband had multiple angiodyplastic lesions in the stomach and also hematochezia, indicating that vascular lesions had spread to the lower GI tract. In addition, close monitoring for GI bleeding is needed. Capsule endoscopy and conventional endoscopy may provide important information on whether these drugs can induce regression of existing vascular lesions.

In summary, we report the case of a patient in whom we found multiple gastric angiodyplastic lesions. With both clinical evaluation and genetic screening, we confirmed that the patient was suffering from HHT2. Family history and other HHT symptoms should be carefully evaluated when a patient shows multiple angiodyplastic lesions. Genetic screening has tremendous benefit not only for confirming the diagnosis but also in preventing asymptomatic family members developing life-threatening complications.

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