Choi et al.; Headache and Epistaxis Associated with Ischemic Stroke

Family History of Headache and Epistaxis Associated with Ischemic Stroke

İskemik İnme ile İlişkili Ailede Baş Ağrısı ve Epistaksis Öyküsü

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Abstract

A 34-year-old woman presented to the emergency room with symptoms of transient right arm weakness, hemoptysis, headache, and seeing stars. She revealed a long history of epistaxis. Despite receiving electro-coagulation therapy twice, her epistaxis redeveloped. We examined her chest and brain using computed tomography (CT) and magnetic resonance imaging (MRI). Her chest CT scan showed an arteriovenous malformation (AVM) in the right apex and the right lower lung, and the brain MRI indicated an AVM in her frontal head. After the surgical treatment of her pulmonary AVMs, her epistaxis was significantly improved. In addition, her pedigree suggested that her condition might be hereditary. Further investigations revealed that she had hereditary hemorrhagic telangiectasia (HHT) with mutations in the endoglin gene. Both the patient and her mother were affected. It is known that pulmonary arteriovenous fistulas (PAVF) can cause intrapulmonary right-to-left shunts, which can lead to transient ischemic attacks. However, PAVFs may also cause critical neurologic disorders such as permanent hemiparesis, brain abscesses, and meningoencephalitis when not adequately treated. This case study demonstrates the need for surgical intervention to control pulmonary AVMs and their associated neurologic complications. Furthermore, patients with recurrent epistaxis or hemoptysis with a family history may benefit from genetic testing for HHT.

Keywords: Pulmonary arteriovenous malformation, transient ischemic attack, hereditary hemorrhagic telangiectasia, transcranial Doppler, endoglin gene mutation

Öz


Anahtar Kelimeler: Pulmoner arteriyovenöz malformasyon, geçici iskemik atak, herediter hemorajik telenjiektazi, transkranial Doppler, endoglin gen mutasyonu

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Introduction

A pulmonary arteriovenous malformation (PAVM), also referred to as a pulmonary arteriovenous fistula (PAVF), is an atypical connection between an artery and a vein in the pulmonary circulation (1,2). A PAVM causes a high-flow, low-pressure shunt, comprising a feeding artery connected through an aneurysmal sac to a draining vein (3). PAVMs may lead to the development of a brain abscess by permitting bacteria to easily access the systemic circulation via the right-to-left pulmonary vascular shunt without undergoing the pulmonary capillaries’ filtering processes (4). If left untreated, PAVMs may lead to critical neurologic disorders such as brain abscesses and meningitis (5). PAVMs may present as a symptom of hereditary hemorrhagic telangiectasia (HHT), also referred to as Rendu-Osler-Weber disease, which is an autosomal dominant genetic disorder featuring vascular malformations (6).

Case Report

A 34-year-old woman presented to the emergency room with the primary symptom of transient right arm weakness. She was also experiencing hemoptysis, headache, and seeing stars in her vision. She had a history of light headaches and epistaxis since middle school. Her mother and aunts also experienced frequent migraines and nasal bleeding but had never received any diagnostic testing for their conditions (Figure 1). Although the patient received electro-coagulation therapy twice to treat her frequent epistaxis during her military service, her epistaxis redeveloped.

The patient underwent computed tomography (CT), magnetic resonance imaging (MRI), and chest radiography, which revealed numerous AVMs. She was referred for chest surgery for video-assisted thoracic surgery wedge resection to remove the AVMs in her right lower lung and right apex. In addition, she underwent surgical removal of her cerebral AVM. Following surgical procedures, her epistaxis and hemoptysis were significantly improved.

An examination of her family history led to genetic testing for HHT.

Neurological Examination, Neuroradiologic Findings, and Genetic Testing

In the neurologic examination, she was alert and aware of time, place, and persons.

There were no pathologic reflexes from her extremities but she had left-arm motor weakness and paresthesia. She was afebrile (body temperature 36.5°C) and her blood sampling revealed normal liver function and stable C-reactive protein levels. However, her chest PA results indicated nodular opacities at the right upper lung and right lower lung, and a radiologist recommended a chest CT scan for a closer examination (Figure 2). A T2-weighted brain MRI revealed irregular cystic cerebromalacia and peripheral dark hemosiderin deposits surrounding reactive gliosis at the right frontal white matter area. A brain MRA showed a nodule with a tortuous and ectatic draining vein on the paramedian frontal region (Figure 3). Moreover, the patient’s axial chest CT scan demarcated a large (>1 cm) AVM nidus in the right lower lung as well as a small lingular nodule, which was likely an intrapulmonary lymph node (Figure 4). The transcranial Doppler sonogram revealed microembolic signals: 170 embolic tracks during normal respiration and 250 embolic tracks when the patient was performing the Valsalva maneuver (Figure 5). This indicated the existence of right-to-left shunts in the patient’s lung and she was referred to chest surgery for video-assisted thoracic surgery wedge resection to remove the AVMs in the right lower lung and the right apex. She also underwent surgical removal of her cerebral AVM. Furthermore, the patient and her mother underwent whole-blood genetic testing. For the first time in South Korea, the c.859_858AC>G transition mutation and the p.Asn286fs frameshift deletion mutation were detected (Figure 6). No mutations were found in the ALK1 gene. Thereafter, the patient regularly visited the outpatient clinic for prescriptions of antiplatelet and antiepileptic medications.

Discussion

This case study highlights the importance of aggressive treatment of pulmonary AVMs to prevent critical neurologic complications (1,7). It also demonstrates that patients with recurrent epistaxis or hemoptysis with a family history may benefit from genetic testing for HHT. In this instance, the patient’s pedigree suggested that her condition was inherited and whole-blood genetic testing of the patient and her mother revealed that both had HHT with mutations in the endoglin (ENG) gene.

Figure 1. The pedigree showing the family history of migraine and epistaxis of the patient’s mother and aunts

Figure 2. Chest radiograph showing suspicious nodular opacities at the right upper lung and right lower lung
PAVFs cause the formation of abnormal right-to-left, high-flow, and low-pressure shunts, which comprise a single feeding artery connecting via an aneurysmal sac to a draining vein (2,3,5). Consistent with our findings, PAVMs have been reported in previous studies to be a symptom of HHT. From the Cognard classification of dural AVFs, this case may be the type IV to have cortical venous drainage with venous ectasia. PAVFs have been reported to be associated with HHT in 88% of PAVM cases (2).

Previous studies increased our understanding of the diagnostic methods of PAVMs. Kawano et al. (8) used transcranial color Doppler sonograms with saline-contrast-medium infusion to detect PAVFs. Furthermore, Swanson et al. (9) used echocardiogram with indocyanine green dye to diagnose extracardiac right-to-left shunts in 26 (90%) of 29 tested patients. Furthermore, chest PA with or without a CT scan of 93 patients with PAVF demonstrated abnormalities in 87 (94%) patients and revealed a PAVF diagnosis in 68 patients (73%) (9).

Swanson et al. (9) further examined the etiology and symptoms of PAVF. They showed that 52 (56%) patients had a history of HHT. Thirty-four (37%) of the patients with PAVF had neurologic disorders including brain abscesses, seizures, and TIAs (9). Other clinical symptoms were dyspnea (n=53, 57%), epistaxis (n=46, 49%), pulmonary bruits/murmurs (n=32, 34%), cyanosis (n=27, 29%), clubbing (n=18, 19%), and hemoptysis (n=4, 15%) (9).

Other researchers investigated the outcomes of PAVF. Pollak et al. (10) stated that a set of the primary determinants of stroke and abscess risks were not correlated with PAVM severity. To reach this conclusion, they examined a cohort study of 323 patients, 219 of whom were diagnosed as having PAVF and 305 were diagnosed as having HHT (10,11). Furthermore, male patients showed higher brain abscess rates [hazard ratio: 3.61 (95% confidence interval: 1.58-8.25), p=0.0024]. The analysis of the patients’ interventional histories and bacteriologic isolates pointed to dental sources for the higher brain abscess rates (10). Orofacial surgeons must be careful regarding complications related to dental extractions in patients with HHT because PAVF-related brain abscesses are challenging to diagnose and have the potential to recur. For instance, antibiotics should be used for patients with HHT in such operations according to Corre et al. (12). Oral surgeons are also recommended to prescribe antibiotics to patients with a high risk of bacterial endocarditis because such patients have a high prevalence of PAVFs. In conclusion, oral and maxillofacial surgeons must be aware of the potentially life-threatening complications of dental operations in patients with HHT due to the high prevalence of PAVF (12).

Regarding treatment options, Shioya et al. (11) insisted PAVMs must be adequately managed either by coil embolization and/or by surgery because of the association of recurrent brain abscesses and PAVM in patients with HTT. It is important to evaluate clinical and anatomic outcomes after PAVM embolization to check for persistent, reperfused, and enlarging lesions. In particular, the latter are common occurrences (10). Although patients with ongoing, reperfused, or enlarging lesions often show symptoms, some patients are asymptomatic (10). Therefore, it is necessary to examine the cause of brain abscesses to prevent their recurrence (12).

Due to the associated dangers, Byrne et al. (13) suggested that patients with both pulmonary and cerebral vascular malformations should undergo lifelong screening every 3-5 years using CT scanning with contrast-enhancement of the chest to ensure definitive treatment of recurrent fistulae and prevent cerebral complications (13).

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**Figure 3.** Brain magnetic resonance imaging and MRA revealing the nidus with a tortuous and ectatic draining vein in the paramedian frontal region

**MRA:** Magnetic resonance angiography

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**Figure 4.** Enhanced chest computed tomography showing the lungs and mediastinum, revealing a large (>1 cm) nodule in the right lower lung
Appropriate precautions and countermeasures must be taken for such patients because PAVMs or HHT pose great risks to their health. Although the patient in this case report did not have any clinical symptoms directly suggestive of HHT, further examinations enabled us to diagnose HHT and the patient was able to receive genetic counseling (4, 14). Knowledge of whether the patient is has HHT1 or HHT2 would help determine the expected phenotypic expressions and serve as a useful predictor of disease progression (13). For instance, patients with HHT1 show a more severe disease progression with a greater frequency of cerebral and pulmonary malformations, and thus, a greater frequency of complications associated with these conditions (13). Previous studies have shown that mutations in three genes are associated with HHT: ENG (ENG on chromosome 9), ACVRL1 (activin A receptor type II-like 1: activin-like kinase 1 on chromosome 12), and SMAD4 (SMAD family member 4; Co- SMAD on chromosome 18) have been identified to underlie HHT1, HHT2, and the juvenile polyposis-HHT overlap syndrome, respectively (4, 14). Therefore, even for patients with a diagnosis of HHT, further examinations are recommended to determine the exact genotype (13).

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Ethics
Informed Consent: The signature was obtained after explaining the purpose of this article.
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Authorship Contributions

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