

Pearls & Oy-sters: Cerebral Abscess Secondary to Pulmonary Arteriovenous Malformation in Hereditary Hemorrhagic Telangiectasia

Jodie I. Roberts, MD, MSc, Kristine Woodward, MD, MSc, Adam Kirton, MD, MSc, and Michael J. Esser, MD, PhD

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Correspondence

Dr. Roberts
jirobert@ucalgary.ca

Abstract

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant condition that is linked to a myriad of neurologic complications arising from vascular malformations of the brain, spinal cord, and lungs. Our case describes a previously healthy 3-year-old male who presented to hospital with fever of unknown origin and was found to have a brain abscess stemming from a pulmonary arteriovenous malformation (PAVM). This etiology was identified after a period of diagnostic delay; the medical team was suspicious for a proximal embolic source due to the presence of multiple tiny infarcts seen on MRI of the brain, but transthoracic echocardiogram and head and neck angiogram were unremarkable. Fortunately, an enhanced CT of the chest was performed, identifying a moderately sized PAVM. PAVMs are associated with intracranial abscesses due to shunting and loss of the normal filtering effects of the lung capillary bed. Impaired pulmonary filtration can permit paradoxical thromboemboli and septic microemboli to enter systemic circulation, predisposing patients with PAVMs to cerebral abscess and ischemic stroke. Screening for PAVMs with contrast-enhanced echocardiogram or enhanced CT of the chest may be considered in patients with cryptogenic brain abscess or recurrent embolic stroke of unknown origin. PAVMs are often associated with hereditary hemorrhagic telangiectasia (HHT). As many features of HHT have delayed clinical manifestation, genetic testing for HHT should be considered in all people with PAVM, even in the absence of other clinical features. In our case, genetic testing returned positive, confirming a new diagnosis of HHT type 1.

Pearls

- Pulmonary arteriovenous malformations (PAVMs) produce a continuous right-to-left shunt, which allows a proportion of systemic venous blood to bypass pulmonary bed filtration.
- Impaired pulmonary filtration can permit paradoxical thromboemboli and septic microemboli to enter systemic circulation, predisposing patients with PAVM to cerebral abscess and ischemic stroke.
- PAVMs are often associated with hereditary hemorrhagic telangiectasia (HHT).

Oy-sters

- Screening for PAVM with contrast echocardiogram or CT chest may be considered in patients with cryptogenic brain abscess or recurrent embolic stroke of unknown origin.
- Many features of HHT have delayed clinical manifestation, and genetic testing for HHT should be considered in all people with PAVM, even in the absence of a history of epistaxis or telangiectasias.

Case Report

A 3-year-old male was hospitalized with a 4-week history of fever of unknown origin. He was previously healthy and developmentally normal. At onset, he had a high-grade fever (Tmax

From the Department of Clinical Neurosciences (J.I.R., A.K.); Department of Pediatrics (K.W., A.K., M.J.E.), Cumming School of Medicine, University of Calgary; Alberta Children's Hospital Research Institute (A.K., M.J.E.), University of Calgary; Hotchkiss Brain Institute (A.K., M.J.E.), University of Calgary, Alberta, Canada.

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≥39°C) associated with persistent emesis and headache. He first presented to hospital after 4 days of illness and received 3 doses of IV antibiotics but was discharged with a diagnosis of viral gastroenteritis after blood and urine cultures returned negative and fever resolved. He was readmitted 3 days later due to recurrent fever. Although complete blood counts were normal, he had mild elevations in erythrocyte sedimentation rate (14 mm/hour [normal ≤10]) and C-reactive protein (19.2 mg/L [normal ≤8.0]). CSF was notable for 9 white blood cells (78% lymphocytes) with normal protein (0.26 g/L) and glucose (3.5 mmol/L). He received 3 days of antibacterial and antiviral therapy, which was discontinued after CSF viral panel and culture returned negative. He was discharged home with a diagnosis of fever of unknown origin. He was readmitted 1 week later, and the possibility of an atypical pneumonia or sarcoidosis was queried due to intermittent oxygen requirements and a questionable focal opacity in the left lower lobe on chest x-ray (Figure, 1A). Repeat respiratory panels and blood and urine cultures were negative. He was transferred to our tertiary care center for further investigation.

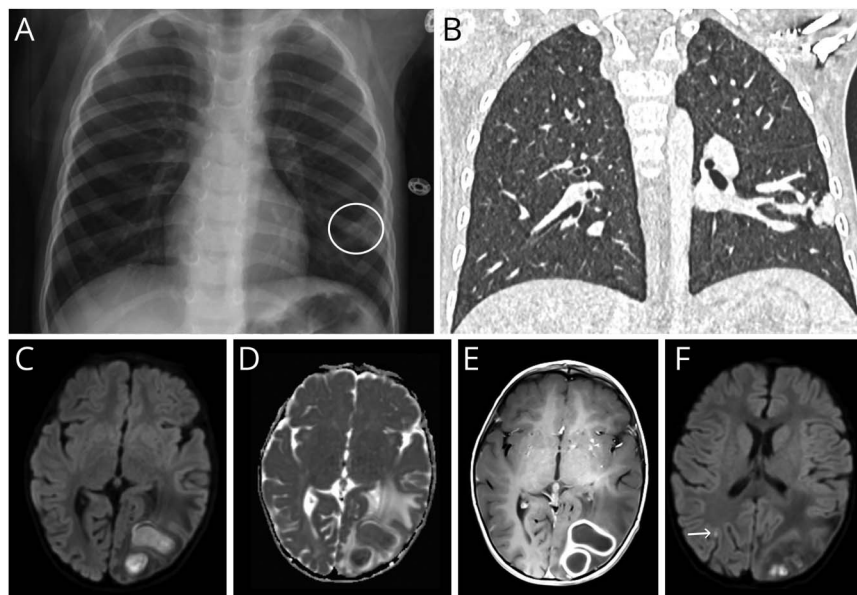
Ophthalmologic assessment was performed for new-onset ocular misalignment. Examination was limited by cooperation. Fundoscopic examination revealed blunting of the left optic disc margin. Visual acuity and confrontational fields could not be assessed. Pupils were equal and reactive. Ocular ductions appeared full, but an intermittent comitant right esotropia was seen. Enhanced MRI of the brain was subsequently ordered, which revealed a large left parieto-occipital abscess and tiny infarcts in multiple vascular territories (Figure, 1C–F). As there were no abnormalities in the brainstem or significant mass effect, his acute onset strabismus was hypothesized to represent

an adaptation to an undetected homonymous hemianopia from parieto-occipital brain abscess.

Aspirate from the abscess cultured *Streptococcus anginosus* (a subgroup of viridans streptococci), which was susceptible to treatment with IV ceftriaxone. The source of infection was unclear; dentition was normal, and sinuses were clear on MRI. Given multiple tiny infarcts seen on brain MRI, the possibility of a proximal embolic source was considered. Transthoracic echocardiogram with bubble study did not reveal a source of embolus or shunt. Neck ultrasound and cerebral angiogram were additionally unremarkable. An enhanced chest CT was ordered to investigate for a pulmonary shunt; this demonstrated a moderately sized left lower lobe pulmonary arteriovenous malformation (PAVM), which corresponded to the focal opacity previously seen on chest x-ray (Figure, 1B). An additional focus of ground-glass change was seen at the right lung base, which raised suspicion for a second tiny PAVM (not shown). The source of cerebral abscess was concluded to be paradoxical emboli in the setting of PAVM-associated right-to-left shunt and loss of the pulmonary capillary bed filtering. He underwent successful catheter embolization of his left lower lobe PAVM and had resolution of his ocular misalignment.

Although there was no known history of affected relatives, epistaxis, telangiectasias, or gastrointestinal bleeding, a diagnosis of hereditary hemorrhagic telangiectasia (HHT) was considered. Genetic testing confirmed a c.991G>A heterozygous pathogenic variant in *ENG* consistent with a diagnosis of HHT type 1. Surveillance imaging did not identify any AVMs of the brain or liver. He was referred to a specialized HHT center for ongoing management.

Figure Pulmonary Arteriovenous Malformation as a Source of Cerebral Microemboli and Abscess



(A) Anterior-posterior chest radiograph demonstrating a subtle opacity in the left lower lobe (circle). (B) Enhanced CT of the chest demonstrating a pulmonary arteriovenous malformation corresponding to the area of opacity seen on chest x-ray. (C and D) Axial brain MRI demonstrating a mature, multilobulated parieto-occipital abscess with associated central diffusion restriction on (C) diffusion-weighted imaging and (D) apparent diffusion coefficient maps, with substantial perilesional edema. (E) Thick, smooth ring enhancement is present on T1 postgadolinium sequences with central hypointensity. (F) Multiple punctate foci of diffusion restriction were additionally seen, suggestive of tiny emboli (arrow).

Discussion

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, is an autosomal dominant multisystem vascular disease with a prevalence of 1:5,000 to 1:10,000, which is associated with a myriad of primary and secondary neurologic complications.^{1,2} Pathogenic gene variants in *ENG* (HHT type 1), *ACVRL1* (HHT type 2), and *SMAD4* (juvenile polyposis overlap syndrome) disrupt transforming growth factor- β (TGF- β) signaling pathways on vascular endothelial cells, leading to vascular fragility and malformations.³ A diagnosis of HHT can be made through identification of a causative variation or by application of the Curaçao criteria (Table).⁴ The 4 Curaçao criteria include (1) spontaneous and recurrent epistaxis; (2) multiple mucocutaneous telangiectasias of the lips, oral cavity, fingers, or nose; (3) visceral lesions (gastrointestinal telangiectasias or pulmonary/hepatic/cerebral/spinal AVMs); and (4) a first-degree relative with HHT.⁵ HHT is considered possible or suspected with 2 criteria present and definite with 3 or more positive criteria.⁵

People with HHT experience primary neurologic complications secondary to vascular malformations in the brain or spinal cord. Although cerebral vascular malformations (CAVMs) are found in nearly a quarter of people with HHT,⁶ spinal AVMs are uncommon and not routinely screened for.⁷ Although natural history varies by AVM type, the overall annual hemorrhage rate for unruptured CAVMs is 2.2% (95% CI 1.7%–2.7%).⁸ Symptomatic CAVMs may also present with seizure or headache.⁹ Expert guidelines recommend screening for brain vascular malformations with brain MRI in all people with possible or definite HHT.⁴ Surgical management is considered on a case-by-case basis.⁹

Secondary neurologic complications arising from pulmonary arteriovenous malformations (PAVMs) are a much more frequent cause of neurologic sequela in HHT. PAVMs are abnormal blood vessels found in approximately 50% of people with HHT, which directly connect pulmonary arteries and veins, producing a continuous right-to-left shunt and allowing for a proportion of systemic venous blood to bypass

pulmonary bed filtration and gas exchange.¹⁰ Partial loss of pulmonary capillary filtering impairs systemic prevention of paradoxical emboli, resulting in an increased risk of ischemic stroke; 1 UK study reported ischemic stroke in 12% of persons with a PAVM.¹⁰

Although rare in the general population, the odds of developing a cerebral abscess are substantially elevated (OR 30.0, 95% CI 3.1–288) in people with HHT,¹ with 6% of individuals with a PAVM experiencing a cerebral abscess.¹⁰ The presence of a right-to-left shunt allows septic microemboli to bypass the filtering effect of the pulmonary capillaries, yielding a direct path to the cerebral circulation. The possibility of PAVM should be considered in people with cerebral abscess that do not have predisposing risk factors such as immunocompromised state, history of head trauma or neurosurgery, dental infection, ENT infection, or congenital heart disease.¹¹

In our case, the finding of a cryptogenic brain abscess did not immediately raise suspicion for the possibility of a PAVM or HHT. Missed or delayed diagnoses of HHT are common, with an average time lag between development of HHT manifestations and diagnosis nearing 3 decades.² Although this reflects lack of disease awareness, another culprit is delayed clinical expression of common HHT manifestations. Although nearly all people (>90%) with HHT eventually develop recurrent epistaxis, the mean age at onset is 12 years.¹² Similarly, mucocutaneous telangiectasias do not occur until after puberty and may not occur until adulthood.¹³ Importantly, as nearly all PAVMs are due to HHT, all people with PAVMs should be screened for HHT, even in the absence of other clinical manifestations.¹⁴

Although our patient's PAVM was found using CT imaging of the chest, recommended first-line screening for PAVMs in patients with possible or confirmed HHT is with transthoracic contrast echocardiography.⁴ Because of the risk of new PAVM development, enlargement of existing PAVMs, or progression of previously embolized PAVMs, pediatric-specific guidelines recommend repeating pulmonary AVM screening at 5-year intervals.⁴ In the adult setting, it is recommended that all PAVMs are

Table Summary of Highlighted Diagnostic and Surveillance Recommendations in Hereditary Hemorrhagic Telangiectasia

Consideration	Recommendation
Diagnostic	<ul style="list-style-type: none">• An underlying diagnosis of HHT should be considered in all persons with a PAVM.¹⁴• An underlying diagnosis of HHT should be considered in persons meeting 2 or more Curaçao criteria⁵:<ol style="list-style-type: none">(1) Spontaneous and recurrent epistaxis;(2) Multiple mucocutaneous telangiectasias of the lips, oral cavity, fingers, or nose;(3) Visceral lesions (gastrointestinal telangiectasias or pulmonary/hepatic/cerebral/spinal AVMs);(4) A first-degree relative with definite HHT.
Targeted screening	<ul style="list-style-type: none">• PAVM screening should be performed at the time of HHT diagnosis (adult/pediatric patients) and repeated at 5-y intervals (pediatric patients only).⁴• All adults with possible or definite HHT should receive MRI screening for brain vascular malformations at the time of diagnosis.⁴• Spinal arteriovenous malformations are not routinely screened for.⁷

Abbreviations: HHT = hereditary hemorrhagic telangiectasia; PAVM = pulmonary arteriovenous malformation.

treated with transcatheter embolotherapy; whereas in the pediatric setting, PAVMs are only treated if they are large or associated with reduced oxygen saturation.⁴ Regardless of whether pulmonary AVMs are treated or untreated, patients should receive antibiotic prophylaxis for procedures with risk of bacteremia (such as dental procedures), take precautions against air embolism during IV administration, and avoid SCUBA diving.⁴

Although HHT prognosis varies by individual disease severity, overall survival is only modestly reduced, with a median age of survival of 77 years.¹ Risk of death is highest in the first 3 years after diagnosis, reflecting that most patients are diagnosed after presenting with a complication.¹ Although current interventions are largely surgical, several potential therapeutic targets have been recently identified,¹⁵ and a stage 3 clinical trial of bevacizumab, a monoclonal antibody that targets the vascular endothelial growth factor (VEGF) signaling pathway, is underway (NCT 03227263).

Our case highlights the importance of screening for PAVM in patients with cryptogenic brain abscess or recurrent embolic stroke of unknown origin. Particularly in younger patients, additional clinical manifestations of HHT may not yet be apparent, and detection of a PAVM allows for appropriate management and surveillance.

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Appendix Authors

Name	Location	Contribution
Jodie I. Roberts, MD, MSc	Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary, Alberta, Canada	Drafting/revision of the manuscript for content, including medical writing for content
Kristine Woodward, MD, MSc	Department of Pediatrics, Cumming School of Medicine, University of Calgary, Alberta, Canada	Drafting/revision of the manuscript for content, including medical writing for content

Appendix (continued)

Name	Location	Contribution
Adam Kirton, MD, MSc	Department of Clinical Neurosciences, Cumming School of Medicine, University of Calgary; Department of Pediatrics, Cumming School of Medicine, University of Calgary; Alberta Children's Hospital Research Institute, University of Calgary; Hotchkiss Brain Institute, University of Calgary, Alberta, Canada	Drafting/revision of the manuscript for content, including medical writing for content
Michael J. Esser, MD, PhD	Department of Pediatrics, Cumming School of Medicine, University of Calgary; Alberta Children's Hospital Research Institute, University of Calgary; Hotchkiss Brain Institute, University of Calgary, Alberta, Canada	Drafting/revision of the manuscript for content, including medical writing for content

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