A 25-Year-Old White Woman With a Cerebrovascular Accident and a Right-to-Left Shunt

Richard W. Smalling, MD, PhD; Wilson SooHoo, MD; Phebe Chen, MD

History

The patient is a 25-year-old woman transferred to Hermann Hospital 3 days after admission to an outlying facility. The patient initially woke up at 3 AM with acute onset of nausea, mild headache, hemoptysis (1/3 cup of fresh blood), and worsening shortness of breath. She then noticed weakness in the right half of her body associated with dysarthria. She had no associated chest pain or palpitations. In the past, she had experienced recurrent episodes of transient weakness of her limbs on the right side and one episode of transient left hemianesthesia. None of the episodes were associated with any permanent sequelae, and she had not sought medical attention for them. She had a history of asthma since childhood worsened by mild to moderate exertion, for which she used a Ventolin inhaler. She denied a history of cyanotic spells, squatting, or syncopal episodes. She did describe a history of intravenous drug abuse (cocaine) and alcohol abuse until 5 years before admission. She smoked one pack of cigarettes per day for the past 10 years. Over the past 2 to 3 years, she described occasional episodes of epistaxis.

Past Medical History

The patient has a history of right arm fracture as a child and multiple rib fractures after blunt trauma more than 10 years before admission. She was on no medications.

Physical Examination

The patient was a young white woman of normal stature; on admission to Hermann Hospital, she was awake and oriented but tachypneic. She was not in obvious acute distress. Her temperature was 97.8°F, pulse was 64 beats per minute, blood pressure was 116/68 mm Hg, and respirations were 20 per minute. Examination of the head, eyes, ears, nose, and throat revealed a right upper motor neuron facial weakness. Carotid pulsations were normal, and jugular venous pressure was not elevated. Chest examination revealed lungs normal to percussion, and she had normal fascicular breath sounds. Cardiovascular examination revealed a nondisplaced apical impulse. S1 was within normal limits. S2 split normally. There were no gallops, murmurs, or clicks. There was a 2/6 holosystolic murmur at the apex that radiated to the axilla. Abdominal examination was unremarkable. Neurological examination demonstrated dysarthria with 3/5 power in all groups of the right upper and lower limbs. Power in the left limbs was normal. Sensory examination was normal. There was sustained clonus of the right ankle and bilateral upgoing plantar responses. Examination of the extremities demonstrated clubbing and cyanosis of the fingernails on both hands without edema.

Laboratory Values

Pertinent laboratory values are listed in Table 1. Arterial blood gasses on 4 L nasal oxygen demonstrated a pH of 7.47, Pco2 of 34, Po2 of 52, bicarbonate of 26, with an oxygen saturation of 89%. The ECG, illustrated in Fig 1, demonstrated normal sinus rhythm with normal P and QRS morphology as well as a normal axis. There were nonspecific T-wave abnormalities over the precordial leads.

Radiological Evaluation

Phebe Chen, MD, Assistant Professor of Medicine, Department of Radiology

The initial chest radiograph (Fig 2) was interpreted as showing no evidence of an acute cardiopulmonary process. A ventilation-perfusion scan obtained the same day (Fig 3, left and right) showed significant activity in the abdomen and in the brain. The ratio of radioactivity of the lungs to the periphery suggested a 33% right-to-left shunt. A magnetic resonance image (MRI) of the brain (Fig 4, left and right) performed 5 days later showed abnormal T2 hyperintensity within the pons, which enhanced after administration of gadolinium, consistent with an early subacute infarct. Demyelinating or neoplastic processes were thought to be less likely.

Clinical Discussion

Richard W. Smalling, MD, PhD, Professor, Department of Medicine

Important Historical Clues

The patient complained of dyspnea on exertion since childhood. She had previously been told that her symptoms of dyspnea on exertion were secondary to asthma;
however, on closer questioning, she did not remember ever having symptoms of overt wheezing. Her symptoms were such that she could not play sports in school. Complicating her early history of dyspnea was the more recent history of drug abuse, including cocaine, alcohol, and cigarette smoking. She specifically denied cyanotic episodes, squatting, palpitations, or syncope that might be seen with some forms of congenital heart disease, specifically tetralogy of Fallot. Her presenting symptoms included headache, worsening shortness of breath, right-sided weakness, dysarthria, and hemothysis, a constellation of symptoms and findings not readily ascribable to a single diagnosis.

**Pertinent Physical Examination and Laboratory Findings**

On physical examination, the patient was tachypneic but not in distress. She had a normal blood pressure. Her jugular venous pressure was not elevated, and her chest was clear—specifically, she had no wheezing. Cardiac examination revealed no evidence of right ventricular hypertrophy, there was no right ventricular lift, S₂ was normally split, and P₂ was not accentuated. Furthermore, there was no evidence for cardiomegaly. A soft holosystolic murmur at the apex was the sole abnormal cardiac finding. She did have definite right-sided weakness and dysarthria consistent with recent symptoms.

**TABLE 1. Pertinent Laboratory Values**

<table>
<thead>
<tr>
<th>Chemistry</th>
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| Na        | 138  
| K         | 4.5 T prot 7  
| Cl        | 103 Alb 3.3  
| CO₂       | 25 Ferritin 5 ng/mL  

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<tr>
<th>Hematology</th>
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| Hb         | 10.1 MCV 66 WBC 7.1  
| Hct        | 32.2 MCH 20.8 Plt 397 000  
| Coagulation |  
| PT         | 12.4 AT III 86%  
| PTT        | 30.7 Prot C 94%  
| Serology   | VDRL NR, RA factor -ve, ANA +ve 1:40, Anti ds DNA -ve, Anti SM -ve, Anti RNP -ve, Lupus anticoagulant panel +ve, HIV -ve, C3&C4 WNL  
| Blood culture | Sterile  

AT indicates antithrombin; Prot, protein.
cerebrovascular accident, and she had clubbing in her fingers but no edema.

Important laboratory abnormalities included the presence of an iron-deficiency anemia; however, the patient was a menstruating female. She reportedly had a history of epistaxis and hemoptysis. She had normal clotting studies except for a positive lupus anticoagulant. Despite significant supplemental oxygen administration, she had marked hypoxemia. As previously mentioned, this was despite her appearing relatively comfortable, a finding that suggests that her hypoxemia might have been a chronic condition. Surprisingly, her ECG was essentially normal. Specifically, there was no evidence for right ventricular hypertrophy, which might have been expected with some of the more common forms of cyanotic congenital heart disease. Her chest radiograph demonstrated no evidence for shunt vascularity; it confirmed the physical impression of a normal heart size, and there was no evidence for pulmonary hypertension. The ventilation-perfusion scan showed clear-cut uptake in the brain, liver, and kidneys, which indicated right-to-left shunting. An echocardiogram demonstrated normal heart size, normal chamber sizes, and normal valvular function. A bubble contrast study suggested the presence of a right-to-left shunt at the atrial level. The MRI study of the brain confirmed a

![Fig 3. Ventilation-perfusion scan shows significant activity outside the lungs, compatible with a right-to-left shunt.](image)

![Fig 4. Magnetic resonance image of the brain shows abnormal T2 hyperintensity within the pons, with contrast enhancement compatible with a subacute infarct.](image)
circumscribed infarct of the pons consistent with a thromboembolic event.

**Synthesis Based on History and Physical and Laboratory Values**

The patient’s long history of dyspnea, physical findings of clubbing and peripheral cyanosis despite oxygen administration, and a ventilation-perfusion scan that confirmed the presence of a right-to-left shunt suggested that the patient had a long-standing significant right-to-left shunt. Interestingly, the cardiac examination, chest radiograph, and ECG were relatively unremarkable; none of these suggested the presence of pulmonary hypertension. In the presence of a right-to-left shunt, her thromboembolic stroke was probably secondary to paradoxical embolization.

**Cerebral Infarction**

The differential diagnosis of cerebral infarction might include atherothrombosis or thromboembolism. Emboli of cardiac origin typically occur in the presence of atrial fibrillation, after myocardial infarction, with bacterial endocarditis, or in association with mitral valve prolapse. The patient had no evidence for any of the above, as previously discussed. Other causes include generalized cerebral hypoxia; thrombosis due to coagulation abnormalities; arthritis; and paradoxical embolization. Clotting disorders leading to cerebral thrombosis include pregnancy; oral contraceptive use; cancer; polycythemia vera; antithrombin-3, protein C, or protein S deficiencies; or the lupus anticoagulant. The patient did have positive lupus anticoagulant titers, suggesting that her cerebral embolic event was secondary either to paradoxical embolization or to in situ thrombosis secondary to lupus anticoagulant or both.

**Cyanotic Congenital Heart Disease Encountered in Adults**

In general, cyanotic congenital heart disease in adults can be characterized by lesions with normal pulmonary vascular resistance, those with increased pulmonary vascular resistance, or other, rare anatomic anomalies. Normal pulmonary vascular resistance lesions include tetralogy of Fallot, pulmonary atresia with ventricular septal defect, pulmonary stenosis with atrial septal defect, and others. The absence of murmurs or right ventricular lift on physical examination and normal ECG, chest radiograph, and echocardiogram ruled out any of the above anomalies. Increased pulmonary vascular resistance occurs in atrial or ventricular septal defects or patent ductus with the Eisenmenger reaction. Given the absence of evidence for pulmonary hypertension, it is unlikely that the patient had one of these lesions.

Other rare anomalies include total anomalous pulmonary venous return, congenital vena cava–to–left atrium communication, congenital pulmonary arteriovenous (AV) fistula(s), and others. Eighty percent of children born with total anomalous pulmonary venous return die before 1 year of age if left untreated. In this syndrome, cardiac murmurs are not prominent; however, S2 is usually widely split. The right atrium and right ventricle are usually dilated, and the left atrium is usually small. Given the normal S2 and normal chamber sizes, it is unlikely that the patient had total anomalous pulmonary venous return.

Congenital vena cava–to–left atrium communication is often associated with other congenital abnormalities such as ventricular septal defect or tetralogy of Fallot. In this condition, the right heart flow and pressures are normal or low, while systemic flow is normal. The chamber sizes are usually normal, and there is symmetrical cyanosis and clubbing. Survival to adulthood with minimal symptoms is common. The ECG can be normal, and the second heart sound may be single. This diagnosis fits fairly well with the physical examination and laboratory findings in this patient.

Pulmonary AV fistulas usually are recognized in adulthood, although the symptoms begin in childhood. Cyanosis is usually seen first, followed by dyspnea and fatigue. One third to three quarters of these patients have associated telangiectasias (Rendu-Osler-Weber disease). Epistaxis and hemoptysis are common, and anemia is frequent. Murmurs from these fistulas occur most frequently in the lower posterior aspect of the lung fields and are low in intensity and are usually continuous in quality. However, cyanosis and clubbing are common. The ECG is normal, and the chamber sizes are normal on echocardiogram. The fistulas most frequently involve the lower lobes or right middle lobe and may be seen on plain chest radiograph if large. This constellation of findings also fits well with the findings in this patient.

**Clinical Synthesis**

The findings in this patient—cyanotic heart disease, definite right-to-left shunting, normal ECG, normal heart size, normal chamber sizes, and absence of ventricular septal defect—suggest the differential diagnosis of (1) congenital vena cava–to–left atrium communication, (2) pulmonary AV fistula(s), or (3) total anomalous pulmonary venous return (unlikely). The combination of the above features, including the positive history of epistaxis, hemoptysis, and anemia, suggests Rendu-Osler-Weber disease, “hereditary hemorrhagic telangiectasia,” with pulmonary AV fistula as the leading diagnosis. The cerebrovascular accident was probably secondary to paradoxical embolization possibly compounded by the presence of the lupus anticoagulant.

**Hospital Course**

The patient was taken to the cardiac catheterization laboratory for angiographic and hemodynamic assessment. Oxygen saturation data and hemodynamics are listed in Table 2. The patient had no evidence for left-to-right shunting. A small right-to-left shunt (0.6 L/min) was calculated using an assumed pulmonary oxygen venous saturation. The intra-atrial septum could not be crossed with extensive catheter probing, which argued against the presence of an atrial septal defect. A levo-phase pulmonary arteriogram demonstrated normal anatomy of the pulmonary veins. Injections into the superior vena cava and inferior vena cava ruled out anomalous vena cava–to–left atrium communication, and selective pulmonary angiography demonstrated a large pulmonary AV malformation with aneurysm formation in the left lower lobe, as illustrated in Fig 5.
TABLE 2. Cardiac Catheterization and Hemodynamic Data

<table>
<thead>
<tr>
<th>Oximetry</th>
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<tbody>
<tr>
<td>Cardiac catheterization data</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(patient on 2 L O₂ NC)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SVC</td>
<td>59</td>
<td>8.2</td>
</tr>
<tr>
<td>IVC</td>
<td>65</td>
<td>9.0</td>
</tr>
<tr>
<td>Mid RA</td>
<td>63</td>
<td>8.7</td>
</tr>
<tr>
<td>Mid RV</td>
<td>62</td>
<td>8.6</td>
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<tr>
<td>Left PA</td>
<td>65</td>
<td>9.0</td>
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<tr>
<td>Right PA</td>
<td>95</td>
<td>13.2</td>
</tr>
<tr>
<td>PV (assumed)</td>
<td>100</td>
<td>13.9</td>
</tr>
</tbody>
</table>

Hemodynamics

RA 2 mm Hg
RV 19/3 mm Hg
Aortic pressure 120/55 (66) mm Hg
PA 15/5 (9) mm Hg
PCWP 6 mm Hg
SVR 1249 d · s⁻¹ · cm⁻⁵
PVR 65 d · s⁻¹ · cm⁻⁵

SVC indicates superior vena cava; IVC, inferior vena cava; RA, right atrium; RV, right ventricle; PA, pulmonary artery; PV, pulmonary vein; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance; and PVR, pulmonary vascular resistance. Values in parentheses are mean pressures.

Clinical Management

After extensive discussions, it was elected to proceed with a segmental resection of the left lower lobe AV malformation. At the time of surgery, a small wedge resection of the lingula was also carried out because of the presence of obvious AV malformations on the surface of the lung in that region as well. Postoperatively, the patient continued to have severe oxygen desaturation. At this point, additional selective pulmonary angiography was performed, which revealed other small AV malformations in the left upper lobe, right lower lobe, and right upper lobe. These AV malformations were embolized successfully during several sessions, and the patient has returned home with markedly improved systemic oxygenation and exercise tolerance, although she still requires occasional supplemental oxygen. She recovered totally from her cerebrovascular accident.

Pathological Findings:

Wilson E. SooHoo, MD, Assistant Professor, Department of Pathology

The specimen consisted of the lower lobe of the left lung with suture tags identifying the arterial and venous components of the lesion. Most of the specimen consisted of normal lung. Toward the base was a 3.0×2.0×1.5-cm subpleural ill-defined area that was firmer than the surrounding parenchyma and covered by tan pleura. Within this firm area was a 1.0-cm roughly spherical saccular lesion that had direct communication with the tagged arterial and venous structures (Fig 6). Within the venous limb was a small adherent blood clot.

Histological sections revealed essentially normal pulmonary parenchyma with the exception of aberrant vascular structures, including the tagged feeding and draining vessels, the saccular lesion, and numerous enlarged arteries and veins in the area of the saccular lesion (Fig 7). Some of the vessels were surrounded by loose fibrous tissue, and some had mild fibrous intimal thickening similar to that seen in early atherosclerosis. The wall of the saccular lesion focally was slightly thicker and contained more fibrous change than the walls of the rest of the lesion. The elastic-tissue component of a Movat stain highlighted an abrupt transition from arterial to venous architecture (Fig 8). The native peribronchial arteries, arterioles, and veins appeared dilated, suggesting that there was communication between the abnormal and native circulations.

Diagnosis: pulmonary AV malformation.

Pathological Discussion

Pulmonary AV malformations are nonneoplastic, possibly hamartomatous, lesions of the lung that usually result in direct connections between branches of the pulmonary artery and pulmonary vein. They were first
They have been called angioma, pulmonary aneurysm, pulmonary AV fistula, pulmonary angioma, cavernous hemangioma, and pulmonary hamartoma. Most cases are congenital, although they may be acquired as a consequence of chest surgery, trauma, actinomycosis, schistosomiasis, cirrhosis, and metastatic carcinoma.1

A classification of pulmonary AV malformations has been suggested by Anabtawi et al,2 as well as a discussion of the possible embryology of these lesions. The possibilities range from multiple microscopic AV malformations, which they suggest could be due to abnormal development of the capillary system, to large aneurysmal lesions, such as the present case, which they suggest could result from abnormal development of the primitive venous plexus with the persistence of large ectatic vascular channels. Approximately 4% of lesions are associated with systemic arterial supply or anomalous venous drainage. Most cases are seen in the lower lobes and are near visceral pleura. Most cases involve single lesions, but a sizable minority (8% to 42%) can be bilateral.1 Multiple small lesions can be difficult to diagnose by chest radiography and angiography.3

Rendu-Osler-Weber disease is a condition that is characterized by the triad of (1) repeated episodes of hemorrhage, (2) multiple telangiectasias in skin and mucous membranes, and (3) a family history of these lesions. It has an autosomal-dominant inheritance pattern with high penetrance and affects both sexes equally.4 There is an association of pulmonary AV malformation and Rendu-Osler-Weber disease. Rendu-Osler-Weber is present in 36% to 57% of patients who have pulmonary AV malformation. Conversely, pulmonary AV malformation is present in 15% of patients with Rendu-Osler-Weber disease.1

References

Key Words • Clinicopathological Conferences • cerebral infarction
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