An Anomalous Unilateral Single Pulmonary Vein Associated with a Bone Morphogenetic Protein Receptor II Gene Mutation

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Abstract

Anomalous unilateral single pulmonary vein (AUSPV), a rare congenital anomaly, is associated with an aberrant course but normal drainage, and resembles arteriovenous malformation (AVM). We treated a 26-year-old man with AUSPV in the right lung and an anomalous segmental pulmonary vein in the left lung. CT revealed a tortuous vascular shadow with an enhancement pattern identical to that of the pulmonary vein, suggesting AUSPV. This was confirmed by pulmonary angiography. Although pulmonary AVMs were not detected on angiography, microvascular AVMs could not be excluded because delayed bubbles appeared on contrast echocardiography. A genetic examination revealed a missense mutation in BMPR2.

Key words: anomalous unilateral single pulmonary vein, pulmonary arteriovenous malformation, pulmonary varix, CT, pulmonary angiography, BMPR2


Introduction

An anomalous unilateral single pulmonary vein (AUSPV) is a rare congenital anomaly. The vein has an abnormal course, but normal drainage (1, 2), and is often confused with other pulmonary abnormalities, such as arteriovenous malformations (AVMs) (3). AUSPV is a variation of the normal anatomy, but causes no alteration in the physiological function; therefore, a careful differential diagnosis is required to avoid unnecessary intervention. We herein present a case of AUSPV in the right lung that was associated with an anomalous segmental pulmonary vein with normal drainage in the left lower lobe in a 26-year-old man. Further diagnostic exploration revealed a novel missense mutation in the bone morphogenetic protein receptor II gene (BMPR2) and wild-type activin receptor-like kinase 1 (ALK1).

Case Report

During a routine health check, an abnormal chest shadow was found in a 26-year-old man. He had a past medical history of congenital cataract and retinopathy and a smoking history of 2.5 pack-years. He was clinically stable, with a SpO2 of 99%. His respiratory and heart sounds were normal. A chest X-ray showed a curved tubular structure in the right middle lung field (Fig. 1). Contrast-enhanced computed tomography (CT) scans of the chest revealed a tortuous vascular shadow in the right lung. The vessel originated in the hilum of the right upper lobe, coursed through the right middle lobe in a loop configuration and drained into the left atrium, together with the right lower pulmonary vein.
The vascular shadow was initially interpreted as an AVM originating from the pulmonary artery, but its enhancement pattern was slightly different from that of the adjacent pulmonary artery, and was the same as that of the pulmonary vein (Fig. 3). This suggested that it originated from venous structures, as was later confirmed. Another anomalous vascular shadow was detected in the left lower lobe (Fig. 2).

Because the vascular shadow was initially interpreted as an AVM, further diagnostic exploration was performed for AVM and hereditary hemorrhagic telangiectasia (HHT). There was no significant superficial telangiectasia. The patient’s blood chemistry values were normal, including the level of brain natriuretic peptide (4.7 pg/mL), D-dimer (0.9 μg/mL), and fibrinogen degradation products (<2.5 μg/mL). Lung function testing yielded normal results: his vital capacity was 3.65 L (90% of the predicted value), his forced expiratory volume in 1 second was 3.25 L (88% of the predicted value) and the pulmonary diffusing capacity for carbon monoxide was 20.8 mL/min/mm Hg (85% of the predicted value). Lung perfusion scanning (99mTc-pertechnetate-labeled macroaggregated albumin) suggested a shunt fraction of 13.7% and slightly decreased perfusion of the right upper lobe (Fig. 5a). The electrocardiographic findings were normal (Fig. 5b). Echocardiography showed normal wall motion, and the estimated pulmonary artery pressure was 27 mm Hg. Contrast echocardiography revealed a slight entry of microbubbles into the left atrium, with a significant delay after several cardiac cycles, suggesting right-to-left shunting via the pulmonary vasculature. The delayed appearance of microbubbles was not influenced by the position of the patient. The microbubbles did not appear immediately, which excluded the presence of intracardiac shunting, such as that seen in atrial septal defects. Although the patient had no neurological complications, brain magnetic resonance imaging showed multiple cerebellar infarctions, without brain AVMs (Fig. 5c). The patient’s six-minute walk distance was 455 m, without desaturation in the SpO2 (99% at rest to 98% with exercise). The score on the Borg dyspnea scale was 0 (none at all).

The patient was referred to interventional radiology for pulmonary angiography and embolization. Pulmonary angiography showed normal pulmonary arteries, with no evi-
Figure 3. Contrast-enhanced chest CT scans showed different enhancement patterns for the abnormal vascular shadow and the adjacent pulmonary artery (which was the same as the pulmonary vein), suggesting that it originated from venous structures.

Figure 4. Chest 3D-CT scans showed the gross features of the dilated tortuous vascular shadows in the right upper and middle lobes (a, b) and in the left S6 segment (c, d). The blue vasculature represents pulmonary veins; the red vasculature represents pulmonary arteries.

dence of AVMs. On venous-phase images, the right upper lobe pulmonary vein ran toward the dilated and tortuous collateral vein in the middle lobe (Fig. 6). The anomalous pulmonary vein appeared to drain normally into the left atrium, together with the right lower pulmonary vein. In the left lower lobe, an anomalous segmental pulmonary vein drained the superior segment (S6) via a tortuous collateral, into the basal segmental pulmonary vein (Fig. 6). AUSPV in the right lung and an anomalous segmental pulmonary vein with normal drainage in the left lung was diagnosed, and the patient was discharged without further evaluation.

A genetic examination was conducted before pulmonary angiography for suspected multiple AVMs and possible HHT, with the informed consent of the patient. The exami-
Congenital anomalies of the pulmonary veins can be classified as veins with a normal course and normal drainage, those with an abnormal course and abnormal drainage (scimitar syndrome) and those with an abnormal course and normal drainage (pseudoscimitar syndrome) (4). AUSPV is characterized by a single pulmonary vein that drains an entire lung and enters the left atrium. It is categorized as an anomalous vein with normal drainage and an abnormal route in the lung. AUSPV is caused by atresia or hypoplasia of a pulmonary vein, and results in drainage of the whole lung to the left atrium. It is categorized as an abnormal drainage (pseudoscimitar syndrome) (4). AUSPV is characterized by a single pulmonary vein that drains an entire lung and enters the left atrium. It is categorized as an anomalous vein with normal drainage and an abnormal route in the lung. AUSPV is caused by atresia or hypoplasia of a pulmonary vein, and results in drainage of the whole lung via the other collateral vein (2, 5).

The condition was first described in 1968, in a six-year-old girl (6), and 32 patients, including the present patient, have been reported since (1, 2, 4). The right lung is more commonly involved than the left lung (n=22). AUSPV is usually an asymptomatic anomaly that is fortuitously detected by radiological examination. Its dilated collateral vein has been described as an arc-like opacity (7), a curved tubular structure (1), a meandering pulmonary vein (8) and as pseudoscimitar syndrome (9). AUSPV has been confused with other pulmonary abnormalities, such as hypogenetic lung (scimitar) syndrome (9), dilated varices (10), bronchopulmonary sequestration (11), and more recently, as AVMs (3) or pulmonary nodules (1), even after CT examination.

AUSPV is a variant of the normal anatomy, which nonetheless maintains normal physiological function. It therefore requires a careful differential diagnosis in order to avoid unnecessary intervention. Pulmonary angiography still appears to be the gold standard for the diagnosis of AUSPV, while thin-section CT and its various reconstructed images are the less-invasive alternatives. Chwang et al. (7) maintained that knowledge of this anomaly should prompt careful tracing of the course of vessels on CT, which allows for differentiation of an AUSPV from a pulmonary AVM, without the need for angiography. Hidvegi and Lapin (12) reported that spiral multidetector CT (MDCT) showed spatial resolution superior to the three-dimensional reconstruction of helical CT images (3D-CT). We also prefer MDCT because of its enhancement information, which is helpful in distinguishing closely adjoined structures at the hilum. Thus, we propose that dynamic enhancement CT scans of the hilum would be useful for observing and diagnosing AUSPV respect.

A pulmonary varix is another pulmonary abnormality, and should be considered in the differential diagnosis, although there is some controversy regarding the definition of the condition. Primary pulmonary varices are generally subdivided into three groups (3): idiopathic dilation of normally draining central pulmonary veins, dilated central pulmonary veins with abnormal insertion into the left atrium, and the absence of a lobular pulmonary vein with the presence of a dilated (variceal) collateral vein. The third group would have the same features as AUSPV and its related anomalies. Despite the controversy concerning definitions, these anomalous vascular structures are physiologically normal, and unnecessary intervention or surgery should be avoided.

In the present patient, multiple AVMs and possible HHT were considered first as the differential diagnosis, and genetic examination for BMPR2 and ALK1 revealed a missense mutation of BMPR2. Pulmonary arterial hypertension (PAH) and HHT are autosomal dominant disorders of the vascular system caused by germline mutations in genes encoding members of the transforming growth factor (TGF)-beta superfamily, BMPR2 in the case of PAH and ALK1 or endoglin (ENG) in the case of HHT (13, 14). While PAH and HHT are reported to be distinct clinical entities, and ALK1 mutations predominate in cases with coexisting PAH and HHT (15), Fujiwara et al. (16) reported a high number of ALK1 mutations in pediatric PAH patients without HHT. They proposed that ALK1 has as notable a role as BMPR2 in the etiology of PAH. On the other hand, Rigelsky et al. (13) reported a rare case of BMPR2 mutation in a patient with HHT with multiple AVMs and PAH. They suggested that individuals with HHT alone who are negative for mutations in ALK1 and ENG should also be tested for mutations in BMPR2.

Only 10-20% of known carriers of BMPR2 mutations de-
Figure 6. Pulmonary angiography showed the dilated collateral anomalous veins in the right upper and middle lobes (a-d), and in the left lower lobe (e, f). These findings confirmed the diagnosis of an anomalous unilateral single pulmonary vein and anomalous segmental pulmonary vein.

velop clinical PAH (17). This suggests that the development of PAH requires a subsequent “second hit”. Rarely, associations of \textit{BMPR2} mutations with abnormalities have been reported in patients with atrial septal defects (18). This was not the case in the present patient. An association with pulmonary veno-occlusive disease was also reported, although this too appears to be rare (19). The present case could be the first described case of \textit{BMPR2} mutation-associated AUSPV. However, it cannot be excluded that this patient is currently an asymptomatic carrier of the \textit{BMPR2} mutation, and that he might develop pulmonary hypertension as a result of this mutation in the future.

In the present case, the possibility of a small, subclinical right-to-left shunt also cannot be excluded, although the abnormal vasculature was an AUSPV, not AVMs. The patient was asymptomatic and clinically stable, but lung perfusion scanning showed a shunt fraction of 13.7%. Although the radionuclide method of shunt calculation was reported to be sensitive and to have several advantages (it is simple, noninvasive, and non-operator-dependent) (20), radiopharmaceutical impurities and particle dissolution could lead to incorrect estimation of the shunt ratio (21). Sugiyama et al. indicated
that a shunt ratio of 10-15% on pulmonary perfusion scanning might be significant (21). The calculated shunt ratio in our patient, 13.7%, might therefore be considered borderline. Contrast echocardiography may also show limited entry of microbubbles, but this could be “overdetection of a clinically unimportant AVM” (20). Although the right-to-left shunt was of borderline clinical significance because the patient had no hypoxemia or shortness of breath on exertion, brain magnetic resonance imaging showed multiple cerebellar infarctions. Hence, the patient should be monitored for possible paradoxical emboli caused by a small, undetectable right-to-left shunt. A histological examination might be helpful for assessing the presence and severity of diffuse microvascular AVMs (22), but further invasive examinations did not seem to be warranted for this patient.

During an observation for possible AVM development, the influence of AVMs on borderline PAH should be considered. The development of pulmonary AVMs has been reported to cause a subsequent decrease in the pulmonary artery pressure, which could lead to underestimation of the PAH-related vasculopathy in AVMs and borderline PAH (14). The present patient will continue to be closely monitored due to his risk of developing PAH or AVMs and paradoxical infarction.

The authors state that they have no Conflict of Interest (COI).

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