

# Coexistence of pulmonary arteriovenous malformation and inferior vena cava agenesis in a patient presenting with hemoptysis

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- Hemoptysis,
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## SUMMARY

**INTRODUCTION:** Pulmonary arteriovenous malformations (PAVMs) are abnormal vascular connections, mostly associated with hereditary hemorrhagic telangiectasia (HHT), an autosomal vascular disorder. Inferior vena cava (IVC) agenesis is a rare congenital abnormality, reported to be associated with idiopathic deep venous thrombosis and pulmonary embolism in young patients. A coexistence of pulmonary arteriovenous malformation with IVC agenesis has only been described once in published literature. **CASE PRESENTATION:** We present the case of a 24-year-old, Greek male with a history of recurrent episodes of hemoptysis. Evaluation confirmed the coexistence of a pulmonary arteriovenous malformation with IVC agenesis. The patient underwent a right lower lobectomy and remains asymptomatic at follow-up. **CONCLUSION:** PAVMs are rare causes of hemoptysis. Given the very limited epidemiologic evidence of IVC agenesis, we could not theorize that this entity presents a true association. As unanswered questions remain regarding the pathogenetic correlation of these vascular malformations, further investigation is needed on PAVMs and their pathogenesis.

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## INTRODUCTION

Pulmonary arteriovenous malformations (PAVMs) are abnormal vascular structures that connect a pulmonary artery to a pulmonary vein, thus bypassing the normal pulmonary capillary bed<sup>1</sup>. Population-wide screening programs using thoracic computed tomography scans suggest a prevalence of 1 in 2630 individuals<sup>2</sup>. The majority of PAVMs are congenital and associated with hereditary hemorrhagic telangiectasia (HHT) also known as Osler-Weber-Rendu syndrome. HHT affects on average one in two to 10000 people, although the incidence is reported to be higher in certain geographic areas<sup>3</sup>. HHT may lead to abnormal development of arteriovenous

communications in virtually every organ<sup>3</sup>. Arteriovenous malformations and smaller telangiectatic vessels develop at multiple sites, including nasal, mucocutaneous, pulmonary, hepatic, gastrointestinal, and cerebrovascular beds. PAVMs can also occur as isolated entities, but this diagnosis should not be considered until HHT has been formally sought in the proband and family members<sup>1</sup>. Non-HHT-related PAVMs are idiopathic or associated with acquired causes such as chest surgery, schistosomiasis, cirrhosis, metastatic carcinoma and mitral stenosis<sup>4</sup>. PAVMs can also occur secondary to hepatopulmonary syndrome<sup>5</sup>.

Congenital anomaly of the inferior vena cava (IVC) is an uncommon vascular malformation. This entity was first recognized by Abernethy in 1793, who described a congenital mesocaval shunt and azygos continuation of the IVC in a 10-month-old infant with dextrocardia<sup>6</sup>. IVC agenesis has an estimated prevalence of less than 1% in the general population<sup>7</sup> and is often discovered incidentally during imaging studies performed for other purposes<sup>7,8</sup>. IVC agenesis cases have been published mainly as case reports or case series<sup>7</sup>, mostly associated with idiopathic deep venous thrombosis (DVT) and pulmonary embolism in young patients<sup>7,9,10</sup>.

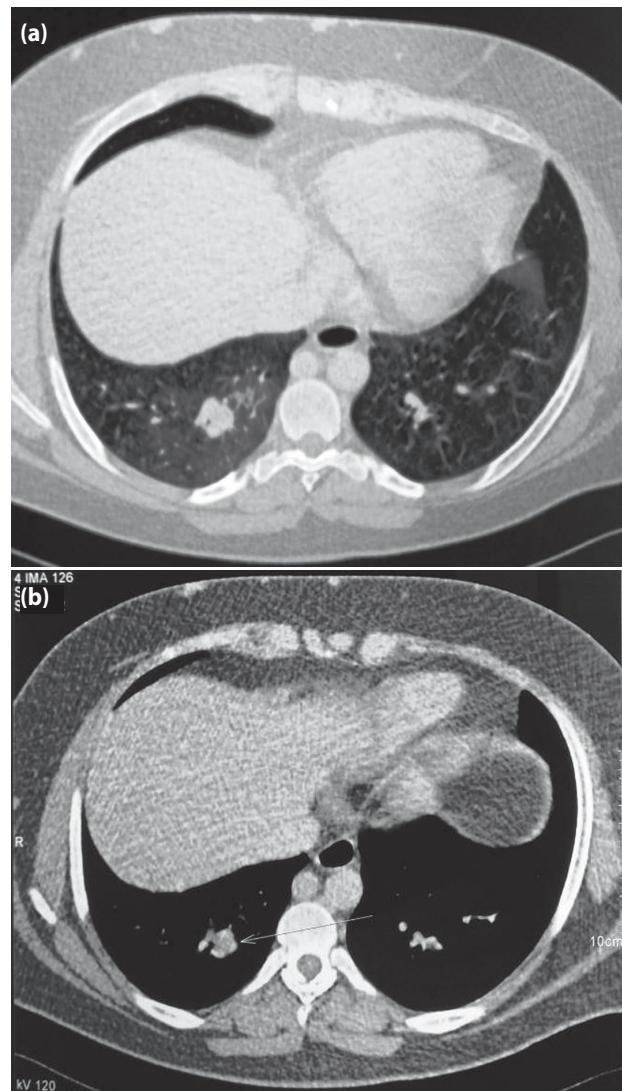
Even if IVC agenesis has been recognized as predisposing factor of DVT<sup>9,11</sup>, the combination of pulmonary arteriovenous malformation and IVC agenesis has been mentioned only once in published literature<sup>12</sup>. Herein, we describe the interesting case of an adult patient with pulmonary arteriovenous malformation, whose evaluation revealed an underlying IVC agenesis.

## CASE PRESENTATION

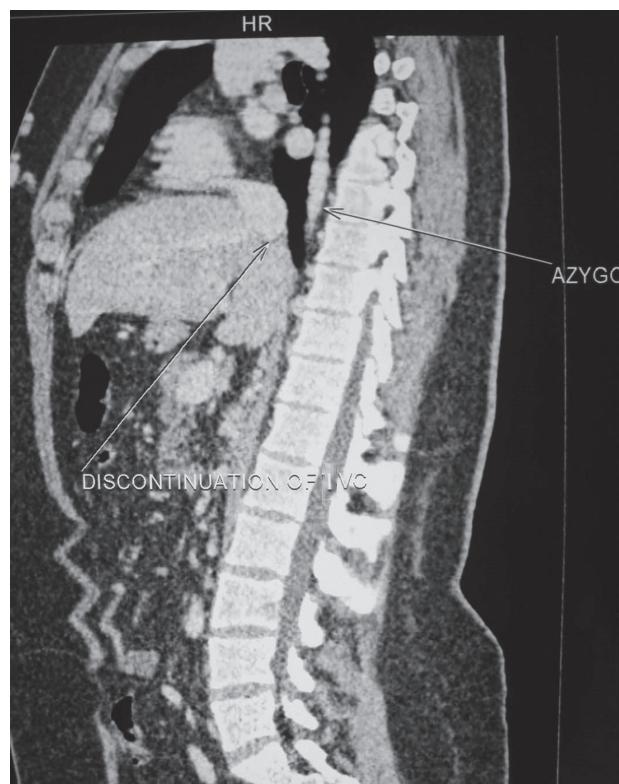
A 24-year-old, Greek, non-smoker, obese (BMI >30), otherwise healthy male was admitted to hospital for investigation of recurrent episodes of hemoptysis. He denied any associated symptoms of chest pain, fever or breathlessness. On admission, he had a pulse rate of 90 beats per minute, blood pressure of 120/75 mm Hg, temperature of 37.2° C, and pulse oximetric saturation of 92% on breathing ambient air. A widening of the superficial vascular network in the abdominal area was observed. The rest of the physical examination was normal. Apart from a total leukocyte count of 15.000/mL, with a predominance of neutrophils, no remarkable findings resulted from the rest of laboratory tests. Immunological tests (ANA, ANCA, RF, C3, C4, immunoglobulins) did not provide any abnormal findings. Chest radiograph was normal. High resolution

chest CT scan was performed, revealing a lesion in the posterior basal segment of the right lower lobe along with an extensively dilated azygos vein (Figures 1, 2). CT pulmonary angiography excluded pulmonary embolism. Flexible bronchoscopy was performed with normal findings. Sputum smears were persistently negative for acid-fast bacilli by Ziehl-Neelsen technique. Sputum culture grew out of normal oropharyngeal flora.

In order to investigate the azygos vein dilation, an abdominal ultrasonography was performed illustrating a liver of normal size, no evidence of portal hypertension



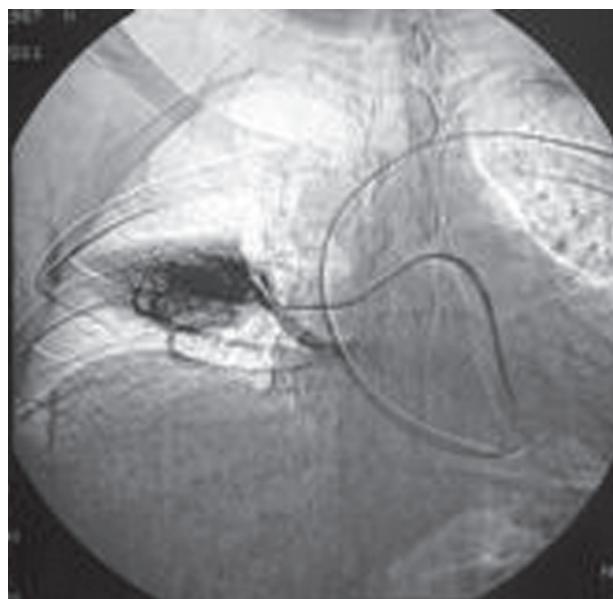
**FIGURE 1.** Chest CT demonstrates a tubular lesion in the posterior basal segment of the right lower lobe in lung window (1a) and mediastinal window after i.v administration (1b).



**FIGURE 2.** Chest CT (sagittal view) demonstrates the discontinuation of inferior vena cava along with an extensively dilated azygos vein.

and absence of IVC depiction under the mesogastrium. An abdominal CT scan revealed IVC agenesis and widening of the azygos and lower epigastric veins, signs of adjacent vein system development. The findings of IVC absence in combination with the widening of azygos system and the presence of the pulmonary lesion raised the suspicion that a certain vascular malformation could be the cause of hemoptysis. A selective right pulmonary angiography was subsequently performed and depicted a lesion in contact with a bronchopulmonary bundle, supplying from one of the branches of pulmonary artery (Figure 3). Transthoracic contrast echocardiography with agitated saline also revealed a right to left shunt.

The patient's skin, oral and nasal cavities were carefully examined, but there were not identified telangiectatic lesions. There were no family members who had been diagnosed with visceral arteriovenous malformations before. Gastroscopy and colonoscopy ruled out gastrointestinal telangiectasia, while brain MRI did not show any enhancing lesions. As there were no evidences suggesting the diagnosis of HHT, the patient was regarded as having



**FIGURE 3.** Pulmonary angiography demonstrates a lesion supplying from one of the branches of pulmonary artery.

non-HHT-related pulmonary arteriovenous malformation.

The patient was managed with intravenous fluids, tranexamic acid, cough suppressants and antibiotics. Due to the current unavailability of embolization method in our hospital, the patient was initially referred to an expert center. However, further episode of massive hemoptysis was observed and the patient eventually underwent a right lower lobectomy. Histopathology of the excised specimen was consistent with a pulmonary arteriovenous malformation. Postoperative period was uneventful and the patient remains asymptomatic at follow-up.

## DISCUSSION

PAVMs may be single or multiple, unilateral or bilateral, simple or complex and are usually located at the lower lobes<sup>4</sup>. Asymptomatic hypoxemia due to right-to-left shunting is the most common manifestation. Platypnea is frequent, attributed to basal predominance of PAVMs and occasionally masked by obesity<sup>13</sup>. Hemoptysis or hemothorax are rarely presented, though these episodes tend to be more common and fatal during the period of pregnancy<sup>1</sup>. Neurological events due to paradoxical emboli are common and include ischemic strokes, brain abscesses and/or migraine headaches<sup>1</sup>. Interestingly, these manifestations may precede the official PAVM diagnosis for years<sup>1</sup>.

The majority of PAVMs (80-90%), as previously mentioned is hereditary and associated with HHT, an autosomal dominant vascular disorder. HHT diagnosis can be difficult and rely mostly on clinical criteria, known as Curaçao criteria which consist of the following four components<sup>14</sup>: (1) epistaxis (spontaneous, recurrent); (2) telangiectases (multiple at lips, oral cavity, fingers or nose); (3) visceral lesions, including gastrointestinal telangiectasia (with or without bleeding), pulmonary, hepatic, cerebral, and spinal arteriovenous malformations; and (4) family history of a first-degree relative with HHT according to these criteria. Three of these four criteria confirm the diagnosis<sup>14</sup>. Our patient did not have any evidence suggesting the diagnosis of HHT.

The pathogenesis of PAVMs is highly interesting and includes several mechanisms. The vascular system is remarkably well regulated and malformations are fortunately rare; however disruption in pathways involved in vascular stability can occur. Biological data from endothelial cells derived from arteriovenous malformations, show a high proliferation rate and absence of sensitivity to inhibitory cytokines, such as interleukin (IL)-1b, tumour necrosis factor-a (TNF-a), transforming growth factor-b (TGF-b) and interferon-g (IFN-g). Therefore, genes that regulate angiogenic processes, and more specifically proliferation and/or apoptosis, may be involved in the etiopathogenesis of AVMs. Other probable candidates are genes encoding proteins that are essential for vessel identity, such as ephrin B2, expressed in arteries, and its specific receptor, Eph-B4, present in veins<sup>15</sup>. The genes mutated in HHT encode proteins which are involved in the TGF- b superfamily signaling pathway<sup>5</sup>.

The diagnosis of PAVMs on the basis of radiological findings is generally straightforward; however, several pulmonary parenchymal diseases and congenital anomalies that closely resemble pulmonary arteriovenous malformations may cause diagnostic confusion<sup>16</sup>. Radiographic appearances on a plain chest radiograph range from normality to a mass with visible feeding or draining vessels while the gold standard method for diagnosis has been pulmonary angiography as well as the use of both pulmonary angiography and CT scan<sup>5,16</sup>. Simple PAVMs appear as well-defined peripheral nodules, which may be rounded or multilobulated, into which one feeding artery, and from which one or more draining veins, can be clearly visualized<sup>16</sup>. In case of complex PAVMs, they may consist of one or more lobulated venous sacs of variable size supplied by more than one feeding artery,

often arising from adjacent segmental pulmonary artery branches and from which there are usually several draining veins. For the diagnosis of either simple or complex PAVMs, both feedings and draining vessels should be present; otherwise diagnosis cannot be confirmed by CT and more invasive investigations are requested<sup>16</sup>.

PAVMs pose unique management challenges. Treatment options include surgery and embolization, with the latter being currently the preferred technique<sup>5</sup>. Percutaneous Transcatheter Embolization is the gold standard for the treatment usually performed by an interventional radiologist. PAVMs with a feeding artery of 3 mm in diameter detected by chest CT scan should be considered for therapy with this technique<sup>5</sup>. Severe pulmonary hypertension remains a contraindication<sup>1</sup>. Surgery is used as an emergency procedure to control bleeding and when loss of lung is justified<sup>5</sup>. The decision for surgical resection in our case was made on the basis of the massive hemoptysis combined with the unavailability of embolization method. Recurrence of PAVM occurs after 15% of embolizations and results from recanalization of occluded PAVMs, collateralization from adjacent arteries, or missed accessory pathways<sup>5</sup>. As for the follow-up period, it is recommended to perform CT scan 6 to 12 months after embolization and then every 3 to 5 years<sup>1,5</sup>.

Interestingly, anomalies of the IVC are extremely rare and present only in 0.3-0.5% of healthy individuals<sup>17</sup>. About 90% of congenital IVC malformations involve the hepatic and suprarenal segments, whereas only about 6% involve the renal or infrarenal segments<sup>18</sup>. IVC agenesis has an incidence of less than 1% and may occur as isolated entity or coexist with anomalies of other anatomic structures, mainly the heart (situs inversus, dextrocardia) or the spleen (polysplenia, asplenia)<sup>17</sup>. In our case, the patient did not have any associated congenital heart or splenic defects. IVC agenesis is divided into 3 segments (retrohepatic, renal and postrenal segments) and is often associated with azygos and/or hemiazygos continuation which allow drainage into the caudal segment up to the right atrium through the connection with the superior vena cava<sup>17</sup>.

Several mechanisms are involved in the pathogenesis of IVC agenesis. The IVC and adjacent urogenital drainage system undergo complex embryogenesis between weeks 6 and 8 of embryonic life. Two hypotheses have been described to explain the origin of the malformation: changes during the process of embryogenesis or intrauterine/

perinatal thrombosis that consecutively influences the postnatal development of the venous system<sup>19</sup>.

The clinical importance of these congenital anomalies lies in the fact that they have been particularly associated with unprovoked DVT in young patients, although they are usually not considered because of their rarity. Indeed, it has been reported an incidence of IVC agenesis of about 5% in young patients affected by DVT<sup>9</sup>. Accordingly, Ruggeri et al suggest a thorough investigation with a CT scan or venous angiography in all young patients with idiopathic DVT affecting the inguinal and iliac region, for exclusion of this abnormality<sup>9</sup>. However, apart from a few cases of pulmonary embolism<sup>8,10</sup>, no connection with pulmonary disorders has ever been described.

In conclusion, to the best of our knowledge, there is only one description of the combination of PAVM with

IVC agenesis in published literature<sup>12</sup>. Indeed, given the very limited epidemiologic evidence of IVC agenesis, we could not theorize that this entity presents a true association rather than an interesting coincidence. Nevertheless, physicians should be mindful of the possibility of an undiagnosed pulmonary arteriovenous malformation in adults presenting with hemoptysis; the possibility of associated anatomic abnormalities and multiorgan anomalies should also be considered. Furthermore, as unanswered questions remain regarding the pathogenetic correlation of these vascular malformations, further investigation is needed on PAVMs and their pathogenesis.

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

## ΠΕΡΙΛΗΨΗ

### Πνευμονική αρτηριοφλεβώδης δυσπλασία με συνύπαρξη αγενεσίας κάτω κοίλης φλέβας σε ασθενή με αιμόπτυση

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**Εισαγωγή:** Οι πνευμονικές αρτηριοφλεβώδεις δυσπλασίες αντιπροσωπεύουν ένα φάσμα ανώμαλων επικοινωνιών μεταξύ πνευμονικών αρτηριών και πνευμονικών φλεβών. Στη πλειοψηφία τους συνδυάζονται με τη Συγγενή Αιμορραγική Τηλεαγγειεκτασία, μια κληρονομική διαταραχή ανάπτυξης του αγγειακού δικτύου. Η αγενεσία της κάτω κοίλης φλέβας είναι μια εξαιρετικά σπάνια συγγενής ανωμαλία και έχει αναφερθεί σε περιστατικά νεαρών ενηλίκων με εν τω βάθει φλεβοθρόμβωση ή πνευμονική εμβολή. Η παρουσία πνευμονικής αρτηριοφλεβώδους δυσπλασίας με ταυτόχρονη αγενεσία κάτω κοίλης φλέβας έχει περιγραφεί μια μόνο φορά στη παρούσα βιβλιογραφία. **Παρουσίαση περιστατικού:** Παρουσιάζουμε τη περίπτωση 24χρονου άνδρα που εισήχθη στη Κλινική μας λόγω υποτροπιαζόντων επεισοδίων αιμόπτυσης. Κατά τη διερεύνηση, διαπιστώθηκε αρτηριοφλεβώδης δυσπλασία δεξιού κάτω λοβού με ταυτόχρονη αγενεσία κάτω κοίλης φλέβας. Η βλάβη αφαιρέθηκε χειρουργικά και ο ασθενής είχε καλή μετεγχειρητική πορεία, χωρίς νέο επεισόδιο αιμόπτυσης. **Συμπέρασμα:** Οι αγγειακές δυσπλασίες του πνεύμονα θα πρέπει να συμπεριλαμβάνονται στη διαφορική διάγνωση της αιμόπτυσης, ιδιαίτερα σε νεαρούς ενήλικες. Επιπλέον, δεδομένης της περιορισμένης βιβλιογραφίας, δεν μπορούμε να γνωρίζουμε αν οι δυο ανωμαλίες συνδέονται παθογενετικά και περαιτέρω έρευνα είναι ενδεχομένως απαραίτητη για τις αρτηριοφλεβώδεις δυσπλασίες και τη παθογένεση τους.

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**Λέξεις - Κλειδιά:** Σύνδρομο Αποφρακτικής Άπνοιας Ύπνου, Εκτελεστικές λειτουργίες, Νευρογνωστικές συστοιχίες, Νευρογνωστικές λειτουργίες

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