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CASE REPORT

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When you hear hoofbeats, think zebras – pulmonary veno-occlusive disease: A case report

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Abstract

Pulmonary veno-occlusive disease (PVOD) is a rare disease. It may be idiopathic or associated, in particular, with connective tissue disease, or it may develop after radiation exposure; in heritable forms of PVOD, the inheritance is autosomal recessive due to the presence of homozygous or compound heterozygous pathogenic variants in the EIF2AK4 gene. We describe the case of a young man whose PVOD was initially misdiagnosed as chronic thromboembolic pulmonary hypertension despite worsening after riociguat, nonspecific computed tomography pulmonary angiogram findings, and parental consanguinity could suggest an autosomal recessive disease. The correct diagnosis and the correct treatment are crucial given the high mortality rate of this disease.

KEYWORDS
cardiovascular diseases, pulmonary heart disease, transplantation, vascular remodeling

INTRODUCTION

Pulmonary veno-occlusive disease (PVOD) is a very rare form of pulmonary hypertension (PH) currently classified in group 1′ PH (1′.2.1).[1] Although PVOD is described as characterized by preferential remodeling of the pulmonary venules, the disease is panvascular involving arterial, venous ad capillary vessels. It may be idiopathic or associated, in particular, with connective tissue disease, or it may develop after radiation exposure; in heritable forms of PVOD, the inheritance is autosomal recessive due to the presence of homozygous or

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compound heterozygous pathogenic variants in the *EIF2AK4* gene.[2,3]

We describe the case of a young man whose PVOD was initially misdiagnosed as chronic thromboembolic pulmonary hypertension (CTEPH) despite findings at computed tomography pulmonary angiogram (CTPA) should have suggested a correct diagnosis as well as worsening of clinical conditions after the beginning of pulmonary arterial hypertension (PAH) specific therapy.

CASE DESCRIPTION

In December 2018, a 28-year-old male complained of progressive fatigue and breathlessness (World Health Organization [WHO] functional class III) lasting 6 months. His past medical history was silent, as was his family history. After physical examination, electrocardiogram (EKG), chest X-ray, two-dimensional-transthoracic echocardiogram (2D-TTE), and CTPA scan, he was diagnosed with CTEPH with distal lesions. He was given warfarin (International normalized ratio target: 2–3), furosemide 25 mg od, and riociguat 1 mg tid. Despite treatment, the patient's clinical conditions deteriorated after 6 months and, in August 2019, he was addressed to our center to evaluate the eligibility for pulmonary endarterectomy due to our expertise in CTEPH patients with distal diseases.[4] On admission, the clinical scenario was that of congestive heart failure with dyspnea at rest, jugular vein distention, ascites, and severe peripheral edema. Oxygen saturation was 85% in oxygen therapy. Their blood pressure was 90/60 mmHg. At auscultation, heart rate was fast with a fixed split S2 tone, diffuse pulmonary rales were present. The EKG showed sinus tachycardia (105 bpm), first-degree atrioventricular block, tall and peaked P waves, and ST–T segment changes consistent with ventricular overload. Chest X-ray demonstrated mild right pleural effusion and signs of vascular and interstitial congestion. The 2D-TTE showed an estimated pulmonary artery systolic pressure (PASP) of 115 mmHg; right ventricular (RV) dilation, hypertrophy, and systolic dysfunction (RV end-diastolic area: 41 cm^2; RV outflow tract diameter: 52 mm, maximum thickening of RV free wall: 10 mm), tricuspid annular plane systolic excursion: 14 mm; fractional area change: 17%, severe tricuspid regurgitation [TR]); right atrium dilation (area: 32 cm^2), dilated and poorly collapsible inferior vena cava (IVC, diameter = 25 mm), and pericardial effusion. The left ventricle was small (end-diastolic volume: 69 ml), with a normal ejection fraction and abnormal septal motion due to RV pressure overload (Figure 1a). Laboratory tests showed mild renal impairment – estimated glomerular filtration rate 82 ml/min/1.73 m^2 – and mild anemia (hemoglobin value 12.8 g/dl), with elevated values of *N*-terminal pro-brain natriuretic peptide (3834 pg/ml). The patient was carrier of the heterozygous variants R506Q in factor V Leiden and A1298C in the methylenetetrahydrofolate reductase. At right heart catheterization (RHC), mean pulmonary artery pressure was 50 mmHg with normal wedge pressure (12 mmHg) and low cardiac index (1.3 L/min/m^2), mean atrial pressure (right atrial pressure) was 18 mmHg, and calculated pulmonary vascular resistance was 18.3 WU. Treatment with rioc iguat was stopped, since deterioration with PAH-specific therapy may be observed in PVOD, and inotropic support with dobutamine (5 mcg/kg/min) and dopamine (2 mcg/kg/min) was started.

Ventilation/perfusion scintigraphy did not show a clear ventilation/perfusion mismatch (ventilation rate: 46% left lung, 54% right lung; perfusion rate: 46% left, 54% right). A repeated CTPA scan excluded CTEPH but showed the signs of pulmonary edema which should typically raise the suspicion of PVOD: septal thickening, ground-glass opacities, mediastinal lymph nodes enlargement, and pleural effusion (Figure 1b).[5] These signs were also identified at a critical re-examination of the previous CTPA images. On the third day of hospitalization, after the abdominal ultrasound, a paracentesis followed by albumin infusion lowered the ascites grade. After a transient clinical improvement, the patient's conditions redeteriorated requiring dobutamine uptitration and oxygen therapy up to FiO_2 60%; furthermore, after the first paracentesis, ascites progressively reworsened, which was not unexpected due to the hemodynamically severe PH.

Considering the young age, the absence of major comorbidities, the inotropic dependence of the labile hemodynamic stability – WHO Class IV – and the absence of alternative treatments, the patient was included on the national transplant waiting list (National Emergency Program) on September 23rd. On September 30th, he underwent uncomplicated double-lung transplantation through Clamshell thoracotomy. Due to the critical hemodynamic status, the patient was put on femoro-femoral venous-arterial extracorporeal membrane oxygenation before inducing general anesthesia. RHC performed 3 weeks after transplant showed normalization of hemodynamic profile. He was discharged in good clinical status 44 days after the transplant. During the posttransplantation period (1–3–6 months), routine surveillance endoscopy with bronchoalveolar lavage and transbronchial biopsies ruled out acute rejection and graft infections. Immunosuppressive therapy was well-tolerated. The functional class remained stable in WHO Class I. He was discharged in good clinical status 44 days after the transplant. He's

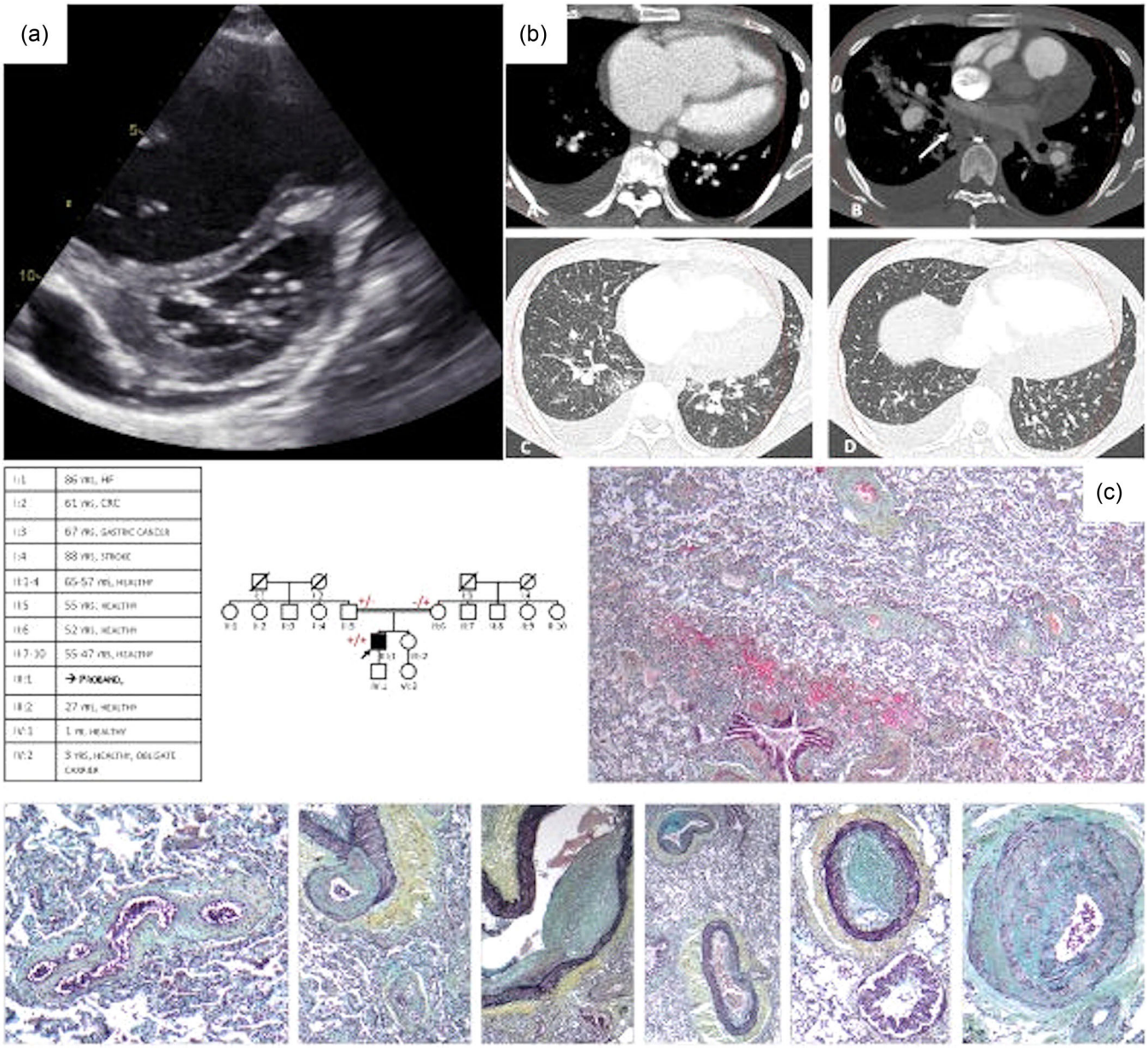

FIGURE 1 (a) Transthoracic echocardiography (parasternal short axis) showing RV dilation and hypertrophy, LV compression, and pericardial effusion. (b) (A, B) Axial CT images at mediastinal window setting showing: (A) RV dilation and hypertrophy, septal bowing, and LV compression, (B) subcarinal mediastinal lymph nodes enlargement (arrow) and bilateral pleural effusion; (C, D) axial CT images at lung parenchyma window setting displaying septal thickening and centrilobular ground-glass opacities. (c) Family pedigree highlights the consanguinity of the parents (double line linking the parents) and the absence of other affected relatives. The young son (IV:1) is obviously a healthy heterozygous carrier of the paternal variant. Both parents (II:5 and II:6) were heterozygous carriers of the mutation. The pathology panels show the spectrum of vascular lesions diffusely involving lung vasculature, arteries, capillaries, and veins. CT, computed tomography; LV, left ventricular; RV, right ventricular.

still doing well at 2-years follow-up. The last TTE performed on April 2021 showed mildly dilated and hypertrophic (maximum thickening of RV free-wall 7 mm) RV with normal estimated PASP in the absence of TR or IVC dilation and rejection.

The pathologic study of the lungs excised at transplantation showed a panvascular pulmonary disease involving arteries, capillaries, and veins, both large and small (Figure 1c). These findings confirmed the diagnosis of PVOD.

Genetic testing included the analysis of both bone morphogenetic protein receptor 2 and eukar yotic translation initiation factor 2 alpha kinase 4 (EIF2AK4) genes. The known p.(Arg1136*) homozygous pathogenic variant (P, according to the American College of Medical Genetics and Genomics criteria) was identified in the *EIF2AK4* gene, which is associated with the autosomal recessive PVOD.[2,3] Genetic counseling demonstrated parental consanguinity (Figure 1c) which, if not missed at first visits, should have raised the suspicion of an autosomal recessive disease. He was the only affected member of the family since both parents were healthy and had no signs of disease, as were the younger sister (whose carrier status is unknown) and the maternal and paternal relatives.

DISCUSSION

This case highlights the clinical relevance of a timely and accurate etiologic diagnosis of PH to provide the appropriate, life-saving treatment.

PVOD is a rare autosomal recessive disease associated with homozygous or compound heterozygous mutations in the *EIF2AK4* gene. Although the preferential involvement of the pulmonary venous system, all three compartments of the pulmonary circulation (venous, capillary, and arterial) are affected. Venular lesions include intimal fibrosis of small preseptal venules. Capillary lesions are characterized by the proliferation of endothelial cells. Arterial lesions resemble those of PAH, with intimal fibrosis and medial hypertrophy.

PVOD is clinically characterized by the harmful, paradoxical response to PAH therapy and the risk of pulmonary edema.[5] This is one of the reasons why its clinical course is usually very aggressive with a mortality rate of up to 72% within one year of diagnosis.[6] Given the difficult diagnosis, the prevalence is still a matter of debate, reaching 1–2 cases per million inhabitants with an annual incidence rate of ~0.1–0.5 per million.[7] To date, the only available treatment for PVOD is lung transplantation.

Our clinical case describes a challenging clinical scenario, in which several red flags such as CTPA findings, parental consanguinity suggestive of an autosomal recessive disease, and worsening after PAH-specific vasodilator therapy, might have raised the suspicion of PVOD. The correct diagnosis and the correct treatment option were only reached when the patient was referred to a specialized center.

AUTHOR CONTRIBUTIONS

Laura Scelsi: Conceptualization, data curation, and writing – original draft. **Giuseppe Lanzillo:** Conceptualization, data curation, and writing – original draft. **Eloisa Arbustin:** Writing – review and editing, and genetic and histopathology data curation. **Andrea D'Armini:** Writing – review and editing, and clinical and surgical data curation. **Alessandra Greco:** Writing – review and editing, and clinical data curation. **Federica Meloni:** Writing – review and editing, and clinical data curation. **Annalisa Turco:** Writing – review and editing, and clinical data curation. **Adele Valentini:** Writing – review and editing, and clinical and imaging data curation. **Luigi Oltrona Visconti:** Writing – review and editing, and clinical data curation. **Stefano Ghio:** Data curation, writing – original draft, writing – review and editing, and supervision.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

The patient signed informed consent for use in an anonymous form of clinical data for research.

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