

Pneumologia

Dyspnoea – a valuable clue in a rare disease diagnosis

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Abstract

English:

Pulmonary veno-occlusive disease (PVOD) is a rare microvasculopathy associated with dyspnoea, pulmonary arterial hypertension (PAH) and poor prognosis. A 42-year-old female, with a known history of cured thyroid neoplasm, complained of severe inspiratory progressive dyspnoea, chest pain, dry cough and asthenia. The initial investigations established the diagnosis of idiopathic PAH. Specific associated vasodilator treatment was initiated but with sildenafil intolerance. The clinical condition continued deteriorating, and thus the investigations were extended. DLCO was unnaturally low (24%). Angiography detected a minimal left distal CTEPH (not suitable for balloon angioplasty). Genetic test came positive for biallelic mutations of EIF2AK4, suggestive for PVOD. Finally, the diagnostic was changed to PAH in the PVOD context. A decision was made to refer the patient for lung transplant and to associate treprostinil treatment (with slight clinical improvement). Therefore, severe dyspnoea, hypoxia, decreased DLCO and poor response to vasodilator treatment compel physicians to search for PVOD and refer to lung transplant.

Keywords

dyspnoea • pulmonary hypertension • pulmonary veno-occlusive disease • EIF2AK4 • lung transplantation

Dispneea – un indiciu valoros în diagnosticul unei boli rare

Rezumat

Romanian:

Boala veno-ocluzivă pulmonară (PVOD) este o microvasculopatie rară asociată cu dispnee, hipertensiune arterială pulmonară (HTAP) și prognostic nefavorabil.

Caz clinic: femeie 42 ani, cunoscută cu neoplasm tiroidian vindecat, care acuza dispnee inspiratorie severă progresivă, dureri toracice, tuse seacă, astenie. Investigațiile inițiale au stabilit diagnosticul de HTAP idiopatică. A fost inițiat tratament specific vasodilatator asociat, dar cu intoleranță la Sildenafil. Starea clinică a continuat să se deterioreze, astfel că investigațiile au fost extinse: DLCO nefiresc de scăzut (24%), angiografia cu CTEPH distal stâng minim (nu se pretează pentru angioplastia cu balon), testul genetic pozitiv pentru mutațiile bialelice ale EIF2AK4, sugestive pentru PVOD. În final, diagnosticul s-a schimbat în HTAP în contextul PVOD. Tratamentul a fost suplimentat cu Treprostinil (cu ușoară îmbunătățire clinică) și este în evaluare pentru transplant pulmonar. Dispneea severă, DLCO scăzut, răspunsul slab la tratamentul vasodilatator ridică suspiciunea de PVOD, necesitatea unor investigații tinite și adresarea pentru transplant pulmonar.

Cuvinte-cheie

dispnee • hipertensiune pulmonară • boală veno-ocluzivă pulmonară • hipoxie • EIF2AK4 • transplant pulmonar

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Introduction

Pulmonary veno-occlusive disease (PVOD) is a rare pulmonary microvasculopathy entity, with a very poor prognosis, that is usually mistaken with idiopathic pulmonary arterial hypertension (PAH). The pathological process is an obliteration of small pulmonary veins by fibrous intimal thickening and irregular capillary proliferation (1). Similar to other types of obstructive pulmonary vascular diseases, PVOD leads to a progressive increase in pulmonary vascular resistance (PVR), causing right heart failure and finally death (2). PVOD accounts for 5%–10% of the histological forms of cases initially considered to be idiopathic pulmonary hypertension (PH) (3). If we apply this frequency to the idiopathic PH incidence rate, it leads to an estimated incidence rate of 'idiopathic' PVOD of 0.1–0.2 cases per million (3). PVOD can also exist in patients with comorbidities, including connective tissue disease, sarcoidosis, HIV infection, bone marrow transplantation or pulmonary Langerhans cell granulomatosis, suggesting that PVOD may have a much higher prevalence than indicated by the current registries (3). Even though the first well-documented case of PVOD was described more than 70 years ago, the characteristics and pathophysiology of this disease remain poorly understood regarding diagnosis, treatment and evolution (4). The accurate diagnosis of PVOD is often delayed due to the nonspecific clinical presentations, the absence of clear diagnostic criteria and the lack of non-invasive confirmatory tests. A major discovery in PVOD diagnosis was the recessive mutations in the epithelial translation initiator factor 2 α K type 4 (*EIF2AK4*) gene that was co-segregated with PVOD, and these are found in 100% of familial cases and 25% of sporadic cases of histologically confirmed PVOD (5). In this article, we report a case of PH in middle-aged women, wherein ruling out almost all common aetiologies finally established the diagnosis of PVOD.

Case report

We describe the case of a 42-year-old female patient, without any vices, known with thyroid neoplasm operated in 2014 and treated with radioactive iodine, cured, and being at the moment under substitution treatment with levothyroxine. Since 2020, she has been complaining of progressively worsening inspiratory dyspnoea, currently in severe form – 3/4 MRC grade, with desaturation at rest ($\text{SaO}_2 = 87\%$). She also complains of diffuse chest pain, dry cough and asthenia. Patient examination shows facial and extremities cyanosis and slightly digital hipocratism. In the first investigations, chest X-ray and spirometry were within normal limits. EKG detects pulmonary P, right deviation of QRS axis and minor right branch bundle block. Echocardiography reveals dilated

right ventricle (with double values compared to left cavities) with a normal ejection fraction of 62% and severe PH (estimated systolic pulmonary artery pressure [PAP] at 115 mmHg). Thoracic computed tomography (CT) angiography excludes pulmonary embolism but reveals obvious signs of PH, with a pulmonary trunk/aorta ratio of 1.58 (Figure 1), and excludes other lung diseases (suggestive for interstitial pulmonary oedema, Figure 2). The N-terminal pro B-type natriuretic peptide (NT-proBNP) value was greatly increased (4268 pg/mL versus the normal value of 130 pg/mL). The 6-min walk test (6MWT) was a paradox, in that the patient walked 520 m (87% of the predicted distance) despite her desaturation to an SaO_2 of 75%. She was also investigated by oncology and endocrinology for a possible relapse of thyroid neoplasm and it was excluded.

Currently, she has a normal thyroid function, being under substitution treatment with levothyroxine. Right heart catheterisation confirms the diagnosis of severe PAH, with a PAP systolic/diastolic of 83/37 mmHg, a mean PAP of 54 mmHg, a low pulmonary capillary wedge pressure (PCWP) of 14 mmHg and a very increased PVR of 18.3 mmHg/L/min, as well as the preservation of cardiac output. Unfortunately, there was no possibility of a vasoreactivity test due to a lack of resources. Screening for autoimmune diseases, vasculitis, HIV infection and thrombophilia were all negative, and thus it was considered to be an idiopathic PAH form. We initiated

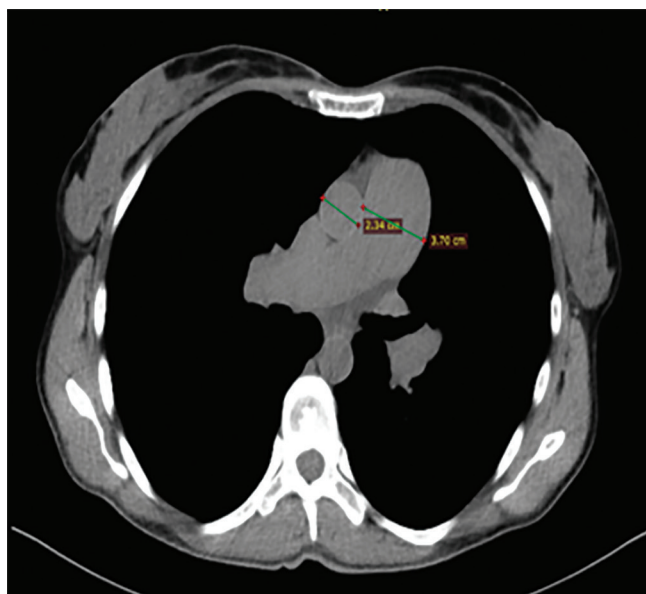


Figure 1. Thoracic CT angiography reveals obvious signs of PH, with a pulmonary trunk/aorta ratio of 1.58. CT, computed tomography; PH, pulmonary hypertension.

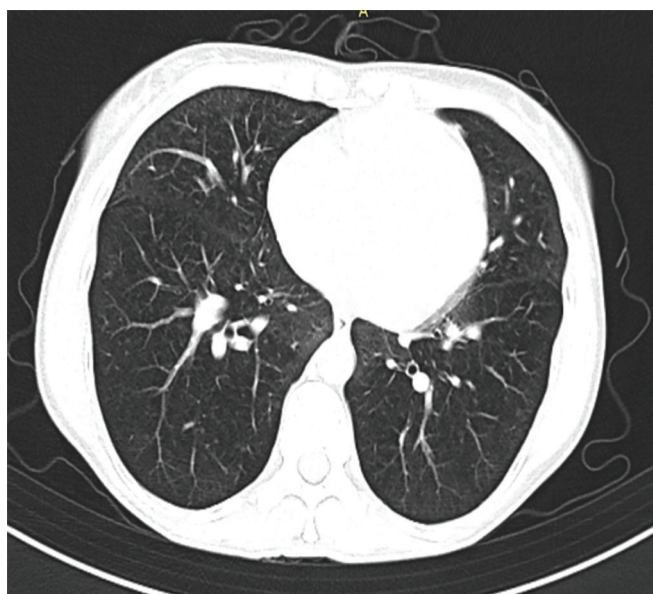


Figure 2. Thoracic CT angiography excludes other lung diseases but is suggestive for interstitial pulmonary oedema with interlobular septal thickening. CT, computed tomography.



Figure 4. Treprostinil subcutaneous pump treatment.



Figure 3. Angiography from AKH Vienna Clinic (May 2022) detects a distal CTEPH particularly visible in the side view, with small visible anterior–posterior changes, but without peripheral loss. CTEPH, chronic thromboembolic pulmonary hypertension.

specific vasodilator treatment with an endothelin receptor antagonist (macitentan) and a phosphodiesterase 5 inhibitor (sildenafil), the last of these being stopped immediately due to intolerance (worsening dyspnoea with signs of pulmonary oedema). The clinical condition continued deteriorating, and thus the investigations were extended. We also performed a test for the diffusing lung capacity for carbon monoxide (DLCO), which was found severely decreased at 25%.

Angiography detected minimal left distal chronic thromboembolic pulmonary hypertension (CTEPH) and was not suitable for balloon angioplasty (Figure 3). Upon encountering this finding, a differential diagnosis was considered, and against this backdrop the possibilities of various diseases were discussed, such as pulmonary capillary haemangiomatosis, chronic interstitial pneumonia, chronic passive congestion, idiopathic pulmonary haemosiderosis, lymphangiomatosis and IPAH due to the mixed pattern of lung involvement. The next step was to perform a genetic test. It came with a potentially positive result for autosomal recessive PVOD and associated PAH (two pathogenic variants were identified at the *EIF2AK4* gene level). We reconsider the final diagnosis as being a PAH with features of PVOD involvement, in high-risk class, with heart failure New York Heart Association (NYHA) III. Additional treatment with treprostinil subcutaneously through pump was initiated with resources

Table 1. Recommendations for PAH with signs of venous/capillary involvement

Recommendations	Class ^a	Level ^b
A combination of clinical and radiological findings, ABG, PFTs and genetic testing is recommended to diagnose PAH with signs of venous and/or capillary involvement (PVOD/PCH) ⁵⁹¹	I	A
Identification of biallelic <i>EIF2AK4</i> mutations is recommended to confirm a diagnosis of heritable PVOD/PCH ^{158,59}	I	A
Referral of eligible patients with PVOD/PCH to a transplant centre for evaluation is recommended as soon as the diagnosis is established	I	C
In patients with PVOD/PCH, the use of drugs approved for PAH may be considered with careful monitoring of clinical symptoms and gas exchange	IIb	C
Lung biopsy is not recommended to confirm a diagnosis of PVOD/PC	III	C

ABG, arterial blood gas analysis; *EIF2AK4*, epithelial translation initiator factor 2α K type 4; PAH, pulmonary arterial hypertension; PCH, pulmonary capillary haemangiomatosis; PFT, pulmonary function test; PVOD, pulmonary veno-occlusive disease.

^aClass of recommendation.

^bLevel of evidence.

from outside the country. Currently, the patient presents a partial improvement of clinical condition, without systemic side effects but with local pain and rash (Figure 4). Once this diagnosis was established, the patient was informed about the need for the simultaneous initiation of lung transplant procedures, but she refused. Besides the specific vasodilator treatment, the patient also received treatment with diuretics, anticoagulant and long-term oxygen therapy.

Discussion

PVOD is often labelled as an idiopathic form of PAH, having a similar clinical presentation with PAH, but it is important to differentiate between these two conditions since PVOD carries a worse prognosis (the 1-year mortality is as high as 72% and the mean survival is estimated at 1–2 years) (6). Also, in this case, the detection of a minimal distal CTEPH in the left does not explain the patient's clinical condition, severe PAH and the lack of response to the specific treatment, being considered an unfortunate association. This patient presented with typical manifestations of PVOD, with unexplained severe dyspnoea, rapid clinical deterioration, hypoxaemia, arterial PH and very low DLCO. Lung biopsy is theoretically the gold standard that confirms the diagnosis but currently is not recommended due to the increased risk of bleeding in the setting of fragile pulmonary veins (6). The presence of the biallelic mutations of the *EIF2AK4* gene was associated with a heritable form of PVOD (4,7) and confirms the diagnosis (according to the ESC/ERS 2022 PAH guidelines recommendations, Table 1) (7). Treatment with vasodilators in PVOD patients is controversial and may be fatal because it may induce life-threatening pulmonary oedema. Pharmacological management is only a bridge to lung transplantation, which remains the final solution. Referral of eligible patients with PVOD/PCH to a transplant centre for evaluation is recommended as soon as the diagnosis is established (7). Most cases of PVOD appear spontaneously

without having an obvious cause. Multiple factors such as toxic and radiation exposures, malignancies, inflammatory/connective tissue disorders and immune-mediated, infectious and genetic alterations have been identified as possible risk factors for the development of PVOD (8). Based on the aetiology, alongside genetic determination, a connection with thyroid cancer therapy with radioactive iodine or levothyroxine is a possible scenario in our case. Therefore, starting from an inexplicable dyspnoea, with rapid clinical deterioration, we ended up with a very rare disease with an extremely reserved prognosis. The case has a special dramatic element to it, highlighting a young patient, who has overcome cancer but now can die suddenly in the context of PVOD, especially if she does not undergo the transplant in time.

Conclusions

Severe inexplicable dyspnoea with hypoxaemia, rapid clinical degradation and a marked decrease in DLCO, with reduced response to specific vasodilator therapy, are key elements that compel physicians to search for a possible PVOD. Early diagnosis in suspected cases of PVOD, with referral to a transplant centre as soon as the diagnosis is established, should be the primary purpose.

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Authors' contributions

Larisa Dobrescu drafted the article and contributed to data acquisition and interpretation. Nicoleta Bertici drafted and critically revised the article and gave final approval. All authors approved the final version of the article as submitted.

Conflicts of interest

The authors declare no conflict of interest.

Institutional review board statement

Not applicable.

Informed consent statement

Informed consent for patient information to be published in this article was not obtained because our institution does not require informed consent for individual case reports.

Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

References

1. Pietra GG, Capron F, Stewart S, Leone O, Humbert M, Robbins IM, et al., Pathologic assessment of vasculopathies in pulmonary hypertension. *Journal of the American College of Cardiology*. 2004;43(12 Suppl): 25S–32S. doi:10.1016/j.jacc.2004.02.033.
2. Simonneau G, Gatzoulis MA, Adatia I, Celermajer D, Denton C, Ghofrani A, et al. Updated clinical classification of pulmonary hypertension. *Journal of the American College of Cardiology*. 2013;62(25 Suppl): D34–D41. doi:10.1016/j.jacc.2013.10.029.
3. Huertas A, Girerd B, Dorfmueller P, O'Callaghan D, Humbert M, Montani D. Pulmonary veno-occlusive disease: advances in clinical management and treatments. *Expert Review of Respiratory Medicine*. 2011;5(2): 217–231. doi:10.1586/ers.11.15.
4. Montani D, Price LC, Dorfmueller P, Achouh L, Jaïs X, Yaïci A, et al. Pulmonary veno-occlusive disease. *European Respiratory Journal*. 2009;33: 189–200. doi:10.1183/09031936.00090608.
5. Eyries M, Montani D, Girerd B, Perret C, Leroy A, Lonjou C, et al. EIF2AK4 mutations cause pulmonary veno-occlusive disease, a recessive form of pulmonary hypertension. *Nature Genetics*. 2014;46: 65–69. doi:10.1038/ng.2844.
6. Masters K, Bennett S. Pulmonary veno-occlusive disease: an uncommon cause of pulmonary hypertension. *BMJ Case Reports*. 2013;2013: bcr2012007752. doi:10.1136/bcr-2012-007752.
7. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *European Heart Journal*. 2022;43(38): 3618–3731. <https://doi.org/10.1093/eurheartj/ehac237>.
8. Balko R, Edriss H, Nugent K, Test V. Pulmonary veno-occlusive disease: an important consideration in patients with pulmonary hypertension. *Respiratory Medicine*. 2017;132: 202–209. doi:10.1016/j.rmed.2017.10.015.