COMPLEX ETIOLOGY IN A CASE OF PULMONARY HYPERTENSION

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Rezumat

Hipertensiunea porto-pulmonară este asocierea dintre hipertensiunea portală secundară bolii hepatice sau unei etiologii extra-hepatice și hipertensiunea pulmonară. Prevalența acesteia variază între 2 și 16%^{1,2} și diagnosticul său necesită excluderea cauzelor alternative de hipertensiune pulmonară, lucru care poate fi uneori dificil, în special în contextul unei game largi de comorbidități pe care un pacient cu boală hepatică cronică le poate prezenta.

Prezentăm cazul unui bărbat în vârstă de 72 de ani cu un tablou clinic de insuficiență cardiacă dreaptă și semne de hipertensiune pulmonară severă obiectivate la examinarea ecocardiografică. Testele de sânge au fost pozitive pentru anticorpi anti-HCV iar imagistica prin computer tomograf a arătat semne de ciroză și hipertensiune portală. Examenele complementare și revizuirea literaturii au permis excluderea altor cauze potențiale care constituie diagnosticul diferențial al hipertensiunii pulmonare la acest pacient.

Cuvinte cheie: hipertensiune porto-pulmonară, hipertensiune pulmonară, insuficiență cardiacă dreaptă, ciroză.

Abstract

Porto-pulmonary hypertension (PPH) is the association between portal hypertension (PoH) due to liver disease or extra hepatic etiology and pulmonary hypertension (PH). It's prevalence ranges between 2 and 16 %^{1,2} and it's diagnosis requires the exclusion of alternative causes of PH which can be sometimes challenging, especially in the context of a wide range of comorbidities that a patient with chronic liver disease can present with. We describe a 72 years-old man with a clinical presentation of right heart failure and signs of severe PH shown by the echocardiography. The blood tests were positive for anti-HCV antibodies and CT-imaging showed signs of cirrhosis and PoH. Complementary exams and review of the literature allowed use to rule out other potential causes constituting the differential diagnosis of the PH in this patient.

Keywords: porto-pulmonary hypertension, pulmonary hypertension, right heart failure, cirrhosis.

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Clinical cases

Case description

A 72 year-old man was admitted in the cardiology department for worsening dyspnea and bilateral leg edema. He didn't smoke and had no other cardiovascular risk factors.

His medical history consisted in permanent atrial fibrillation, tuberculosis, pulmonary interstitial fibrosis, suspected chronic obstructive pulmonary disease (COPD), chronic virus C hepatitis and several previous admissions in the hospital for dyspnea and leg edema. He was anticoagulated with Apixaban and had a history of previous epistaxis episodes.

The physical exam showed normal blood pressure (120/80 mmHg), atrial fibrillation with controlled heart rate (62bpm), 95% oxygen saturation with no need for oxygen supplementation, bilateral leg edema, jugular turgescence, hepatojugular reflux, moderate systolic murmur on the left sternal border and at the level of the xiphoid appendix. The abdomen was mildly distended, the liver was enlarged, with firm consistency and painless.

The ECG showed atrial fibrillation, right axis deviation, complete right bundle branch block and secondary repolarization changes (Figure 1).

The chest X-ray showed cardiomegaly with broad vascular pedicles and bilateral

peribronchial cuffing; bilateral apical tuberculosis sequelae (Figure 2).

The transthoracic echocardiography (TTE) showed preserved systolic function of the left ventricle, difficult evaluation of the diastolic function because of the atrial fibrillation and marked enlargement of the right ventricle (RV) with a basal diameter superior to the left ventricle basal diameter (Figure 3).

The right atrium (RA) was also dilated (43.4 square centimeters) (Figure 4). The pulmonary artery was enlarged (3 cm) (Figure 5) and pulmonary accelerated time was short (88 msec) (Figure 6). There was a flattening of the interventricular septum, a severe tricuspid regurgitation with high velocity (3.38 m/s). The RV-RA gradient was 45.63 mmHg (Figure 7). We noted a dilated inferior vena cava (2.1cm) with less than 50% inspiratory collapse (Figure 8), estimated RA filling pressures at 15 mmHg and systolic pulmonary arterial pressure (PAPs) at 60 mmHg. All of these echocardiographic criteria suggested a high probability of severe PH, according to the ESC guidelines⁽⁹⁾.

The blood tests showed anemia, no leukocytosis, mildly raised CRP, hyponatremia, mildly altered hepatic function tests with raised spontaneous INR, low total cholesterol and the presence of

Figure 1. Electrocardiography: atrial fibrillation, right axis deviation with complete right bundle branch block and secondary repolarization changes

Figure 2. Chest X-ray: cardiomegaly with broad vascular pedicles and bilateral peribronchovascular cuffing

Figure 4. TTE: Dilated RA (43.4 square centimeters)

Figure 3. TTE: Right ventricle (RV) with a basal diameter superior to the left ventricle basal diameter

Figure 5. TTE: The pulmonary artery was dilated (3cm)

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anti-HCV antibodies, negative HBS antigen, high NT-proBNP and normal TSH levels. Arterial blood gas analysis showed mild respiratory alkalosis (Table 1).

An abdominal CT showed hypertrophy of the caudate lobe of the liver with irregular micronodular contour and a heterogeneous structure with imprecise borders in the sixth segment with hypodense signal before and after contrast injection; no abdominal lymphadenopathy, portal vein with a diameter of 1.36 cm and dilated splenic vein. The CT described also important cardiomegaly by predominant dilation of right cavities and right lateral pericardial effusion (Figure 9).

An upper gastrointestinal endoscopy was also performed, in the context of cirrhosis and imagistic signs of portal hypertension, showing esophageal varices.

Pulmonary function tests did not reveal bronchial obstruction, ruling out COPD.

The positive diagnosis is severe PH, permanent atrial fibrillation, complete right bundle branch block, interstitial pulmonary fibrosis, tuberculosis sequelae, decompensated cord pulmonary, virus C cirrhosis of the liver complicated with portal hypertension; tumor of the liver; chronic anemia.

At this moment the most important problem was the differential diagnosis of the etiology

regarding the severe pulmonary hypertension.

We took into consideration: left ventricular diseases; pulmonary disease (suspected COPD, pulmonary fibrosis, tuberculosis sequelae, obstructive sleep apnea); chronic thromboembolic disease; grown-up congenital heart disease; porto-pulmonary arterial hypertension (PoPH). There are arguments and counterarguments for each of the presumed causes (Table 2).

A thoracic computed tomography angiography was performed showing the following: suspicion of pulmonary arterial hypertension with dilation of the pulmonary trunk (diameter of 4.1 cm, pulmonary arteries and intrapulmonary branches (Figure 10); bilateral pulmonary interstitial infiltration, fibrous lesions with microcalcifications and bilateral bronchiectasis, cardiomegaly and hypertrophy of the left liver lobe with micronodular surface. There were no signs of emboli in the pulmonary circulation.

We concluded thus that the most probable cause of severe PH in this case was PoPH.

Unfortunately the patient passed away by right heart failure unresponsive to treatment before a right heart catheterization could take place.

The final diagnoses were: PoPH, decompensated chronic right heart failure,

Figure 6. TTE: Pulmonary accelerated time was short (88 msec)

Figure 9. Abdominal CT scan. Cardiomegaly by predominant dilation of straight cavities with right lateral pericardial effusion

Figure 7. TTE: Tricuspid regurgitation velocity was high (3.38 m/s) with a gradient between the RV and right atrium (RA) of 45.63 mmHg

Figure 10. Thoracic CT scan: Dilation of the pulmonary trunk

Figure 8. TTE: The vena cava was dilated (2.1cm) with insufficient inspiratory collapse (less than 50%) and RA filling pressures estimated at 15 mmHg

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permanent atrial fibrillation, complete right bundle branch block, pulmonary fibrosis, sequelae of pulmonary tuberculosis, bilateral bronchiectasis, hepatic postnecrotic cirrhosis with hepatic virus C and portal hypertension, suspicion of hepatocellular carcinoma, anemia most probably by mixed mechanism (both iron and folic acid deficiency).

Discussion

PoPH is as a type of pulmonary arterial hypertension belonging to the first group of etiologies as classified by the ESC 2015 Guidelines for Pulmonary Hypertension. Its definition relies on:

1. Confirmation of the PH (with the following criteria by right heart catheterization, which is the the gold standard: Mean Pulmonary Artery Pressure (mPAP) > 20mmHg with Pulmonary Capillary Wedge Pressure <15 mmHg and Pulmonary Vascular Resistance (PVR) > 3 uW (240 dynes/sec/cm⁵). The criteria of increased vascular resistance is important because it allows the exclusion of those cases in which the increased cardiac output is the sole responsible for the raised pulmonary pressures (by raised pulmonary flow) as those cases are associated with normal pulmonary vascular resistances and do not meet the definition of PPH.

2. Exclusion of alternative etiologies.
3. Confirmation of the PoH (clinically, imagistically or in rare cases, by hepatic vein catheterization).

It's prevalence ranges between 2 and 16 %^(1,2). The risk factors for the occurrence of PoPH are female sex, autoimmune hepatitis and primitive biliary cirrhosis but not age or severity of hepatic dysfunction⁽²⁾. In real life most patients have cirrhosis but PoPH can be associated with other causes of PoH. According to medium pulmonary artery pressure values (mPAP), PoPH is classified in **mild** (mPAP 25-35 mmHg), **moderate** (mPAP 35-44 mmHg) and **severe** (mPAP ≥45 mmHg).

Anatomical changes in PoPH occur in the precapillary pulmonary arterioles: muscle hypertrophy, endothelial proliferation, adventitial proliferation, plexiform lesions, in situ thrombosis, pulmonary arterioles microaneurysms^(6,7).

The exact mechanism of PPH is not completely understood. There are however many theories, some of them regarding the role of the direct passage, through the newly-formed portosystemic shunts, of either vasoconstrictive substances (which are no longer normally metabolized because of liver dysfunction) or thrombi, some take into account the role of the hyperdynamic circulation while others highlight the importance of systemic inflammation.

Test	Results	Normal values
Hemoglobin	8.6 g/dL	13+/-2 g/dL
Leucocytes	6.2 10 ³ /ul	4.5-10.5 10 ³ /ul
CRP	10.5 mg/l	0-5 mg/L
Creatinine	1.02 mg/dl	0.6-1.2 mg/dL
Estimated DFG	73 ml/min/1.73 m ²	90-125 ml/min/1.73m ²
Sodium	119.4 mmoli/l	135-145 mmoli/L
Potassium	4.06 mmoli/l	3.5-5 mmoli/L
AST	60.47 UI/L	8-40 UI/L
ALT	20 UI/L	8-40 UI/L
Total bilirubin	1.36 mg/dL	0.1-1 mg/dL
Direct bilirubin	0.82 mg/dL	0-0.3 mg/dL
INR	1.80	0.2-1.2
Total cholesterol	55.3 mg/dL	< 200 mg/dL
HVC antibodies	prezent	absent
HBSAg	absent	absent
NT-proBNP	13 846 pg/mL	< 300 pg/ml
TSH	3.608 uIU/mL	0.27-4.2 uIU/mL
Arterial blood pH	7.47	7.35-7.45
Arterial blood pO ₂	85 mmHg	75-100 mmHg
Arterial blood pCO ₂	32 mmHg	35-45 mmHg
Arterial blood Base excess	0.4 mmol/L	+/- 3 mmol/L

Table 1 Blood test results

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Presumed etiology of the PH	Arguments	Counterarguments
Causes of left ventricular dysfunction	History of permanent atrial fibrillation. PH possible in left ventricle diseases irrespective of ejection fraction.	Non-dilated and non-hypertrophied left ventricle. No valvular heart diseases.
Pulmonary disease	History of interstitial pulmonary fibrosis, sequelae of pulmonary tuberculosis. Chronic pulmonary diseases associates most frequently mild PH ^{4,5} .	High severity of the PH, unappropriated in the context COPD or interstitial pulmonary fibrosis.
Chronic thromboembolic disease	Patient with low mobility.	Under anticoagulation for permanent atrial fibrillation.
Porto-pulmonary arterial hypertension (PoPH)	Virus C cirrhosis of the liver with suspicion of hepatic tumor. Portal hypertension at the abdominal CT scan.	More often in women, autoimmune hepatitis and biliary cirrhosis.
Grown-up congenital heart disease	Sometimes there is an unexpected discovery of unknown atrial septal defect or aberrant pulmonary vein drainage in adults with unexplained PH.	No congenital cardiac defect showed by the TTE.

Table 2. Differential diagnosis of the etiology of the PH

Vasoconstriction of the pulmonary arteries can be induced by high cardiac output increasing parietal shear stress, endotoxins reaching the pulmonary circulation from the gastro-intestinal tract, endothelin 1 acting on ET_A receptors within the pulmonary arteries, TXA₂, IL-6, TNF alpha, serotonin^(6,7). There could be also a genetic predisposition.

The occurrence of PoPH worsens the patient's outcome. There are some good results with Epoprostenol, Iloprost, type 5 phosphodiesterase blockers. The endothelin receptor antagonists cause hepatic cytolysis and are indicated only in patients with mild hepatic impairment. Liver transplantation is contraindicated if mPAP values are more than 35 mmHg and PVR more than 250 dyn sec cm⁻⁵. Our patient had also other possible causes of PH: interstitial pulmonary fibrosis, bronchiectasis, sequela of pulmonary tuberculosis but these causes do not provide severe PH. The lack of left heart disease history and the TTE data do not support the hypothesis of left ventricular dysfunction or congenital heart diseases as causes of PH. The high value of NTproBNP was due to the right heart decompensation. Unfortunately the patient did not have a right heart catheterization.

Learning points

- Porto-pulmonary hypertension is the association of pulmonary arterial hypertension with portal hypertension, caused by liver disease or an extra-hepatic cause, and should be suspected whenever alternative causes of pulmonary hypertension have been excluded.
- Clinical presentation, blood test and transthoracic echocardiography should guide the diagnosis of pulmonary hypertension but invasive measurement by right heart catheterization is mandatory in order to confirm the diagnosis while portal hypertension is usually diagnosed by combining careful history taking, physical examinations, blood and imaging tests and it seldom requires hepatic venous pressure gradient measurement by hepatic venous catheterization.

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