Case Report

Pulmonary Circulation

Idiopathic hypereosinophilic syndrome with pulmonary hypertension

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Abstract

Hypereosinophilic syndrome is a myeloproliferative disorder characterized by persistent eosinophilia with involvement of multiple organs. The occurrence of severe pulmonary hypertension (PH) in the setting of hypereosinophilic syndrome is very uncommon. A 43-year-old man with documented idiopathic hypereosinophlic syndrome presented to the hospital with symptoms of paroxysmal chest discomfort and progressive exertional dyspnea. Physical examination showed distended jugular veins, cyanosed lips, increased P2 sound, and moderate pitting edema of the lower extremities. Echocardiography revealed enlarged right atrium, enlarged right ventricle, increased pulmonary artery systolic pressure, and decreased right ventricular systolic function. Venous ultrasound of the lower extremities, computed tomography pulmonary angiography, and right heart catheterization (RHC) were negative for thrombus. The pulmonary artery systolic pressure was found severely increased during the RHC. Treatment included prednisolone, ambrisentan, diuretics, and digoxin. The involvement of the pulmonary artery in patients with idiopathic hypereosinophilic syndrome is an uncommon finding. The patient presents with clinical manifestations of right ventricular systolic dysfunction resulted from severely increased PH.

Keywords

idiopathic hypereosinophilic syndrome, pulmonary hypertension, right heart catheterization

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Introduction

Idiopathic hypereosinophilic syndrome (IHES) is characterized by the persistent elevation of blood eosinophils without any recognizable causes such as allergies, parasitic infections, drugs, connective tissue diseases, vasculitis, or malignancies.[1] It can affect many organs such as the heart, skin, nervous system, gastrointestinal tract, lungs, or bone marrow.[2] Among them, cardiac involvement is the most common and major cause of morbidity and mortality. The incidence of pulmonary hypertension (PH) in IHES patients is rarely seen, which lacks clinical specificity. It has a poor prognosis if timely diagnosis and proper management are not executed.[3] Here, we introduce a case of a 43-year-old man with PH secondary to IHES.

Case report

A 43-year-old man with documented IHES presented to the hospital with paroxysmal chest discomfort, exertional dyspnea, orthopnea, occasional fever, and skin rashes. He reported a ten-year history of hepatitis B and was on entecavir without history of parasitic infections, bronchial asthma, hypertension, or diabetes mellitus. Physical examination showed stable vital signs, distended jugular vein, cyanosed lips, increased cardiac borders, clear lungs, and

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increased P2 sound, but no cardiac murmurs, soft, non-tender abdomen, non-palpable liver and spleen, and moderate edema on the bilateral lower limbs. Routine blood test showed normal white blood cell (WBC) count with increased eosinophils 2.42×10^9/L (reference range = 0.02–0.52×10^9/L), red blood cell (RBC) count 3.86×10^9/L (reference range = 4.3–5.8×10^9/L), hemoglobin 124 g/L (reference range = 130–175 g/L), platelet 56×10^9/L (reference range = 125–350×10^9/L). Other lab reports consisted of: AST 59.1 U/L (reference range = 15–40 IU/L); ALT 112.7 U/L (reference range = 9–50 IU/L); ALP 178.2 U/L (reference range = 45–125 IU/L); albumin = 26.5 g/L (reference range = 40–55 g/L); globulin 43.9 g/L (reference range = 20–40 g/L); total bilirubin 56.6 umol/L (reference range = 6.8–30 umol/L); direct bilirubin 20.3 umol/L (reference range = 0–8.6 umol/L); indirect bilirubin 36.3 umol/L (reference range = 5.1–21.4 umol/L); PT 26.5 s (reference range = 9–23 s); INR 2.26 (reference range = 0.60–1.20); ESR 37/1 h (reference range = 0–15/1 h); BNP 2090 pg/mL (reference range = 0–100 pg/mL); D-dimer 3660 ng/mL (reference range = 100–600 g/mL); arterial blood gas with pH 7.46 (reference range = 7.35–7.45); pO2 106 mmHg (reference range = 83–108 mmHg); and pCO2 28 mmHg (reference range = 35–48 mmHg). Among anti-phospholipid antibodies, anti β2-glycoprotein I antibody 34 RU/mL (0–20 RU/mL) and anticardiolipin IgA antibody 24 U/mL (reference range = 0–10 U/mL), while anticardiolipin IgM antibody and anticardiolipin IgG antibody were within normal limits. Anti-nuclear antibody, anti-neutrophil antibody, and thyroid function tests were also within normal limits. We conducted routine urine and stool tests that did not show any evidence for parasitic infections.

ECG showed sinus tachycardia and right ventricular hypertrophy. Echocardiography revealed enlarged right atrium (67 × 55 mm), enlarged right ventricle (45 mm), normal left ventricle (38 mm), normal ejection fraction (62%), increased pulmonary artery systolic pressure (83 mmHg), decreased right ventricular systolic function (TAPSE 11 mm), and mild pericardial effusion. There were no valvular abnormalities found on echocardiography. Abdominal ultrasonography revealed hepatic congestion, gall bladder wall edema, splenomegaly, and ascites. Venous ultrasound of lower extremities was normal. Pulmonary artery CTA was negative for thrombus. The patient did not give consent for ventilation/perfusion scan. The pulmonary function test was normal. Bone marrow smear revealed significantly active nucleated cell proliferation, increased eosinophil line 38%, eosinophils in different stages with unbalanced development of nucleoplasm of some eosinophils like megaloblastic degeneration. Right heart catheterization (RHC) revealed right atrial pressure 22/18/20 mmHg, right ventricle pressure 91/23/53 mmHg, pulmonary artery pressure 91/47/67 mmHg, and mean pulmonary arterial wedge pressure 14 mmHg. Cardiac output and pulmonary vascular resistance were not measured due to limited lab support. Normal saline was used during RHC. Finally, the patient was further diagnosed with precapillary PH and right heart failure. Treatment included prednisolone 10 mg daily for hypereosinophilic syndrome, ambrisentan 10 mg daily for PH, and diuretics and digoxin for the right heart insufficiency. The patient could not appear for follow-up visits; hence, information was obtained over the phone that he had significant improvement of the exertional dyspnea and chest discomfort. The lower limb edema also subsided.

This case has been approved for reporting and publication by the Ethical Committee of the First Bethune Hospital of Jilin University.

Discussion

IHES refers to a disease with persistent eosinophilia (peripheral blood eosinophil count > 1.5×10^9/L) that can involve several organs,[4] most commonly seen in the heart, skin, and nervous system. Among them, cardiovascular involvement is the major cause of death in IHES patients.[5,6] The pathological changes of the heart due to eosinophil infiltration include granuloma formation, necrotic vasculitis, myocardial necrosis, and interstitial and endomyocardial fibrosis. Clinical manifestations can be asymptomatic or can present with angina, myocardial infarction, endocarditis, myocarditis, valvular changes, cardiac insufficiency, atrioventricular block, and even sudden cardiac death. This patient presented to our hospital with symptoms of progressive exertional dyspnea and his medical history revealed a documented diagnosis of IHES. Echocardiography revealed an increased pulmonary artery systolic pressure, which was later confirmed by RHC. According to the World Symposium (Nice, France, 2013), the classification of PH is divided into five groups:[7] (1) pulmonary arterial hypertension (PAH); (2) PH due to left heart disease; (3) PH due to lung disease and/or hypoxia; (4) chronic thromboembolic PH; and (5) PH with unclear multifactorial mechanisms (hematologic disorders, systemic disorders, metabolic disorders). Based on the lung computed tomography (CT), pulmonary CT angiography (CTA), and pulmonary function test of this patient, the third and fourth groups of PH can be excluded. Studies show both V/Q scanning and modern pulmonary CTA are accurate methods for detection of chronic thromboembolism.[8] In our case, due to limited consent given by the patient, pulmonary CTA and RHC were performed to rule out possible thromboembolic disease and to establish the diagnosis of PH. In this case, BNP was increased significantly, but the echocardiography showed normal left ventricular ejection fraction and no valvular disease or restrictive cardiomyopathy. Similarly, pulmonary capillary wedge pressure (PCWP) was <15 mmHg in RHC examination; hence, the second group of PH was also excluded. The fifth group of PH includes myelodysplasia type of hematologic disorder-induced PH. In our case, the patient had documented IHES for several years and recently developed manifestations of right heart

insufficiency and PH. Hence, we considered PH was due secondary to hematologic disorder, i.e. IHES. For this patient, we assume liver function abnormality, elevated bilirubin, and low albumin were all manifestations of the right ventricular systolic dysfunction. We did not find significant clinical manifestations and abdominal ultrasonography findings that would strongly suggest portal hypertension and hepatic cirrhosis. Splenomegaly could be one of several manifestations of the hypereosniophilic syndrome.

As mentioned earlier, IHES commonly involves the cardiovascular system; however, cases with hypereosinophilic syndrome accompanied by severe PH are rarely seen.[9,10] Out of 149 cases with hypereosinophilic syndrome diagnosed during 30 years in the Peking Union Medical College (PUMC), only six cases were found to have PH; among them, severe PH was found in only one case.[11] The main pathological change in PH is vascular remodeling. The mechanisms include proliferation and remodeling of small arteries, and formation of thrombus in situ.[12] The mechanisms behind IHES inducing PH include: (1) pulmonary vascular remodeling: studies show that inflammatory response mediated by eosinophils plays important role in the vascular remodeling. Using adiponectin, Weng et al.[13] created pulmonary hypertensive mouse models, and found infiltration and aggregation of eosinophil cells leading to the pulmonary arterial remodeling; (2) thrombus formation: blood coagulation tendency in IHES patients is high – eosinophil cells release some cytokines, which promote in situ thrombus formation; alkaline protein is the major cytokine that stimulates platelet activation and aggregation. The eosinophilic cationic proteins can inhibit anticoagulant activity of thrombomodulin, platelet activating factor, and leukotrienes. They increase vascular permeability, damage endothelial cells, and result in thrombus formation.[14] Although there is microthrombotic pathophysiology associated with this disorder, the PT and INR of this patient were significantly high. We thought that use of any anticoagulants may increase the bleeding risk of the patient; (3) cardiac involvement: IHES affecting the heart leads to valvular diseases, restrictive cardiomyopathy, or cardiac insufficiency.

In this patient, both anti β2-glycoprotein I antibody and anticardiolipin IgA were found positive; hence, they needed to differentiate from the antiphospholipid syndrome (APS). APS is a systemic non-inflammatory autoimmune disorder related to recurrent thrombus formation and complications during pregnancy with positive anticardiolipid antibody. For the diagnosis of APS, there should be one of the clinical criteria (thrombus formation, pregnancy complication) and one of antiphospholipid antibodies (anticardiolipid antibody, lupus anticoagulant, anti β2-glycoprotein I antibody) positive after being performed twice 12 weeks apart. In this patient, both antiphospholipid antibodies were found positive, but there were no clinical manifestations of venous thrombosis. Hence, diagnosis of APS cannot be made and is considered a secondary change caused by IHES-induced immunological disorder.

Based on the 2015 ESC guideline on PH, treatment for patients diagnosed with group 5 hypertension is secondary.[15] There was no randomized trial regarding the use of PAH-approved drugs. It was emphasized for further study for the effectiveness of pulmonary vasodilators including endothelin receptor antagonists, prostacyclin analogues, and phosphodiesterase type 5 inhibitors for PAH in this setting.[16] Pre-capillary PH mostly shares a similar pathophysiology with that of PAH. Our patient who was diagnosed with pre-capillary PH from RHC was administered ambrisentan 10 mg daily. The patient was also administered diuretics and digoxin for the management of right heart insufficiency. The ultimate aim of IHES therapy is to prevent the consequences which can lead to poor prognosis. The clinical symptoms and peripheral blood absolute eosinophil count (AEC) are used to guide the therapeutic decision.[17]

Conclusion

The involvement of the pulmonary artery in patients with IHES is not common. Clinically, patients develop manifestations of right heart failure due to severe PH. Severe PH has a poor prognosis. Although there is a lack of evidence for using PH therapies, pre-capillary PH shares a similar pathophysiology with PAH. Hence, treating PH with PH drug (ambrisentan) might be an option, which needs further studies.

Conflict of interest

The author(s) declare that there is no conflict of interest.

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