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Unexpected causes of pulmonary hypertension in a previously healthy Thai rural man with right-sided heart failure

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Male, 52
Final Diagnosis: Pulmonary hypertension
Symptoms: Diarrhea • dyspnea • jaundice
Medication: —
Clinical Procedure: —
Specialty: Endocrinology and Metabolic

Objective: Unusual clinical course

Background: Hyperthyroidism is one of the important causes of high-output failure and reversible pulmonary artery hypertension. Severe pulmonary artery hypertension is rarely found in associated with hyperthyroidism due to the small number of cases reported. We present an interesting case with multiple unexpected findings of the possible causes of severe pulmonary artery hypertension: hyperthyroidism, pulmonary embolism, and ostium secundum atrial septal defect.

Case Report: We present the case of a previously healthy rural Thai man who progressively developed dyspnea on exertion, chronic diarrhea, and jaundice for the previous 3 months. Physical examination revealed right-sided predominate chronic heart failure with signs of pulmonary hypertension. The investigation demonstrated autoimmune hyperthyroidism, cholestatic jaundice, moderate tricuspid regurgitation, ostium secundum atrial septal defect, and severe pulmonary artery hypertension. After treatment with an anti-thyroid drug and closure of the ostium secundum atrial septal defect, his symptoms of jaundice and pulmonary artery pressure were completely resolved.

Conclusions: Severe pulmonary artery hypertension may not solely be a result of hyperthyroidism. Further investigation for other causes is recommended.

MeSH Keywords: Hypertension, Pulmonary • Ostium Secundum Atrial Septal Defect • Hyperthyroidism • Pulmonary Embolism

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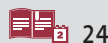
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Background

There are many causes of right-sided predominate chronic heart failure with pulmonary artery hypertension (PAH), such as primary pulmonary hypertension, secondary pulmonary artery hypertension from left heart disease, pulmonary disease, and high-output failure. Hyperthyroidism is an important cause of high-output failure and can bring about uncommonly associated conditions such as cholestatic jaundice and pulmonary embolism. The literature suggests that some hyperthyroid patients may develop reversible pulmonary artery hypertension and isolated right heart failure that resolved with treatment of hyperthyroidism. Furthermore, previous studies showed that hyperthyroidism was associated with hypercoagulable state and has a 2.31 times greater risk of pulmonary embolism during 5-year follow-up [1]. We describe an interesting case of hyperthyroidism with pulmonary artery hypertension that presented with isolated right heart failure and cholestatic jaundice. Here we present unexpected findings of the possible etiologies of severe pulmonary artery hypertension: hyperthyroidism, chronic pulmonary embolism, and ostium secundum atrial septal defect (ASD).

Objective

To remind physicians that there can be multiple causes of pulmonary hypertension in a single patient, especially in a patient with severe pulmonary hypertension.

Case Report

Description

A 52-year-old man was admitted to the hospital with complaints of worsening dyspnea on exertion, with edema, chronic diarrhea, and jaundice during the previous 3 months. His past medical history was unremarkable and he had no history of smoking, pharmaceutical or herbal medications, infections, abuse of alcohol, blood transfusion, or traveling. On admission, he was afebrile with a regular heart rate of 108 beats per minute, normal blood pressure, and no desaturation. Physical examination revealed agitation, moderate jaundice, pitting edema in both legs equally, no sign of chronic liver disease, JVP distension, apical and RV heaving, pan-systolic murmur grade III/VI at the left sternal border with positive Carvallo's sign, normal S1, loud P2, a small amount of ascites, positive hepato-jugular reflux, no hepatomegaly, no splenomegaly, diffuse thyroid gland enlargement without bruit (about 25 gm), onycholysis of ring fingers of both hands, and no clubbing of fingers. Chest radiography demonstrated cardiomegaly; especially RV enlargement, increased pulmonary artery vasculature, no pulmonary infiltration, and mild right pleural effusion. His

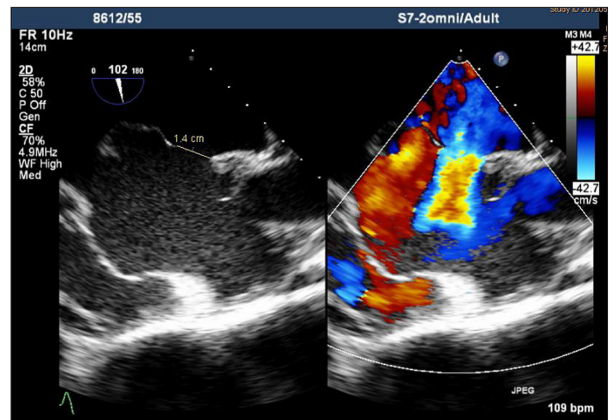


Figure 1. Transesophageal Echocardiography demonstrates secundum ASD, size 1.4 cm.

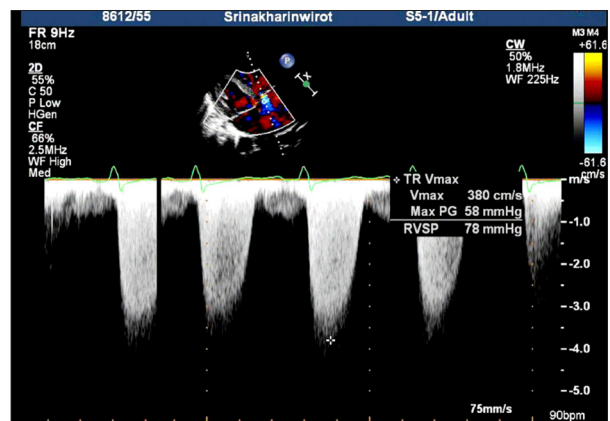


Figure 2. Moderate tricuspid regurgitation and severe pulmonary HT (RVSP 78 mmHg).

electrocardiography showed sinus tachycardia, normal axis, incomplete RBBB, no atrial dilatation, no RVH, and no LVH.

Laboratory test results showed high free T4 (4.86 ng/dL; reference range 0.93–1.71), mild elevation of free T3 (4.83 pg/mL; reference range 1.80–4.60), and low serum thyroid-stimulating hormone (TSH)(0.008 mIU/L; reference range 0.27–4.21). Autoantibody profile revealed high anti-thyroglobulin antibody 101 IU/ml (reference range <34.0 IU/ml) and elevation of antimicrosomal antibody (anti-thyroid peroxidase) 24 IU/ml (reference range <12.0 IU/ml).

The liver function test (LFT) result was compatible with cholestatic jaundice: total bilirubin 12.29 mg/dl (reference range 0.0–1.0), direct bilirubin 10.27 mg/dl (reference range 0.0–0.2), alkaline phosphatase 191 U/L (reference range 40–129), aspartate aminotransferase (AST) 44 U/L (reference range 0–40), alanine aminotransferase (ALT) 25 U/L (reference range 0–40), albumin 2.69 g/dL (reference range 3.5–5.2), globulin 3.9 g/dL (reference range 1.5–3.5), prolonged prothrombin time, and anti-smooth muscle antibody was negative. Serology for

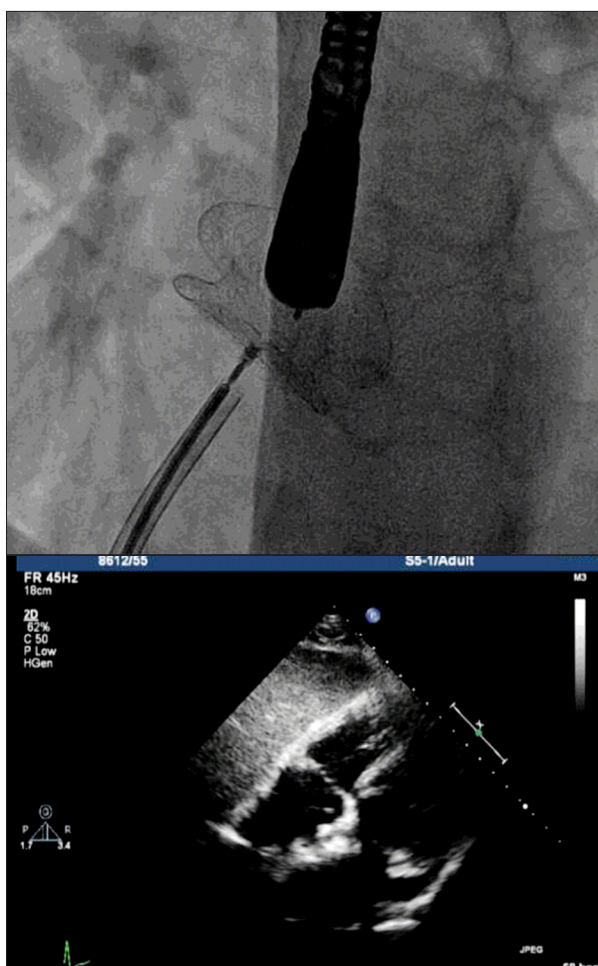


Figure 3. Closure of ASD with ASD device (Cocoon®).

hepatitis A, B, and C and autoantibody profiles for ANA were also negative.

The abdominal ultrasound examination showed that the size and the parenchyma of the liver were normal. Intrahepatic duct and common bile duct were not dilated. Prominent size of spleen was noted. Pancreas and both kidneys appear normal. There was minimal ascites.

Right thoracentesis was performed and pleural fluid profile revealed transudate feature with lymphocytic predominant and negative for malignancy. Ascitic fluid showed wide serum ascitic albumin gradient (SAAG=2.27) and high protein content (protein=12.2 g/L). These findings suggested that the ascites was the result of cardiac failure.

Therefore, his initial diagnosis was hyperthyroidism with pulmonary hypertension, right-sided predominate chronic heart failure, and cholestatic jaundice. Hyperthyroidism *per se* manifests as clinically reversible pulmonary hypertension and isolated right heart failure, but we confirmed the diagnosis of

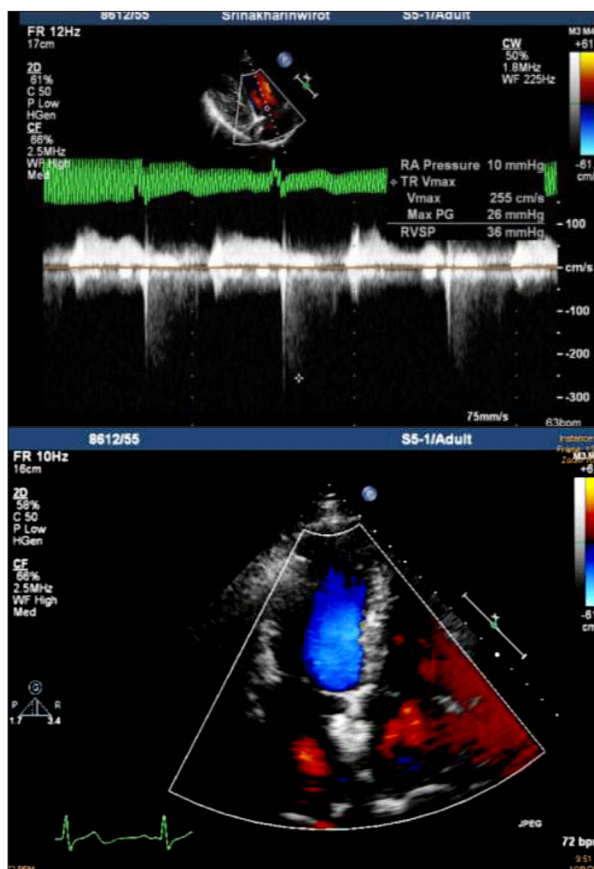


Figure 4. Dramatically fall of RVSP from 78 to 36 mmHg after treatment of hyperthyroidism pulmonary embolism and closure of ASD.

pulmonary hypertension and searched for other possible causes. Hence, transthoracic and transesophageal echocardiography were performed and showed dilatation of right atrium and right ventricle, and moderate size of ostium secundum ASD (Figure 1). The defect size measured about 1.4 cm, with significant left to right shunt, moderate tricuspid regurgitation, and severe pulmonary hypertension (right ventricular systolic pressure (RVSP) =74 mmHg (Figure 2). Intracardiac thrombus was not present. Left ventricular and right ventricular systolic functions were both preserved. Computerized tomography angiography of pulmonary arteries revealed intraluminal filling defect at the segment branch of the left upper lobe and left lower lobe pulmonary arteries. Main, right, and left pulmonary arteries measured about 3.0, 2.8, and 2.5 cm, respectively. No pulmonary infiltration, pulmonary mass lesion, or mediastinal or hilar adenopathy were noted.

Finally, the patient was treated as having both hyperthyroidism and chronic pulmonary embolism. We considered that cholestatic jaundice had developed secondary to hyperthyroidism. During hospitalization, anti-thyroid drug (Propylthiouracil) treatment was initiated at a daily dose of 300 mg in 3 divided

doses with an anticoagulant drug (warfarin) 18.5 mg/week. Small doses of furosemide and spironolactone were given to control symptoms of heart failure. After 10 weeks of treatment, LFT returned to normal and clinical right-sided predominate chronic heart failure was improved. The patient could ride a bicycle about 2 kilometers per day, the same as before his illness. The ostium secundum ASD was later closed with a size 28 mm Cocoon® ASD closure device (Figure 3). Surprisingly, when transthoracic echocardiography done 2 month after ASD closure, RVSP dramatically fell from 78 to 36 mmHg, which was consistent with his improved clinical symptoms (Figure 4).

Discussion

We describe a rare case of autoimmune hyperthyroidism presenting with multiple, uncommon, associated conditions: severe pulmonary artery hypertension, isolated right-sided heart failure, secondary pulmonary embolism, and cholestatic jaundice. Unexpected findings of ostium secundum ASD were also revealed during work-up for the possible causes of pulmonary hypertension. The patient had a dramatic hemodynamic and symptomatic recovery and a marked lowering of right ventricular systolic pressures after anti-thyroid drug treatment and ASD closure.

Several mechanisms have been suggested in the pathogenesis of pulmonary artery hypertension in patients with hyperthyroidism, including an autoimmune process associated with endothelial damage or dysfunction, increased cardiac output resulting in endothelial injury, and increase metabolism of intrinsic pulmonary vasodilating substances [2] but with normal pulmonary artery resistance [3].

This case demonstrates the coexistence of pulmonary embolism with hyperthyroidism, which has rarely been reported. A comparison cohort study in Taiwan reported that hyperthyroidism has a 2.31 times greater risk of pulmonary embolism during the 5-year follow-up period [1]. Hypercoagulability was found and associated with hyperthyroidism; this may be the possible cause of secondary pulmonary embolism.

The severity of pulmonary artery systolic pressure (PASP) in this case prompted us to seek for other explanations for the pulmonary hypertension. In studies that evaluated patients recently diagnosed with hyperthyroidism, the prevalence of PAH was found to be 35–43% [4,5] and the prevalence of autoimmune thyroid disease (AITD) in patients with PAH was as high as 49% [6]. Furthermore, reports have demonstrated that mean pulmonary artery systolic pressure (PASP) in most hyperthyroidism patients with pulmonary hypertension is mildly elevated (30.4 ± 8.5 mmHg) [7,8], and in 1 study, 16

of 39 patients (41%) had pulmonary arterial systolic pressure ≥ 35 mm Hg [9]. Severe PAH could only be found in a small number of case reports with right ventricular systolic pressure 69–80 mmHg [10,11] and normalized following the initiation of anti-thyroid treatment for 6 months. The potential pathogenic mechanisms of hyperthyroidism-related PAH remain unclear [12–16].

Pulmonary artery hypertension in adults with hyperthyroidism is increasingly being reported. Although the mechanism is uncertain, the reversal of pulmonary artery hypertension following restoration to a euthyroidism state supports a causal relationship. Therefore, pulmonary artery hypertension should be considered in hyperthyroid patients with dyspnea. All patients with pulmonary artery hypertension should be screened for hyperthyroidism, because this combination has a good prognosis, the increase in the pulmonary artery pressure is usually slight, and it reverses after treatment of the thyroid disease. A possible explanation includes an influence of thyroid hormones, which affect growth and maturation of vascular cells, and enhanced catecholamine sensitivity causing pulmonary vasoconstriction.

Several case reports and case-control studies support an association between venous thrombosis and hyperthyroidism, but the absolute risk is low [17], as in the population-based control study that included 4494 patients with venous thrombosis and 5896 controls. Deep-venous thrombosis was reported in 57% of patients and pulmonary embolism in 30%, according to the abstracts [18]. Persistent elevation of factor VIII levels have been shown to be independently associated with both initial and recurrent venous thromboembolism [19,20]. The most biologically plausible mechanism for a causal link between hyperthyroidism and VTE is related to significant but reversible elevation of factor VIII. In our case, the elevation in factor VIII and vWF resolved a few weeks after treatment, suggesting a direct role of hyperthyroidism in elevation of factor VIII and vWF activity [21,22]. Erem et al. [23] showed statistically significant elevations in vWF, factor IX, antithrombin III, fibrinogen, and plasminogen activator inhibitor-1 (PAI-1) levels, and reduction in factor X and tissue plasminogen activator (tPA) levels in hyperthyroidism subjects compared to euthyroidism controls. Other putative mechanisms such as changes in endothelial function [23,24] and enhanced platelet plug formation-2 in hyperthyroidism have been also suggested.

Conclusions

Hyperthyroidism *per se* may not be the only cause of pulmonary artery hypertension – pulmonary embolism may also be a cause, especially in rare cases presenting with severe form of pulmonary hypertension.

Learning point

- Multiple causes of pulmonary artery hypertension can be discovered in a single case.
- The coexistence of pulmonary embolism with hyperthyroidism is rarely seen.

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