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Case Report

Reversible pulmonary arterial hypertension due to Graves disease: A case report

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Pulmonary arterial hypertension (PAH) is defined as a mean pulmonary arterial pressure (mPAP) greater than 25mmHg at rest [1]. The extensive aetiological causes can be classified into left-heart disease, lung disease, chronic-thromboembolic phenomena, connective tissue diseases and medication. Thyrotoxicosis is recognized as a rare cause of PAH with a multitude of hypothesized mechanisms. Unlike other diseases, successful control of thyroid disease often results in reversal.

Case presentation

A 70-year-old woman with well-controlled diabetes mellitus type II presented with bilateral lower limb oedema associated with dyspnoea for one week. The oedema progressively extended to midcalf with periorbital swelling. There was no frothy urine or oliguria. She complained of atypical chest pain at rest and exertional dyspnoea worsening over a week's duration. Furthermore, palpitations and semi-solid stools for 2 months were present.

She had proptosis, exophthalmos with lid-lag and fine finger tremors suggestive of hyperthyroidism along with a diffuse non-tender goitre. The pulse was regular at 100 beats/min with raised jugular venous pressure and blood pressure of 120/60 mmHg. A loud pulmonary component of the second heart sounds with a pan-systolic murmur, best heard in the left sternal edge suggestive of tricuspid regurgitation (TR), raised the possibility of pulmonary hypertension. Lungs were clear on auscultation. The rest of the systemic examination was unremarkable.

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Hyperthyroidism, as a possible aetiology for heart failure, was strongly suspected. Cardiac ischaemia was excluded with a normal electrocardiogram (ECG) and normal repeated cardiac troponin levels. Her blood investigations are summarized in Table 1.

Table 1: Summary of blood investigations

Investigation	**Result**	**Normal range**
White blood cells (/µl)	6,900	4,500 - 11,000
Haemoglobin (g/dL)	11.1	12 – 15
Platelet (/µL)	155,000	150,000 – 400,000
CRP (mg/L)	5	<5
ESR (mm 1st hr)	20	<10
Serum creatinine (µmol/L)	43	74 – 110
Serum sodium (mEq/L)	138	135 – 145
Serum potassium (mEq/L)	3.9	3.5 - 5.3
TSH (mIU/mL)	<0.0025	0.5-5.0
T_4 (pmol/L)	27	6.5-13.0
TPO Antibodies	Negative	
TSH receptor antibodies (IU/L	5.1	<0.9
AST (U/L)	55	<50
ALT (U/L)	30	<50
ALP (U/L)	300	40- 150
GGT (U/L)	44	<55
Total bilirubin (µmol/ L)	60	5-17
Direct bilirubin (µmol/ L)	29	1.7 - 5.1
Albumin (g/L)	28	35 – 55
Globulin (g/L)	36	20 – 35

The significantly suppressed TSH levels, with raised T4 levels (primary hyperthyroidism) along with diffuse goitre with characteristic eye signs, led to a diagnosis of Graves thyrotoxicosis. Ultrasonography of goitre demonstrated diffusely reduced echo-pattern and increased vascularity compatible with Graves disease. TSH-receptor antibodies were raised. Transthoracic echocardiography (TTE) confirmed moderate-severe PAH with grade 2 TR (TR peak gradient - 55 mmHg) with a dilated right atrium and ventricle. However, left ventricular systolic function was normal (ejection fraction - 60%).

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Intravenous frusemide was initiated, with carbimazole 15mg daily for thyrotoxicosis. Propranolol was introduced at 20mg bd later. The patient symptomatically improved with treatment and was subsequently followed up in the clinic. High-resolution computed tomography (HRCT) and CT pulmonary angiogram yielded negative in the search for an alternative diagnosis. She was euthyroid by four months (T_4 8.1 pmol/L and TSH 1.0 mIU/mL) and the repeat TTE revealed resolution of PAH. The patient was planned for elective total thyroidectomy.

Discussion

The effects of thyrotoxicosis on the cardiovascular system are multiform, mostly due to alteration of haemodynamics by increased sympathetic tone, resulting in atrial dysrhythmias and heart failure [2]. Although the association between PAH and hyperthyroidism was first described in 1980, the prevalence is unknown. However, studies have shown prevalence rates ranging from 41% to 65%, suggesting the importance of considering thyrotoxicosis as an aetiology for PAH. One of the largest studies, comprising 114 patients with hyperthyroidism, found a prevalence of mild PAH of 43%.[3] Yanai-Lindau *et al* reported antithyroglobulin antibodies in 30% of 40 patients with PAH.[4] Based on these studies, PAH among hyperthyroid patients was a frequent observation. However, most of these patients were asymptomatic.

Although the pathogenesis of PAH in hyperthyroidism remains unclear, several hypotheses have been proposed including (1) enhanced catecholamine sensitivity causing pulmonary vasoconstriction, reduction of pulmonary artery compliance and increase in pulmonary vascular resistance, (2) increased metabolism of intrinsic pulmonary vasodilating substances, (3) decreased or impaired metabolism of vasoconstrictors and (4) autoimmune disease-causing endothelial damage or dysfunction. However, the exact pathophysiology of PAH in thyrotoxicosis is yet to be described [3,5].

Treatment of thyrotoxicosis plays an important role in the resolution of PAH, which was demonstrated in our patient. Among the different options for treatment, such as medical therapy, radioactive iodine and surgery, there is limited data on the optimal method of treatment to reduce pulmonary pressure. Certain studies have shown that treatment with methimazole resulted in a more rapid normalization of pulmonary arterial pressure compared to surgery [3]. This might be due to the direct vasodilator properties of methimazole. However, further studies are needed to evaluate the optimal treatment modality.

Conclusions

Pulmonary hypertension with associated right heart failure can be a clinical presentation of Graves thyrotoxicosis. Effective treatment and achieving an euthyroid state will result in the reversal of pulmonary hypertension. Thus, it is of paramount importance to consider thyrotoxicosis as an aetiological cause of PAH.

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