

Pulmonary hypertension and thyrotoxicosis

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Abstract

Thyrotoxicosis is listed as a cause of pulmonary arterial hypertension (PAH). The aetiopathogenesis remains largely uncertain, but an autoimmune mechanism has been postulated, among others. In this setting, other causes of PAH need to be actively sought and excluded prior to attributing it to the thyrotoxicosis. The importance of recognising this condition is that it is usually reversible with restoration of a euthyroid state. We describe three patients who presented with thyrotoxicosis and features of PAH in whom other causes were excluded with various investigations. We also demonstrated reversibility of the pulmonary hypertension upon restoration of a normal thyroid state.

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Introduction

Hyperthyroidism is associated with an increased morbidity and mortality from cardiovascular disease.¹ Heart failure occurs in between 6-16% of hyperthyroid patients.²⁻⁴ Thyrotoxicosis is commonly associated with exacerbation of underlying coronary heart disease, with atrial fibrillation and systolic dysfunction.⁵ It is less well appreciated that hyperthyroidism is also associated with pulmonary arterial hypertension (PAH) and right heart failure.

We describe three patients who presented with thyrotoxicosis and features of PAH in whom other causes of PAH had been excluded. We also demonstrate reversibility of the pulmonary hypertension upon restoration of the euthyroid state. The possible aetiology and clinical significance of this association will be discussed.

Case 1

A 55-year-old female presented with evidence of severe Graves' thyrotoxicosis, complicated by proximal muscle weakness and mild thyroid eye disease. She had a past history of left breast carcinoma, for which she simultaneously underwent a left radical mastectomy and radiotherapy. She was also a smoker, known to have mild chronic obstructive lung disease (COPD), and was on treatment for systemic hypertension. Further clinical examination revealed marked bipedal oedema, as well as an elevated jugular venous pressure (JVP) (15 cm) and loud pulmonary component of the second heart sound. Scattered bilateral wheezing was present, with a central trachea. The mastectomy scar was noted on the left. Chest radiography showed hyperinflation and evidence of the previous surgery on the left (Figure 1).

Further tests revealed an FT4 of 65.7 pmol/l (10.3-21.9), FT3 > 30.8 pmol/l (3.1-6.8) and thyroid-stimulating hormone (TSH) < 0.01 mIU/l (0.35-4.5). She had a TSH receptor antibody titre of > 40 (0-1.75) and a technetium thyroid uptake scan that is typical of Graves' disease. An echocardiography showed an elevated pulmonary arterial systolic pressure of 64 mmHg (normal values on echocardiography < 30 mmHg), no valvular pathology, a mildly dilated left ventricle with mild impairment of systolic function (left ventricular ejection fraction 45%), and an element of diastolic dysfunction.

Investigations were carried out to establish the cause of the elevated pulmonary pressure. A normal ventilation/perfusion (V/Q) scan excluded pulmonary embolism. Her spirometrical parameters were within normal limits [forced expiratory volume in one second (FEV1)/forced vital capacity (FVC) 71.13 and FEV1 83.8%]. However, TL_{CO}c (diffusion capacity) was decreased at 58% (normal > 70%). In view of this, as well as the previous history of radiation therapy, we proceeded to carry out a high-resolution computed tomography (CT) scan of her chest. This showed no evidence of interstitial lung disease.

Initially, she was started on carbimazole, and then treated with radioactive iodine (RAI). Subsequently, the clinical signs of cor pulmonale resolved, and an echocardiography that was performed when she was euthyroid demonstrated that the pulmonary pressure had normalised to 25 mmHg.

Case 2

A 44-year-old male, who was previously well, presented with severe thyrotoxicosis and a five-month history of progressive dyspnoea, orthopnoea, bilateral leg swelling, loss of weight and generalised weakness.

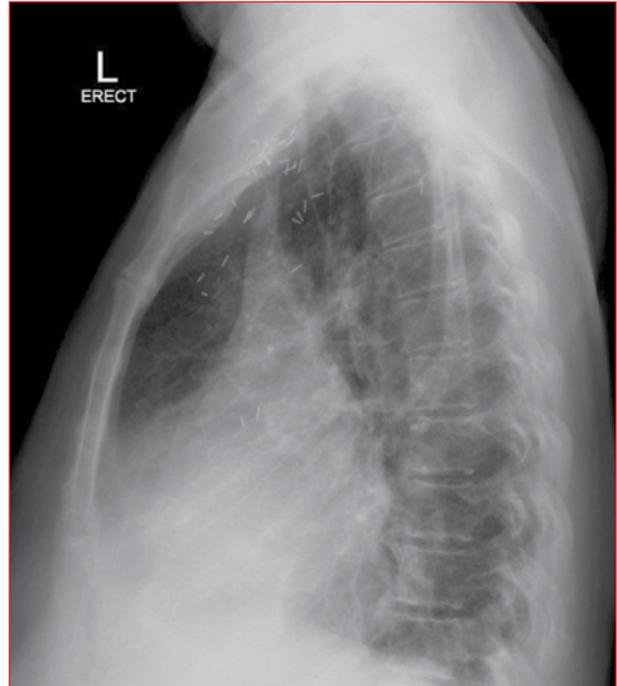


Figure 1: The posteroanterior and lateral views of the chest radiograph of patient number 1 showed hyperinflation, left ventricular hypertrophy, a small right-sided pleural effusion and surgical clips from a left mastectomy

He had atrial fibrillation and clinical evidence of right ventricular enlargement and pulmonary hypertension (parasternal heave and loud second heart sound), and severe right heart failure (gross bipedal oedema, hepatic congestion and markedly elevated JVP). He also had evidence of a right-sided pleural effusion. No thyromegaly or evidence of thyroid eye disease was present.

Thyroid function tests showed an FT4 of > 155 pmol/l, FT3 of > 30.8 pmol/l and TSH < 0.01 mIU/l. A technetium

thyroid scan was consistent with Graves' disease, and revealed an increased uptake of 16% (normal: 0.75-4%). Chest radiography (Figure 2) demonstrated an enlarged right ventricle, as well as a right-sided pleural effusion. Analysis of the fluid showed that it was a transudate.

Echocardiography demonstrated a severely dilated right atrium and ventricle, moderate tricuspid regurgitation and good left ventricular function. Pulmonary arterial pressure was 50 mmHg.

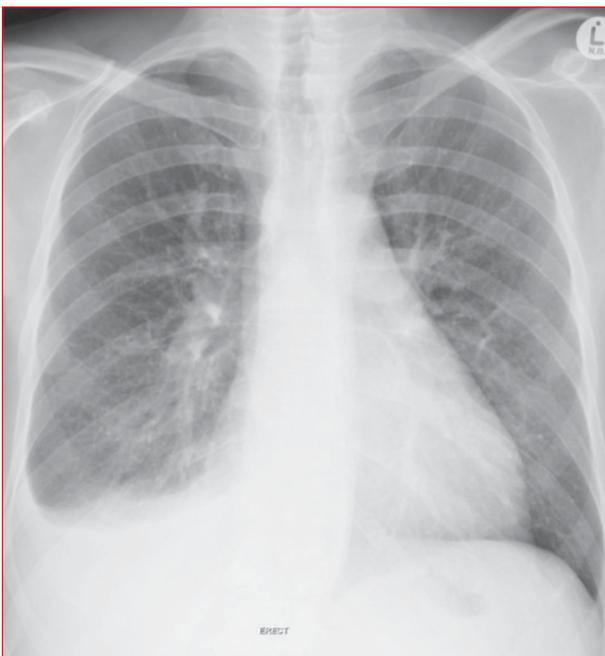


Figure 2: The posteroanterior and lateral views of the chest radiograph of patient number two revealed right ventricular hypertrophy with a moderate right-sided pleural effusion

In view of the marked cor pulmonale, a pulmonary CT-angiography was performed, and this excluded any thromboembolic disease. However, in the light of his atrial fibrillation, a decision was made to anticoagulate him with low-molecular-weight heparin and warfarin. The patient was treated with RAI, and subsequently became hypothyroid. His cardiac status improved markedly and the pleural effusion cleared, although he did remain in atrial fibrillation. Currently, he is on thyroid replacement therapy and warfarin, and anti-failure medication has been significantly decreased.

A subsequent echocardiography, at a time when he was euthyroid, demonstrated improvement in his right ventricular dilatation and function. He still had biatrial enlargement. This is most likely to be due to remodelling. The pulmonary arterial pressure had normalised to 30 mmHg.

Case 3

A 72-year-old female presented to us with clinical features of thyrotoxicosis. Medical therapy with carbimazole had apparently been initiated six months before. She had no features of heart failure, but had evidence of pulmonary hypertension with a right ventricular heave, and a loud pulmonary component of the second heart sound. The rest of the clinical examination was normal. Previous medical history was unremarkable, with no history of smoking.

Thyroid function tests revealed an FT4 of 43.0 pmol/l and FT3 of 8.5 pmol/l, with a TSH < 0.01 mIU/l. The TSH receptor antibody titre was markedly increased at 23.44 (0-1.75). Chest radiography was normal. An echocardiography showed a normal left ventricular ejection fraction of 67%, slight diastolic dysfunction, and raised pulmonary arterial pressure of 54 mmHg.

The patient was treated with RAI, and remained

euthyroid thereafter. A subsequent echocardiography showed that pulmonary artery pressure had nearly normalised to 37 mmHg (Table I).

Discussion

Although hyperthyroidism is classically associated with left ventricular dysfunction and heart failure, awareness that this disease may also at times predominantly, if not exclusively, involve the right heart has increased over the past few years.⁶⁻⁸ However, the true prevalence and clinical significance of this complication remain unclear. Isolated case reports, often involving patients presenting with acute cor pulmonale, suggest that the association of thyrotoxicosis and PAH is rare. However, a limited number of observational studies have documented the prevalence of PAH in hyperthyroidism to range from 41-65%. The largest observational study, by Marvisi et al, evaluated 114 patients with hyperthyroidism (47 with Graves' disease and 67 with toxic nodular goitre), and found mild PAH in 43%, and no case of PAH in the control group.⁹ More recently, Siu et al evaluated 75 patients with hyperthyroidism and normal left ventricular systolic function, and found that up to 47% had (asymptomatic) pulmonary hypertension, either due to PAH with increased cardiac output or pulmonary venous hypertension with elevated left ventricular filling pressure.¹⁰

Usually, these observational studies have documented only mild degrees of PAH in patients presenting with thyrotoxicosis primarily. Conversely, a retrospective study found a significantly higher prevalence of thyroid disease in 356 patients presenting with severe pulmonary hypertension, compared with an appropriately matched control group [odds ratio (OR) 2.53, 95% confidence interval (CI) 1.55-4.08, p-value < 0.001].¹¹ Interestingly, most patients had mild thyroid disease and were often not hyperthyroid, but hypothyroid.

Most reports have focused on middle-aged females, although the association between hyperthyroidism and PAH has also been reported in men.¹² Our second patient, who presented with the most severe degree of right heart failure and hyperthyroidism, was a male.

The aetiology of the pulmonary hypertension that has been observed in subjects with hyperthyroidism remains unclear, but various mechanisms have been proposed. These include endothelial injury due to the high cardiac output that often accompanies the hyperthyroid state.^{6,13} Given the fact that PAH may also develop in the absence of an increased cardiac output, this proposed mechanism clearly does not explain all cases. Hyperthyroidism-induced vasospasm has been suggested by some,¹⁴ although little objective evidence exists to support this theory. Likewise, it has been hypothesised that an increased metabolism of intrinsic pulmonary vasodilators may underlie the PAH, but scant data support this concept.¹³ Hyperthyroidism

Table I: Thyroid functions and pulmonary artery pressures

Characteristics	Case 1	Case 2	Case 3
Age (years)	55	44	72
Gender	Female	Male	Female
FT4 (10.3-21.9 pmol/l)	65.7	> 155	43
TSH (0.35-4.5 mIU/l)	< 0.01	< 0.01	< 0.01
TSH R Ab (0.00-1.75 IU/l)	> 40	-	23.44l
Microsomal ab (0-9 IU/ml)	-	1:1 600	-
PAP before (< 30 mmHg)	64	50	54
PAP after (< 30 mmHg)	25	30	37

microsomal ab: microsomal thyroperoxidase antibody, PAP: pulmonary arterial pressure, TSH: thyroid-stimulating hormone, TSH R ab: thyroid-stimulating hormone receptor antibody, microsomal or thyroperoxidase

is commonly associated with hypercoagulability and an increased prevalence of deep vein thrombosis,¹⁵ as well as a two- to threefold increased prevalence of pulmonary embolism, even after correcting for confounders.¹⁶ Thus, pulmonary embolism may account for a definite number of patients presenting with PAH, and always needs to be excluded. However, as was evident in our own patients, PAH has been adequately documented in hyperthyroid patients in the absence of any pulmonary embolism. Therefore, it cannot account for the vast majority of cases.

An attractive hypothesis to explain the association between PAH and thyroid disease relates to autoimmunity. In a series of 40 patients with apparent primary pulmonary hypertension, Yanai-Landau et al found an eightfold increase in the incidence of anti-thyroglobulin antibodies over that of the general population.¹⁷ Therefore, the question arises as to whether immune activation in hyperthyroidism may account for endothelial damage or dysfunction, causing pulmonary hypertension. In another study of 63 consecutive patients with pulmonary arterial hypertension, it was found that half the patients had evidence of autoimmune thyroid disease or a family history thereof.¹⁸ Most of these studies have assessed anti-thyroglobulin or microsomal anti-thyroperoxidase antibodies, and we are not aware of studies which measured TSH receptor antibodies. Some apparent cases of primary or idiopathic PAH in children have, in retrospect, been shown to precede, by five years or more, the development of autoimmune polyglandular endocrine syndromes comprising type 1 diabetes and hyperthyroidism.¹⁹ The autoimmune thyroid diseases, such as Graves and Hashimoto's thyroiditis, have been shown to be more frequently associated with PAH, than multinodular goiter has, for example, lending credence to a possible autoimmune basis for this association. In fact, Sahin et al found euthyroid Hashimoto's patients to have higher pulmonary arterial pressures, than controls (31.6 ± 5 vs. 25.6 ± 4.5 mmHg, p -value = 0.005).²⁰

Reversibility of PAH upon treatment of the underlying thyrotoxicosis has been demonstrated consistently in the vast majority of cases.^{10,21} In one study, it was demonstrated that a more rapid drop in pulmonary arterial pressures could be achieved with anti-thyroid drugs, compared with partial thyroidectomy, suggesting a possible role for the anti-thyroid drugs per se.⁹ However, in our patients, normalisation of the pulmonary pressures was achieved in all three cases with RAI.

Conclusion

Thyroid disease, in particular Graves' disease, should be recognised as a cause of PAH and cor pulmonale. The exact prevalence, pathophysiology, and clinical significance of this association is yet to be determined. In this setting, it is imperative to exclude other causes of pulmonary hypertension, especially pulmonary

embolism, which is known to occur more frequently in hyperthyroidism. The importance in recognising the association between PAH and hyperthyroidism lies in the fact that reversibility of the pulmonary hypertension is usually achieved upon restoration of the euthyroid state. Therefore, all patients presenting with apparent primary pulmonary hypertension should be screened for thyroid disease. Given the fact that, especially in children, the PAH may precede the development of the thyroid disorder by many years, it may be prudent to repeat thyroid function tests after a period of time in these individuals.

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