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Published online 2015 December 09. **Case Report**

Shortness of Breath and Lower Limb Edema in a 54-Year-Old Woman, Is There Any Cure?

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Introduction: Pulmonary hypertension is common among patients with hyperthyroidism, and Graves' disease constitutes the most common cause of thyrotoxicosis.
Case Presentation: We report the case of a female patient admitted to the cardiology department with shortness of breath and pretibial myxedema. The diagnostic work-up revealed combined pre- and post-capillary pulmonary hypertension due to Graves' disease superimposed on left ventricular diastolic dysfunction. Restoration of thyroid function led to normalization of the pulmonary pressure and symptom resolution.
Conclusions: Thyroid disease is a cause of reversible pulmonary hypertension and thus should be appropriately considered in the diagnostic algorithm in patients with dyspnea, clinical signs of hyperthyroidism and elevated pulmonary pressure.

Keywords: Dyspnea; Myxedema; Hypertension

1. Introduction

Pulmonary hypertension is defined as an increase in mean pulmonary arterial pressure ≥ 25 mmHg as assessed by right heart catheterization (1-3), and can be present in 35% of patients with hyperthyroidism. Graves' disease is the most common cause of thyrotoxicosis (4). Successful treatment of Graves' disease usually normalizes the elevated pulmonary artery pressure and some parts of the right heart failure that accompanies hyperthyroidism (5).

We report the case of a female patient with a history of Graves' disease that was admitted to the cardiology department with shortness of breath and pretibial myxedema.

2. Case Presentation

A 54-year-old woman presented to the emergency department because of dyspnea after moderate exertion and exacerbation of bilateral lower limb edema. Her medical history included Graves' disease, which was being treated with methimazole (20 mg/24 h).

Physical examination revealed a large diffuse goiter and fine finger tremor. A bilateral, non-pitting edema with multiple erythematous nodules was evident in the pretibial area, ankles, and dorsal area of both feet (Figure 1A). No ophthalmopathy was observed. Cardiac auscultation revealed a high-pitched systolic murmur in the left parasternal region and an accentuated S2. Blood pressure was 140/70 mmHg with a regular heart rate of 80 beats/min. Body temperature was normal and oxygen saturation was 99%. A 12-lead resting electrocardiogram showed non-specific ST changes in the precordial leads.

Echocardiography reported normal left ventricular dimensions and systolic function (ejection fraction = 60%), mild left ventricular diastolic dysfunction, mild right ventricular dilatation (34mm at 4 chamber view at the tips of the tricuspid leaflets), normal right ventricular function as estimated by tissue Doppler imaging, mild tricuspid regurgitation, and significantly elevated pulmonary artery systolic pressure (PASP = 55 mmHg, Figure 1B). Thyroid function tests showed hyperthyroidism [TSH < 0.01 μIU/mL (0.27 - 4.20), T3 = 4.9 ng/mL (0.8 - 2.0), and FT4 = 3.9 ng/dL (0.8 - 2.0)]. Thyroperoxidase (TPO) and thyroglobulin (Tg) antibodies were negative [anti-TPO = 30 IU/mL (< 34.0) and anti-Tg = 66 IU/mL (< 115)], while thyroid-stimulating immunoglobulin was positive [TSI = 40.0 IU/L (< 1.75)]. Computed tomography (CT) pulmonary angiogram and functional lung tests were normal. Diagnostic work-up did not reveal any other causes of pulmonary arterial hypertension.

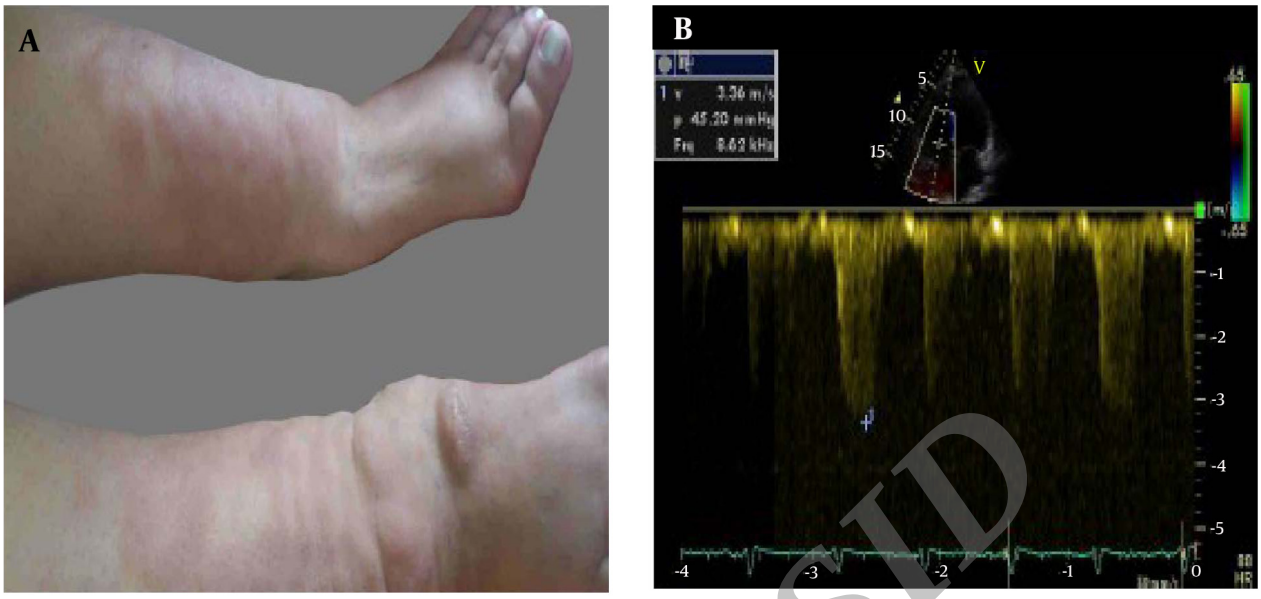

Figure 1. A, Pretibial Myxedema; B, High Tricuspid Regurgitation Velocity Corresponding to the Calculated Right Ventricular-Pulmonary Artery Systolic Pressure of 55 mmHg at Admission

The patient was referred for right heart catheterization for further investigation, which revealed the following: systolic pulmonary artery pressure (PAP) = 50 mmHg, mean PAP = 33 mmHg, diastolic PAP = 26 mmHg, pulmonary capillary wedge pressure (PCWP) = 18 mmHg, transpulmonary gradient (TPG) = 15 mmHg, and diastolic pressure difference (DPD) = 8 mmHg. However, elevated TPG (mean PAP minus mean PCWP) and DPD (diastolic PAP minus PCWP) were suggestive of combined pre- and post-capillary pulmonary hypertension (PH) (1). In particular, the aforementioned out-of-proportion PH (mean PAP > 25 mmHg, PCWP >15 mmHg, and TPG > 12 mmHg) underscored the existence of an additional factor, superimposed on left ventricular diastolic dysfunction, which contributed to PAP elevation. Given that the patient had hyperthyroidism, the diagnosis of PH due to Graves' disease was established (group 5) (2, 3).

The diagnosis of pretibial myxedema was confirmed histologically by biopsying the limb nodules. The patient was discharged with an increased dose of methimazole, propranolol, and furosemide, with a recommendation for thyroidectomy after restoration of euthyroidism. Gradual improvement of the clinical and laboratory findings, with the exception of pretibial myxedema, was observed, and the patient ultimately underwent thyroidectomy. Postoperatively, thyroxine replacement therapy was initiated. During follow-up, the patient was dyspnea free. Repeat echocardiography reported normal left ventricular systolic dimensions and function (ejection fraction = 60%), normalized right ventricular diameter (30 mm at 4 chamber view at the tips of the tricuspid leaflets), and normal right ventricular function as estimated by tissue Doppler imaging. There was still mild tricuspid regurgitation, but pulmonary artery pressure was normal (30 mmHg, Figure 2).

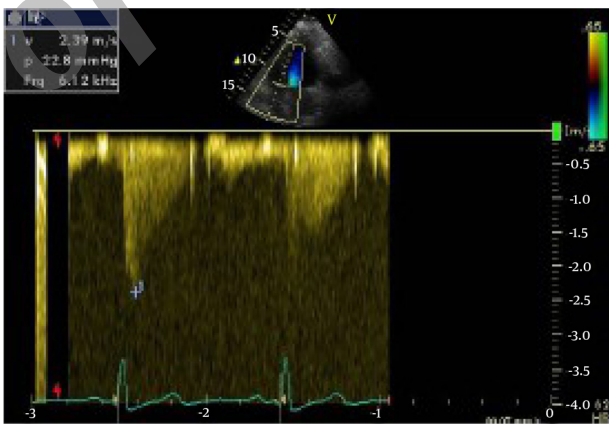

Figure 2. Right Ventricular-Pulmonary Artery Systolic Pressure was Normalized (30 mmHg) After Thyroidectomy

3. Discussion

Graves' disease is the most common cause of thyrotoxicosis and has a female to male ratio of approximately 8:1 and a peak incidence between the ages of 20 to 40 years (4). Pretibial myxedema occurs in about 2% - 3% of patients with Graves' disease and is usually associated with significant opthalmopathy and a very high TSI titer (4). Therefore, it is remarkable that our patient did not exhibit ophthalmopathy.

The effects of the thyroid hormone on the cardiovascular system include increased heart rate, left ventricular contractility, and blood volume, and decreased systemic vascular resistance (6). The symptoms and signs of

Graves' disease result not only from effects of the thyroid hormone but also from autoimmune processes. Hyperthyroidism has been associated with PH, but the underlying mechanisms remain to be clearly elucidated (6). Studies have shown the presence of PH in 35% of patients with hyperthyroidism; it is usually reversible. PH is defined as an increase in mean pulmonary arterial pressure ≥ 25 mmHg as measured by right heart catheterization (2, 3). Elevated PCWP (> 15 mmHg) defines post-capillary PH, while an elevated TPG (> 12 mmHg) and DPD (> 7 mmHg) characterize combined pre- and post-capillary PH, which is suggestive of intrinsic changes in the pulmonary circulation that override the passive increase in PCWP due to left heart disease (1, 3).

Increase in cardiac output and pulmonary vascular resistance are the main pathophysiologic factors that contribute to PAP elevation. Increased cardiac output is mediated through increased heart rate and myocardial contractility due to the effects of the thyroid hormone on the sympathetic nervous system, while decreases in the systemic vascular resistance are driven by excessive nitric oxide production. In contrast to the effect of thyroid hormone in decreasing systemic vascular resistance, pulmonary vascular resistance is not decreased by hyperthyroidism (6).

Possible pathways through which hyperthyroidism can lead to pulmonary hypertension include augmented sensitivity to catecholamines causing increased pulmonary vascular resistance (5). Increased catabolism of pulmonary vasodilating agents (prostacyclin, nitric oxide) and decreased catabolism of vasoconstrictors (serotonin, endothilin-1 and thromboxane) elevate pulmonary vascular tone (5). Hyperthyroidism has been associated with low levels of phospholamban, a Ca^{2+} balance regulator, resulting in smooth muscle cell Ca^{2+} overload and increased contractility (5). In addition to the effects of thyroid hormone on the cardiovascular system, autoimmune-mediated pulmonary vascular remodeling may play a role in Graves' disease-mediated elevated pulmonary systolic arterial pressure (6). Antithyroid antibodies are a marker of generalized immune activation, and a high prevalence in PH may suggest an autoimmune pathogenic link. Immune-mediated injury and endothelial cell destruction result in the generation of rapidly proliferative apoptosis-resistant endothelial cells, leading to vascular remodeling and the development of PH (6). Successful treatment of Graves' disease, as in our patient, usually normalizes elevated pulmonary artery pressure and some of the components of right heart failure that accompany hyperthyroidism (7).

Additionally, left ventricular diastolic dysfunction, as expressed by specific echocardiographic indices (E/E' > 15, E' < 9 cm/sec, left atrium-(LA) volume index > 34 mL/m^2) (8, 9), may be a cause of PH (3). Current therapy includes a number of drugs (diuretics, beta-blockers, angiotensin converting enzyme inhibitors, and inotropes) that may lower pulmonary artery pressure through a drop in left-sided filling pressures (10).

In conclusion, our patient exhibited a combined pattern of pre- and post-capillary PH, underlining intrinsic changes in the pulmonary circulation caused by Graves' disease that overrode the passive increase in PCWP due to left heart disease. Treatment of hyperthyroidism reverses PH. Thus, thyroid disease should be considered in the diagnostic algorithm of PH.

Authors' Contributions

All authors participated in the management of the patient. Alexandra Frogoudaki and Andreas S. Triantafyllis: acquisition, analysis, interpretation of the data and drafting of the manuscript. Evangeline Vassilatou, Charalampos Tsamakis and Achilles Zacharoulis: acquisition, interpretation of the data and critical revision of the manuscript. John Lekakis: interpretation of the data and critical revision of the manuscript.

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