Case Report with Review of Literature

Hyperthyroidism: A rare cause of pulmonary embolism: Report of two cases

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ABSTRACT

Several disorders of coagulation and fibrinolysis have been widely reported in patients with hyperthyroidism. Most reports have focused on only the venous thromboembolism risk, and few of them have studied specifically the association between hyperthyroidism and pulmonary embolism (PE). We report two cases of Graves' disease complicated by PE. The first patient is a 32 year-old man, and the second patient is a 23-year-old female. PE was suspected on the basis of pulmonary hypertension in patient one, and clinical presentation in the other patient. The first patient had also right heart failure. PE was confirmed in both patients by a lung perfusion-ventilation scan test. Thrombophilia screen revealed normal findings in the first patient and an elevation in coagulation factor VIII in the second one. Both patients received heparin, followed by oral anticoagulant therapy. In addition, they were treated with radioactive iodine resulting in partial recovery from hyperthyroidismforpatient oneand clinical euthyroidism for patient two.The former died of acute heart failure secondary to a chest infection, while the later was lost to follow-up. In conclusion, hyperthyroidism is associated with increased risk of venous thromboembolism, including PE. Potential mechanisms involved in this association include endothelial dysfunction, decreased fibrinolytic activity, and increased coagulation factors levels. Thyroid evaluation is recommended in patients with unprovoked venous thromboembolic events. Conversely, the diagnosis of venous thromboembolism should be considered in patients with hyperthyroidism, particularly if additional prothrombotic risk factors are present.

Key words: Hyperthyroidism, pulmonary embolism, venous thromboembolism, factor VIII levels

Introduction

The prethromboticstates include various primary as well as secondary clinical disorders characterized by an increased tendency for thromboembolism.[1] Primary hypercoagulable states include relatively rare inherited disorders of coagulation, such as protein C and protein S deficiency and abnormalities of the fibrinolytic system. Secondary hypercoagulable states are generally acquired, and include different conditions, such as pregnancy, malignancy, myeloproliferative syndromes, and systemic diseases.[1] Still, in 25 to 50% of patient with first-time venous thrombosis, no readily identifiable risk factor can be found.[2]

Several previous studies suggest that hyperthyroidism represent a potential hypercoagulable and hypofibrinolytic state, which may contribute to the increased risk of thromboembolism.[3-6] Most reports have focused on only the venous thromboembolism risk, and few of them have studied specifically the association between hyperthyroidism and pulmonary embolism (PE).[7-10]

In this report, we describe two patients with Graves' disease complicated by PE. We also discuss the potential mechanisms involved in this association.

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Case Reports

Patient 1

A 32 year-old man, with a family history of Graves' disease in a maternal aunt, was admitted to the hospital with a history of weight loss, excessive sweating, palpitation, tremors of the hands and irritability of sixmonths duration.

On clinical examination, he was found to be toxic. Pulse was 132 per minute and irregular. Blood pressure (BP) was 110/70 mmHg. He had moderate bilateral exophtalmos associated with a large elastic vascular goiter. He also had clinical signs of right heart failure, including edema of lower limbs, hepatomegaly and hepatojugular reflux. Laboratory tests revealed normocytic normochromic anemia with a hemoglobin level of 11.8 g/dL. The rest of the laboratory results were within normal range. Thyroid function tests confirmed a state of thyrotoxicosis with free T4 (FT4) of 51 pmol/L (reference range 10-24), and TSH of 0.07 μU/mL (reference range 0.4-4.5). High titer of antithyroid-stimulating antibodies confirmed the diagnosis of Graves' disease. Electrocardiogram (ECG) showed complete arrhythmia due to atrial fibrillation (CA/FA). A cervicothoracic scan indicated a non-compressing and non-dipping homogeneous goiter.

Echocardiography revealed dilated right cavities, mild tricuspid insufficiency, and elevated pulmonary pressure reaching 64 mmHg. There were no signs of left ventricular enlargement or reduced function.

The diagnosis of PE was suspected by the presence of significant pulmonary hypertension, and was confirmed by a lung perfusion-ventilation scan test that showedhypoperfusion of the left lung [Figure 1].

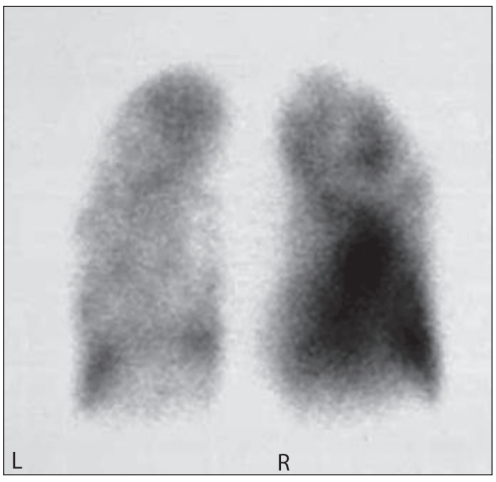

Figure 1: Ventilation-perfusion scintigraphy of the patient n°1 hypoperfusion on his left lung

No conventional venous thromboembolism risk factors were identified. Thrombophilia screen, including protein C and S, antithrombin, activated protein C resistance, lupus anticoagulant, and anti-cardiolipin antibody were negative.

The patient was diagnosed as Graves' disease complicated by cardiothyreosis and PE. The patient received heparin, followed by oral anticoagulant therapy. Benzylthiouracil (Basdène®) treatment was also initiated at a dose of 225 mg daily, associated with beta-blocker propranolol. Two months later, radioactive iodine treatment (8 mCi) was administered, resulting in incomplete recovery from thyrotoxicosis. Repeated echocardiography showed normal pulmonary artery pressure (29 mmHg). The patient died of acute heart failure secondary to a chest infection 2.5 months after radioactive iodine treatment.

Patient 2

A 23-year-old female patient, whose sister was affected by Graves' disease, had been treated since 2007 for Graves' disease. This diagnosis was made on the basis of hyperthyroid symptoms, moderate homogenous and elastic goiter, elevated FT4 level (94.9 pmol/L, normal range 10-24) with suppressed TSH (0.05 μU/mL, normal range 0.4-4.5), and elevated titer of antithyroid-stimulating antibodies (43.3 UI/L, normal range <2).

The patient was put under antithyroid drugs: Benzylthiouracil (Basdène®) at a dose of 225 mg daily in combination with a beta-blocker (Propranolol, 60 mg daily). The patient showed poor compliance and frequent discontinuation of her treatment.Facing the reappearance of hyperthyroidism, she was hospitalized in June 2010. On examination, she had a body mass index of 21.38 kg/m², BP of 140/80 mmHg. In addition to the signs of thyrotoxicosis, the patient had a moderate bilateral exophthalmos associated with a moderate homogenous and vascular goiter. Her ECG showed sinus tachycardia with right axis deviation, and Sokolow-Lyon criteria for left ventricular hypertrophy.

On hormonal investigations, FT4 was higher than 100 pmol/L (normal range 10-24) and TSH was 0.005 μU/mL (normal range 0.4-4.5). During hospitalization, the patient developed a severe chest pain, dyspnea with an exaggeration of tachycardia. ECG showed right bundle branch block. Chest radiography revealed no abnormalities. Arterial blood gas analysis showed hypoxia and hypocapnia. Serum level of D-Dimer was higher than 500 ng/ml. PE was suspected and was confirmed by a lung perfusion-ventilation scan test confirmed which showed several bilateral segmental perfusion defects [Figure 2]. The patient was put under heparin relayed by anticoagulants. In addition, radioactive iodine treatment was administered (7 mCi), and then the

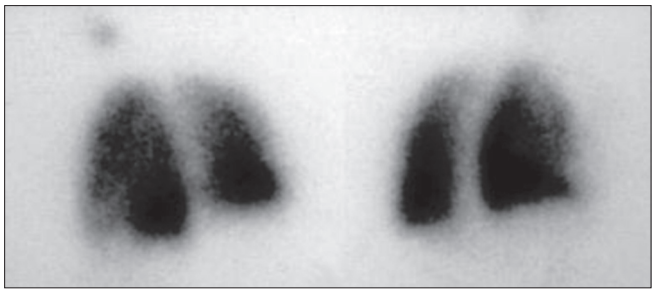

Figure 2: Ventilation-perfusion scintigraphy of the patient n°2 several bilateral segmental perfusion defects

patient was again put under Benzylthiouracile. Etiological investigation of PE has revealed a 200% elevation of plasma concentration of coagulation factor VIII. The patient consulted three months following radioiodine treatment without any hormonal tests. She was clinically euthyroid, and since then she was lost to follow-up.

Discussion

Our two reported cases are in agreement with previous observations of PE and venous thrombosis in patients with hyperthyroidism.[8-10]

In a recent systematic analysis, Franchini *et al.* documented 34 cases of venous thrombosis occurring in patients with overt hyperthyroidism. Cerebral veins were the most common site of thrombi. PE was present in fourpatients. Interestingly, all the thrombotic episodes reported were unprovoked. The authors concluded that there was an increased risk of venous thrombotic complications in overt hyperthyroid patients.[11]

There are few reports of PE associated with hyperthyroidism. A recent study, using a nationwide population-based dataset, aimed to estimate the risk of PE among hyperthyroidism patients during a five year period.[7] The study included 8903 patients with hyperthyroidism as a study cohort and 44515 randomly selected patients without hyperthyroidism as a comparison cohort. After adjustment for potential confounders, the risk of having PE during the five year follow-up period was 2.31 times greater (95% confidence interval 1.20-4.45, $P = 0.012$) for patients with hyperthyroidism than for patients in the comparison cohort.[7]

PE is, in the overwhelming majority, a consequence of deep venous thrombosis; the two together constitute venous thromboembolism (VTE). The incidence of PE thus reflects the presence of risk factors for VTE.[12]

Three primary influences predispose a patient to thrombus formation; these form the so-called Virchow triad, which consists of decreased flow rate of the blood, damage to the blood vessel wall and hypercoagulability.[13]

Possible predisposing factors for the development of venous thrombosis and PE in patients with thyrotoxicosis are also in line with this triad. Indeed, patients with hyperthyroidism may often have accompanying endothelial dysfunction, decreased fibrinolytic activity, and hypercoagulablestates, which contribute to the development of venous thrombosis and increased risk of PE.[5,7,14]

Patients with hyperthyroidism had elevated levels of von Willibrand factor, tissue plasminogen activator inhibitor-1 and antithrombin III, decreased levels of tissue plasminogen activator, shortened activated partial thromboplastin time, increased turnover of coagulation factors II, VII, IX and X, and increased plasma homocysteine and fibrinogen levels.[14-19]

Indeed, many publications have described a high factor VIII activity associated with hyperthyroidism.[20-22]

It is well established that plasma coagulation factor VIII activity positively correlates with tissue metabolic rate and plasma catecholamine levels. An excessive adrenergic activity, occurring in hyperthyroid patients, may directly contribute to an increased production of FVIII, as illustrated by the fact that propanolol may inhibit the increase of FVIII in patients with hyperthyroidism.[11,20] Elevated factor VIII levels seem to be a significant, prevalent, independent, and dose-related risk factor for venous thrombosis.[23,24] This entity may also account for a significant proportion of idiopathic hypercoagulable states. The factor VIII level typically falls as the thyroid function becomes normalized.[20,23] In our first case, the factor VIII could not be determined in the acute phase, while in the second observation; factor VIII was high reaching 200%, thus corroborating the literature data.

Previous intervention studies, performed in healthy volunteers, showed a dose dependent increase in factor VIII and IX levels, von Willebrand factor, and endothelium-associated proteins concentrations during administration of oral thyroid hormones.[25-27] In line with these findings, van Zaane *et al.*, demonstrate a gradual relation between plasma FT4 levels and the risk of venous thrombosis. Notably, the thrombotic risk was substantially increased for FT4 levels well within the physiologic range.[28] Moreover, FT4 levels were particularly associated with the risk of unprovoked deep veinous thrombosis, indicating FT4 as a potential novel risk factor.[28]

In addition to overt hyperthyroidism, subclinical hyperthyroidism seems also to be associated with increased risk of venous thrombosis. In this context, Patane *et al.*, describe a case of recurrent PE associated with subclinical

hyperthyroidism, in an 81-year-old Italian woman.[29] In addition, alterations in fibrinogen and D-dimer levels, and increased factor X activity were reported in patients with subclinical hyperthyroidism.[30] All these findings represent a potential hypercoagulable state, which could contribute to increased thromboembolic risk in subclinical hyperthyroidism.

In summary, hyperthyroidism is associated with increased risk of venous thrombosis, including PE. Our study emphasizes the need for thyroid evaluation in patients with unprovoked venous thromboembolic events. Conversely, the diagnosis of venous thromboembolism and PE should be considered in patients with hyperthyroidism, particularly if additional prothrombotic risk factors are present.

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