

Uncommon Presentation of Combined Graves' Disease and Pulmonary Embolism in a 32-year-old Woman

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Abstract

Pulmonary embolism (PE) is related to hypercoagulable status, such as malignancy, nature anticoagulant deficiency, pregnancy and use of estrogen replacement. It has rarely been reported to be associated with endocrine diseases. We presented a 32-year-old woman with combined Graves' disease and PE. The initial presentation was progressive exertional dyspnea and cough for one month. First impression was Graves' disease complicated with thyrotoxic crisis at the emergency department, but PE was suspected clinically. A dilemma of diagnostic process was the use of iodine-containing contrast media. Increasing iodine uptake of thyroid glands would lead to potential exacerbation of thyrotoxicosis, but PE is usually diagnosed with a contrast-enhancing computed tomography (CT) of chest. We demonstrated a good result of combined treatment for Graves' disease with anti-thyroid drugs and submassive PE with catheter-directed thrombolysis and anticoagulants. After extensive literature review, we hypothesized that hyperthyroidism per se may contribute to the development of PE. (J Intern Med Taiwan 2019; 30: 351-357)

Key Words: Graves' disease, Hyperthyroidism, Pulmonary embolism, Hypercoagulability

Introduction

Graves' disease is an autoimmune thyroid disease mostly manifested as palpitations, heat intolerance, tremor, and weight loss¹. The disease might also involve gastrointestinal, hematological, neurological and cardiopulmonary systems². It may lead to atrial fibrillation and hypercoagulable states,

thus increase the risk of cardioembolic stroke; but the association with deep vein thrombosis (DVT) and/or PE was rare.

Case

A 32-year-old woman, previously healthy, presented to the emergency department with progressive exertional dyspnea and cough for one month.

In the following two months, progressive shortness of breath developed, associated with intermittent cough, rhinorrhea, stuffy nose, and loose stools. Medications for the relief of symptoms were all ineffective. She was frequently awakened at night because of sudden breathlessness, palpitations, and flushing. Three days before admission, she visited the other hospital, and hyperthyroidism was diagnosed there. She was treated with carbimazole, propranolol and furosemide, but her dyspnea worsened gradually. Thus, she came to the emergency department of National Taiwan University Hospital for help.

At triage, her vital signs were as follows: blood pressure 134/99 mmHg, pulse rate 154 beats per minute, respiratory rate 25 breaths per minute, body temperature 38.1 degrees Celsius, and peripheral oxygen saturation 92% while breathing supplemental oxygen via nasal cannula. Physical examination showed bilateral coarse breathing sounds and a grade III systolic heart murmur at the right upper sternal border. Lab data showed leukocytosis (WBC 19.35 k/ μ L), hyperbilirubinemia (total bilirubin 2.8 mg/dL), elevated C-reactive protein (5.37 mg/dL), elevated NT-proBNP (8309 pg/mL) and elevated D-dimer (4.13 μ g/mL). Thyroid function showed primary hyperthyroidism with high free T₄ (>5.4 ng/dL) and undetectable TSH (<0.004 μ IU/mL). Thyroid autoantibody profile revealed high anti-thyroperoxidase antibody (anti-TPO Ab) of 603 IU/mL (normal < 5.6) and thyrotropin-binding inhibiting immunoglobulin (TBII) of 93.2% (normal <10%), compatible with Graves' disease. Chest plain film revealed cardiomegaly. Electrocardiogram showed sinus tachycardia and right heart strain pattern (Fig. 1(A)). According to the Burch-Wartofsky Point Scale, her total score was 70 (>45), highly suggestive of thyroid storm. Based upon the clinical impression of Graves' disease with thyrotoxic crisis, she was admitted and treated with propylthiouracil (PTU), hydrocortisone, and propranolol, followed

by diluted Lugol's solution one hour later, considering its beneficial effect to rapidly decrease both T₄ and T₃ levels. We were cautious with Lugol's solution since it may exacerbate hyperthyroidism; it was much safer to start Lugol's solution one hour after thionamides¹. Because of her respiratory distress, fever and leukocytosis, empiric antibiotic with ceftriaxone was administered for coverage of community-acquired pneumonia.

However, her fever, diaphoresis, orthopnea, hemoptysis and dyspnea persisted and worsened in the following three days. We upgraded antibiotics to piperacillin/tazobactam for suspicion of hospital-acquired pneumonia. The electrocardiogram showed right heart strain pattern with SIQ3 in the limb leads. Transthoracic echocardiography showed fair contractility (LVEF 74.1%), elevated right heart systolic pressure (tricuspid regurgitation pressure gradient, TRPG 60.5 mmHg), moderate to severe tricuspid regurgitation, and D-shaped left ventricle (Fig. 1(B)). PE was highly suspected. Because iodine may exacerbate hyperthyroidism, iodinated contrast-enhanced CT was replaced by pulmonary perfusion scintigraphy, which showed multiple moderate to large segmental wedge-shaped perfusion defects in bilateral lungs. The patient was started on enoxaparin. A follow-up contrast-enhanced CT scan, after achieving euthyroidism status one week later, revealed thrombi at both pulmonary arteries and both branches, (Fig. 1(C), (D)) with wedge-shaped infarction, but no obvious consolidation. Moreover, there was left common femoral vein thrombosis; further vascular duplex ultrasound showed compatible findings and even more extensive lesions of lower extremities.

For submassive pulmonary embolism, she underwent catheter-directed thrombolysis therapy (CDT) with EKOS® catheter and implantation of IVC filter two weeks later. Meanwhile, surveys for other causes of hypercoagulability including antiphospholipid syndrome were all negative,

except for elevated factor VIII procoagulant activity (VIII:C) of 322.2% (normal 53-152%). The treatment course was complicated with hospital acquired pneumonia and suspicious antibiotics-related leukopenia and/or anti-thyroid drug-induced agranulocytosis. Thus, anti-thyroid medication was shifted to lithium. We prolonged the duration of thrombolysis and applied EKOS in both pulmonary arteries for higher treatment efficacy. Venogram at the 3rd week after CDT procedure showed improvement with little residual thromboembolism of the left lower pulmonary artery. Her symptoms improved gradually; follow-up electrocardiogram showed sinus tachycardia only with no more right heart strain, and echocardiogram revealed no more D-shaped left ventricle and decreased TRPG (36.2 mmHg) comparing to previous study, suggestive of improvement in right heart dysfunction.

Before discharge, she underwent radio-iodine ablation (12 mCi) with premedication of intramuscular injection of 1.1 mg recombinant thyrotropin, considering previous excessive iodine exposure due to repetitive use of contrast media and diluted Lugol's solution. Subsequently, elevated thyroxine levels occurred, so lithium was changed back to carbimazole. Thyroid function profile improved gradually, and there was no recurrence of leukopenia or neutropenia. In a stable condition, she was discharged on admission day 57, and subcutaneous injection of enoxaparin was switched to oral anti-coagulant rivaroxaban for extended-duration treatment of PE. During follow-ups at the outpatient department, she noticed to have intermittent dry cough and worsening lower leg redness and swelling. For persistent disease activity of Graves' hyperthyroidism and dermopathy, she received pulse steroid therapy with

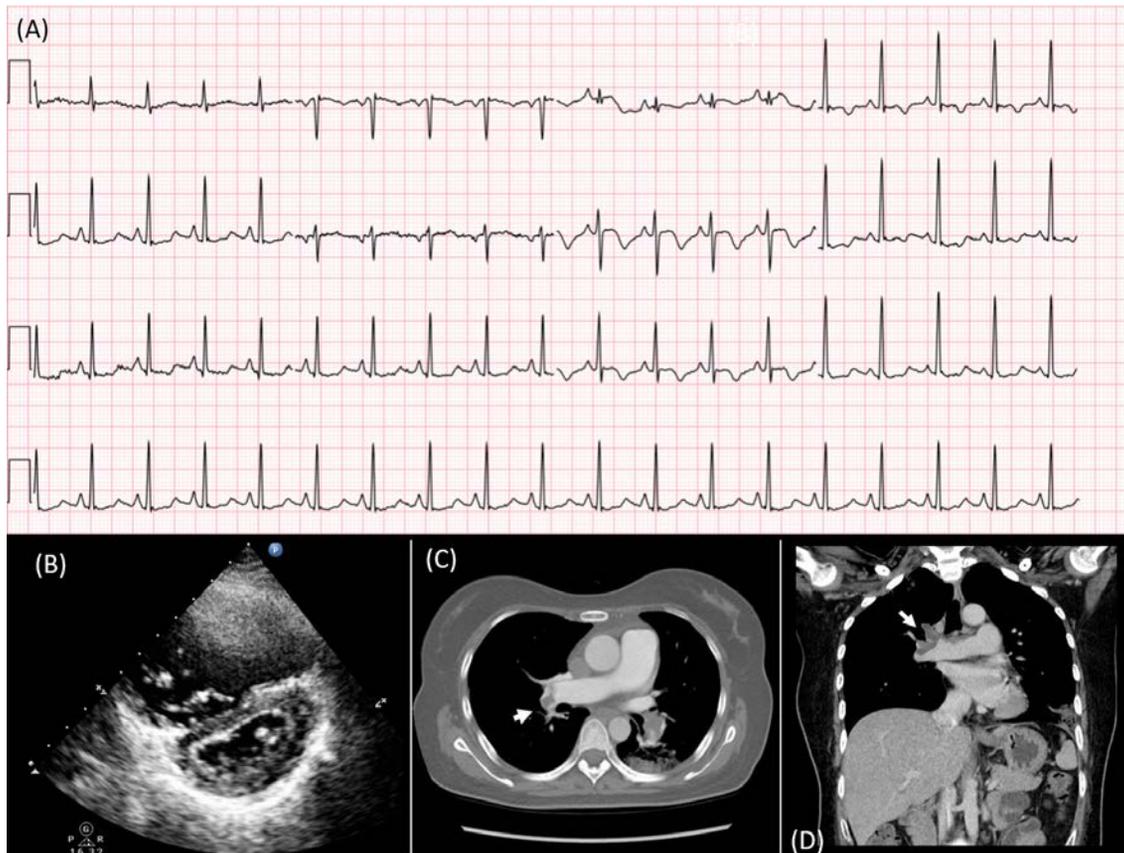


Figure 1. (A) showed sinus tachycardia and S1Q3 pattern in limb leads. (B) showed D-shaped left ventricle from parasternal short axis view on echocardiogram. (C) and (D) showed filling defects in the right pulmonary artery on contrast-enhanced chest computed tomography, as the arrows pointed.

IV infusion of methylprednisolone 500 mg weekly for 4 weeks, and then 250 mg weekly for another 8 weeks. Her general condition gradually improved after the treatment. Reviewing her history, the left leg swelling and redness might be a presentation of Graves' dermopathy but was misdiagnosed as varicose veins before.

In the out-patient clinics, she remained euthyroid throughout the entire follow-up period. Rivaroxaban was maintained for her PE which did not reoccur thereafter. We removed her IVC filter smoothly six months later. Follow-up factor VIII procoagulant activity returned to 144% (normal 53-152%).

Discussion

In this case, the patient visited the emergency department for symptoms and signs of PE, but the initial impression was thyrotoxic crisis, or thyroid storm. Concerning excessive iodine exposure might aggravate hyperthyroidism, iodinated contrast-enhanced computed tomography was postponed until after stabilization of thyroid functional status. Gadolinium-based contrast-enhanced MRI may be an alternative option because its resolution is comparable to multi-detector CT (MDCT)³. We performed chest CT examination after stabilization of hyperthyroidism, but delayed diagnosis of PE may prolong the whole treatment course. Submassive pulmonary embolism could progress to massive pulmonary embolism associated with compromised hemodynamics, which is a devastating life-threatening condition. Early diagnosis with ensuing prompt management and aggressive intervention might be the key to treatment success.

In previous studies, coagulation system was affected by thyroid hormone (Fig. 2). Overt and even subclinical thyrotoxicosis rendered the hemostatic system in favor of hypercoagulable and hypofibrinolytic state, via elevating serum levels of factors VIII, IX, fibrinogen, von Willebrand factor,

and plasminogen activator inhibitor-1⁴⁻⁵. Even though hypercoagulable status might be associated with thyrotoxicosis, whether hyperthyroidism led to increased risk of venous and/or PE was uncertain *in vivo*⁶. The serum levels of free thyroxine were correlated with higher risk of PE in literature review⁷. However, the most common site of thromboembolism was the cerebral vascular system in hyperthyroidism according to the previous report⁸. On the other hand, there were several case reports of combined occurrence of DVT and hyperthyroidism⁹. But the incidence of symptomatic PE in hyperthyroidism was extremely low¹⁰. The contribution of hyperthyroidism to DVT and/or PE was still controversial. Because of the low prevalence of thromboembolism event in hyperthyroidism, the routine implementation of primary prevention with oral anticoagulants was not advised. However, PE should be considered as one of the critical differential diagnoses if patients with hyperthyroidism present with unexplained dyspnea, especially when DVT is documented.

Moreover, the patient had been suspected to have agranulocytosis while being treated with anti-thyroid medication, which was a rare but fatal drug complication that should be kept in mind. Incidence of agranulocytosis in patients with Graves' disease receiving antithyroid drugs was 0.2-0.5%¹¹. Drugs, including PTU, carbimazole, and its active metabolite methimazole, may lead to agranulocytosis. The adverse effect of methimazole was dose-dependent, while such relationship was not existed in PTU¹². The mechanisms included direct toxicity and immune-mediated responses. Immediate suspension of culprit drug, initiation of antibiotics and consideration of administration of hematopoietic growth factors were the next step¹³. Substitution with lithium for antithyroid medication might be an option due to the safety profile of lithium. Lithium carbonate had been reported to successfully increase the white cell counts in a psychiatric patient with

clozapine-induced neutropenia¹⁴. I-131 therapy was an optimal treatment modality in patients intolerant of ATDs; however, after I-131, her hyperthyroidism relapsed. We recommenced antithyroid drug carbimazole, instead PTU, before discharge and closely monitored the hemogram. Fortunately, no more neutropenia recurred until now and it worked well for controlling her hyperthyroidism.

Hormone replacement therapy (HRT) was the most common trigger factor of DVT/PE in young female. However, the patient denied recent use of HRT, but previous short course of HRT for amenorrhea was uncertain. Other common risk factors included prior thromboembolism event, pregnancy, obesity, major surgery, multiple trauma, family history, congestive heart failure, immobilization, malignancy, coagulopathy, elderly, and foreign

body in venous system¹⁵. Regarding this case, there was only increased factor VIII activity documented during detailed clinical survey, which returned to normal after achieving euthyroid status. Thus, we hypothesize hyperthyroidism per se contributes to her hypercoagulable status, leading to the catastrophic thromboembolism event.

Conclusion

We reported a patient with hyperthyroidism complicated by submassive PE. We proposed that hyperthyroidism per se would contribute to the development of DVT and PE event. To avoid excessive thyroid gland uptake of iodine due to iodinated contrast media in the CT study, we might choose diagnostic modality of venous duplex, ventilation-perfusion scan, or gadolinium-based con-

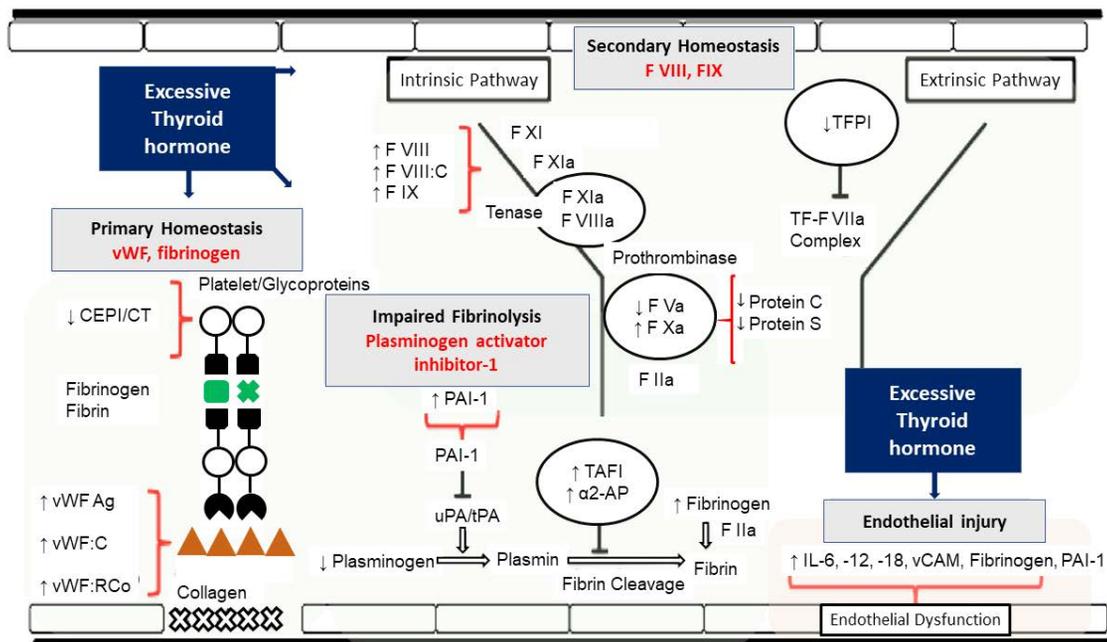


Figure 2. Illustrated changes in hemostatic parameters associated with hypercoagulability in overt and subclinical hyperthyroidism^{16,17}. (Adapted from Arash Ordookhani, Kenneth D. Burman Hemostasis in Overt and Subclinical Hyperthyroidism. *Int J Endocrinol Metab.* 2017 Jul; 15(3): e44157, Fig. 2)

Abbreviations: Ag, antigen; α 2-AP, α -2 antiplasmin; CEPI/CT, collagen and epinephrine closure time; F, coagulation factor; F VX:C, F X activity (X indicates individual Roman numerals of the coagulation factor); F Xa, activated F X (X indicates individual Roman numerals of the coagulation factor); PAI-1, plasminogen activator inhibitor-1; TAFI, thrombin activatable fibrinolysis inhibitor; TF, tissue factor; TFPI, tissue factor pathway inhibitor; tPA, tissue plasminogen activator; uPA, urokinase type plasminogen activator; vCAM-1, vascular cell adhesion molecule-1; vWF, von Willebrand factor; vWF:C, vWF activity; vWF:RCo, von Willebrand factor ristocetin cofactor activity.

trast-enhanced MRI instead. Once achieving the euthyroid status, contrast-enhanced chest CT could be performed safely without exacerbation of the disease. Catheter-directed thrombolysis is a safe and efficacious intervention, which may be considered if high bleeding risk precludes the use of systemic thrombolysis and/or as a rescue intervention after failed thrombolysis. The duration of anticoagulant therapy should be individualized according to the risk of bleeding and PE recurrence.

References

1. Dan L. Longo Graves' Disease. *NEJM* 2016; 375(16):1552-65.
2. Hegazi MO, Ahmed S. Atypical clinical manifestations of Graves' disease: an analysis in depth. *J Thyroid Res* 2012; 2012: 768019.
3. B. Hochegger, J Ley Zaporozhan, E Marchiori. Magnetic resonance imaging findings in acute pulmonary embolism. *Br J Radiol* 2011; 84(999): 282-7.
4. Danka JF, Stuijver, Bregje van Zaane, Erica Romnualdi, et al. The effect of hyperthyroidism on procoagulant, anticoagulant and fibrinolytic factors: A systematic review and meta-analysis. *Thromb Haemost* 2012; 108(06): 1077-88.
5. Monika Homoncik, Alois Gessl, Arnulf Ferlitsch, et al. Altered Platelet Plug Formation in Hyperthyroidism and Hypothyroidism. *J Clin Endocrinol Metab* 2007; 92(8): 3006-12.
6. L.P.B. Elbers, B. van Zaane, V.E.A. Gerdes. Venous thromboembolism in overt hyperthyroidism - a direct association with clinical implications? *Neth J Med* 2014; 72(4): 242-4.
7. van Zaane, Squizzato A, Huijgen R, et al. Increasing levels of free thyroxine as a risk factor for a first venous thrombosis: a case-control study. *Blood* 2010; 3; 155(22): 4344-9.
8. Franchini M, Lippi F, Targher G. Hyperthyroidism and venous thrombosis: a casual or causal association? A systemic literature reviews. *Clin Appl Thromb Hemost* 2011;17(4):387-92.
9. Umezu T, Ashitani K, Toda T, et al. A patient who experienced thyroid storm complicated by rhabdomyolysis, deep vein thrombosis, and a silent pulmonary embolism: a case report. *BMC Res Notes* 2013; 20; 6: 198.
10. D.D.W. Kim, S. Chunilal, S. Young, et al. A study of venous thrombosis incidence in patients with acute hyperthyroidism. *Intern Med J* 2013; 43(4): 361-5.
11. Nakamura H, Miyauchi A, et al. Analysis of 754 cases of antithyroid drug-induced agranulocytosis over 30 years in Japan. *J Clin Endocrinol Metab* 2013; 98(12): 4776-83.
12. Copper DS. The side effects of antithyroid drugs. *Endocrinologist* 1999; 9(6): 457-67.
13. Nuno Vicente, Luis Cardoso, et, al. Antithyroid Drug-induced Angranulocytosis: State of Art on Diagnosis and Management. *Drugs R. D.* 2017; 17(1): 91-6.
14. Chathurie Suraweera, Raveen Hanwella, et al. Use of lithium in clozapine-induced neutropenia: a case report. *BMC Res Notes* 2014; 7(1): 635.
15. Frederick A, Anderson JR, et al. Risk Factors for Venous Thromboembolism. *Circulation* 2003; 107(23): 19-16.
16. Arash Ordoorkhani, Kenneth D. Burman Hemostasis in Overt and Subclinical Hyperthyroidism *Int J Endocrinol Metab* 2017; 15(3): e44157, Fig2.
17. Stuijver DJ, van Zanne B, et al. The effect of hyperthyroidism on procoagulant, anticoagulant and fibrinolytic factors: a systematic review and meta-analysis. *Thromb Haemost* 2012; 108(6): 1077-88.

罕見臨床表現： 一名三十二歲女子同時併有葛瑞夫茲病及肺栓塞

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摘 要

葛瑞夫茲氏病(Graves' disease)是一種自體免疫性的甲狀腺疾病，患者的表現多以甲狀腺亢進的病徵為主。肺栓塞(pulmonary embolism)則多與高凝固性血液(hypercoagulability)、惡性腫瘤(malignancy)及靜脈血液滯留(venous stasis)有相關性，而治療方面則以抗凝血劑的使用為主。我們的病例報告中，病人同時合併有葛瑞夫茲氏病及肺栓塞，使我們面臨診斷工具上的困境，因為以注射含碘顯影劑之電腦斷層來診斷肺血栓栓塞，可能會惡化甲狀腺亢進的病徵。在適時診斷後，經過抗甲狀腺藥物(anti-thyroid drugs)及導管導引血栓溶解(catheter-directed thrombolysis)和抗凝血劑(anticoagulants)等治療後，患者的病情獲得良好的改善及控制。經由廣泛文獻回顧，我們提出假設，甲狀腺亢進本身可能導致患者的高凝固性血液狀態。