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Case Report

Should We Screen Patients with Unprovoked Venous Thromboembolism for Hyperthyroidism? Report of Several Paradigmatic Clinical Cases from the RIETE Registry

Abstract

Unprovoked venous thromboembolism (VTE) is defined as a VTE appearing in the absence of the common risk factors including cancer, surgery, hypomobility, oestrogen use or pregnancy. Around 40% of VTE patients have unprovoked VTE in real life. However, a number of additional clinical conditions may be associated to ahypercoagulable state and induce VTE, though they are less often considered in clinical practice such as the abnormalities of the thyroid function. Here we report three relevant case-reports that we found in the RIETE registry in which overt hyperthyroidism is the only apparent cause of haemodynamic unstable acute pulmonary embolism (PE).

Background

Unprovoked venous thromboembolism (VTE) is defined as a VTE appearing in the absence of the common risk factors, including cancer, surgery, hypomobility, oestrogen or pregnancy [1]. Around 40% of VTE patients have unprovoked VTE in real life [2-4]. In clinical practice around 40-50% of VTE cases are classified as unprovoked VTE in most clinical trials and \ or registries [4-6]. For this reason. For this reason, unprovoked VTE is still matter of discussion. Screening for occult cancer and for congenital thrombophilias in fact are routinely suggested in patients with unprovoked VTE [1,7,8], and long term anticoagulation is recommended anticoagulant in international guidelines in idiopathic VTE in order to avoid the risk of recurrences and their associated morbidity and mortality [1,9].

However, several other clinical conditions may be associated with VTE but, are not usually considered for daily screening as a potential cause of VTE, nor are reported as common cause of VTE in large randomized clinical trials and registries including nephrotic syndrome, inflammatory bowel disease, connectivitis and others [10-12].

We here report three clinical case reports patients with a severe VTE and hyperthyroidism as the only co-morbidity of detected VTE during follow up. Although hyperthyroidism has been associated to hypercoagulable state and thrombotic disease, it is rarely considered for evaluation as a cause of otherwise unprovoked VTE.

Case 1

A 62-year old male with history of hypertension was admitted at Emergency Ward because he referred hypotension, tachypnea and palpitations. ECG revealed sinus rhythm with 105 bpm, hypotension was confirmed (i.e. 85\40 mmHg), pulse-oxymetry was 90% AA and breath frequency 28 per minute. Sweating, tremors and exophtalmus were not present at physical examination nor clinical signs of right hearth failure. Laboratory tests performed revealed only a strong increase of d-dimer levels (i.e. >2800 mcg\dL) and an overt hyperthyroidism with TSH levels < 0.001microU\mL. A CT scan

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was performed and revealed a severe PE. Anticoagulant therapy was immediately started with intravenous unfractionated heparin 35.000 U daily. Clinical improvement was quickly obtained and anticoagulation was also associated to anti-hormone treatment with tapazole (3 tablets daily). A further scan with scintigraphy of thyroid gland revealed a Plummer's adenoma.

In order to evaluate the risk for future VTE recurrences, hypomobility, recent surgery, potential presence of occult cancer, were ruled out. Inherited or acquired thrombophilic defects were absent [Table 1], so hyperthyroidism was the only underlyingdisease associated to PE.

Case 2

A 38-year old woman was admitted at the Emergency Ward with a personal anamnesis of palpitations, tremors, irritability, frequent sweating and insomnia during the last 3 months. Her history was negative for recent pregnancy or prolonged contraceptive drugs. Clinical signs showed low blood pressure (.e. 90\60 mmhg), tachycardia with 128 bpm with sinus rhythm on the ECG, 26 breaths per minute, pulse-oxymetry 93% AA. Other clinical signs were mildexophtalmus and initial signs of right hearth failure (i.e. hepatomegaly, lower limbs oedema and cianosis).

Laboratory tests showed increased d-dimer (i.e. > 1800 mcg\dL) and dysfunction of the thyroid with hyperthyroidism and thyrotoxicosis. Thyroxicosis was certified by increase of free FT4 (i.e. 68 pMOL) and decreased level of TSH (i.e. < 0.05 microU\mL) due to the increase of antibodies toward thyroid cell receptors (i.e. Thyroyd Receptor autoantibodies, TRAb) so suggesting a Grave's disease. On the other hand, the presence of dyspnea with clinical signs of right hearth failure and increased d-dimer levels suggested us to perform a perfusion\ ventilation lung scan that revealed a bilateral lPE.

Immediately a combined treatment based on anti-hormonal drugs for thyrotoxicosis (i.e. tapazole 4 tablets daily) and low molecular weight heparin (i.e. enoxaparin 120 mg daily) was started. A thorough anamnesis to look for acquired thrombotic risk factors as bed rest or hypomobility, recent surgery, pregnancy or hormonal treatment was performed without further findings; the further screening for acquired or inherited thrombophilia did not reveal any abnormality [Table 1]. Thus, thyrotoxicosis was the only clinical condition associated to PE.

Table 1: Thrombophilic tests of the reported patients.

Test	Case 1	Case 2	Case 3	N.V.
Prothrombin A20210G	Absent	Absent	Not tested	Absent
Factor V Leiden	Absent	Absent	Not tested	Absent
Hyperhomocysteinemia (microM/L)	10.1	8	Not tested	(5-15)
Protein S (%)	74%	98%	Not tested	(80-120)
Protein C (%)	92%	104%	Not tested	(80-120)
AT III (%)	99%	90%	Not tested	(80-120)
Anticardiolipin IgG\IgM (U/DL)	2 IgG / 3 IgM	5 IgG / 4 IgM	Not tested	< 10
LAC	Absent	Absent	Not tested	absent

Legend to table 1. LAC : lupus anticoagulant; N.V. normal values

Case 3

A 67-year old smoking woman with chronic lung disease was referred to emergency room for increasing of dyspnea with bad clinical pharmacological response to classic medication and because these symptoms were associated with paresthesia localized to left side. Blood pressure was 90\50 mmHg, ECG revealed an atrial fibrillation at 146 bpm, breath rate 22 per minute and pulse-oxymetry was 88% AA, fever was absent; chest X-ray examination did not reveal signs of pneumonia and\or pleural effusion. Blood tests found increased levels of d-dimer and troponin, and normal white blood cells count. A ventilation\perfusion lung scan revealed signs of pulmonary embolism and cerebral CT scan did not reveal cerebral ischaemia. She started antithrombotic treatment with i.v. amiodarone (200 mg three times daily) and unfractionated heparin30000 U daily with a PTT monitoring every 6 hours.

12 hours after she felt a light improvement in breathing but nor for heart rhythm. 18 hours later she felt aphasia and full hemiparesis of the same side where previously she felt, paresthesia as clinical signs of acardioembolic stroke. A new cerebral CT scan was planned after 4 hours and revealed radiological ischaemic signs; an echocardiography was performed and showed global enlargement of both atrial areas with spontaneous echo contrast in left atrial camera so confirming the cardioembolicorigin of ischaemic stroke; pulmonary pressure was determined and raised in 90 mmHg, confirming the pulmonary hypertension due to the recent pulmonary embolism.

Further laboratory tests revealed clinically overt hyperthyroidism as likely cause of arrhythmia and PE with TSH levels < 0.005 U\L; ultrasound scan of thyroid revealed a single adenoma, mimicking Plummer's adenoma but thyroideal scintigraphy was not performed because of the recent double embolism with haemodynamic involvement. Tapazole was added to antithrombotic and antiarrhythmic therapy, but three days later the patient felt an irreversible cardiogenic shock and died. Thrombophilic screening was not performed due sudden death of the patient.

Discussion

When the common risk factors for VTE are not found in a patient with VTE, and if thrombophilia is not found after the right time of observation, we may define it as an unprovoked VTE. According to this definition several studies record a nearly 40-50% of unprovoked VTE in real life [5] and according to common thrombotic risk factors suggested by guidelines 2014; yet other clinical conditions are well known as conditions that may predispose for VTE as inflammatory bowel disease, immunopathological disease and/or connectivitis, nephritic syndrome and others [10-12].

Is it useful a registry on venous thromboembolism? Previous articles of the RIETE registry underlined as nearly

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40-50% of patients with VTE show unprovoked VTE and as for as in nearly 25% of cases there are not available guidelines to suggest the better clinical approach! [5,15]. RIETE is an ongoing independent international registry on VTE gathering data about epidemiology, risk factors, diagnosis, treatment and outcome of patients with documented VTE in the real life. Patients with VTE already enrolled in randomized clinical trials are not enrolled in the registry while all other type of patients with VTE are present recruited. The risk factors considered in the database are not only the commonly known risk factors suggested by the guidelines. Padua score is a score suggested by the guidelines [13] that underlines clinical conditions at risk for VTE that may benefit of pharmacological thromboprophylaxis: other clinical conditions at risk for VTE are included in the registry in a special section. This section is dedicated to thrombophilia or other medical diseases as inflammatory bowel diseases, immunological diseases, hormonal diseases and others.

The percentage of40-50% of unprovoked VTE in the registry is similar to that reported in other studies [16]. However, the literature does not offer the chance to understand the percentage of other medical condition associated to VTE as minor thrombotic risk factor such as inflammatory bowel diseases [10], immunopathological disease/connectivitis [11], hormonal disease including hyperthyroidism [17] and so on.

Yet, less frequent conditions associated to VTE are recorded in the RIETE registry and here we reported 3 cases of VTE associated to hyperthyroidism and without presence of the common thrombotic risk factors. Hyperthyroidism, in fact, has been already associated to several abnormalities of coagulation and fibrinolysis [18-21] with a trend to hypercoagulation thus suggesting a potential role in pathophysiology of VTE.

Furthermore, several cases are present in the literature that confirm the association between hyperthyroidism and VTE, so suggesting not only the increased thrombotic risk demonstrated on pathophysiological evidences but also a clinical evidence of thrombotic complications [17,22].

Cases we reported underlined the clinical association of overt hyperthyroidism and severe PE in all described patients in absence of further thrombotic risk factor. Also in other case reports of VTE described in the literature, there was not an association with other thrombotic risk factors other than hyperthyroidism.

For this reason the main issue that we may suggest before defining an unprovoked VTE, is to check also hormonal abnormalities, such as hyperthyroidism, particularly if the patient is haemodynamically unstable; VTE, in fact, may appear suddenly in the absence of other medical conditions that predispose to VTE; on the other hand this association should be better screened in all registries for VTE and in future clinical trials.

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