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Massive Pulmonary Embolism as the Initial Presentation of Acromegaly: Is Acromegaly a Hypercoagulable Condition?

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Conflict of interest: None declared

Patient: Male, 21
Final Diagnosis: Massive pulmonary embolism and acromegaly
Symptoms: Chest pain and syncope
Medication: Thrombolysis and Anticoagulation
Clinical Procedure: Computerized tomography pulmonary angiogram and magnetic resonance imaging of pituitary
Specialty: Endocrinology and Pulmonology

Objective: Unusual clinical course

Background: The clinical presentation in acromegaly is usually insidious, with headaches or visual disturbances being the most common symptoms. Previous studies have shown higher fibrinogen levels, lower protein C and S activity values, and enhanced platelet function in patients with acromegaly compared to a normal population. Nevertheless, the link between hypercoagulability and acromegaly is often overlooked and rarely reported in the literature.

Case Report: We report a case of a young man with a massive pulmonary embolism as the initial presentation of acromegaly. Extensive workup excluded other causes of thrombophilia. Furthermore, the diagnosis of acromegaly was confirmed by the patient's clinical features as well as laboratory and radiological testing. A literature review on the link between hypercoagulability and acromegaly was performed.

Conclusions: This case report shed light on hypercoagulability as an under-recognized serious complication of acromegaly and paves the road for future studies on this topic.

MeSH Keywords: Acromegaly • Embolism and Thrombosis • Pulmonary Embolism • Thrombophilia

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Background

Acromegaly is a rare disease with a prevalence of 2.8 to 13.7 cases per 100 000 populations. It results from excessive growth hormone (GH) secretion. Most patients present late, with a mean delay in diagnosis of 4.5 to 5 years, resulting from the insidious course of the disease [1]. Common clinical manifestations in cases of acromegaly include: acral enlargement (86% of cases), maxillofacial changes (74%), excessive perspiration (48%), arthralgia (46%), and headache (40%). Other manifestations, such as hypogonadal symptoms, fatigue, weight gain, and galactorrhea, can also be seen [2]. A wide range of complications can result from acromegaly including: hypertension, left ventricular hypertrophy, cardiomyopathy, obstructive sleep apnea, insulin resistance, and neoplasia (such as colon cancer) [2]. Manifestations can also be as serious as visual loss and loss of pituitary function related to a direct pressure effect. Venous thromboembolism (VTE) encompasses deep vein thrombosis (DVT) and pulmonary embolism (PE). It is the third most frequent cardiovascular disease with an overall annual incidence of 100 to 200 per 100 000 inhabitants [3–5]. Pulmonary embolism is a major cause of mortality, morbidity, and hospitalization worldwide. In 2004, VTE killed over 317 000 people in 6 European countries with a total population of 454.4 million [4,5]. Pulmonary embolism is classified as “massive” or “high-risk” if it results in hypotension; “sub-massive” or “intermediate-risk” if there is associated right ventricular strain; or “low-risk” if there is no evidence of right ventricular strain or hypotension [5]. Previous studies have shown that patients with acromegaly tend to have higher fibrinogen levels, lower protein C and S activity values, and enhanced platelet function compared to a normal population. In addition, some of these studies correlated high insulin-like growth factor (IGF-1) levels with these hemostatic parameters [6,7]. Nevertheless, the link between acromegaly and hypercoagulability is rarely reported in the literature. Furthermore, acromegaly is seldom mentioned among the risk factors for VTE or thrombophilia. In this paper, we report a case of a young man with a massive pulmonary embolism as the initial presentation of acromegaly. Extensive

workup excluded other causes of thrombophilia. Furthermore, the diagnosis of acromegaly was confirmed by the patient's clinical features as well as laboratory and radiological testing.

Case Report

A 21-year-old male presented to the emergency department with sudden acute chest pain and dizziness that was followed by syncope of 1-hour duration. Upon presentation, he was hypotensive (82/49 mmHg), with tachypnea, tachycardia, and oxygen saturation in the blood on room air (SpO₂) of 90%. Electrocardiography showed incomplete right bundle branch block (RBBB) and ST segment changes (Figure 1). Echocardiography showed right ventricular strain. Immediate blood work showed a troponin T level of 580 ng/L (N ≤10.0 ng/L), a D-dimer of 30 mcg/mL (N ≤0.5 mcg/mL) and a pro-BNP of 2986 pg/mL (N ≤100 pg/mL). An urgent computed tomography pulmonary angiogram revealed bilateral extensive pulmonary embolism (Figure 2). Urgent thrombolysis with alteplase was provided in the intensive care unit (ICU) and consequently, the patient was started on low molecular weight heparin (LMWH). The patient denied any history of recent travel, previous thrombosis, or family history of thrombosis. During the physical examination, he was observed to have clinical features indicative of acromegaly with frontal bossing, coarse facial features, wide nose, large spade-like hands, large feet, deep voice, and prognathism. Perimetry revealed a bitemporal hemianopia. On questioning the patient, he denied having acromegaly or any other endocrine disorders prior to this presentation. Blood level of GH was found to be 28.60 mcg/L (N=0.00–10.00) and IGF-1 was 908.1 mcg/L (N=187.9–400.0). Furthermore, during a growth hormone suppression test (GHST), the patient's GH was non-suppressible with a 75 g oral glucose tolerance test (OGTT). Other pituitary hormone levels were not affected (Table 1). Pituitary magnetic resonance imaging showed a pituitary macro-adenoma with supra-sellar extension, secondary upward displacement of the optic chiasm and splaying of the circle of Willis (Figure 3).

Figure 1. Electrocardiography showing incomplete right bundle branch block (RBBB) and right axis deviation.

Figure 2. Computed tomography pulmonary angiogram showing bilateral extensive pulmonary embolism. Filling defects in right and left main pulmonary arteries (arrows).

Ultrasound of the abdomen and pelvis did not detect any tumor, and his colonoscopy was unremarkable. Thrombophilia workup including peripheral blood flow cytometry for paroxysmal nocturnal hemoglobinuria (PNH), lupus anticoagulant and anti-nuclear antibodies (ANA), anti-thrombin activity, protein C activity, fibrinogen level, prothrombin gene, and factor V Leiden studies were all unremarkable. Protein S activity (extracted after initiation of anticoagulation) was 25.3% (N=60–130).

In the context of his recent pulmonary embolism, and current anticoagulation therapy, we initiated medical management with a plan to undertake trans-sphenoidal surgery after 6 months. The patient was evaluated by the endocrine team and was started on 0.5 mg cabergoline twice weekly, and 50 mcg octreotide subcutaneously 3 times daily for 2 weeks, followed by a monthly maintenance injection. He was then discharged

Figure 3. Pituitary magnetic resonance imaging showing a pituitary macro-adenoma.

in a stable condition on the aforementioned therapy as well as indefinite warfarin therapy.

Discussion

In 1912, Coffey and Cummins were the first to suspect a link between acromegaly and the risk of VTE. Following sudden deterioration and death of their acromegalic patient (who proved to have pulmonary embolism and thrombosis on autopsy),

Table 1. Patient's blood hormone levels.

Test	Patient values	Reference values
FSH	8.46 IU/L	1.00–19.0 IU/L
LH	3.76 IU/L	1.00–9.00 IU/L
Prolactin	175 mIU/L	73–407 mIU/L
TSH	0.8 mIU/L	0.45–4.50 mIU/L
FT4	11.20 pmol/L	9.0–20.0 pmol/L
Ferritin	0.205 nmol/L	0.175–0.700 nmol/L
IGF-1	908.1 mcg/L	187.9–400 mcg/L
Growth Hormone Suppressions Test (GHST)	Baseline: 19.60 mcg/L 60 min: 10.20 mcg/L 120 min: 7.90 mcg/L	– Value falls to 1 mcg/L within 2 hours
Cortisol Stimulation Test (CST)	Baseline 277 nmol/L 30 min: 576 nmol/L 60 min: 623 nmol/L	– Baseline $\times$ >138 nmol/L – 497–552 nmol/L or incremental increase of 193.2 nmol/L over baseline value

they postulated that the increase in serum calcium level in patients with the hypophyseal disease could have increased the risk of thrombosis [8]. Recent studies have revealed many serum coagulation abnormalities in acromegalic patients that can be a potential for hypercoagulable and hypofibrinolytic state and hence augment the risk for thrombosis. In a study of 22 patients with acromegaly and a similar number of controls, Erem et al. found increased serum fibrinogen, tissue plasminogen activator (t-PA) and tissue plasminogen activator inhibitor-1 (PAI-1) levels, and decreased protein S and plasma tissue factor pathway inhibitor (TFPI) levels in acromegalic patients compared to controls [9]. Landin-Wilhelmsen et al. showed that the high fibrinogen levels in acromegalic patients correlated positively with serum IGF-I levels and that these levels decreased significantly following treatment for acromegaly [7]. In a recent study of 39 patients with active acromegaly, Colak et al. found higher fibrinogen levels, lower protein C and S activity values, and enhanced platelet function compared to controls [6]. Since the report of first VTE case in an acromegalic patient by Coffey and Cummins in 1912 [8], there have been only a few reported cases in the literature. In 2015, Al Dahmani et al. reported 3 cases of VTE in patients with uncontrolled acromegaly in the absence of other risk factors for VTE [10]. In an attempt to estimate the risk of complications of acromegaly, Dal et al. examined a cohort of patients with acromegaly from health registries in Denmark and recorded an increased overall risk of VTE in this group of patients [11]. The correlation between serum IGF-1 levels and risk of thrombosis is conflicting and poorly understood. While higher IGF-1 levels have been reported in some studies to be associated with early carotid artery atherosclerosis [12], other studies reported that low circulating IGF-1 levels were associated with increased carotid intima-media thickness and atrial fibrillation [13,14]. The presence of low protein C and protein S activities and enhanced platelet function in patients with acromegaly have been found in other studies to correlate with the high IGF-1 levels, and the tendency toward hypercoagulability has been attributed to these effects [6]. All VTE incidents in patients with acromegaly have been reported in patients with the uncontrolled disease. While a significant decrease in hyperfibrinogenemia has been found following medical and surgical treatment of acromegaly and achievement of biochemical remission, the effect of such treatment on the risk of thrombosis remains unknown [7,10,15,16]. Besides the serum coagulation abnormalities, 2 more important conditions that

can contribute to hypercoagulability risk in acromegaly are the associated risk of malignancy and obstructive sleep apnea. Studies have shown that patients with acromegaly are at increased risk of developing certain types of malignancies such as colon, thyroid, and renal malignancies [17–19]. Cancer is one of the best-established risk factors for VTE and accounts for about 20% of all first VTE events. It induces a systemic hypercoagulable state that elevates the baseline thrombotic risk of affected patients [20]. Sleep apnea is a common cause of snoring and daytime sleepiness in acromegaly. It may affect as many as 60% of unselected acromegalic patients and 93% of acromegalic patients referred for suspicion of sleep apnea. The vast majority of cases are due to anatomical narrowing of the upper respiratory airways seen in acromegaly [21]. Multiple studies have proven that sleep apnea as an independent risk factor for VTE and patients with this disease exhibit a higher risk of subsequent DVT and pulmonary embolism [22,23]. To the best of our knowledge, our case report is the first report of a massive pulmonary embolism as the initial presentation of acromegaly. Other causes of inherited thrombophilia in this patient were excluded by detailed history and extensive laboratory workup. Our case report augments the previous hypothesis that acromegaly carries a risk of VTE and should help increase awareness among physicians of this serious condition in this group of patients. Nevertheless, an important limitation of this case report was that protein S activity was measured following the initiation of warfarin therapy and thus we were not sure if this low level was the effect of anticoagulation or it was part of abnormal coagulability states encountered in acromegaly. Furthermore, we did not perform a sleep study to confirm or exclude sleep apnea as a risk factor for thrombosis in this patient.

Conclusions

Hypercoagulability is an important and under-recognized complication of acromegaly and can result in serious consequences. Future research on acromegaly should consider this complication, identify its magnitude, and exact pathophysiologic mechanisms and preventive measures.

Conflict of interest

None.

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