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CASE REPORT

Is Clomiphene the Culprit?

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Pulmonary embolism is a well known culprit in the medical world with a mortality as high as 30% for untreated population [1]. Multiple risk factors have been described including, but not limited to immobility, trauma, oral contraceptive use, drugs, and malignancy. One of the most common risk factors widely recognized is oral contraceptive use in females. However, there are only limited case reports of pulmonary embolism associated with hormone use therapy in males [2-4]. Here, we describe a case of a middle aged male with hypogonadism treated with clomiphene that developed pulmonary embolism. After recognizing Clomiphene as a plausible cause, the drug was discontinued, and the patient was treated with intravenous heparin while in the hospital and subsequently discharged on a direct oral anticoagulant. His workup was negative for malignancy, thrombophilia, and infection. He did not have other known risk factors for pulmonary embolism including trauma, recent surgery, or immobilization. Pulmonary embolism (PE) is a common occurrence resulting in significant morbidity and mortality. Clinical pictures of pulmonary embolism can vary ranging from asymptomatic incidental findings to sudden cardiac death [5].

Pulmonary embolism can be categorized as provoked or unprovoked. Common causes of provoked pulmonary embolism are recent trauma, surgery, immobilization, longair travel, autoimmune disease, and inherited thrombophilia [6]. Medications such as hormonal contraceptives, other hormonal therapy, and glucocorticoids can increase the risk for pulmonary embolism. While less common, there are a few cases reported for Clomiphene citrate associated with pulmonary embolism. Clomiphene citrate has also been associated with other thromboembolic complications like central retinal vein occlusion and intracranial venous thrombosis [7,8].

A 44 year male with a past medical history of obstructive sleep apnea on continuous positive airway pressure and hypogonadism presented with a complaint of exertional dyspnea for 2 days, which was associated with fatigue, non productive cough, and weakness. He denied fever, chest pain, and palpitations. Family history was absent of coagulopathies and cancer. He reported no tobacco or other recreational drug use. He drinks alcohol occasionally. On examination, his vital signs were stable and the physical exam was normal. Lab studies were negative for leukocytosis and anemia. Chest X-ray was unremarkable with no evidence of pneumonia. PCR for Coronavirus-19 and Influenza tests were negative. As his D-dimer was elevated (> 1050 ng/mL), a chest computed tomography angiogram (CTA) was performed which revealed pulmonary embolism involving the second and third-order branches bilaterally, infiltrate in the right lower lobe posterior segment, extensive mediastinal and hilar adenopathy with the largest nodes measuring up to 3.5 centimeters. While looking for the etiology we performed CT scan of the abdomen and pelvis which revealed portocaval lymph nodes measuring up to 1.8 cm and porta hepatis lymph nodes measuring up to 1.0 cm with hepatic steatosis, no inguinal lymphadenopathy was noted.

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Pulmonology consultation was requested, and the patient underwent endobronchial ultrasound (EBUS) with biopsy which was negative for malignant cells, lymphoma and sarcoidosis.

Autoimmune work up performed and was unremarkable. The patient was started on Heparin while in the hospital and was discharged on Xarel to 15 mg BID for a total of 21 days, and then 20 mg daily thereafter to continue for 3 months. Clomiphene citrate was discontinued. He followed up regularly with a pulmonologist and hematologist. No other obvious reason for his pulmonary embolism emerged over time, and on reviewing his medication list it was presumed that that clomiphene was likely the plausible cause. As per the Naranjo algorithm, the event scored 5 which implies that Clomiphene citrate was the probable cause for hypercoagulable state. The patient had follow up visits in the pulmonary and hematology clinic where the repeat chest CT scan showed stable mediastinal and hilar lymphadenopathy.

Clomiphene citrate is a selective estrogen receptor modulator (SERM) that acts at the level of the hypothalamus, occupying cell surface and intracellular estrogen receptors (ERs) for durations longer than that of estrogen [9]. This activity interferes with receptor recycling, effectively depleting hypothalamic estrogen receptors and inhibiting normal estrogenic negative feedback. Impairment of the feedback signal results in increased pulsatile gonadotropin-releasing hormone (GnRH) secretion from the hypothalamus and subsequent pituitary gonadotropin (Follicle-stimulating hormone and luteinizing hormone) release, causing the growth of the ovarian follicle, followed by follicular rupture. It is sometimes used off-label in males for male infertility, erectile dysfunction, and hypogonadal symptoms [10]. Its side effects are not well studied. There are reported cases of venous thromboembolism with the use of Clomiphene [11]. In this particular case, clomiphene had been prescribed to the patient for about 10 years, with an increase in dose 2 years ago to 100 mg daily to treat hypogonadism, which may have increased his risk for a thromboembolic event. No other identifiable risk factors were noted in our patients for pulmonary embolism and hypercoagulable workup was negative. Hypercoagulable workup is particularly necessary to determine the duration of therapy with anticoagulants. Our patient was treated with Xarel to for 3 months and clomiphene was discontinued. This case highlights the importance of awareness of rare risk factors and being mindful of the possibility of venous thromboembolism with clomiphene use.

Clomiphene is used in both women and men for different conditions. It can cause venous thromboembolism in different organs of the body including pulmonary embolism. Pulmonary embolism is a common clinical disease with variable clinical presentation. The author wants to highlight the importance of early recognition of this adverse effect of clomiphene and discontinuing it sooner than later along with early initiation of anti-coagulants.

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