

## A Case of Acute Pulmonary Thromboembolism after Taking Tadalafil

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Tadalafil is a phosphodiesterase-5 inhibitor (PDE5I), which is widely used to treat erectile dysfunction. Although PDE5Is have excellent safety profiles, and most of the side effects are mild, rare serious adverse events have been reported in association with PDE5Is. Thrombosis is one of those events, and a few previous reports have suggested the association of PDE5Is with thrombosis. We report the case of a 61-year-old male who developed pulmonary embolism combined with pulmonary infarction directly after taking tadalafil. Both the patient and the physician suspected tadalafil as the culprit drug, as the patient was in an otherwise healthy condition. However, after extensive evaluation, we noticed that factor VIII levels were elevated. Prior reports suggesting the association between thrombosis and PDEIs either lack complete information on coagulation factors, or show inconsistencies in their results. Physicians should operate caution prior to accepting the diagnosis of adverse drug reaction.

**Key Words:** Pulmonary Embolism; Pulmonary Infarction; Tadalafil; Phosphodiesterase 5 Inhibitors; Factor VIII

### Introduction

Phosphodiesterase-5 inhibitors (PDE5Is)-sildenafil and tadalafil-have been prescribed worldwide to treat male erectile dysfunction<sup>1,2</sup>. They are in fact among the 75 most popular prescription drugs dispensed in the United States<sup>3</sup>. Based on postmarketing data, PDE5I generally have excellent safety profile and most of the commonly reported side effects are mild such as headache, flushing and dyspepsia<sup>4</sup>. Nevertheless, PDE5I use has been reported in association with rare but serious adverse events such as thromboembolism<sup>5-7</sup>. We report a case of a 61-year-old male who developed pulmonary throm-

boembolism combined with pulmonary infarction shortly after taking tadalafil.

### Case Report

A 61-year-old man experienced sudden onset of right lower chest pain before visiting the emergency room. The chest pain began 2 days ago and was aggravated the next day, followed by blood tinged sputum. He smoked 1 pack of cigarette every day for 13 years and had no other identified cardiovascular risk factor. He was diagnosed with chronic hepatitis B virus infection 30 years ago. He had been taking tadalafil for 2 years, usually once a week for erectile dysfunction. He denied taking any other medications.

Approximately 15 hours before developing chest pain, he took one dose of tadalafil before attempt of sexual contact. Afterwards he had sexual intercourse with two different women with time interval of about 8 hours. Few hours after the second sexual intercourse he experienced sudden onset of right lower chest pain. The pain aggravated the next day and hemoptysis occurred the day afterwards which led him to visit the

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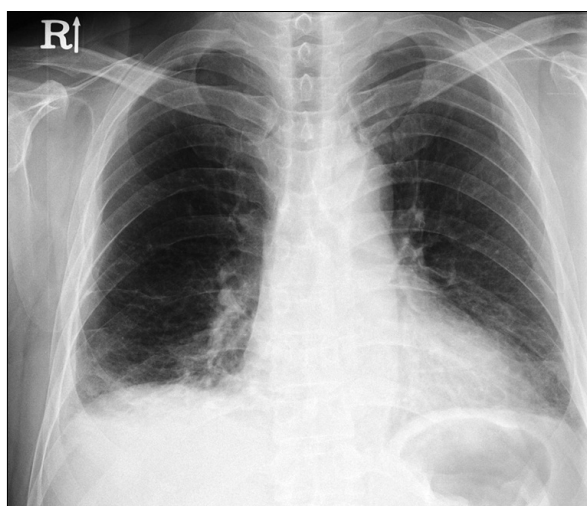
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emergency room.

His initial blood pressure was 123/99 mm Hg, heart rate 69 beats/min, respiration rate 20 frequencies/min, body temperature 36,8°C, oxygen saturation 96%. The mental status was oriented. Auscultation revealed no heart murmur but breathing sound was decreased on his right lower lung field. There was no pitting edema or clubbing seen in the four limbs. The chest X-ray showed ill-defined density in the right lower lung zone with blunted costophrenic angle (Figure 1). Electrocardiography revealed Q wave in lead III and aVF and poor R progression. D-dimer was increased to 0,6  $\mu$ g/mL (normal, less than 0,4) and chest computed tomography was performed with suspicion of acute pulmo-

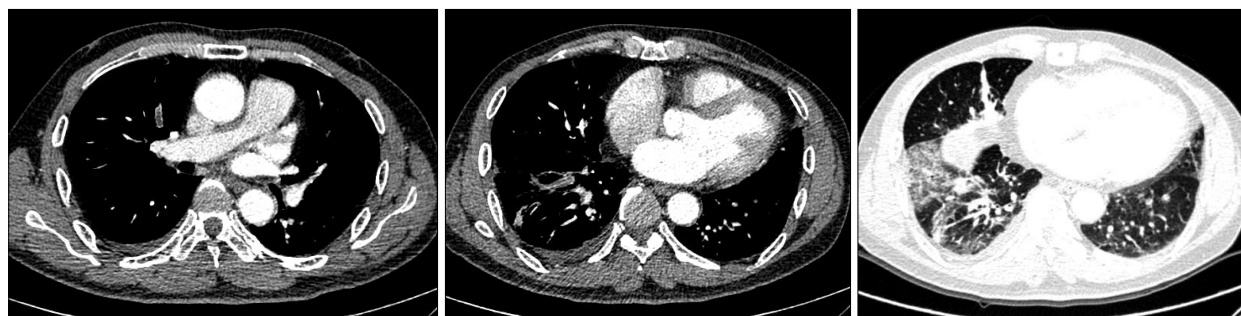


**Figure 1.** Chest x-ray shows ill-defined density in the right lower lung with blunted costophrenic angle.

nary thromboembolism. Thrombus was seen at right ascending and descending subsegmental pulmonary arteries along with wedge-shaped lesion in right lower lobe. Small amount of right pleural effusion was also noted (Figure 2). Blood analysis showed normal concentrations of protein C (98%), protein S (83%), antithrombin III (97%), factor XI (124%) and elevated concentrations of factor VIII (222%). Tests for lupus anticoagulants, factor V Leiden mutation and anticardiolipin antibodies were also negative. The patient was treated with anticoagulation therapy of 80 mg of enoxaparin (1 mg/kg) subcutaneous injection every 12 hours and oral warfarin. When the warfarin dosage was adjusted to keep prothrombin international normalized ratio between 2 and 3, enoxaparin was no longer used. Oral anticoagulation was maintained for 6 months and the patient made full recovery confirmed by chest computed tomography.

## Discussion

Tadalafil is a selective, reversible oral PDE5I commonly used to treat male erectile dysfunction in a diverse population of patients. It has a long half-life of 17.5 hours and is effective for treating erectile dysfunction for up to 36 hours after dosing<sup>8</sup>. Tadalafil has a satisfactory long-term safety profile and is known to be well tolerated: most common side effects are headache, flushing, dyspepsia, myalgia; they are generally mild and reversible<sup>2</sup>. Although sildenafil and tadalafil are



**Figure 2.** Chest computed tomography demonstrates filling defect at right ascending and descending subsegmental pulmonary arteries, along with a wedge-shaped lesion in the right lower lobe.

both approved by the Food and Drug Administration for pulmonary arterial hypertension treatment, there are several alarming reports that suggest PDE5Is may rarely cause thromboembolism. There were reports of acute myocardial infarction, transient ischemic attack and stroke, branch retinal artery occlusion and recurrent venous thrombosis after taking sildenafil. Recently, a report of pulmonary embolism after tadalafil use arose some concern<sup>7</sup>.

The presented case also shows acute pulmonary thromboembolism shortly after tadalafil ingestion, which made both the patient and the attending physician suspect tadalafil as the culprit at initial assessment. However, the full study on coagulation factors showed elevated factor VIII levels. Factor VIII is a non-enzymatic plasma protein and is an essential factor for normal blood coagulation. Deficiency of factor VIII activity results in hemophilia A and increased levels is a well-recognized risk factor for thrombosis<sup>9</sup>. Therefore, it is reasonable to assess elevated factor VIII levels as the most likely cause of acute pulmonary thromboembolism in this patient.

Giving a second look at prior case reports, the evaluation of possible congenital or acquired thrombotic risk factors were mostly not complete and reports with data for extensive evaluation showed abnormal results. Rufa et al.<sup>5</sup> reported a case of a subject with recurrent venous thrombosis over a 12-month period of sildenafil use but the patient had reduced plasma levels of antithrombin III and protein S. Chen et al.<sup>7</sup> suggested tadalafil as a probable risk factor for acute pulmonary embolism in a previously healthy 54-year-old man but he also had low level of protein C. This puts into question the causal relationship between sildenafil/tadalafil and adverse thromboembolic events.

The estimation of the probability that a certain drug

caused an adverse side effect is usually based on clinical judgment. Physicians should be careful before accepting the diagnosis of adverse drug reactions, and should do his or her best to find other relevant causes. Large-scale studies are needed to prove the relationship between drug intake and its possible side effect.

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