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A Case Report of Pulmonary Vascular Dilation and Multilevel Bronchial Mucosal Bleeding Contributed to Long-term Administration of Sildenafil

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Abstract: Although sildenafil is approved for erectile dysfunction (ED) and pulmonary arterial hypertension (PAH), its association with pulmonary side effect has not been previously reported. This case underscores the potential risk of pulmonary vascular dilation, tortuosity, and airway mucosal bleeding associated with chronic sildenafil administration. This case report describes a 44-year-old male presenting with a 1-year history of cough and productive sputum, which worsened over the past 3 days. The patient reported no smoking history but had been using sildenafil for 7 years to manage ED. Electronic bronchoscopy identified diffuse punctate hemorrhagic spots in the multilevel-bronchial mucosa. Three-dimensional contrast-enhanced CT angiography of the thoracic aorta revealed dilated and tortuous pulmonary bronchial arteries, along with focal dilation of the pulmonary arterioles and venules. After ruling out alternative diagnoses, chronic sildenafil administration was identified as the culprit cause of pulmonary vascular dilation and mucosal bleeding in this patient. At the 6-month follow-up after sildenafil discontinuation, the patient reported complete resolution of cough. Repeat bronchoscopy: No residual hemorrhagic spots in the tracheobronchial mucosa. Clinicians should maintain heightened vigilance for pulmonary vascular dilation and subsequent hemorrhage risk associated with chronic sildenafil use. The diagnosis of pulmonary vascular abnormalities and airway bleeding necessitates explicit consideration of sildenafil exposure in the differential diagnosis.

1. Introduction

Pulmonary vascular dilation constitutes a clinically significant finding that warrants meticulous clinical evaluation. The lungs' extensive vascular network, combined with attenuated vessel walls in dilated states, predisposes to catastrophic hemorrhagic complications with life-threatening potential. Etiologies of pulmonary vascular dilation include: Congenital vascular malformations (e.g., pulmonary arteriovenous fistula[1]); Compensatory dilation in chronic hypoxic states (e.g., chronic pulmonary embolism[2]); Pro-inflammatory cytokines inducing vascular smooth muscle relaxation, predominantly affecting the capillary (e.g., pulmonary inflammation); Autoimmune-mediated vasculopathies (e.g., Interstitial pneumonia[3]). Sildenafil, one of the approved phosphodiesterase-5 (PDE5) inhibitors, has been widely used to treat patients with erectile dysfunction (ED) or pulmonary arterial hypertension (PAH).[4] Importantly, this case first presents pulmonary vascular dilation and multilevel bronchial mucosal bleeding in a 44-year-old male following long-term oral sildenafil administration.

2. Case description

2.1 Patient history

A 44-year-old male presented with a 1-year history of chronic cough and productive sputum, which had worsened progressively over the preceding 3 days. He denied fever, chest pain, hemoptysis, or dyspnea. Notably, the patient reported no prior medical interventions and had no smoking history. Medication history revealed long-term sildenafil administration (25-50 mg orally 2-3 times weekly) for ED management over 7 years. Physical examination revealed no remarkable findings.

2.2 Laboratory tests

Routine blood test: White blood cell count 5.35 * 10^9/L (reference range: 3.5-9.5 * 10^9/L), neutrophil count 3.62 * 10^9/L (reference range: 1.8-6.3 * 10^9/L), platelet count 149 * 10^9/L (reference range: 125-350 * 10^9/L), hemoglobin 145 g/L (reference range: 130-175 g/L). Coagulation profile: Prothrombin time (PT) 11 seconds (reference range: 9.8-12.1 seconds), activated partial thromboplastin time (APTT) 27.7 seconds (reference range: 23.9-31.9 seconds), fibrinogen (Fbg) 2.85 g/L (reference range: 1.8-3.5 g/L), D-dimer 0.06 μg/mL (reference range: 0-0.55 μg/mL). Allergen testing: Aspergillus fumigatus (m3) specific IgE 0.03 kUA/L (reference range: <0.35 kUA/L), Alternaria alternata (m6) specific IgE 0.01 kUA/L (reference range: <0.35 kUA/L), total IgE 125 kUA/L (reference range: <60 kUA/L). Tumor markers: Neuron-specific enolase (NSE) 11.04 ng/mL (reference range: 0-16.30 ng/mL), carcinoembryonic antigen (CEA) 2.96 μg/L (reference range: 0-5 μg/L), squamous cell carcinoma antigen (SCC) 1.90 ng/mL (reference range: 0-2.5 ng/mL). Autoimmune serology: p-ANCA (-), c-ANCA (-), anti-dsDNA (-), anti-Sm (-), antinuclear antibody (ANA) (-), anti-SSB (-), anti-Scl-70 (-), anti-SSA (-), anti-Ro52 (-). Humoral immunity: Complement C3 0.98 g/L (reference range: 0.7-1.4 g/L), C4 0.21 g/L (reference range: 0.1-0.4 g/L). Bronchoalveolar lavage fluid: Cultures revealed normal flora with no fungal growth; acid-fast bacilli stain negative; Mycobacterium tuberculosis complex DNA not detected.

2.3 Imaging examination

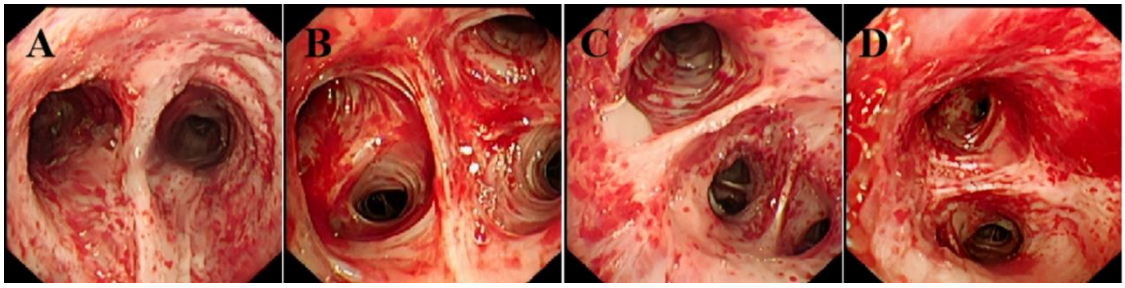

Figure 1. Electronic bronchoscopy revealed extensive mucosal hemorrhagic spots in the bilateral multilevel bronchi. (A) Carinal. (B) Right superior lobar bronchus. (C) Right middle lobar bronchus. (D) Left superior lobar bronchus.

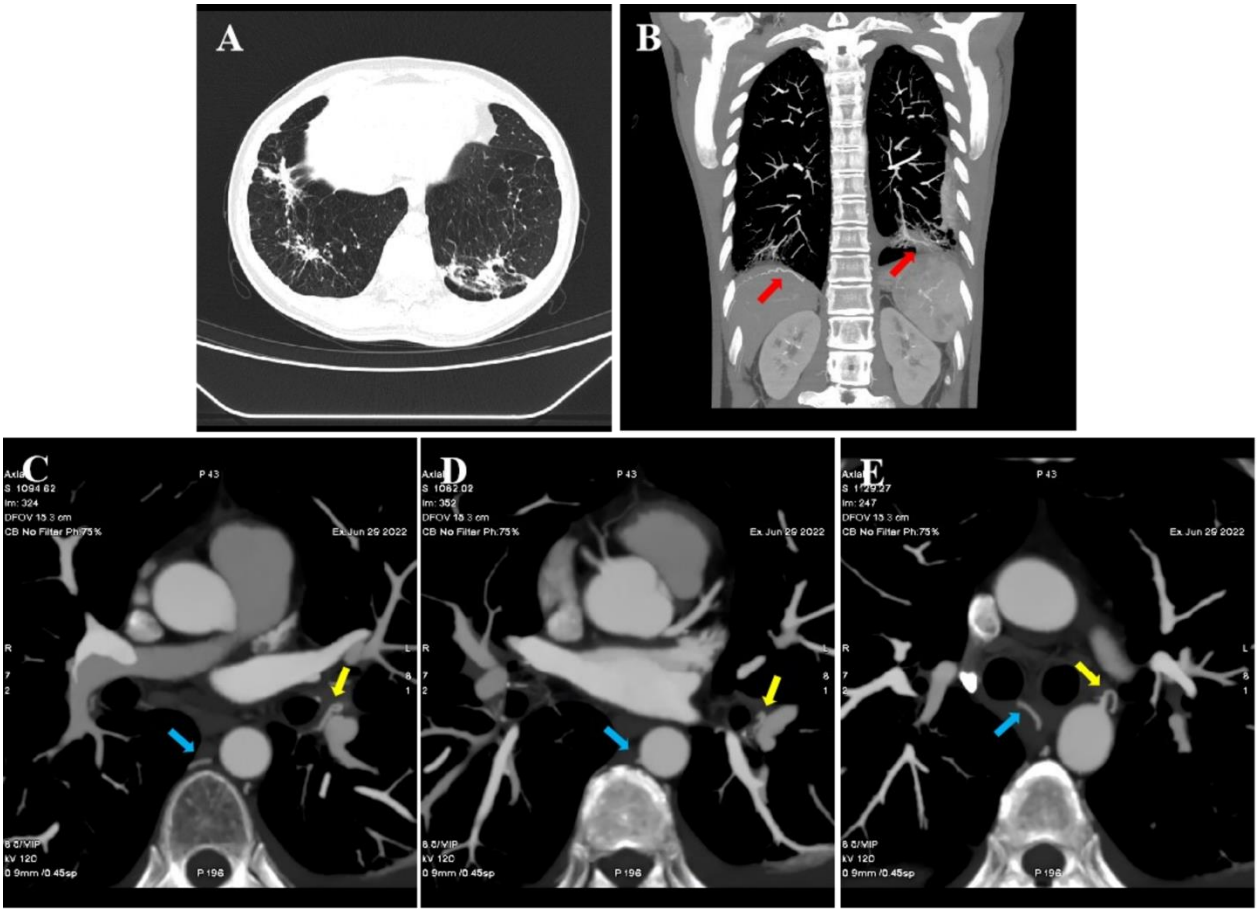

Figure 2. CT: Dilated and tortuous bilateral bronchial arteries. (A) Non-contrast chest CT revealed multiple areas of increased attenuation opacities in the bilateral lower lobes. (B) CT angiography: Dilation of pulmonary arteries and veins within the left lower lobe lesion. Tortuous dilation of the inferior phrenic artery (red arrow). (C-E) CT angiography: Dilated and tortuous bilateral bronchial arteries: Right bronchial artery (blue arrow); Left bronchial artery (yellow arrow).

Electronic bronchoscopy revealed extensive mucosal bleeding spots in the bilateral multilevel bronchi, with smooth mucosal surfaces and patent lumina. Minimal thin secretions were observed without evidence of neoplastic lesions (Fig. 1A-D). Non-contrast chest CT demonstrated multiple small nodular, patchy, and linear opacities with ill-defined borders in the bilateral lower lobes, accompanied by areas of consolidation and mild tractional dilation of bronchial walls, suggestive of infectious/inflammatory etiology (Fig. 2A). Three-dimensional thoracic aortic CTA identified (Fig. 2B-E): Pulmonary vasculature: Dilation of pulmonary arteries and veins within the left lower lobe lesions, and dilation of the inferior phrenic artery (Fig. 2B). Right bronchial artery: Originating from the right lateral wall of the descending aorta at the T6 vertebral level (diameter: 2.3 mm), coursing tortuously superiorly before descending toward the right pulmonary hilum. Left bronchial artery: Arising from the anterior wall of the descending aorta at the T5 vertebral level (diameter: 1.3 mm), extending to the left pulmonary hilum and surrounding the left lower lobar bronchus, with focal luminal dilation measuring 2.3 mm in diameter near the bronchial bifurcation (Fig. 2C-E). Transthoracic echocardiography revealed no structural or functional abnormalities.

2.4 Management and Follow-up

Given the absence of evidence for vascular malformations, infection, thromboembolic disease, or autoimmune disorders, chronic sildenafil administration was identified as the probable etiology underlying pulmonary vascular dilation and multilevel bronchial mucosal bleeding. The patient was advised to discontinue sildenafil and underwent close clinical surveillance.

At the 6-month follow-up, repeat bronchoscopy demonstrated complete resolution of previously revealed: Diffuse hemorrhagic spots, with residual findings limited to chronic bronchitis (Fig. 3A-D). CT revealed: Resolution of bilateral scattered ground-glass opacities. Stable chronic inflammatory changes in the left upper lobe anterior segment and bilateral lower lobes, consistent with prior imaging (Fig. 3E); Retracted vessels (Fig. 3F&G).

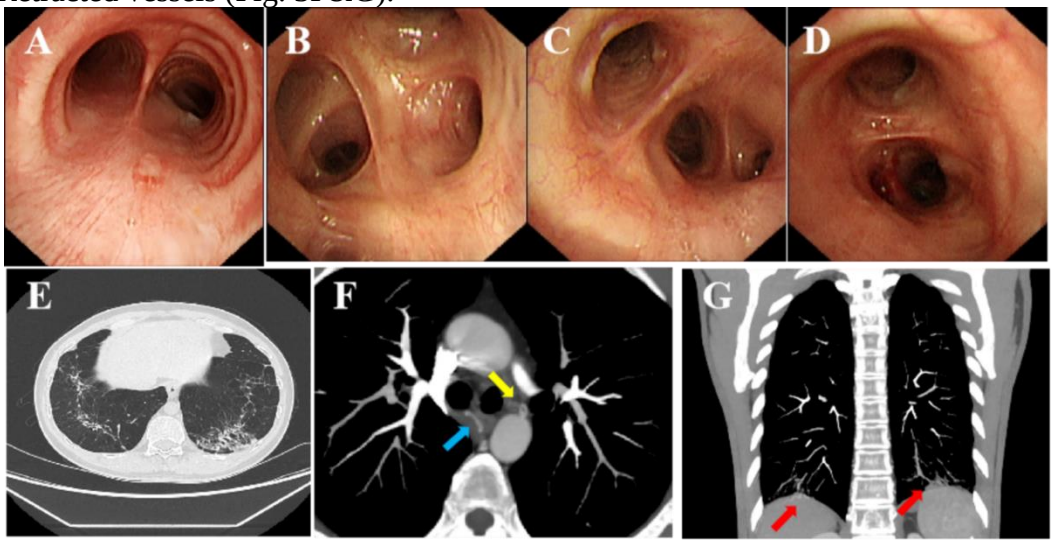

Figure 3. Bronchoscopy imaging of (A) the Carinal, (B) right superior lobar bronchus, (C) right middle lobar bronchus and (D) left superior lobar bronchus. (E) Non-contrast chest CT. Contrast-enhanced chest CT: Retracted left (yellow arrow) and right (blue arrow) bronchial artery (F), as well as pulmonary arteries and veins within the left lower lobe lesions and inferior phrenic artery (G).

3. Discussion

Sildenafil is a PDE5 inhibitor approved by the FDA for the treatment of ED and PAH.[4,5] As a highly selective PDE5 inhibitor, sildenafil targets PDE5—an enzyme abundantly expressed in the corpus cavernosum of the penis and pulmonary vascular endothelium, but minimally in other tissues (including platelets, vascular and visceral smooth muscle, and skeletal muscle).[6] By selectively inhibiting PDE5, sildenafil enhances the nitric oxide (NO)-cGMP pathway, increasing cGMP levels and leading to smooth muscle relaxation and vascular dilation.

For ED, the dosage may be titrated upward to a maximum of 100 mg. The most commonly reported adverse reactions in patients taking sildenafil include headache, flushing, dyspepsia, nasal congestion, back pain, myalgia, nausea, dizziness, and rash.[4] Sildenafil has also been associated with color vision changes, altered light perception, and blurred vision.[7] Currently, routine monitoring is generally not considered necessary for sildenafil use. However, patients may be advised to monitor blood pressure and heart rate after initiating sildenafil therapy, following dose escalation, or when concomitant CYP3A4 inhibitors are introduced.[4]

Several types of bleeding events have been reported in association with sildenafil, including bloody cough[8], epistaxis[9], hemoptysis[10], ocular haemorrhage[11], rectal bleeding[12], variceal bleeding[13], arterial dissection[14,15], intracranial haemorrhage[16,17], and postoperative bleeding[18]. The age distribution of affected patients shows no distinct pattern, with reported cases ranging from infants[18] to elderly individuals over 70 years old[19]. Some studies suggest that concurrent use of CYP3A4 inhibitors (e.g., nifedipine for hypertension) may elevate sildenafil concentrations by impairing its metabolism, thereby increasing the likelihood of bleeding events. Research[20] has also explored the hypothesis that prolonged sildenafil use may progressively compromise vascular elasticity, potentially contributing to aneurysm expansion. Notably, while two patients[11,21] experienced bleeding shortly after their first sildenafil dose, most reported cases involved repeated or long-term administration of the drug, highlighting potential risks associated with chronic therapy.

Normal bronchial arteries are small, measuring less than 2 mm in diameter at their origin and less than 0.5 mm distally as they enter bronchopulmonary segments.[1] Pathologically dilated bronchial arteries exceed 2 mm in diameter and typically exhibit tortuous mediastinal courses. On multidetector CT (MDCT) or MR imaging, these appear as nodular or linear enhancing structures. Due to their winding paths, they are best visualized using multiplanar or three-dimensional volume-rendered imaging. Pulmonary vascular dilation has diverse etiologies. In congenital thoracic anomalies (e.g., interrupted proximal pulmonary arteries), systemic hypoxia, pulmonary infarction, or inflammatory lung diseases, bronchial artery dilation may enhance oxygenated blood supply to ischemic lung tissue.[2] In pulmonary infections, inflammatory mediators promote capillary dilation. Additionally, idiopathic pulmonary vascular changes must be differentiated from interstitial pneumonia.[3] Drug-induced pulmonary vascular dilation is a diagnosis of exclusion, lacking specific symptoms, signs, or laboratory findings. The most critical evidence is a documented history of drug use.

Although sildenafil is used to treat PAH, no cases of sildenafil-related pathological pulmonary vascular dilation or tracheal mucosal bleeding have been reported. In this case, the patient's bronchial artery and localized pulmonary arteriovenous dilation are hypothesized to result from sildenafil's selective action. Dilated vessels exhibit thinned walls and increased fragility, predisposing them to rupture and hemorrhage. On CT imaging, high-density shadows were observed near the dilated pulmonary vessels. Bronchoscopy revealed extensive mucosal bleeding points in the tracheobronchial

tree, interpreted as evidence of vascular rupture. These findings resolved upon patient recovery, supporting our conclusion.

4. Conclusion

Pulmonary vascular dilation directly leads to wall thinning, which predisposes to capillary rupture and life-threatening hemoptysis under conditions of severe coughing or inflammation. This case underscores two critical clinical implications: Vasodilator pharmacotherapy (e.g., sildenafil) must be included in the differential diagnosis of pulmonary vascular dilation to prevent diagnostic oversight. Clinicians should exercise caution in prescribing long-term sildenafil therapy. Patients on chronic regimens require vigilant monitoring for pulmonary manifestations, with contrast-enhanced chest CT and electronic bronchoscopy employed as necessary to assess vascular integrity.

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Written informed consent was obtained for publication of the patient's data and images in this case report.

Author contributions

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Statement

The manuscript has been read and approved by all the authors. The authors have no conflicts of interest to disclose.

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