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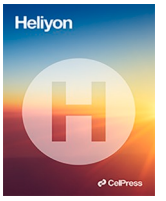

Acute exacerbation of postoperative idiopathic pulmonary fibrosis in a patient with lung cancer caused by invasive mechanical ventilation: A case report

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ABSTRACT

Study design and objection: Idiopathic pulmonary fibrosis (IPF) is a progressive chronic disease characterized by damage to alveolar epithelial cells and abnormal deposition of the extracellular matrix. Although the disease course for most patients with IPF is progressive, in some cases the disease may appear as an acute exacerbation. Mechanical ventilation life support plays an important role in the treatment of patients with IPF but is associated with an increased risk of acute exacerbation of IPF (AE-IPF). Treatment is controversial and is not supported by sufficient clinical evidence. AE-IPF after lung cancer surgery is extremely rare, and the etiology and mechanism remain unclear, and its clinical manifestations are very similar to acute pulmonary edema and are easily misdiagnosed.

Summaryof background data: We describe a 66-year-old male patient with IPF complicated with lung cancer who underwent thoracoscopic resection of the right upper lobe of the lung. Seventy-two hours after surgery, chest computed tomography indicated that AE-IPF in the mechanically ventilated lung was significantly greater than that in the operated lung. The patient's own lung was used as a control and proved that mechanical ventilation can lead to AE-IPF.

Results and conclusions: By highlighting the clinical characteristics of patients with acute exacerbation of idiopathic pulmonary fibrosis, this article will enhance the vigilance of clinicians on AE-IPF caused by mechanical ventilation. Importantly, preoperative nintedanib therapy should be applied in advance to prevent AE-IPF on in patients with mild IPF. Precise pulmonary protective ventilation strategies need to be formulated for patients with IPF to reduce mortality.

1. Introduction

Idiopathic pulmonary fibrosis (IPF) is a chronic progressive interstitial lung disease with an unclear etiology. The histopathological manifestations are obvious damage and fibrosis of the lung structure, often accompanied by subpleural honeycomb changes [1]. In 2016, Collard et al. [2] redefined the condition as an acute and significant deterioration of respiratory symptoms due to new diffuse

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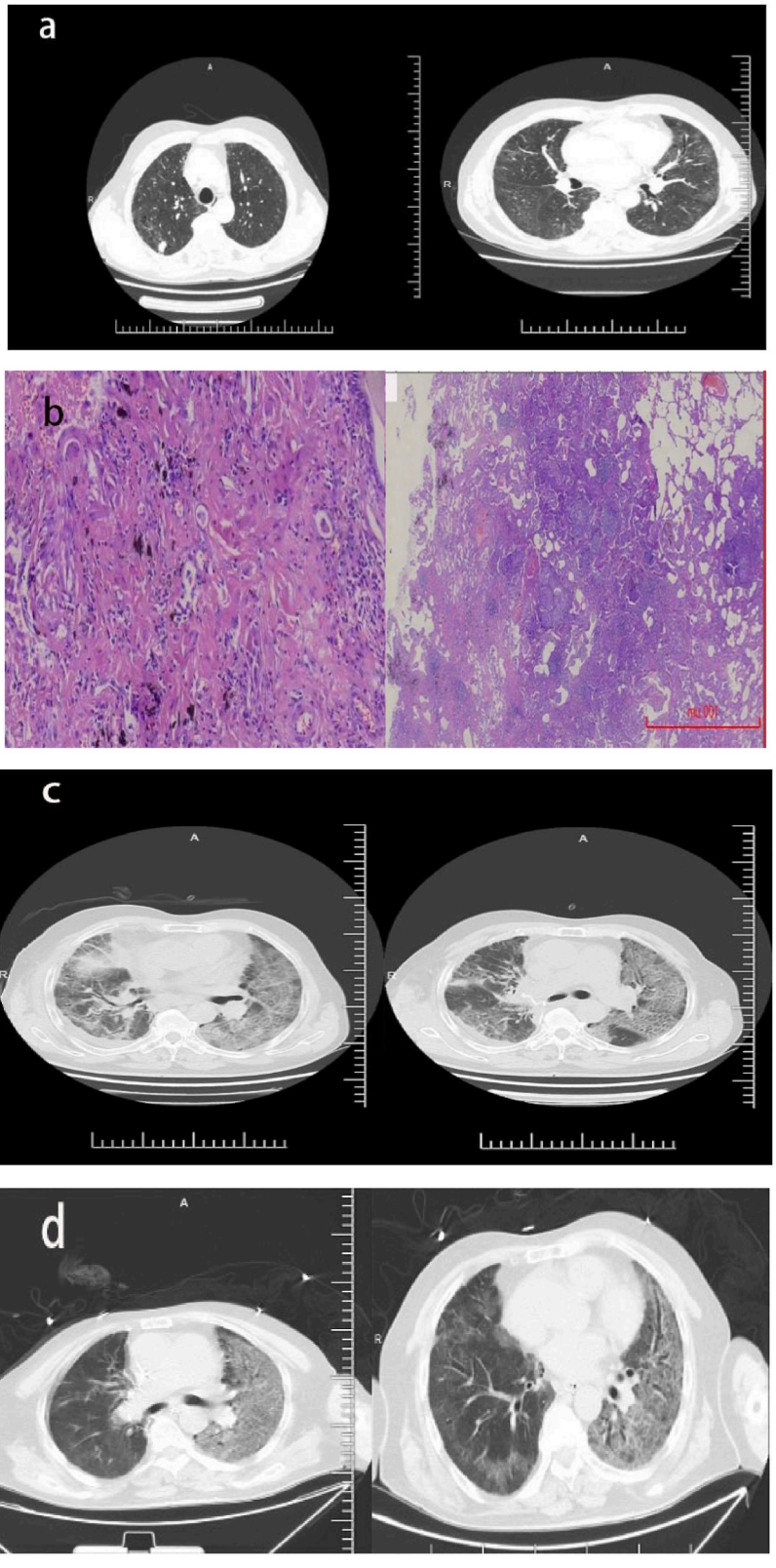

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Fig. 1. A 66-year-old man with acute exacerbation of postoperative idiopathic pulmonary fibrosis. a. Preoperative chest computed tomography (CT) shows a nodule in the upper lobe of the right lung, measuring 20 × 11 mm. Multiple ground glass opacities and grid-like shadows are visible in both lungs. b. Histopathological examination of the surgical specimen indicates lung adenocarcinoma and idiopathic pulmonary fibrosis (hematoxylin and eosin staining; original magnification, 200×). c. CT and angiography of the pulmonary artery on August 19 showing diffuse grid-like shadows and multiple ground glass opacities in both lungs, with no obvious embolism in the pulmonary artery. d. Chest CT performed on August 30 shows an increase in the diffuse grid-like shadows and ground glass opacities in the right lung.

abnormal alveolar changes. The annual incidence rate of AE-IPF is 13–20%, and the mortality rate within 90 days is about 50% [3]. AE-IPF can result from pulmonary surgery; however, only a few cases have been reported, and the specific mechanisms of its development are unclear [1,3,4]. Currently,we found that mechanical ventilation may lead to AE-IPF,and introduced the pathogenesis.

2. Case report

2.1. General condition

A 66-year-old man was hospitalized with a nodule in the right superior lobe with pulmonary interstitial fibrosis. On 10 November 2021, a lung nodule sized 18 × 9 mm was found on a chest computed tomography (CT) scan. The patient refused a CT-guided lung biopsy and was placed under regular observation. On 8 August 2022, the follow-up CT revealed an enlarged nodule sized 20 × 11 mm. Bilateral ground-glass opacification was detected (Fig. 1a). His medical history included intermittent coughing, no dyspnea, and a 40-year history of smoking, averaging 10 cigarettes/day. The force expiratory volume in 1 s (FEV1) was 2.538 L, which was 96.2% of the predicted value. The forced vital capacity (FVC) was 3.052 L, which was 90.3% of the predicted value. The FEV1/FVC ratio was 83.2%, and the DLCO was 79%.The patient actively cooperated throughout the treatment process.

2.2. Course of treatment

Before surgery, We did airway preparation for 3 days, oxygen inhalation at 30% concentration,6 h/day. Given the pulmonary nodules, patient history, and imaging findings, the final diagnosis was early lung cancer. Treatment guidelines [5] indicated thoracoscopic right upper lobe resection under general anesthesia, which was performed on 15 August 2022. The operation lasted 120 min. Invasive mechanical ventilation was used, selective pulmonary ventilation with double intracavitary tubes, positive end-expiratory pressure of 5 cmH_2O in the ventilator side lung, FiO_2 of 80% in a single lung, tidal volume of 6 mL/kg, respiratory rate of 12 times/min, airway pressure limit of 25 cmH_2O. Before tracheal intubation was removed, pulmonary re-expansion was performed using the pinch ball method and the adjustable pressure limit valve door was adjusted to 30 cmHg. Histopathological examination revealed invasive adenocarcinoma and idiopathic pulmonary fibrosis (IPF) (Fig. 1b).

2.3. Disease outcome

On 19 August, the patient developed cough, wheezing, and shortness of breath. Physical examination revealed moist lung rales, 90% oxygen saturation of the fingertip, and chest computed tomography angiography (CTA) showed new diffuse grid shadows and multiple ground glass shadows in both lungs,and the severity of pulmonary disease in the left lung was worse than that in the right lung (Fig. 1c). The patient was screened negative for infectious pathogens, including in the bronchoalveolar lavage fluid (BALF).

Acute exacerbation of IPF (AE-IPF) [1,3,6] was diagnosed. According to the AE-IPF treatment guidelines [1,6], the patient received sodium succinate 120 mg (once daily) and nintedanib 150 mg (twice daily). Dyspnea was reduced and oxygen saturation reached 92%. The patient's condition worsened again with the chest CT on 30 August showed increased grid-shaped and ground glass shadows in the right lung (Fig. 1d). The postoperative severity of left lung disease was significantly greater than that of the right lung (Fig. 1d). On 3 September, dyspnea worsened, blood oxygen saturation dropped to 70% and he died from respiratory failure.

3. Discussion

AE-IPF is defined as an acute, clinically significant acceleration of IPF caused by unknown causes [6]. Currently, etiology and mechanisms are not clear, which may include infection and surgery [6,7]. The incidence is 13%–20% and mortality within 90 days is 50% [2,6,7]. Most patients with AE-IPF experience respiratory failure; however, the use of mechanical ventilation remains controversial. Although invasive mechanical ventilation may not benefit patients with AE-IPF, non-invasive mechanical ventilation may improve the oxygenation status of a small number of patients with respiratory failure [2,7]. In this case, the patient had complications with IPF. To reduce the occurrence of surgical complications, we adopted lung protection strategies; however, the patient still developed an AE-IPF. The monitoring results of pathogenic microorganisms in the BALF were negative and infection was excluded. The chest CT showed that the severity of the non-operative lung was significantly worse than that of the affected lung. Due to the continuous mechanical ventilation of the left lung during surgery, it is reasonable to assume that mechanical ventilation may cause AE-IPF.

Currently, the following factors are associated with AE-IPF induced by mechanical ventilation [8]: (1) Improper setting of ventilator parameters including an excessive or inappropriate setting of parameters (such as tidal volume and oxygen concentration)

leading to increased lung injury or inflammatory response; (2) biomechanical changes induced by mechanical ventilation leading to abnormal remodeling of the extracellular matrix (ECM) and progression of IPF. Main mechanism:1. Type II epithelial cells are damaged by mechanical ventilation, which then leads to epithelial-mesenchymal transition (EMT). Epithelial cells are transformed into pro-fibrotic fibroblasts and myofibroblasts [8,9]. 2. Activation of the TGF-β/Smad2/3 pathway induces polarization of M2 macrophages and significant ECM deposition; 3. NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) increases the inflammatory body and then induces EMT [10]. 4. The production of short-chain hyaluronic acid and EMT is induced through the Wnt/β-catenin pathway [11]. 5. Midkine (MK) interacts with Notch2, and participates in the occurrence of EMT through the Nox1/MK/Notch2/ACe-mediated signaling pathway, ultimately inducing AE-IPF [11,12]. Furthermore, hyperoxygenation mainly damages alveolar endothelial cells and pulmonary capillary cells, inducing AE-IPF [2,8,9].

Studies have shown that glucocorticoids, such as methylprednisolone, combined with immunosuppressive drugs can also alleviate hypoxemia in patients with AE-IPF and improve chest imaging findings [6,9]. Clinical trial results involving nintedanib and pirfenidone, both currently approved for the treatment of IPF, suggest that these drugs help prevent AE-IPF [2,4,12]. Our case suggests that nintedanib should be administered in advance to reduce the incidence of acute exacerbations in patients with mild IPF requiring surgery. The clinical symptoms of AE-IPF are very similar to those of acute pulmonary edema, characterized by sudden onset of severe breathing difficulties. Common causes of acute pulmonary edema included acute heart failure and excessive and rapid infusion,the use of diuretics can quickly alleviate respiratory distress symptoms. Patients with AE-IPF do not have acute heart failure, and administering diuretics cannot effectively alleviate respiratory distress symptoms [6–12].

4. Conclusion

The most important prevention and treatment for AE-IPF caused by mechanical ventilation is to optimize the mode and time of mechanical ventilation, individualized ventilation strategy, end-expiratory positive pressure and intermittent manual lung re-expansion and other lung protection strategies, combined with the application of various clinical lung protection preparations to prevent the occurrence of disease progression. This case is a single study and lacks persuasiveness. Future mechanistic studies should be performed to develop new drugs or preventative strategies for the occurrence and development of AE-IPF caused by mechanical ventilation.

Ethics approval

The institutional ethics committee waived the requirement of ethics approval because this was a case report.

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Availability of data and materials

Data included in article/supp. Material/referenced in article. Further information and requests for resources will be available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Bin Qiu: Data curation, Formal analysis, Writing – original draft. **Zhen Liang Zhang:** Writing – original draft, Supervision. **Xiao Hua Zhao:** Writing – review & editing, Funding acquisition, Data curation. **Chun Mei Wang:** Writing – review & editing, Writing – original draft, Conceptualization. **Tong Wang:** Investigation, Resources. **Zhi Peng Wang:** Writing – review & editing, Writing – original draft, Methodology, Data curation.

Declaration of competing interest

The authors have no conflict of interest to declare.

Abbreviations

AE-IPF	acute exacerbation of idiopathic pulmonary fibrosis
CT	computed tomography
CTA	computed tomography angiography
FEV1	forced expiratory volume
FVC	vital capacity
PF	idiopathic pulmonary fibrosis

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