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A rare case of bronchorrhea associated with lung adenocarcinoma

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Abstract. Lung cancer currently ranks second in global incidence. Non-Small Cell Lung Cancer (NSCLC) is the main pathological type of lung cancer, accounting for approximately 80% to 85% of all lung cancer cases. Bronchorrhea is a disease found only in a small number of cancer patients, characterized by a large amount of non-purulent, watery sputum exceeding 100 ml per day. Bronchorrhea may be idiopathic or associated with various pulmonary diseases such as pulmonary tuberculosis, chronic bronchitis, asthma or malignant tumors of the lung. At present, there is no unified and effective treatment plan for bronchorrhea, and the symptomatic treatments adopted have varying clinical efficacies. Given the rarity of this symptom, it should draw the attention of clinicians. This article will report a rare case of a patient with bronchorrhea related to lung adenocarcinoma, hoping to provide new insights for the clinical diagnosis and treatment of bronchorrhea.According to this case and related reports, several patients with lung adenocarcinoma develop bronchorrhea symptoms. Clinically, therapeutic measures taken during the "golden window" period may help prevent or slow down the onset of bronchorrhea in these patients. From a diagnostic perspective, the diagnostic process of this case is challenging.This case report emphasizes the importance of bronchoscopy and pathogen detection in distinguishing bronchorrhea from other conditions in patients with similar presentations.In terms of diagnosis, clinicians are reminded to consider the possibility of bronchorrhea as a rare symptom in patients who present with large amounts of thin watery sputum, especially if the patient is diagnosed with LUAD and is immunosuppressed. These findings suggest that chest CT could eventually be utilized to differentiate between pneumonia and bronchorrhea in the future.Clinicians should also be aware of patients' immunosuppressive status. A remarkable number of patients with bronchorrhea are in an immunocompromised state, influencing the development, diagnosis, and treatment of bronchorrhea.Further case studies and research are essential to deepen comprehension and improve management strategies for patients with bronchorrhea associated with lung adenocarcinoma.

Keywords: bronchorrhea, lung adenocarcinoma, cancer, case report

1. Introduction

Lung cancer currently ranks second in global incidence. Non-Small Cell Lung Cancer (NSCLC) is the main pathological type of lung cancer, accounting for approximately 80% to 85% of all lung cancer cases. Bronchorrhea is a disease found only in a small number of cancer patients, characterized by a large amount of non-purulent, watery sputum exceeding 100 ml per day. At present, there is no unified and effective treatment plan for bronchorrhea, and the symptomatic treatments adopted have varying clinical efficacies.Given the rarity of this symptom, it should draw the attention of clinicians. This article will report a rare case of a patient with bronchorrhea related to lung adenocarcinoma, hoping to provide new insights for the clinical diagnosis and treatment of bronchorrhea.We present the following case in accordance with the CARE reporting checklist.

2. Case presentation

The patient, Lou, a 69-year-old male farmer, presented to the respiratory department of our hospital on October 18, 2024, with a chief complaint of persistent coughing accompanied by a large volume of thin, water-like sputum for 5 months, which had worsened with wheezing one month before his admission to our hospital. He had been diagnosed with lung adenocarcinoma (LUAD) five months earlier following colonoscopy at the Tianjin First Central Hospital (Tianjin, China). In August 2024, the patient underwent two cycles of chemotherapy at the Tianjin Medical University Cancer Institute, receiving individualism 200 mg, bevacizumab 900 mg, pemetrexed disodium 0.8 g, and carboplatin 500 mg. His last chemotherapy session was on August 16, 2024. The patient had a 50-year smoking history (10 cigarettes per day), while had quit smoking over 7 months earlier.

Upon admission, his vital signs were as follows: body temperature of 36.4°C, pulse of 97 beats/min, respiration rate of 20 breaths/min, and blood pressure of 143/104 mm/Hg. He was afebrile. Pulmonary auscultation revealed bilateral coarse breath sounds, diffuse moist rales, and no pleural friction rubs.

3. Laboratory test results

The patient's routine blood test revealed a hemoglobin level (HGB) of 129 g/L (decreased) and a monocyte percentage (MONO%) of 12% (elevated). Blood gas analysis indicated Blood Oxygen Saturation (sO_2) of 91.7%, partial Pressure of Oxygen (pO_2) of 63.4 mmHg (decreased), partial pressure of carbon dioxide (pCO_2) of 37.8 mmHg, and bicarbonate (HCO_3^-) of 24.1 mmol/L. Levels of fibrinogen (FIB), plasma D-dimer, and C-reactive protein (CRP) were 5.71 g/L (elevated), 1535 ng/mL (elevated), and 6.36 mg/L (elevated), respectively. Cytokine analysis revealed elevated levels of IL-5 (10.90), IL-6 (26.85), IFN-γ (125.69), and TNF-α (24.05). The lymphocyte subsets test revealed reduced absolute counts of total T lymphocytes (CD3+#: 159), B lymphocytes (CD19+#: 23), and NK cells (CD16+CD56+#: 48). Screening for COVID-19 antigen, influenza virus antigen, six upper respiratory tract viruses, and Aspergillus antigen returned negative results. No abnormalities were detected in lung tumor markers or sputum culture results.

4. Imaging test results

The patient's chest Computed Tomography (CT) performed five months earlier revealed bilateral pneumonia. Positron Emission Tomography-CT (PET-CT) identified diffuse ground-glass density foci in both lungs, consistent with adenocarcinoma. Multiple high-density lymph nodes were found in the bilateral pulmonary hilum and mediastinum (including paratracheal, main pulmonary artery window, and subcarinal regions) with increased metabolic activity. Chest CT conducted four days prior to admission to our hospital (Figure 1) displayed a slight increase in the density of diffuse ground-glass opacities in both lungs compared with previous imaging, along with mild enlargement of certain mediastinal lymph nodes.

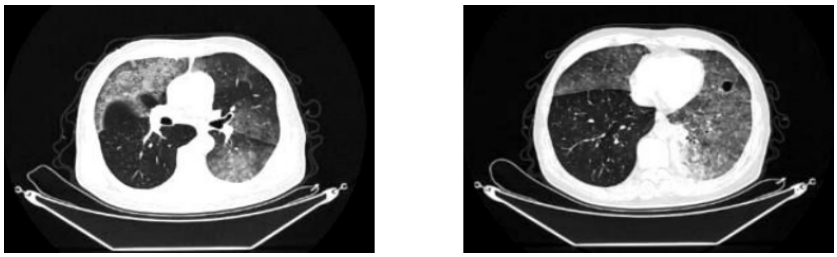

Figure 1. Chest CT performed on October 14, 2024

5. Diagnosis: bronchorrhea associated with lung adenocarcinoma

After admission, relevant examinations were completed. The clinical treatment mainly included anti-inflammatory drugs, cough relief, phlegm reduction, asthma relief, and symptomatic treatment. The treatment included intravenous infusion of cefminox sodium and methylprednisolone sodium succinate for hormone therapy. However, the patient's symptoms did not improve after 3 days of treatment, and bronchoscopy further determined the cause. Both bronchoscopic examinations revealed the distal airways filled with clear, watery secretions, with approximately 200 mL/day of thin, watery secretions observed after thorough aspiration (Figure 2). Cell count, culture, cytological examination, and pathogen gene detection (NGS) yielded no diagnostic findings. According to the patient's medical history and symptoms, bronchorrhea associated with LUAD was regarded. During the hospitalization, octreotide acetate was administered via continuous infusion at a rate of 50 μg/h. The initial dose was 0.5 mg/day, with a daily reduction of 20%. After 3 days of treatment, the patient's clinical wheezing symptoms were significantly alleviated, and the symptoms of coughing and spitting thin water-like sputum were significantly improved.

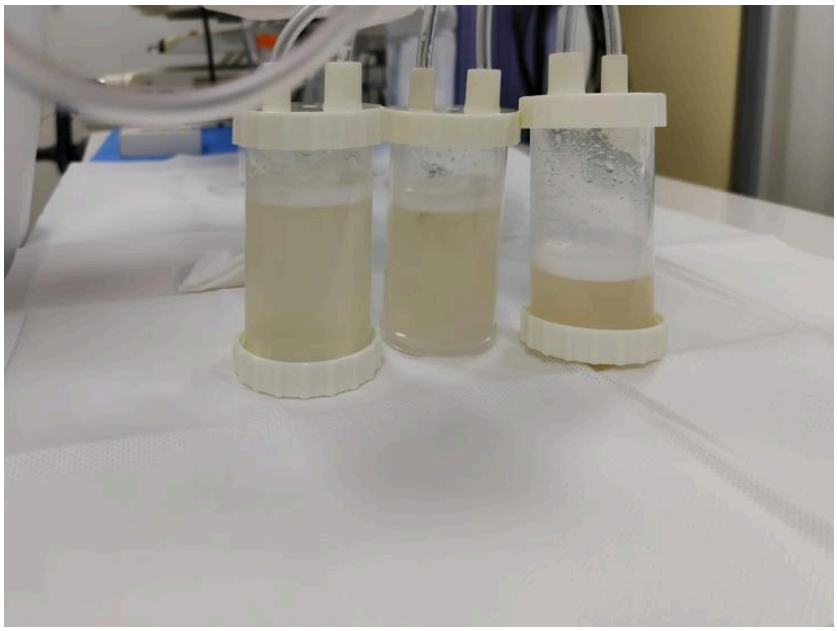

Figure 2. The patient's airway watery secretions

6. Discussion

Bronchorrhea is a rare symptom of lung cancer [1, 2], which is mainly associated with invasive mucinous adenocarcinoma. The first case linked to lung cancer was identified in the 1960s [3].

The clinical manifestations, physical examination, and imaging findings of bronchorrhea are non-specific, including large amounts of non-suppurative watery sputum exceeding 100 ml/d [4], accompanied by dyspnea, cough, and other upper respiratory tract symptoms, such as nasal congestion and clear watery rhinorrhea, which can further lead to hypovolemia, electrolyte disturbance, and respiratory failure [5]. Chest CT findings mainly display alveolar infiltration, diffuse ground-glass opacities, pneumonia-like consolidation, or multifocal patellar consolidation [6]. Bronchoscopy is usually the preferred diagnostic method for bronchorrhea. A diagnosis may be made when characteristic respiratory secretions are observed, clinical symptoms align, and other causes, such as infection, inflammation, or alveolar hemorrhage are ruled out, especially in patients with a history of adenocarcinoma.

Bronchorrhea can be caused by both malignant and non-malignant causes [7], and it is mainly associated with lung diseases, such as asthma, chronic bronchitis, tuberculosis, and malignant tumors [8], among which the most important disease is invasive mucinous adenocarcinoma [9]. Adenocarcinoma is the most common pathological subtype of small cell lung cancer [10], and Invasive Mucinous Adenocarcinoma (IMA) is a distinct subtype of LUAD. In IMA, tumor cells proliferate along the alveolar epithelium, producing large amounts of mucus. The clinical manifestations often resemble pneumonia, presenting with cough and sputum production [2]. IMA accounts for only 2–5% of all LUAD cases and is associated with diagnostic challenges, limited treatment options, high recurrence rates, and poor prognosis [9].

The pathogenesis of bronchorrhea may be related to the proliferation of secretory cells and the metaplasia of normal epithelial cells. Normally, there are few goblet cells which produce mucus among airway epithelial cells. When airway inflammation occurs, the number of goblet cells is increased, and other non-mucinous cells undergo metaplasia, acquiring a mucus-producing phenotype. The process is mediated by molecules and cells of inflammatory pathways, e.g., T-helper lymphocytes, which mediate the release of interleukin-13 (IL-13), IL-10, IL-9, IL-5, and IL-4. In this case, the patient's cytokine test results indicated the elevated IL-5 level, suggesting airway-related inflammation. In addition, for chronic lung diseases, the EGFR pathway is critical for mucus hypersecretion. Previous research indicated that external stimulation of EGFR ligands, e.g., tumor necrosis factor-alpha and transforming growth factor-beta, could induce goblet cell hyperplasia and mucosal metaplasia. Electron microscopy revealed enhanced mucin production activity in tumor cells, supporting the role of EGFR in bronchorrhea pathogenesis [11].

Clinical studies have confirmed that the symptoms of hypoxia caused by severe bronchorrhea could be caused by pulmonary shunting [11]. Severe bronchorrhea, complete filling of the alveoli with mucins, led to a severe ventilator-perfusion mismatch, leading to intractable hypoxia, suggesting that the persistent hypoxemia in this case may be caused by intrapulmonary shingles. In addition, the slow growth of tumors along the surface of the alveoli may also lead to hypoxia in the body.

There is currently no standardized treatment for bronchorrhea. Therapeutic options include systemic and inhaled corticosteroids, mucolytics (e.g., N-acetylcysteine, dornase-alpha, hypertonic saline), macrolide antibiotics, anticholinergics, octreotide, and tyrosine kinase inhibitors [12], such as gefitinib and erlotinib. Severe cases may benefit from chest physiotherapy, assistive devices, or high-frequency chest wall oscillation [13].

Clinical research [14] demonstrated that EGFR pathway inhibitors can help reduce bronchorrhea-related symptoms, as the overexpression of MUC5AC, a key mucin gene, plays a critical role in LUAD. MUC5AC mRNA expression has been inhibited in both the EGF-stimulated and constitutive states in lung mucoepidermoid cancer cell lines (A549 LUAD and NCI-H292), and the effect is more remarkable in the EGF-stimulated state. As EGF stimulation mimics EGFR-mutated lung cancer, EGFR inhibitors may have limited efficacy in treating bronchorrhea in cases of non-EGFR-mutated LUAD [14].

Other clinical studies have found that gefitinib may reduce the mucus production by inhibiting the synthesis of MUC5AC in mucus-secreting cells [14]. In numerous clinical cases, even when EGFR mutations are not detected, and treatment with gefitinib or erlotinib could improve bronchial mucus discharge in patients with newly diagnosed bronchiolar alveolar carcinoma within one week [14].

In summary, there is currently no standardized clinical guideline for managing bronchorrhea associated with LUAD. Clinical treatment strategies and drug recommendations derived from case studies require further investigation to promote evidence-based guidelines.

7. Conclusion and future perspective

According to this case and related reports, several patients with LUAD develop bronchorrhea symptoms, such as the expectoration of large amounts of thin, watery sputum, partly after diagnosis. Clinically, therapeutic measures taken during the "golden window" period may help prevent or slow down the onset of bronchorrhea in these patients. However, no standardized clinical protocol exists, and further research is required to establish effective management strategies.

From a diagnostic perspective, the diagnostic process of this case is challenging. Patients with cough and sputum symptoms are easily misdiagnosed as simple lung infection, mainly because these symptoms overlap in bronchorrhea and pneumonia, which can occur. However, bronchoscopy revealed clear, watery secretions in the distal airways, and Bronchoalveolar Lavage (BAL) with cell count, culture, cytological examination, and pathogen detection yielded no significant findings. As a result, bronchorrhea associated with LUAD was diagnosed. This emphasizes the importance of bronchoscopy and pathogen detection in distinguishing bronchorrhea from other conditions in patients with similar presentations.

This case report has important implications for clinical practice. In terms of diagnosis, clinicians are reminded to consider the possibility of bronchorrhea as a rare symptom in patients who present with large amounts of thin watery sputum, especially if the patient is diagnosed with LUAD and is immunosuppressed. In terms of treatment, although octreotide therapy was somewhat effective, it highlighted the necessity of careful monitoring of adverse reactions and clinical indicators to adjust the treatment plan as needed. Furthermore, long-term follow-up is crucial, as prior reports suggested poor prognosis, low quality of life, and short survival in such patients.

In this case, chest CT images of bronchorrhea associated with LUAD showed multiple flake-like ground-glass opacities in both lungs, which could be mistaken for pulmonary infection due to interstitial changes. However, bronchorrhea was characterized by the presence of large volumes of thin, watery secretions in the lower respiratory tract. These findings suggest that chest CT could eventually be utilized to differentiate between pneumonia and bronchorrhea in the future.

Clinicians should also be aware of patients' immunosuppressive status. A remarkable number of patients with bronchorrhea are in an immunocompromised state, influencing the development, diagnosis, and treatment of bronchorrhea.

There are some limitations in this case report. Firstly, as a single case, the clinical treatment effect was accidental and could not fully represent the clinical characteristics of bronchorrhea associated with LUAD. Secondly, because the patient did not receive further systematic treatment, it remained infeasible to monitor the long-term progression, diagnosis, and treatment effectiveness.

In conclusion, the increasing number of reported cases of bronchorrhea associated with LUAD indicates growing clinical recognition of this condition. Further case studies and research are essential to deepen comprehension and improve management strategies for patients with bronchorrhea associated with LUAD.

List of abbreviations

NSCLC: Non-Small Cell Lung Cancer; LUAD: Lung Adenocarcinoma; BAL: Bronchoalveolar Lavage; CT: Computed Tomography

Declaration

Ethics approval and consent to participate: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for the publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors declare that they have no competing interests.

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Authors' contributions

Yufei Wang and Qiaoning Zhu contributed equally to this manuscript.All authors read and approved the final manuscript.

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(II) Administrative support:Wei Liu,
(III) Provision of study materials or patients:Yufei Wang,
(IV) Collection and assembly of data:Yufei Wang,Qiaoning Zhu
(V) Data analysis and interpretation:Yufei Wang,Zihan Jin,Wei Liu
(VI) Manuscript writing: All authors
(VII) Final approval of manuscript: All authors

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