CHEST

A Woman in Her 60s With Lung Adenocarcinoma Presents With Copious Watery Sputum and Respiratory Failure

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CASE PRESENTATION: A woman in her 60s presented with 1 month of progressive dyspnea, watery rhinorrhea, and paroxysmal cough productive of clear, watery sputum. She was diagnosed with epidermal growth factor receptor (EGFR) mutation-positive lung adenocarcinoma at another institution 1 week prior to presentation and 3 weeks after the onset of symptoms. She was a never-smoker. She denied fevers and had completed a course of antibiotics for presumed pneumonia, without clinical improvement. She presented to the hospital due to increasing severity of her shortness of breath.

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Physical Examination Findings

The patient presented in respiratory distress. Her temperature was 37°C; pulse was 123 beats/min; blood pressure was 154/77 mm Hg; respirations were 25 breaths/min; and arterial oxygen saturation was 79% on room air. Her physical examination was notable for a cough with copious, watery sputum and diffuse rales on lung auscultation. The remainder of her examination was unremarkable.

Diagnostic Studies

Laboratory testing revealed leukocytosis with 13,600 cells/μL (4,000-10,000 cells/μL). Arterial blood gas on a 100% non-rebreather mask showed hypoxemia and hypercapnia (Pao_2, 66 mm Hg; $Paco_2$, 44 mm Hg; pH 7.34). The initial chest radiograph revealed a right upper lobe opacity and large left lower lobe consolidation (Fig 1). The report from a chest radiograph taken 2 weeks prior noted small right upper and left lower lobe infiltrates. Results of sputum microbiology tests and respiratory virus polymerase chain reaction were nondiagnostic, and a cardiac evaluation was normal.

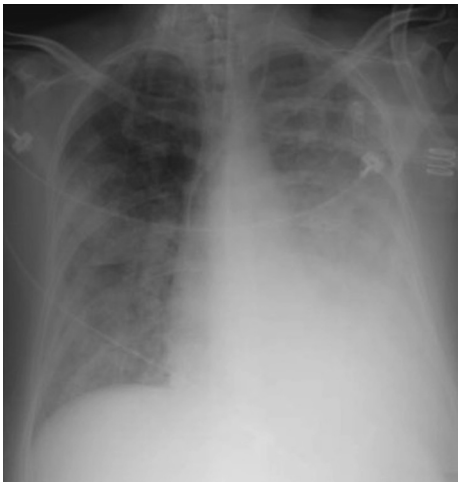

Figure 1 – *Posterioanterior chest radiograph obtained at admission demonstrates a right upper lobe opacity and large left lower lobe consolidation.*

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This case was previously presented in poster format ("Octreotide as Bridging Therapy to Erlotinib in Bronchorrhea-Induced Respiratory Failure") at the American Thoracic Society meeting, May 13-18, 2016, San Francisco, CA.

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The patient required mechanical ventilation (F_{IO_2} of 100%, positive end-expiratory pressure of 20 cm H_2O) and admission to the ICU for hypoxemic respiratory failure. Respiratory secretions suctioned from her endotracheal tube averaged 2.5 L daily (Fig 2). Bronchoscopy revealed distal airways filled with clear, watery secretions. Bronchial lavage cell count, culture, and cytology were nondiagnostic. Her oxygenation failed to improve despite antibiotics, negative fluid balance, and prone positioning.

Figure 2 – *A total of 1,200 mL of respiratory secretions suctioned from the endotracheal tube over 12 h.*

What is the diagnosis?

Diagnosis: Bronchorrhea associated with lung adenocarcinoma

Discussion

Bronchorrhea is most commonly described in non-small cell lung cancer subtype adenocarcinoma in situ (AIS), formerly known as bronchioloalveolar carcinoma. AIS is noninvasive, characterized by its peripheral location and lepidic growth pattern along alveolar septa. The term lepidic adenocarcinoma refers to multifocal tumors that are predominantly lepidic but also have invasive components. Bronchorrhea has also been described in TB, chronic bronchitis, and bronchiectasis. It is defined as the production of $>$ 100 mL of respiratory secretions daily.

The clinical presentation, physical examination, and radiographic findings of bronchorrhea are nonspecific. Typical manifestations include dyspnea and cough productive of characteristic clear, watery secretions. Upper respiratory symptoms, including nasal congestion and clear, watery rhinorrhea, have also been reported. Alveolar infiltrates are seen on chest radiographs and diffuse ground-glass opacities on CT scans. In severe cases, bronchorrhea reportedly causes hypovolemia, electrolyte derangements, and respiratory failure.

The pathophysiology of bronchorrhea in adenocarcinoma remains unknown. Proposed mechanisms include hypersecretion by mucus-producing cells activated by inflammatory stimuli or prostaglandins and abnormal secretin expression resulting in abnormalities in transepithelial transport of chloride and water. Other possible mechanisms include EGFR overexpression, resulting in excessive mucin synthesis and transudation of plasma products into airways.

The management of persistent symptomatic bronchorrhea remains poorly established, being based on expert opinion and case reports. An initial diagnostic approach typically includes bronchoscopy to identify other treatable conditions such as infection, inflammatory processes, or alveolar hemorrhage. A history of adenocarcinoma and the presence of characteristic respiratory secretions should raise clinical suspicion for bronchorrhea after other diagnoses have been excluded.

There is no high-quality evidence to support a specific therapy in the treatment of adenocarcinoma-associated bronchorrhea. Case reports describe variable effects on the alleviation of cough, dyspnea, and reduction of secretion volume using inhaled indomethacin, macrolides, and inhaled and systemic corticosteroids. Two case reports, however, describe treatment of adenocarcinoma-associated bronchorrhea with subcutaneous and IV octreotide, with a decrease in respiratory secretions within 24 h of initiation. In one patient, respiratory secretions decreased from 1 L to 150 mL daily, and in another from 1 L daily to nearly no secretion output. In both cases, there were improvements in cough and dyspnea.

Octreotide is a synthetic analogue of somatostatin that has been used for its antisecretory effects in the palliation of symptoms related to ascites, malignant bowel obstruction, and carcinoid-induced diarrhea. Its proposed mechanism of action in treatment of bronchorrhea is via its inhibition of secretin, which may reduce chloride and water efflux from bronchial epithelial cells. There is no evidence regarding the effectiveness of octreotide in cases of respiratory failure or its impact on mortality.

Additional case reports have reported treatment of bronchorrhea with the EGFR-targeted tyrosine kinase inhibitors gefitinib and erlotinib. Two patients treated with gefitinib reported reductions in secretion volumes of 1 L to 500 mL daily, with improvements in dyspnea, cough, and hypoxemia. Another patient with respiratory failure producing 2.9 L of bronchorrhea daily was treated with erlotinib, with a reduction in secretion output that was not quantified but permitted extubation 2 days later. Interestingly, these agents were effective independent of patients' EGFR-mutation status. These therapies are the standard of care in the treatment of EGFR mutation-positive lung adenocarcinoma. In treating bronchorrhea, their time to treatment effect varied from 24 h to 1 week before reductions in secretion volume and symptoms were observed.

The therapies reviewed have been observed to decrease bronchorrhea volume and improve respiratory symptoms; however, none has been shown to affect survival or reverse respiratory failure. Due to its rapid reduction of the volume of respiratory secretions, IV octreotide is recommended as an initial treatment for severe bronchorrhea.

Clinical Course

Despite the absence of lepidic growth on histologic examination, we suspected the diagnosis of bronchorrhea based on the study patient's known lung

adenocarcinoma and characteristic respiratory secretions and after we excluded other diagnoses. Her respiratory failure was likely multifactorial, due to parenchymal involvement of lung cancer and alveolar filling from large volume bronchial secretions. Increasing alveolar filling may have led to the progression of ventilation/perfusion mismatch to intrapulmonary shunt, resulting in severe hypoxemia.

An octreotide infusion at 25 μg/h was initiated. Twenty-four hours later, the patient's respiratory secretions decreased from 2.5 L to 300 mL daily, with reductions in positive end-expiratory pressure and F_{IO_2}. The dosage was titrated down to 12.5 μg/h to minimize bradyarrhythmias, a known side effect. By reducing the volume of respiratory secretions, octreotide may have decreased the number of fluid-filled alveoli, thus improving gas exchange. Erlotinib, the therapy with more evidentiary support but an un-predictable time to treatment effect, was initiated 2 days later. Further reduction in bronchorrhea was observed with erlotinib 150 mg daily, which persisted after discontinuation of octreotide.

Despite significant progress in the patient's respiratory status, she was unable to be liberated from the ventilator due to the extent of malignant pulmonary disease and a depressed mental status. In accordance with her previously expressed wishes, the patient was terminally extubated.

Clinical Pearls

1. *Although bronchorrhea most often occurs with AIS, the absence of lepidic growth on a lung biopsy specimen does not exclude lung cancer as its etiology because multifocal adenocarcinomas may vary regionally in their invasive vs lepidic histopathologic features.*
2. *Due to the lack of studies, there are no clinical practice guideline recommendations for the treatment of bronchorrhea.*
3. *Octreotide may benefit patients with disabling bronchorrhea associated with lung cancer based on limited case reports that describe a rapid onset of action.*

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Suggested Readings

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