

## A 61-Year-Old Man with Nonresolving Pneumonia and Bronchorrhea

Walid Hadid, MD

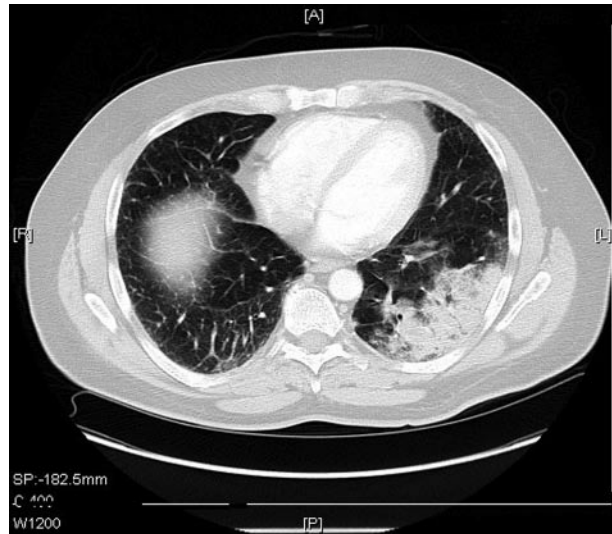
### CASE PRESENTATION

#### Outpatient Course

A 61-year-old man presented to his primary care physician with progressive dyspnea on exertion that was associated with persistent dry cough for 1 week. On review of systems, he denied fever and chills. The patient's past medical history was significant for sarcoidosis diagnosed 20 years ago following lymph node biopsy. At that time, he recovered without complications. The patient also experienced 2 episodes of pulmonary embolism 4 years ago; since then, he has been receiving anticoagulation therapy with warfarin. Extensive evaluation for thrombophilia did not reveal an underlying etiology. The patient was a former smoker (1 pack of cigarettes daily for 10 yr) who quit smoking over 30 years ago. Physical examination was remarkable only for crackles detected over the lower field of the left lung. A sputum sample was obtained and sent for cultures, which were reported as negative. A chest radiograph showed a left lower lobe infiltrate. The patient was given a 2-week course of levofloxacin (500 mg/day) but showed no significant clinical improvement over the following 4 weeks. Therefore, he was referred to a pulmonologist.

At presentation to the pulmonologist, the patient's clinical findings were unchanged. A contrast-enhanced computed tomography (CT) angiogram of the chest was negative for pulmonary embolism but revealed air-space infiltrates in the lower lobe of the left lung (Figure 1). Laboratory evaluation for an underlying cause of the patient's symptoms included bacterial and fungal sputum culture, sputum stain and culture for acid-fast bacilli, blood cultures, and serologic titers for atypical pneumonia. The investigations, which were ordered in coordination between the primary care physician and the pulmonologist, were unrevealing. The patient was treated with amoxicillin/clavulanate (1000 mg orally every 12 hr) without improvement over 10 days.

Bronchoscopy was performed by the pulmonologist after 2 weeks. Bronchoalveolar lavage showed mild neutrophilic and marked histiocytic exudates without atypia or malignant cells. A transbronchial lung biopsy (TBLB) showed mild chronic inflammation without



**Figure 1.** A contrast-enhanced computed tomography angiogram of the chest showed consolidation in the left lower lobe.

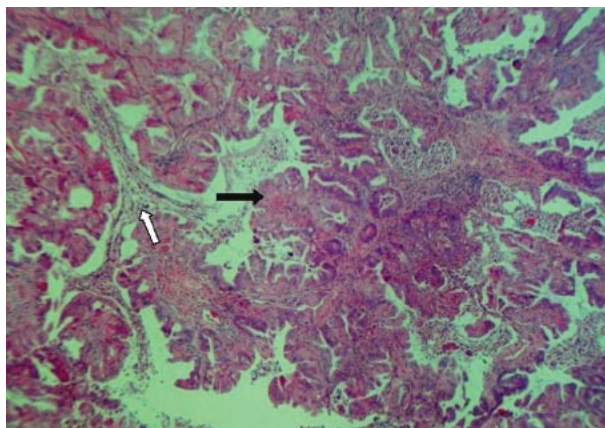
granulomatous process, atypia, or malignant features. Culture of the biopsy samples and special stains (including silver stains and acid-fast bacilli stain) showed no evidence of fungi, *Pneumocystis jirovecii*, or acid-fast bacilli. Antineutrophilic cytoplasmic antibodies and antinuclear antibodies were negative. The patient was scheduled to follow-up with the pulmonologist in 2 weeks at the pulmonary clinic.

#### Hospital Course

Before the patient's scheduled follow-up visit with the pulmonologist, the patient presented to the hospital with increasing dyspnea and a productive cough. He reported that he had produced copious amounts of white-yellowish sputum over the preceding 2 weeks. He still denied fever, chills, and weight loss as well as

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**Figure 2.** Biopsy specimen showing distinctive columnar epithelial cells proliferating within the framework of alveolar septa, forming a papillary appearance (*black arrow*), and mucin with inflammatory cells in the alveolar spaces (*white arrow*).

chest pain and hemoptysis. Physical examination revealed bilateral lung crackles. A complete blood count was ordered, and the results were normal. Chest radiograph showed bilateral interstitial and alveolar opacities in the right upper lobe and left lower lobe of the lungs. High-resolution chest CT showed the old left lower lobe consolidation and new right upper lobe airspace consolidations with a predominantly peripheral distribution. The patient was admitted, and open lung biopsy was performed. Biopsy showed distinctive columnar epithelial cells proliferating within the framework of alveolar septa, forming a papillary appearance (**Figure 2**).

#### WHAT IS YOUR DIAGNOSIS?

- (A) Bacterial pneumonia
- (B) Blastomycosis
- (C) Bronchioalveolar carcinoma, mucinous type
- (D) Cryptogenic organizing pneumonia
- (E) Pulmonary tuberculosis

#### ANSWER

The correct answer is (C), bronchioalveolar carcinoma (BAC), mucinous type.

#### DISCUSSION

The results from the cultures, serologic tests, and biopsy were not consistent with the other potential diagnoses. Given that the patient had a greater than 2-month history of nonresolving pneumonia that had progressed to bilateral consolidations in addition to idiopathic recurrent pulmonary embolism, suspicion for malignancy was high. The pathology was consis-

tent with BAC. Mucin stains and immunostains were performed on the biopsy specimen, which confirmed the diagnosis of mucinous type BAC. The patient had multiple bacterial sputum cultures that were negative, including cultures from the TBLB. He also had negative serology tests for atypical pneumonia and received multiple courses of antibiotics that covered typical and atypical pneumonia without improvement, making the diagnosis of bacterial pneumonia unlikely. Blastomycosis can be diagnosed on histologic evaluation, which reveals large, single broad-based buds with thick walls; this finding was not seen in the case patient. Cryptogenic organizing pneumonia is an inflammatory process histologically characterized by polypoid endobronchial masses of myxoid fibroblastic tissue resembling granulation tissue that fill the distal alveolar spaces.<sup>1</sup> Biopsy results were not consistent with this diagnosis. Detection of acid-fast bacilli was negative on multiple occasions, making the diagnosis of tuberculosis unlikely.

#### CLINICAL COURSE OF THE PATIENT

The patient's clinical course significantly worsened over the 3 weeks following diagnosis. Bronchorrhea became more remarkable, and the patient required continuous oxygen (4 L/min oxygen via nasal cannula). An oncologist was consulted and the treatment options and prognosis were discussed with the patient. The patient refused treatment and requested to be transferred to hospice care. The patient died within 4 weeks following diagnosis with BAC.

#### BRONCHIOALVEOLAR CARCINOMA

BAC is a form of non-small cell lung cancer. Histologically, the World Health Organization (WHO) describes BAC as an adenocarcinoma growing along preexisting alveolar structure (lepidic growth) with no evidence of stromal, vascular, or pleural invasion.<sup>2</sup> In contrast, an adenocarcinoma that has the lepidic growth with invasion to other structures is classified as "adenocarcinoma with prominent bronchioalveolar pattern or mixed subtype adenocarcinomas."<sup>2</sup> Unlike other types of lung cancer, the distribution of disease between men and women is nearly equivalent.<sup>3</sup> Although a significant percentage of patients with BAC have no history of tobacco use (4 of 48 [8%] male patients and 11 of 39 [28%] female patients in 1 study), smoking remains a risk factor for developing BAC, especially with prolonged smoking and starting smoking at an early age.<sup>4</sup>

#### Clinical Features

BAC is often referred to as a masquerader because its clinical features are similar to those of infectious

pneumonia and other inflammatory lung diseases.<sup>5</sup> Although patients with BAC may often be asymptomatic at presentation, symptomatic patients usually complain of dyspnea and cough.<sup>6</sup> Cough may be nonproductive or may be associated with large amounts of sputum,<sup>6,7</sup> which is called bronchorrhea. Bronchorrhea is an uncommon symptom and is defined as production of 100 mL or more of watery or thin sputum.<sup>8</sup> BAC is divided into 3 subtypes: mucinous, nonmucinous, and mixed.<sup>2</sup> The most common subtype is nonmucinous BAC. The mucinous variant represents 25% of all cases of BAC.<sup>2</sup> Bronchorrhea usually occurs in the mucinous type of BAC but may also be present in the mixed type. In some cases, bronchorrhea may be a life-threatening complication due to compromise of respiratory function or electrolyte disturbances.<sup>9,10</sup> Daily sputum production with volumes ranging from 500 to 900 mL has been reported.<sup>11</sup> Bronchorrhea can lead to another rare and serious complication: replacement of the respiratory airspace with mucus, which may cause an intrapulmonary right-to-left shunt that leads to hypoxemia.<sup>9</sup>

BAC also mimics many diseases radiographically and may present as a solitary lesion, consolidations, diffuse interstitial infiltrates, or multiple lesions.<sup>12</sup> The mucinous type of BAC is associated with lobar consolidation as well as multifocal disease.<sup>3</sup> The solitary lesion is more likely to be a nonmucinous subtype of BAC.<sup>2</sup> Kim et al<sup>13</sup> retrospectively reviewed the CT images of 47 patients with focal areas of parenchymal opacification at the lung periphery to determine which features were associated with BAC mimicking pneumonia (n = 18) versus those associated with infectious pneumonia (n = 29). In this study, the presence of bubble-like low attenuation areas within the lesion was associated with BAC, whereas thickening of the bronchial wall proximal to the lesion was associated with pneumonia.<sup>13</sup> Another study that included 21 patients with pathologically proven BAC and 30 patients with infectious pneumonia suggested that the diagnosis is more likely to be BAC rather than pneumonia if CT images show stretching, squeezing, weeping, and widening of the branching angle of the air-filled bronchus within the airspace consolidation or bulging of the interlobar fissure.<sup>14</sup> As BAC may show low or negative avidity on positron emission tomography,<sup>15</sup> this test is not considered valuable.

### **Diagnosis**

The differential diagnosis of the pneumonia-like form of BAC may include infectious pneumonia, eosinophilic pneumonitis, cryptogenic organizing pneumonia, and other types of inflammatory pneumonitis. The diagnosis of BAC can only be made on a pathologic and histologic

basis. Histologically, the mucin-producing adenocarcinomas (eg, some types of gastrointestinal tract, pancreatic, and ovarian cancers) can mimic BAC.<sup>9</sup> Therefore, immunohistochemical stains must be performed to confirm the diagnosis.<sup>9</sup>

Physicians need to consider BAC in the differential diagnosis of nonresolving pneumonia. The clinical symptoms and signs of pneumonia should improve in a range of 3 days (fever) to 14 days (cough) if the appropriate treatment is applied.<sup>16</sup> Radiologic findings may resolve in 7 to 12 weeks, and follow-up with chest radiograph as an outpatient may be recommended for patients who smoke or who have a significant history of smoking or patients who are older than age 40 years.<sup>17</sup> The diagnosis of the underlying cause of nonresolving pneumonia may require extensive investigation. Negative TBLB should not reassure the physician. As mentioned earlier, BAC is a noninvasive adenocarcinoma.<sup>2</sup> The diagnosis of BAC is dependent on confirming lepidic growth without invasion to other structures, which requires examining the entire tumor after resection.<sup>18</sup> As a result, the diagnosis cannot be made or ruled out based on a small biopsy or cytology specimen.<sup>18</sup> On TBLB, the pathology may reveal an adenocarcinoma with BAC-pattern lepidic growth, but this does not confirm the diagnosis. However, if BAC presents radiologically with a ground-glass appearance or as infiltrates and the biopsy demonstrates the BAC-growth pattern, the diagnosis of BAC may be conferred, as non-BAC adenocarcinoma does not present as ground glass.<sup>18</sup>

### **Treatment**

With few treatment options available and with none of these options having been evaluated in any large clinical trials, bronchorrhea represents a challenge in the management of BAC. As inflammation may have a role in causing bronchorrhea, corticosteroids (to inhibit genes from encoding cyclooxygenase-2) and macrolide drugs such as erythromycin and clarithromycin (to decrease glycoprotein secretion) have been used.<sup>11,19,20</sup> Inhaled indomethacin can be helpful in refractory bronchorrhea.<sup>21</sup> Indomethacin usually inhibits the cyclooxygenase pathway, which may decrease transepithelial chloride secretion associated with the pathogenesis of bronchorrhea.<sup>22</sup> Successful treatment of bronchorrhea with epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor and octreotide has also been reported.<sup>23,24</sup>

An in-depth discussion of staging and treatment of BAC is beyond the scope of this review. In brief, treatment options for BAC vary depending on disease stage and extent and may include surgical resection for the

localized form or radiation therapy with or without chemotherapy in unresectable cases.<sup>25</sup> A recent report shows that BAC with mutation of the *EGFR* gene may respond to EGFR tyrosine kinase inhibitors.<sup>26</sup> Many prognostic factors may adversely affect the survival of patients diagnosed with BAC, including advanced stage disease, diffuse malignant invasion, and mucin-producing tumors.<sup>27</sup>

## CONCLUSION

BAC represents a locally noninvasive subtype adenocarcinoma that has several different clinical presentations, including a pneumonia-like variant. This variant of BAC should be considered in the differential diagnosis of nonresolving pneumonia. Treatment of BAC is similar to other forms of lung cancer, which may involve surgery, chemotherapy, and radiation. EGFR tyrosine kinase inhibitors have a role in treating BAC, especially in cases of diffuse and nonresectable BAC.<sup>27</sup> **HP**

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