

## Refractory Hypoxemic Respiratory Failure Due to Adenocarcinoma of the Lung With Predominant Bronchioloalveolar Carcinoma Component

Chakradhar Venkata MBBS, Jesus A Mireles MD, and Saiprakash B Venkateshiah MD

### Introduction

Bronchioloalveolar carcinoma is a subtype of lung adenocarcinoma, characterized by well-differentiated cytology, peripheral location, and characteristic growth of neoplastic cells along intact alveolar septa (ie, lepidic growth pattern). Pure bronchioloalveolar carcinoma, by definition, doesn't invade stroma, pleura, or lymphatic spaces. If there is lymphatic invasion, the tumor is classified as an adenocarcinoma, mixed subtype with predominant bronchioloalveolar carcinoma. Bronchioloalveolar carcinoma can present in various forms, including focal areas of increased lung opacity with ground-glass appearance (either as a single lesion or a confluence of lesions), or as a lobar consolidation mimicking bacterial pneumonia. We report an uncommon presentation of adenocarcinoma with predominant bronchioloalveolar carcinoma component, manifesting as multifocal pulmonary consolidation leading to refractory hypoxemic respiratory failure.

### Case Summary

At Omaha Veterans Affairs Medical Center (an affiliate of Creighton University, Omaha, Nebraska) we saw a 74-

year-old man who had had 4 weeks of worsening shortness of breath, low-grade fever, and productive cough. Fever and cough abated, but shortness of breath progressed to orthopnea and dyspnea at rest, prompting medical attention. He denied exposures to dust, animals, fumes, new medications, or toxins. He did not travel outside the Midwestern United States. His medical history was notable for coronary artery disease and coronary artery bypass graft surgery (performed 15 years ago), hypertension, and elevated prostate-specific antigen. He had 120-pack-year history of smoking, but quit 12 years ago.

His vital signs were normal except for low oxygen saturation (87% on room air). He was in moderate respiratory distress. Cardiac examination was normal. Chest auscultation revealed bilateral diffuse crackles. Mild bilateral ankle edema was noted.

Complete blood count, cardiac enzyme panel, and serum chemistries were unremarkable except for hypoalbuminemia of 3.3 g/dL (normal is 3.5–5.0 g/dL). B-type natriuretic peptide was 135 pg/mL (normal is < 100 pg/mL). A chest radiograph was obtained (Fig. 1). Arterial blood gases while on 2 L/min of oxygen were: pH 7.46,  $P_{aCO_2}$  33 mm Hg, and  $P_{aO_2}$  49 mm Hg. Urinary *Legionella* and *Histoplasma* antigens, serology for human immunodeficiency virus, serum anti-nuclear antibody, anti-neutrophilic cytoplasmic antibody, and anti-glomerular basement membrane antibodies were negative. Sputum cultures grew mixed oropharyngeal flora, and multiple blood cultures in the hospital course were negative. Computed tomography scan of the chest (Fig. 2) revealed multifocal pulmonary consolidation, emphysematous changes, moderate left pleural effusion, and mediastinal lymphadenopathy.

Our patient was admitted with a presumptive diagnosis of congestive heart failure exacerbation and was treated with furosemide and continuous positive airway pressure (10–15 cm H<sub>2</sub>O). When he did not improve, a diagnosis of community-acquired pneumonia was entertained, and levofloxacin (750 mg, intravenous route on day 1, followed by 500 mg intravenous daily) was started. His oxygen requirements continued to increase over the next 2 days. His

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At the time they saw this patient, all the authors were affiliated with the Division of Pulmonary, Critical Care, and Sleep Medicine, Creighton University Medical Center, Omaha, Nebraska, which is affiliated with the Omaha Veterans Affairs Medical Center, Omaha, Nebraska. Chakradhar Venkata MBBS is now affiliated with the Division of Critical Care Medicine, Mayo Clinic, Rochester, Minnesota. Saiprakash B Venkateshiah MD is now affiliated with the Division of Pulmonary, Critical Care, and Sleep Medicine, Atlanta Veterans Affairs Medical Center, Decatur, Georgia. Jesus A Mireles MD is affiliated with the Division of Pulmonary, Critical Care, and Sleep Medicine, Creighton University Medical Center, Omaha, Nebraska.

The authors have disclosed no conflicts of interest.

Correspondence: Saiprakash B Venkateshiah MD, Division of Pulmonary, Critical Care, and Sleep Medicine, Atlanta Veterans Affairs Medical Center, 1670 Clairmont Road, Decatur GA 30033 E-mail: svenkateshiah@gmail.com.



Fig. 1. Chest radiograph showing bilateral infiltrates.

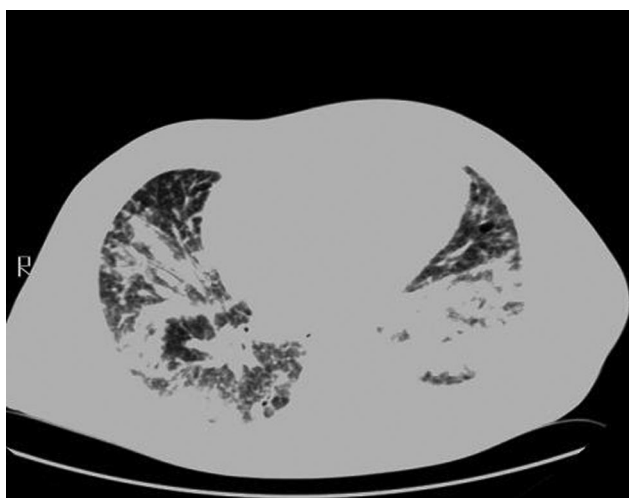


Fig. 2. Computed tomography scan of the chest showing multifocal pulmonary consolidation, emphysematous changes, and moderate left pleural effusion.

antibiotic regimen was expanded to piperacillin-tazobactam (3.375 g intravenous every 6 h) and vancomycin (15 mg/kg intravenous every 12 h). Subsequently, doxycycline (100 mg intravenous every 12 h) was added empirically to cover unusual organisms such as *Brucella* and *Rickettsia* species, even though clinical suspicion was low. Due to lack of improvement on broad-spectrum antibiotic therapy and concern about non-infectious lung conditions, methylprednisolone (1 mg/kg/d intravenous) was started empirically. Despite these interventions, he was intubated on day 6 of hospitalization, due to persistent hypoxia. Neither bronchoscopy for bronchoalveolar lavage nor video-assisted thoracoscopic surgery for lung biopsy could be performed, due to clinical instability ( $P_{aO_2}$  52 mm Hg on positive end-expiratory pressure 17 cm  $H_2O$  and fraction

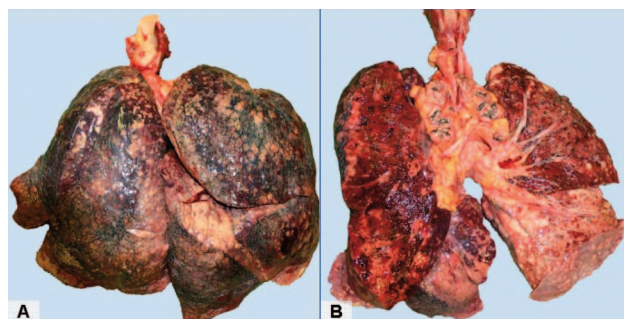


Fig. 3. Gross specimen of lungs (A: frontal view. B: coronal section) showing multifocal consolidations and prominent hilar lymphadenopathy.

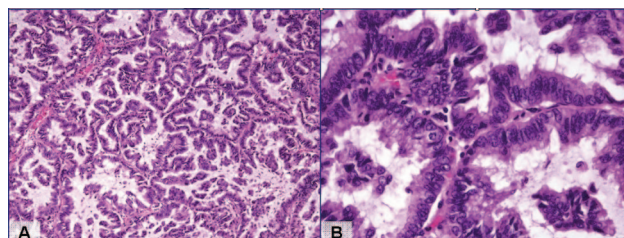


Fig. 4. Histology of lung lesions (hematoxylin and eosin stain, A: 40 $\times$  magnification. B: 200 $\times$  magnification) showing single layer of columnar cells with elongated and hyperchromatic nuclei.

of inspired oxygen 1.0). His family decided to withdraw ventilatory support after 30 days, and the patient died on comfort measures.

Autopsy (Fig. 3) revealed metastatic adenocarcinoma of the lung, with prominent bronchioloalveolar carcinoma component. Histology showed tumor cells growing along the intact alveolar septae (ie, lepidic growth pattern) (Fig. 4). Immunohistochemical staining of lung tissue was positive for cytokeratin 7 and thyroid transcription factor-1, which supported the pathology diagnosis.

## Discussion

Bronchioloalveolar carcinoma is a subtype of lung adenocarcinoma characterized by well-differentiated cytology, peripheral location, growth along intact alveolar septa (lepidic growth pattern), and propensity for both aerogenous and lymphatic spread. Pure bronchioloalveolar carcinoma subtype is defined as those tumors with a pure bronchioloalveolar growth pattern without evidence of invasion of stroma, pleura, or lymphatic spaces. If there is lymphatic invasion, the tumor is classified as an adenocarcinoma, mixed subtype with predominant bronchioloalveolar carcinoma.<sup>1</sup> The proportion of bronchioloalveolar carcinoma can vary widely, from tumors with a predominant bronchioloalveolar carcinoma pattern and minimal invasion to those in which bronchioloalveolar carcinoma

presence is focal. It is unclear whether a distinction between pure bronchioloalveolar carcinoma, minimally invasive bronchioloalveolar carcinoma, and adenocarcinoma with bronchioloalveolar carcinoma features has important clinical implications, but emerging evidence suggests the possibility that an increasing proportion of bronchioloalveolar carcinoma correlates with improved outcomes. The International Association for the Study of Lung Cancer has recommended that any feature of bronchioloalveolar carcinoma in a pathologic specimen would qualify a patient for bronchioloalveolar-carcinoma-specific treatment or clinical trials.

Bronchioloalveolar carcinoma represents less than 4% of all non-small-cell lung cancers<sup>2</sup>; however, as many as 20% of adenocarcinomas of the lung have bronchioloalveolar carcinoma features. Smoking plays a role in the development of some cases of bronchioloalveolar carcinoma, but approximately one third of cases of bronchioloalveolar carcinoma occur in individuals who have never smoked. Other possible etiologic factors include pulmonary scarring (eg, sequelae of bronchiectasis, idiopathic pulmonary fibrosis) and occupational exposures (motor-freight occupations, construction workers, petroleum manufacturers, and sugar cane farmers),<sup>3</sup> although evidence for a definite causal relationship is lacking.

Bronchioloalveolar carcinoma can present as a focal area of increased lung opacity (with ground-glass appearance on computed tomogram), or lobar consolidation (mimicking bacterial pneumonia), or multiple pulmonary lesions.<sup>4</sup> Solitary peripheral lesions may be asymptomatic. More extensive tumors may present with cough, hemoptysis, dyspnea, fever, and weight loss. Two uncommon presentations of bronchioloalveolar carcinoma are bronchorrhea and hypoxemia. Bronchorrhea is the production of > 100 mL of watery sputum per day, which can lead to respiratory distress. Bronchioloalveolar carcinoma presenting with respiratory failure necessitating mechanical ventilation, such as seen in our patient, is rare. There are only 4 published case reports of bronchioloalveolar carcinoma culminating in respiratory failure: one secondary to hemoptysis,<sup>5</sup> others due to progressive lung disease<sup>6</sup> and from intrapulmonary shunting resulting in severe hypoxemia.<sup>7,8</sup>

The diagnosis is established via pathology examination of the surgically resected specimen. For patients who cannot undergo surgical biopsy, the diagnosis of bronchioloalveolar carcinoma should be made only with compatible histopathologic pattern on transbronchial or core-needle biopsy and a computed tomography scan demonstrating a pure ground-glass or pneumonic appearance.<sup>4</sup>

The staging and treatment is similar for bronchioloalveolar carcinoma and adenocarcinoma with a bronchioloalveolar carcinoma component, and is similar to that for patients with other types of non-small-cell lung cancer at

a comparable stage. Surgery is the preferred treatment for patients with stage I or II. Radiation therapy may be considered for patients with early-stage disease who are not surgical candidates, and also as a part of a multimodality treatment for patients with stage III. Advanced disease is treated with combination chemotherapy regimens similar to other types of non-small-cell lung cancer. The presence of epidermal-growth-factor-receptor mutations has been demonstrated in about 26% of bronchioloalveolar carcinoma in one series.<sup>9</sup> This has opened a potential role for small-molecule epidermal-growth-factor-receptor inhibitors as treatment for bronchioloalveolar carcinoma. Epidermal-growth-factor-receptor belongs to a family of cell-surface receptors with intrinsic tyrosine kinase activity, which play a key role in the behavior of malignant cells in a variety of human tumors, including lung cancer. In a non-randomized, phase-II study, treatment with epidermal-growth-factor-receptor inhibitors was associated with a significantly higher response rate and improvement in progression-free survival in patients with epidermal-growth-factor-receptor mutations. These drugs may be considered in patients who failed 1 or 2 prior chemotherapy regimens. The role of small-molecule epidermal-growth-factor-receptor inhibitors as first-line therapy for advanced disease appears promising but awaits randomized studies before this approach becomes standard of care.<sup>10</sup>

Refractory hypoxemia due to intrapulmonary shunting has been reported to improve with the resection of the involved lobe.<sup>7</sup> Corticosteroids, macrolides, inhaled indomethacin, and octreotide have been used to treat bronchorrhea. The survival of patients with bronchioloalveolar carcinoma is better than for those with non-bronchioloalveolar carcinoma non-small-cell lung cancer in all stages. In a large epidemiologic study, the 1-year survival rate for bronchioloalveolar carcinoma patients was 64.9%, and this was both clinically and statistically significant compared to other subtypes (41% and 40% for squamous-cell carcinomas and non-bronchioloalveolar-carcinoma adenocarcinomas, respectively).<sup>2</sup>

### Teaching Points

- Bronchioloalveolar carcinoma is a subtype of lung adenocarcinoma that is characterized by its well-differentiated cytology, peripheral location, and growth along intact alveolar septa, without evidence of invasion of stroma, pleura, or lymphatic spaces. If there is lymphatic invasion, the tumor is classified as an adenocarcinoma, mixed subtype with predominant bronchioloalveolar carcinoma.
- Surgical biopsy is recommended to establish a histopathologic diagnosis of bronchioloalveolar carcinoma. However, if the patient cannot undergo surgical lung biopsy, the presence of certain radiologic features (single or mul-

tifocal lesions with ground-glass appearance or dense pneumonic consolidation), along with histopathologic features compatible with bronchioloalveolar carcinoma on transbronchial or core needle biopsy, can suggest the diagnosis of bronchioloalveolar carcinoma.

- Bronchioloalveolar carcinoma can present as a solitary peripheral lung lesion, lobar consolidation (mimicking bacterial pneumonia), or multiple pulmonary lesions. Bronchorrhoea, hypoxemia due to intrapulmonary shunting, and respiratory failure are rare presentations.
- The presence of epidermal-growth-factor-receptor mutations in about one fourth of these tumors has opened a potential target for small-molecule epidermal-growth-factor-receptor inhibitors as treatment for bronchioloalveolar carcinoma.

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