Bronchioloalveolar Carcinoma Masquerading as Pneumonia

William H Thompson MD

Bronchioloalveolar carcinoma (BAC) is a relatively rare adenocarcinoma that typically arises in the lung periphery and grows along alveolar walls, without destroying the lung parenchyma. It is often multicentric and may arise from a previously stable scar. Because the parenchyma is preserved and because BAC may arise simultaneously in multiple lobes, the chest radiograph and symptoms (cough, chest pain, and sputum production) may be indistinguishable from pneumonia or other noninfectious inflammatory processes (eg, hypersensitivity pneumonitis or bronchiolitis obliterans). The clinician should suspect BAC if what otherwise appears to be pneumonia lacks fever or leukocytosis or does not respond to antibiotics. BAC accounts for 2.6–4.3% of all lung cancers. On a radiograph, BAC often appears as a solitary nodule, but may also appear as patchy, lobar, or multilobar infiltrates, often with air bronchograms indistinguishable from pneumonia. Positron-emission tomography does not help distinguish BAC from pneumonia. Among BAC patients, 62% present without symptoms and with only an abnormal radiograph, whereas 38% present with symptoms of cough, chest pain, and sputum production. Bronchoscopy is usually normal. Preoperative diagnosis with transbronchial biopsy, bronchoscopic cytology examination, or expectorated sputum cytology is more common with the diffuse or multicentric forms. Cure depends on complete resection. A trial of antibiotics and reassessment of clinical findings is a reasonable approach, but biopsy or cytology is the only means of ruling in malignancy and ruling out other etiologies, so biopsy should always be considered when a presumed pneumonia does not respond to antibiotics. I saw a 61-year-old man whose initial diagnosis was pneumonia. He took a 10-day course of oral azithromycin, but his symptoms and chest radiograph were unchanged. A tomogram showed interstitial prominence and peripheral air-space disease in the right upper and lower lobes. Transbronchial biopsy of the right upper lobe showed Clara cells, with substantial atypia and various nuclear-cytoplasmic ratios. The underlying pulmonary architecture was preserved and no invasive component was seen. The diagnosis was changed to nonmucinous BAC. Pneumonectomy was successful and he was cancer-free for about 10 months, after which the cancer returned and from which he eventually died. *Key words: bronchioloalveolar carcinoma, lung cancer, pneumonia.* [Respir Care 2004;49(11):1349–1353. © 2004 Daedalus Enterprises]

Introduction

Bronchioloalveolar carcinoma (BAC) is a relatively rare subtype of adenocarcinoma that typically arises in the periphery of the lung and grows along alveolar walls, without destruction of the underlying parenchyma. It is often multicentric and may arise initially from around a previously stable scar.[1] Because the underlying pulmonary architecture is preserved and because BAC may present simultaneously in multiple lobes, radiographic images may be indistinguishable from pneumonia.[2] Many patients will present with symptoms of cough, chest pain, and sputum production,[2] which again makes it difficult to distinguish BAC from infectious pneumonia and other noninfectious pulmonary inflammatory processes. But its treatment is substantially different from those of other processes, and therefore its recognition by physicians and respiratory therapists is important.

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Case Summary

A 61-year-old man with a history of emphysema and an 80 pack-year history of smoking presented to the outpatient clinic complaining of 2 weeks of increased cough, which was becoming progressively more productive of a thin, white sputum. He had actually collected and presented the whole morning's sputum in a clear vial. On closer inspection, the sputum measured approximately 40 mL, and, except for a thin layer of thick, white, blood-tinged mucus on the top, it was clear and only slightly more viscous than water. On further questioning he admitted that the blood streaks had been present for several weeks and that they had not worsened over that time. Otherwise, he complained of no fever, chills, or sweats. His chronic intermittent left anterior chest pain had not changed, and his substantial dyspnea on exertion had only minimally worsened.

His medical history was remarkable for emphysema, degenerative arthritis, and prior alcohol abuse. He had an 80 pack-year history of smoking and continued to smoke one half pack per day. He denied any history of tuberculosis contacts or risk factors for human immunodeficiency virus. Medications included theophylline, ranitidine, ipratropium via metered-dose inhaler, and albuterol via metered-dose inhaler.

On physical examination, he was a thin man in no acute distress, breathing comfortably, with occasional cough. He was afebrile, with normal blood pressure and heart rate. He had only faint end-inspiratory crackles over the upper anterior and lower posterior chest on the right. There were very mild, scattered expiratory wheezes bilaterally. No dullness was appreciated, and heart tones were regular but distant. Abdominal, extremity, and neurologic exams were all normal.

Laboratory values of note included hemoglobin 17.1 g/dL, white blood cells 9,500/μL, platelets 366,000/μL, and normal chemistry profile and liver function tests. While breathing room air, an arterial blood gas analysis demonstrated pH 7.37, P_{aCO_2} 34 mm Hg, and P_{aO_2} 71 mm Hg. Sputum Gram-stain showed < 25 polymorphonuclear leukocytes and > 10 epithelial cells per low-power field, and 3+ oral flora. The culture eventually grew only 3+ mixed oral flora. Direct fluorescent antibody test of sputum for *Legionella* was negative. The chest radiograph (Fig. 1) demonstrated hyperexpanded lungs, with substantial apical bullous disease, as well as new right mid-lung infiltrates consistent with air-space disease.

A presumptive diagnosis of pneumonia was made, and the patient was placed on a 10-day course of oral azithromycin. Over the subsequent 10 days he had no change in his symptoms or chest radiograph. Besides the underlying emphysematous changes, a chest tomogram demonstrated interstitial prominence and peripheral air-space disease in the right upper and lower lobes (Fig. 2). Bronchoscopy with transbronchial biopsies of the right upper lobe was performed, and pathology examination showed Clara cells with substantial atypia and various nuclear-cytoplasmic ratios. The underlying pulmonary architecture was preserved and no invasive component was seen. Therefore, a presumptive diagnosis of nonmucinous BAC was made.

Further staging demonstrated no evidence of tumor outside the right upper and lower lobes, and pulmonary function tests showed that the ratio of forced expiratory volume in the first second to forced vital capacity (FEV_1/FVC) was 0.58, FEV_1 was 2.94 L (84% of predicted), total lung capacity was 2.77 L (111% of predicted), and the diffusing capacity of the lung for carbon monoxide was 10.31 mL/min/mm Hg (46% of predicted). The patient was subsequently taken for right pneumonectomy. He tolerated surgery well. Pathology evaluation of the entire right lung confirmed the diagnosis of nonmucinous BAC with preservation of the underlying parenchymal structure. Several bullous lesions were lined by malignant cells (Fig. 3). The visceral pleural lining and hilar lymph nodes were free of tumor, while the more distal, intrapulmonary lymph nodes did contain malignant cells. However, approximately 10 months after his original diagnosis he developed recurrent BAC in his left lung. He had a partial response to oral gefitinib (Iressa) but eventually died of his disease.

Discussion

Though BAC makes up at most 2.6–4.3% of all lung cancers,[2,3] it is an important entity in that it can masquerade as pneumonia, and as such, must be listed in the differential of nonresolving "pneumonia." It is characterized as an adenocarcinoma that grows along the alveolar septae without invasion of stromal, pleural, or vascular structures, thus preserving the underlying structure of the lung. The older (1981) World Health Organization classification[4] allowed tumors with invasive growth to be classified as BAC, thus making it difficult to review and compare earlier literature to newer data. Because patients with noninvasive BAC may be cured with surgical resection,[5] the criteria for diagnosis was changed in 1999 to exclude invasive tumors.[6] Some invasive adenocarcinomas have BAC characteristics, especially in metastatic foci and along the periphery of the original tumor mass. However, if any component of invasion exists, the tumor can no longer be considered pure BAC. For that reason, a diagnosis of BAC technically cannot be confirmed until the entire malignancy has been resected and examined histologically.

Three subtypes of BAC are recognized:[6,7] nonmucinous, mucinous, and mixed mucinous and nonmucinous tumors. Ultrastructurally, the nonmucinous type is composed of Clara cells and/or type II pneumocytes, whereas the mucinous cells resemble mucous (goblet) cells. BAC, as in

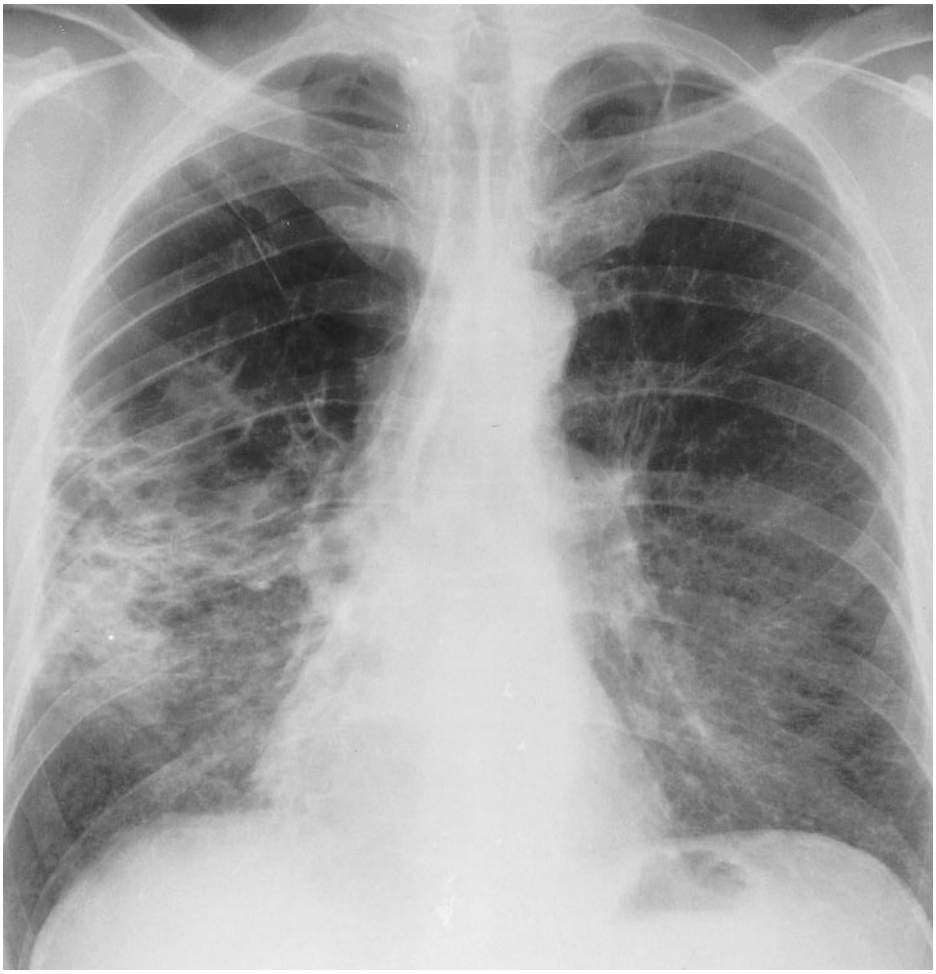

Fig. 1. Initial posteroanterior chest radiograph demonstrating hyperexpanded lungs, apical bullae, and new right mid-lung infiltrates.

this case, is often multicentric, but many disagree as to whether that indicates multifocal origins or aerogenous dissemination of the malignant cells.

Radiographically, BAC often presents as a solitary nodule. However, a radiograph may also demonstrate patchy, lobar, or multilobar infiltrates, often with air bronchograms that are indistinguishable from pneumonia.[2] Positron-emission tomography also does little to distinguish BAC from pneumonia, in that it has a relatively high rate of false negative results in BAC and false positive results in infectious and other inflammatory processes.[8,9] Clinically, 62% of patients present without symptoms and with only an abnormal chest radiograph. The other 38% present with symptoms of cough, chest pain, and sputum production.[2] Bronchoscopic examination is usually normal. Preoperative diagnosis with transbronchial biopsy, bronchoscopic cytology examination, or expectorated sputum cytology is more common with the diffuse or multicentric forms.

Like other pulmonary adenocarcinomas, treatment for cure depends on complete surgical resection.[10] However, because of the propensity of BAC to recur in multiple foci, more emphasis is placed on sparing uninvolved lung, with greater use of wedge resection and lobectomy, rather than more extensive resection.[10] Compared to other lung cancers, BAC tends to have a better prognosis, with 5-year survival up to 100% found in cases in which the tumor had one of the following histologic characteristics: a pattern of lepidic (scale-like) growth of more that 75%, lack of destruction of the elastic fiber framework, or a central scar of $\leq$ 5 mm.[11] Mortality is worse if the tumor has diffuse lesions, as compared to nodular lesions.[2] Statistics of overall prognosis vary considerably, depending on whether the older (ie, pre-1999) or newer diagnostic criteria for BAC are used to define the tumors. Nonetheless, a recent review suggests that complete resection of even multifocal BAC may achieve survival rates similar to those of stages I and II unifocal disease in other forms of non-small-cell lung cancers.[12] As would be expected, subjects with vascular invasion and a component of papillary growth (those who do not meet current criteria for BAC) do not fare as well.

BAC may radiographically and clinically resemble not only pneumonia, but also noninfectious inflammatory pro-

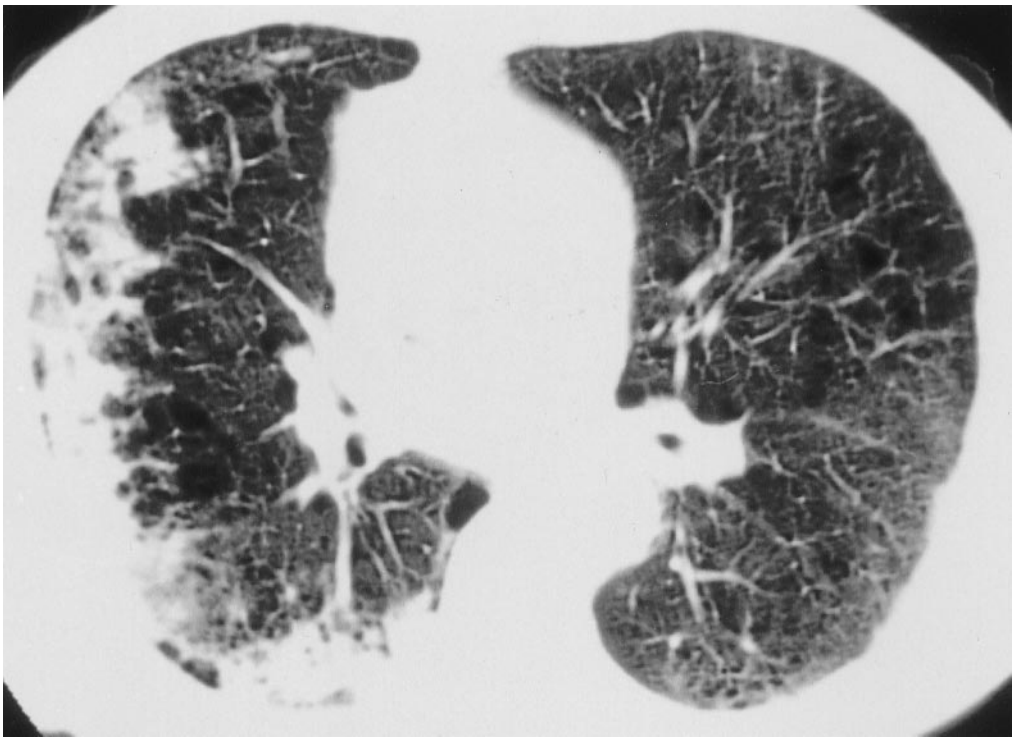

Fig. 2. Tomogram of the patient's chest, demonstrating peripheral air-space disease in the right upper and lower lobes.

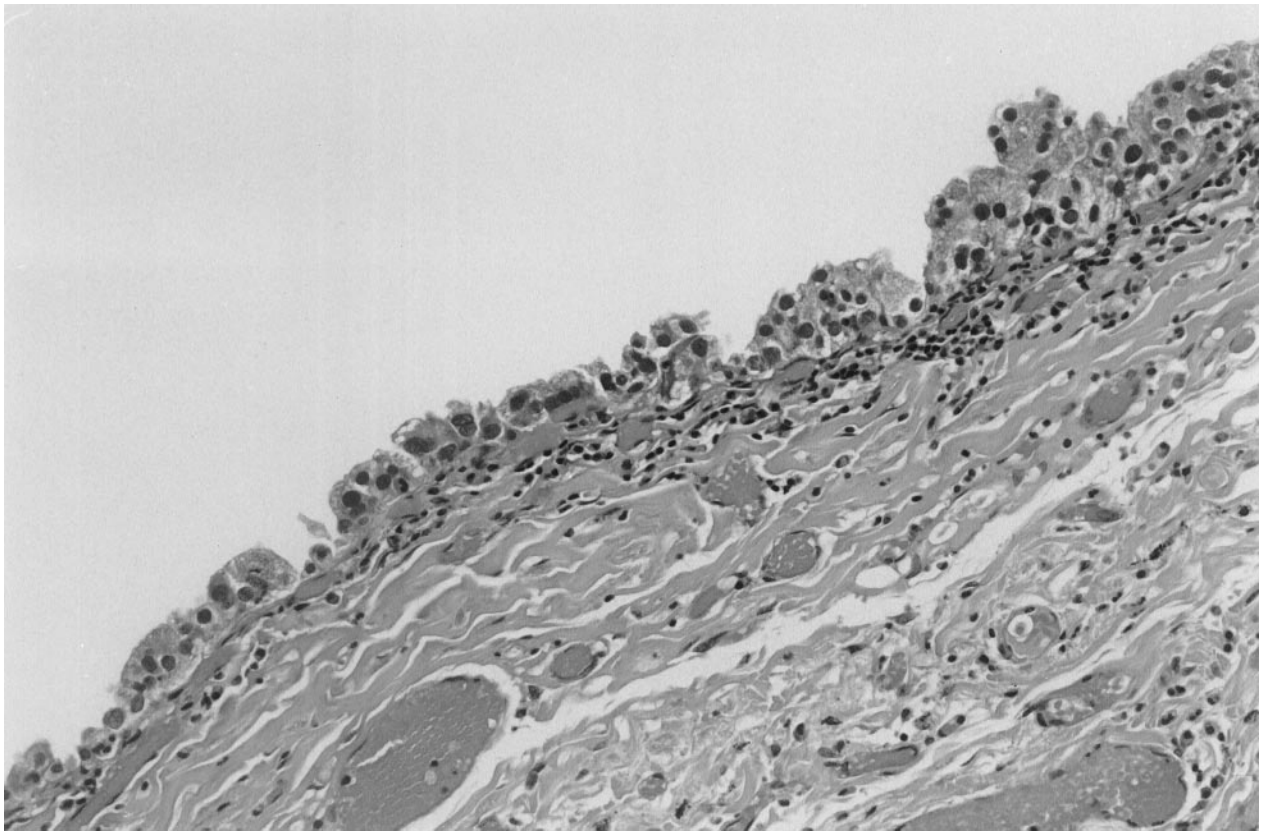

Fig. 3. Photomicrograph of the wall of a bulla. Nonmucinous bronchioloalveolar cells line the otherwise normal wall of the bulla. Note the substantial variation in nuclear-cytoplasmic ratios and lack of invasion.

cesses of the lung, including hypersensitivity pneumonitis, bronchiolitis obliterans, and various vasculitic processes. Lack of fever and leukocytosis should raise suspicion about a diagnosis of infectious pneumonia, and a focal or unilateral infiltrate points against many of the other nonmalignant diseases. An empirical trial of antibiotics and reassessment of clinical findings is a reasonable approach. However, biopsy or cytologic examination is the only means of ruling in a diagnosis of malignancy and ruling out other etiologies. Thus biopsy should always be considered when patients do not respond to antibiotics.

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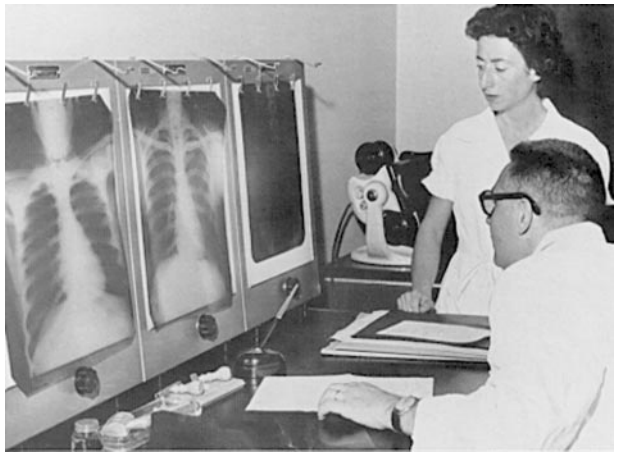

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