Cytopathologic Diagnosis of Bronchioloalveolar Carcinoma
Does It Correlate With the 1999 World Health Organization Definition?

N. Paul Ohori, MD, and Edward L. Santa Maria, MD

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Abstract

We identified 29 bronchial washing, bronchoalveolar lavage, sputum, and fine-needle aspiration specimens with corresponding surgical pathology specimens with features of bronchioloalveolar carcinoma (BAC). Surgical pathology correlates were reclassified according to the 1999 World Health Organization classification into pure BAC, mixed adenocarcinoma–BAC (AD-BAC), and papillary adenocarcinoma (PAP-AD). Twelve cases of invasive pulmonary adenocarcinoma (INV-AD) without a bronchioloalveolar component were reviewed for comparison. The cytology slides were evaluated for 12 features of BAC. No statistically significant feature permitted separation of BAC from AD-BAC or from PAP-AD. However, comparison of BAC with INV-AD identified 9 statistically significant cytologic features: clean background, absence of 3-dimensional clusters, neoplastic cells in flat sheets, orderly arrangement of cells with round uniform nuclei, predominance of mucinous cells, absence of nuclear overlap, absence of irregular nuclear membranes, fine granular chromatin, and nuclear grooves that were features of BAC cases. Although cytologic evaluation cannot prospectively diagnose BAC, the bronchioloalveolar pattern may be recognized and suggests in situ proliferation that is present in BAC, AD-BAC, or PAP-AD. The bronchioloalveolar pattern must be correlated with clinical, radiographic, and histologic parameters to determine whether the tumor is localized, multifocal, or diffuse and whether there is parenchymal invasion.

Bronchioloalveolar carcinoma (BAC) has been a popular topic in the cytopathology literature, and there has been much interest in making a prospective diagnosis by applying the cytomorphic criteria. During the 4 decades since the description of this entity by Liebow,¹ the concept BAC has evolved and the diagnosis has become narrowly defined. The third edition (1999) of Histological Typing of Lung and Pleural Tumours by the World Health Organization (WHO) is the most widely accepted document defining the criteria for pulmonary neoplasms.² By these criteria, BAC shows a pure bronchioloalveolar growth pattern with no evidence of stromal, vascular, or pleural invasion. Because this definition emphasizes architecture, the question arises as to whether a prospective diagnosis of BAC can be made from cytologic specimens. The objectives of the present study were to determine whether the previously stated cytologic features of BAC correlate with the diagnosis of BAC as defined by the 1999 WHO document and to determine the significance of the “BAC pattern” in cytologic specimens.

Materials and Methods

Case Selection

Cases of BAC were identified from the surgical pathology files of the University of Pittsburgh Medical Center-Presbyterian Hospital, Pittsburgh, PA, from January 1983 to December 2002. The term bronchioloalveolar was searched by natural language computer (CoPath-Plus Laboratory Information System, Cerner, Kansas City, MO) search in the “final diagnosis” field of our surgical pathology reports. The surgical
pathology cases were reexamined and classified according to the 1999 WHO classification. The surgical pathology cases originally signed out as “BAC” were reclassified as pure BAC, mixed adenocarcinoma–BAC, and papillary adenocarcinoma. From these cases, the subset with corresponding cytologic specimens (bronchial washing, bronchoalveolar lavage, sputum, and fine-needle aspiration [FNA]) with diagnostic neoplastic cells was identified. The cytology and surgical pathology cases were randomized and coded by our “honest broker,” who is not a coauthor of the present study. For comparison, 12 paired cytopathology and surgical pathology cases of invasive pulmonary adenocarcinoma without a bronchioloalveolar component were identified and analyzed.

**Cytopathologic Analysis**

Without knowledge of the reclassified surgical pathology diagnoses, the cytologic slides were evaluated for the presence or absence of previously described features of BAC, including clean background, 3-dimensional clusters, flat sheets, papillae, orderly arrangement of cells with round uniform nuclei, predominance of mucinous cells, overlapping nuclei, irregular nuclear membranes, fine granular chromatin, macronucleoli, intranuclear cytoplasmic inclusions, and nuclear grooves. A case was determined as having a feature when it was present in the majority of the areas. For example, if a specimen had only 1 flat sheet with numerous single cells, the case was not counted as having flat sheets in Table 1. Both of us participated in reviewing each case. Any difference in opinion was resolved over a double-headed microscope. For statistical analysis, the Fisher exact test was used to compare the results between groups. A P value of less than .05 was defined as the level of significance. The study was reviewed and approved by the institutional review board of the University of Pittsburgh.

**Table 1**

<table>
<thead>
<tr>
<th>Cytologic Feature</th>
<th>BAC (n = 6)</th>
<th>Mixed Adenocarcinoma-BAC (n = 17)</th>
<th>Papillary Adenocarcinoma (n = 6)</th>
<th>Invasive Adenocarcinoma (n = 12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean background</td>
<td>6 (100)</td>
<td>17 (100)</td>
<td>6 (100)</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Three-dimensional clusters</td>
<td>2 (33)</td>
<td>13 (76)</td>
<td>6 (100)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Flat sheets</td>
<td>5 (83)</td>
<td>17 (100)</td>
<td>6 (100)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Papillae</td>
<td>0 (0)</td>
<td>1 (6)</td>
<td>2 (33)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Orderly arrangement of cells with round uniform nuclei</td>
<td>5 (83)</td>
<td>6 (35)</td>
<td>3 (50)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Predominance of mucinous cells</td>
<td>3 (50)</td>
<td>2 (18)</td>
<td>2 (33)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Overlapping nuclei</td>
<td>2 (33)</td>
<td>13 (76)</td>
<td>5 (83)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Irregular nuclear membranes</td>
<td>3 (50)</td>
<td>15 (88)</td>
<td>5 (83)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Finely granular chromatin</td>
<td>6 (100)</td>
<td>9 (53)</td>
<td>3 (50)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Macronucleoli</td>
<td>2 (33)</td>
<td>7 (41)</td>
<td>5 (83)</td>
<td>10 (83)</td>
</tr>
<tr>
<td>Intranuclear cytoplasmic inclusions</td>
<td>0 (0)</td>
<td>7 (41)</td>
<td>4 (67)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Nuclear grooves</td>
<td>6 (100)</td>
<td>14 (82)</td>
<td>3 (50)</td>
<td>3 (25)</td>
</tr>
</tbody>
</table>

BAC, bronchioloalveolar carcinoma.

* Data are given as number (percentage).

**Results**

The distribution of types of cytologic specimens was as follows: FNA, 30; bronchial washing, 4; bronchial brushing, 4; bronchoalveolar lavage, 2; and sputum, 1. Aside from the FNA specimens, the number of the other cytology specimens was too few to perform a meaningful statistical analysis comparing the specimen types.

The presence of each cytologic parameter for BAC, mixed adenocarcinoma–BAC, papillary adenocarcinoma, and invasive pulmonary adenocarcinoma was recorded (Table 1). Of the 6 BAC cases, 3 were of the mucinous and 3 were of the nonmucinous subtype. The typical BAC showed cytologic features including clean background, absence of 3-dimensional clusters, neoplastic cells in flat sheets, orderly arrangement of cells with round uniform nuclei, absence of nuclear overlap, absence of irregular nuclear membranes, fine granular chromatin, and nuclear grooves Image 11. The corresponding resection specimen of BAC showed the proliferation of neoplastic cells without stromal invasion Image 21.

Cytopathologic features of mixed adenocarcinoma–BAC and papillary adenocarcinoma overlapped with BAC Image 31. However, there was a tendency for mixed adenocarcinoma–BAC to show less orderliness of the neoplastic cells and lack of fine granular chromatin Image 41. Interestingly, papillary adenocarcinoma demonstrated a tendency to show more 3-dimensional cell clusters and more intranuclear pseudoinclusions Image 51. The cytologic features of invasive pulmonary adenocarcinoma were strikingly different from those of BAC. Most notably, invasive pulmonary adenocarcinoma lacked the cytologic features associated with BAC, including clean background, neoplastic cells in flat sheets with orderly arrangement of round uniform nuclei, fine granular chromatin, and nuclear grooves Image 61.
Comparison of BAC with the other types of adenocarcinoma by using the Fisher exact test revealed that there was no statistically significant feature that permitted the separation of BAC from mixed adenocarcinoma–BAC and BAC from papillary adenocarcinoma. However, the absence of the features—orderly arrangement of cells with round uniform nuclei and finely granular chromatin—showed a tendency toward significance ($P = .069$ and $P = .058$, respectively) in mixed adenocarcinoma–BAC. In papillary adenocarcinomas, 3-dimensional cell clusters and intranuclear pseudoinclusions were more common, although they were not statistically significant ($P = .061$ for both). Comparison of BAC with invasive pulmonary adenocarcinoma resulted in the identification of 9 statistically significant cytologic features:

**Image 1** Cytologic features of a typical bronchioloalveolar carcinoma included clean background, absence of 3-dimensional clusters, neoplastic cells in flat sheets, orderly arrangement of cells with round uniform nuclei, absence of nuclear overlap, absence of irregular nuclear membranes, fine granular chromatin, and nuclear grooves (Papanicolaou, ×460).

**Image 2** The resected bronchioloalveolar carcinoma showed a pure lepidic growth pattern of the neoplastic cells (H&E, ×230).

**Image 3** A case of the mixed adenocarcinoma–bronchioloalveolar carcinoma subtype that was indistinguishable cytologically from bronchioloalveolar carcinoma (Papanicolaou, ×460).

**Image 4** Some cases of the mixed adenocarcinoma–bronchioloalveolar carcinoma subtype showed a tendency toward less orderly neoplastic cells and lack of fine granular chromatin (Papanicolaou, ×460).
clean background, absence of 3-dimensional clusters, neoplastic cells in flat sheets, orderly arrangement of cells with round uniform nuclei, predominance of mucinous cells, absence of nuclear overlap, absence of irregular nuclear membranes, fine granular chromatin, and nuclear grooves that were features of BAC cases [Table 2].

Discussion

In 1876, Malassez was the first to describe the disease we know today as bronchioloalveolar carcinoma.\(^1\) However, for the next century, there was a lack of consensus in terminology. Synonyms for BAC included bronchiolar carcinoma, alveolar cell carcinoma, and pulmonary adenomatosis. From a modern perspective, Liebow’s\(^1\) article from 1960 is cited often as a landmark document describing this entity. In the article, he described BAC as a “well differentiated adenocarcinoma…with a tendency to spread chiefly within the confines of the lung by aerogenous and lymphatic routes.” Perhaps the important points he stressed were that BACs have a tendency to spread within but remain confined to the lung and that the tumor can produce death without extrapulmonary metastasis. He stated that distinction...
between BAC and conventional adenocarcinoma was difficult, if not impossible, at that time.

Later, the second edition of the WHO Histological Typing of Lung Tumors (1981) included BAC as “an adeno-carciroma in which cylindrical tumor cells grow upon the walls of preexisting alveoli.” Much attention was focused on the recognition of the classic bronchioalveolar (lepidic) growth pattern, which is the characteristic pattern of BAC Figure 1A. However, it is seen also at the periphery of some conventional invasive adenocarcinomas Figure 1B. Owing to the lack of consensus of uniform criteria for BAC, the literature on BAC from the 1980s and 1990s often included invasive adenocarcinomas with a peripheral lepidic growth pattern by neoplastic cells. Also during this period, papillary adenocarcinoma often was included with BAC in a single category.

To improve diagnostic consistency, the third edition of the WHO classification detailed revisions to some of the diagnoses. In this revision, BAC was defined as “an adenocarcinoma with a pure bronchioalveolar growth pattern and no evidence of stromal, vascular or pleural invasion.” Furthermore, the 1999 WHO definition stated “on biopsy or cytology specimens…it will be impossible to make a final histological subclassification since the presence of invasion cannot be excluded.” Also, papillary adenocarcinoma was separated from BAC as “an adenocarcinoma with a predominance of papillary structures that replaces the underlying alveolar architecture.” These neoplasms also have complex secondary and tertiary papillary branches and might show invasion into the lung parenchyma.

During the last 3 decades, a number of studies addressed the issues regarding the diagnosis of BAC by cytologic methods. Because the neoplastic cells of BAC showing mucinous, type 2 pneumocyte, or Clara cell differentiation have a tendency to exfoliate into the airspaces, various procedures, including bronchial washing, bronchoalveolar lavage, sputum collection, and FNA are suitable for procuring the diagnostic material. From these previous studies, the commonly quoted features of BAC included clean background, 3-dimensional clusters, flat sheets, papillae, orderly arrangement of cells with round uniform nuclei, predomiance of mucinous cells, overlapping nuclei, irregular nuclear membranes, fine granular chromatin, macronucleoli, intranuclear cytoplasmic inclusions, and nuclear grooves. Most of these studies stated that it was possible to make the diagnosis of BAC from cytologic specimens. However, these studies were performed before the application of the 1999 WHO criteria, and, therefore, a number of the surgical pathology correlates might have represented mixed adenocarcinoma–BAC or other types of adenocarcinoma.

By evaluating the 12 cytologic parameters in BAC, mixed adenocarcinoma–BAC, papillary adenocarcinoma, and invasive pulmonary adenocarcinoma, we found that no feature represented a statistically significant discriminator when comparing BAC with mixed adenocarcinoma–BAC and BAC with papillary adenocarcinoma. On the other hand, 9 cytologic features, including clean background, absence of 3-dimensional clusters, neoplastic cells in flat sheets, orderly arrangement of cells with round uniform nuclei, predomiance of mucinous cells, absence of nuclear overlap, absence

![Figure 1A](https://example.com/bac_pattern.png)  Bronchioalveolar carcinoma (BAC) with a pure lepidic growth pattern.  
![Figure 1B](https://example.com/adenocarcinoma_pattern.png)  Invasive adenocarcinoma with peripheral areas of a lepidic growth pattern (a, focus of invasion; b, area of fibrosis; c, peripheral lepidic growth [bronchioalveolar] pattern).  
![Figure 1C](https://example.com/multifocal_bac.png)  Multifocal BAC.  
![Figure 1D](https://example.com/diffuse_pneumonic_pattern.png)  Diffuse pneumonic pattern of BAC. This pattern is present most often with the mucinous subtype.
of irregular nuclear membranes, fine granular chromatin, and nuclear grooves, were statistically significant discriminators for distinguishing BAC from invasive pulmonary adenocarcinoma (Table 2).

If pulmonary adenocarcinomas manifested only as pure BAC or invasive pulmonary adenocarcinoma forms, we would be able to distinguish them cytologically. However, under the current 1999 WHO classification of pulmonary neoplasms, we also must consider the possibility of mixed adenocarcinoma–BAC and papillary adenocarcinoma. When differentiating BAC from mixed adenocarcinoma–BAC, radiologic correlation with attention to the possible presence of a peripheral subpleural scar, size of the tumor, and a homogeneous and ground-glass radiographic appearance provides clues. The distinction between BAC and papillary adenocarcinoma would be more difficult, even with clinical and radiologic correlation. If true papillary fronds are present on cytologic samples, the diagnosis of papillary adenocarcinoma might be favored; however, this finding is not consistently present in papillary adenocarcinoma. The cytologic bronchioloalveolar pattern might be recognized; however, the possibility of invasion or presence of another type of in situ growth pattern (eg, papillary) might not be excluded by cytologic evaluation alone. Although the neoplastic cell types (mucinous, Clara, type 2 pneumocyte differentiation) might be recognized cytologically in BAC, mixed adenocarcinoma–BAC, papillary adenocarcinoma, and invasive pulmonary adenocarcinoma, the architectural complexity is best identified on surgically resected specimens.14-16

Although a prospective BAC diagnosis is not realistic, there still is merit to recognizing the bronchioloalveolar pattern on cytologic specimens because the pattern seems to have prognostic significance. BACs often are stated to have a better prognosis. However, prognostication cannot be made by recognition of the cytologic pattern alone but rather requires correlation with clinical and radiologic parameters. Patients with small, localized, solitary BACs that are resected completely may expect long-term survival and potential cure.15,16 Furthermore, Castro et al,17 Higashiyama et al,18 and Terasaki et al19 have shown that for localized adenocarcinomas, the higher the percentage of the bronchioloalveolar component, the better the prognosis. In this respect, the bronchioloalveolar component may be regarded as an in situ component. These studies also showed that the probability of lymph node metastasis was inversely proportional to the amount of the bronchioloalveolar component of the adenocarcinoma.

One of the interesting biologic properties of the bronchioloalveolar proliferation is its propensity to spread aerogenously to other intrapulmonary sites without showing stromal invasion. Multifocality in BAC may manifest as small satellite foci in the same or different lobes as the primary tumor Figure 1Cl. However, in extensive cases, the tumor spreads diffusely, involving the lung fields, and “drows” the patient by uncontrolled intra-alveolar mucin secretions Figure 1Di. In a study by Ebright et al20 the patients with the diffuse pneumonic pattern of BAC had a significantly worse prognosis (median survival, 18.7 months) than patients with localized or multifocal BAC.

The histopathologic definition of BAC has evolved during the last few decades so that currently, no stromal invasion is permitted for a diagnosis of BAC. Although cytologic evaluation cannot prospectively diagnose BAC, the bronchioloalveolar pattern might be recognized and suggests the possibility of in situ proliferation with aerogenous multifocal spread. The cytologic finding of the bronchioloalveolar pattern by itself cannot be used for prognostication but must be correlated with clinical and radiographic parameters and the resected specimen to determine whether the tumor is localized, multifocal, or diffuse and whether there is evidence of parenchymal invasion.

| Table 3I |

Comparison of Architecture and Cellular Detail of Adenocarcinomas by the 1999 World Health Organization Criteria

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Architecture</th>
<th>Cellular Detail</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAC</td>
<td>Pure bronchioloalveolar growth pattern with preservation of alveolar architecture</td>
<td>Nonmucinous cells (Clara cell, type 2 pneumocyte differentiation); intranuclear inclusions might be present; mucinous cells; low nuclear grade</td>
</tr>
<tr>
<td>Mixed adenocarcinoma–BAC subtype</td>
<td>Invasive adenocarcinoma within desmoplastic fibroblastic stroma identified along with bronchioloalveolar growth pattern</td>
<td>Nonmucinous cells (Clara cell, type 2 pneumocyte differentiation); intranuclear inclusions might be present in bronchioloalveolar component; mucinous cells; low to high nuclear grade</td>
</tr>
<tr>
<td>Papillary adenocarcinoma</td>
<td>Secondary and tertiary papillary branches; invasion into lung parenchyma might be present</td>
<td>Low columnar, nonmucinous cells; intranuclear inclusions might be present; tall columnar or cuboidal cells with or without mucin production; intermediate nuclear grade</td>
</tr>
<tr>
<td>Invasive adenocarcinoma (without bronchioloalveolar growth pattern)</td>
<td>Invasive adenocarcinoma within desmoplastic fibroblastic stroma</td>
<td>Nonmucinous cells (Clara cell, type 2 pneumocyte differentiation); mucinous cells; intermediate to high nuclear grade</td>
</tr>
</tbody>
</table>

BAC: bronchioloalveolar carcinoma.
References