Epithelial Cell Atypia in Bronchoalveolar Lavage Specimens from Lung Transplant Recipients

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Key Words: Atypic; Cytology; Harvest injury; Infection; Pulmonary; Rejection; Transplantation; Type 2 pneumocytes

Abstract

In lung transplant recipients, bronchoalveolar lavage (BAL) is mainly performed to detect infectious agents. However, in addition to microorganisms, epithelial cell atypia may be identified, and determination of its significance is necessary. Specimens obtained at BAL in lung and heart-lung transplant recipients (LTRs) between 1991 and 1998 were examined for the presence of significant cytologic atypia in epithelial cells. Ten cases in 9 patients were identified, and these composed the core of our study. These transplant BAL specimens were compared with 4 BAL specimens with carcinoma from non–transplant patients (NTPs). Fourteen cytologic parameters were evaluated, and clinical and biopsy correlation was made in each case. Significant overlap in cytologic features, including background cellularity, number of atypical cell clusters, number of cells in each cluster, size of cell clusters, contour of clusters, 3-dimensionality, tenacious intercytoplasmic connections, multinucleation, nuclear size, nuclear/cytoplasmic ratio, nuclear membrane irregularity, chromatin pattern, intranuclear inclusions, and nucleolar characteristics, was observed between atypical LTR cases and NTP carcinoma cases. Clinically, all LTR cases derived from nonneoplastic conditions including harvest injury (diffuse alveolar damage), acute cellular rejection, and infections. Our study results show that evaluation of cytologic features alone does not permit differentiation of atypical cells found in nonneoplastic conditions from those in malignant conditions. Clinical and histologic correlation and awareness of the range of atypia seen in posttransplant syndromes is important in correct interpretation of these cases.

Among the various procedures used to monitor lung and heart-lung transplant recipients (LTR), bronchoalveolar lavage (BAL) is mainly used to detect infectious agents.[1–3] However, infections and other allograft syndromes may induce an array of cellular changes in the lung allograft, which may result in nuclear atypia observed in BAL. Previous BAL studies in non–transplant patients (NTP) have documented a wide range of nuclear atypia observed in nonneoplastic conditions.[4,5] These changes were commonly observed in the epithelial cells from acute lung injury such as diffuse alveolar damage. At the same time, the efficacy of BAL in making the diagnosis of malignancy (particularly adenocarcinoma) has been addressed.[6–8] The lung allograft is susceptible to both inflammatory and neoplastic processes, and the distinction between these processes is important because management strategies differ. The objectives of this study were to determine the significance of atypical epithelial cells found in BAL specimens from LTR and to correlate BAL findings with allograft syndromes.

Materials and Methods

In LTRs at our institution, BAL was performed during the first month and then at 1- to 4-month intervals or whenever infection or rejection was suspected. Lavage was performed through the subsegmental bronchus of the lobe showing the greatest radiologic abnormality. Fifty-milliliter to 200 mL aliquots of saline solution were injected into the bronchus, and the retrieved fluid was cytocentrifuged for slide preparation. The aliquots were pooled and separated for microbiologic, cytologic, and additional ancillary studies (if volume permitted). Alcohol-fixed slides stained with the Papanicolaou technique were used to assess cytologic characteristics. BAL specimens from LTR from 1991 to 1998 were examined for the presence of significant atypia in epithelial cells. Of 4,880

BAL specimens, 10 from 9 patients were found to harbor atypical epithelial cells with nuclear changes worrisome for the possibility of a neoplastic process. Atypical lymphoid processes such as posttransplant lymphoproliferative disorders were not evaluated in this study. Fourteen cytologic parameters including background cellularity, number of atypical cell clusters, number of cells in each cluster, size of cell clusters, contour of clusters, 3-dimensionality, tenacious intercytoplasmic connections, multinucleation, nuclear size, nuclear/cytoplasmic ratio (N/C), nuclear membrane irregularity, nuclear chromatin pattern, intranuclear inclusions, and nucleolar characteristics were evaluated in each case. Clinical, radiologic, and biopsy correlations were made in each case. These 10 specimens from LTR were compared with 4 BAL specimens with histologically confirmed carcinoma from NTP.

Results

The primary diseases in the patients undergoing transplantation included severe diffuse alveolar damage, emphysema, bronchiectasis secondary to cystic fibrosis, hypersensitivity pneumonitis, and pulmonary hypertension. Clinical correlation revealed that the atypical cells were derived from 3 allograft syndromes: harvest injury, acute cellular rejection (ACR), and infection. None of these LTR cases demonstrated malignancy as the underlying cause of the atypical cells.

At cytology, the background appearance in 5 of the 10 LTR specimens was characterized predominantly by neutrophils; 4 showed predominantly macrophages, and 1 demonstrated numerous lymphocytes. The atypical cells were found both as single cells and in cell clusters. The size of the cell clusters varied from 50 to 300 μm, and 3-dimensionality was noted in 6 cases. The cell clusters demonstrated knobby cytoplasmic borders, and multinucleation was seen in all cases **Image 1**. None of the specimens exhibited intranuclear inclusion. Tenacious intercytoplasmic connection was seen in 1 case **Image 2**. Some of the reactive cells exhibited pronounced atypia with nucleomegaly and marked nuclear membrane irregularities **Image 3**. Others were conspicuous for high N/C and distinct appearance from the background cell population **Image 4**. The nuclear size ranged from 3 to 10 times the size of a small round lymphocyte. The chromatin pattern of the atypical cells was finely granular or coarse with clumping. Variability in cell size and nuclear features was noted in reactive cell populations. In the original cytopathology, reports all 10 BAL specimens were categorized as "atypical" (on a 4-tiered system composed of "negative," "atypical," "suspicious for malignant cells," and "positive for malignant cells" categories). Review of the diagnostic comments made in these reports revealed that a "suspicious" or "positive" diagnosis was not made because the atypical cell clusters were few in number, and in some cases infectious organisms were identified in the BAL specimen or concurrent biopsy tissue sample. When atypical cytologic features were recognized, the BAL specimens were compared with the corresponding biopsy samples, which in such cases revealed histologic

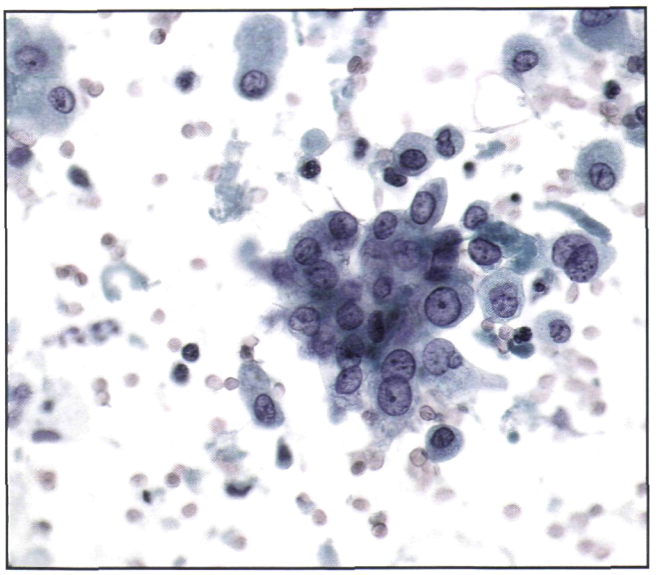

Image 1 Bronchoalveolar lavage specimen from a lung transplant patient with infection. Note 3-dimensional cell cluster with multinucleation and knobby cytoplasmic borders (Papanicolaou, ×500).

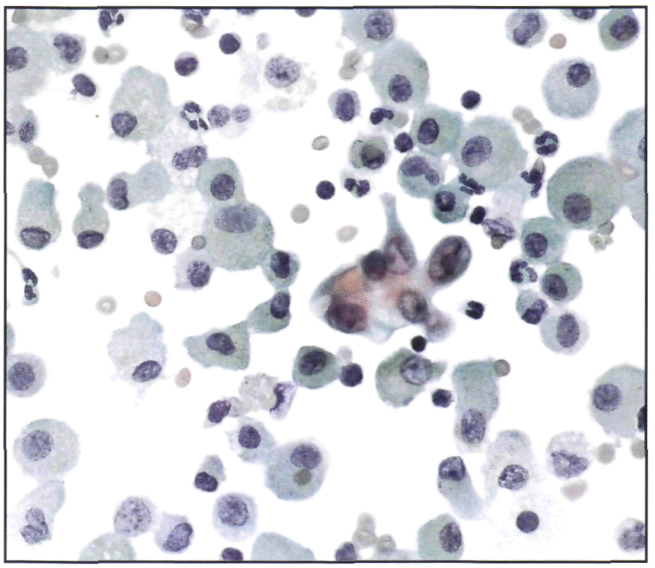

Image 2 Bronchoalveolar lavage specimen from a patient with moderate acute cellular rejection. An atypical reactive epithelial cell with an elongated tenacious intercytoplasmic connection is apparent (Papanicolaou, ×500).

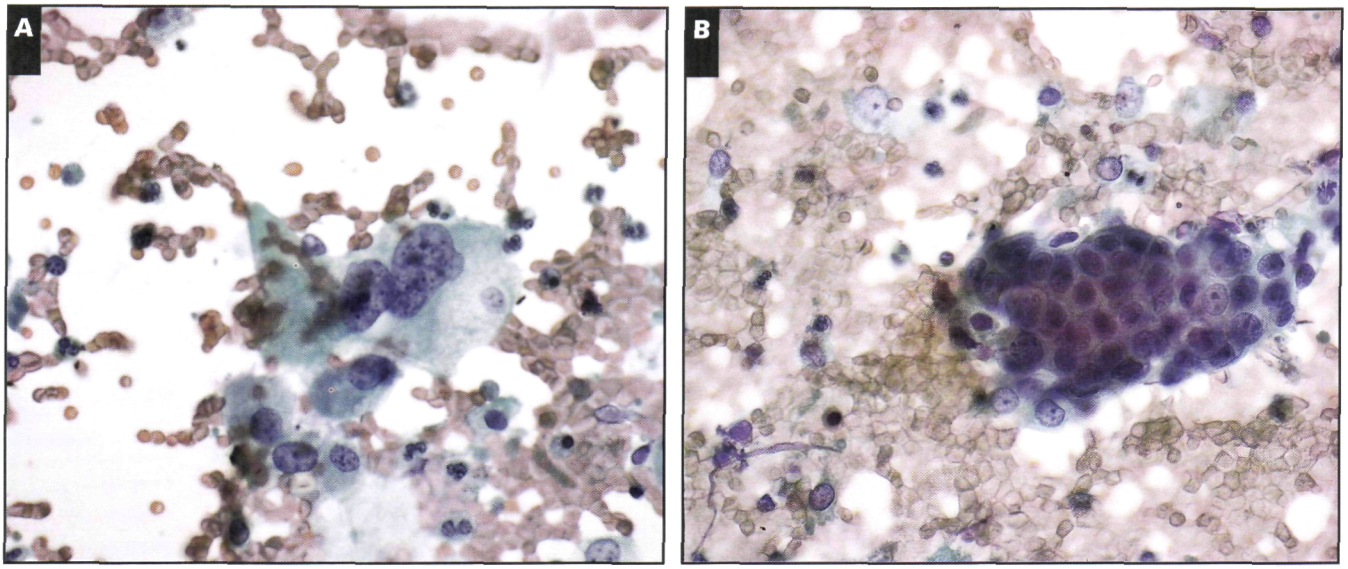

Image 3 Highly atypical cells in bronchoalveolar lavage specimen from a lung transplant recipient with *Aspergillus* infection. A, Markedly enlarged nuclei show irregular nuclear membrane and chromatin clumping. A few neutrophils are noted in the background (Papanicolaou, ×500). B, Same specimen also revealed a cohesive 3-dimensional cluster composed of cells with high nuclear/cytoplasmic ratio, nuclear chromatin clumping, and prominent nucleoli (Papanicolaou, ×500).

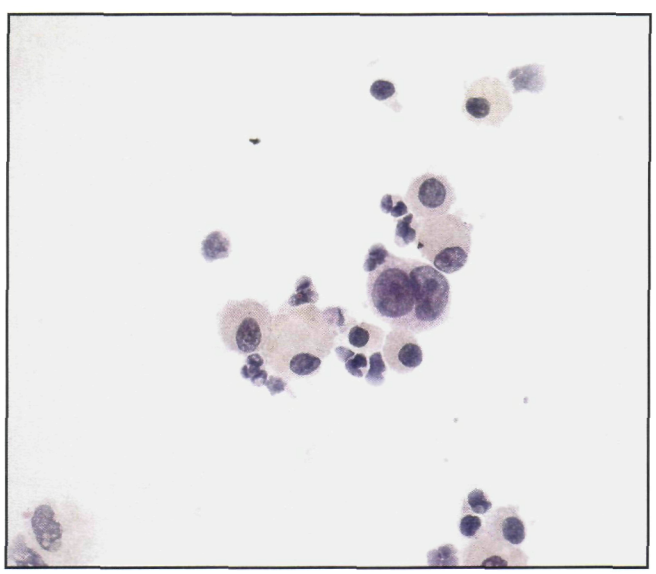

Image 4 Bronchoalveolar lavage specimen in a patient with harvest injury (diffuse alveolar damage), demonstrated isolated cells with high nuclear/cytoplasmic ratio, and prominent nucleoli (Papanicolaou, ×500).

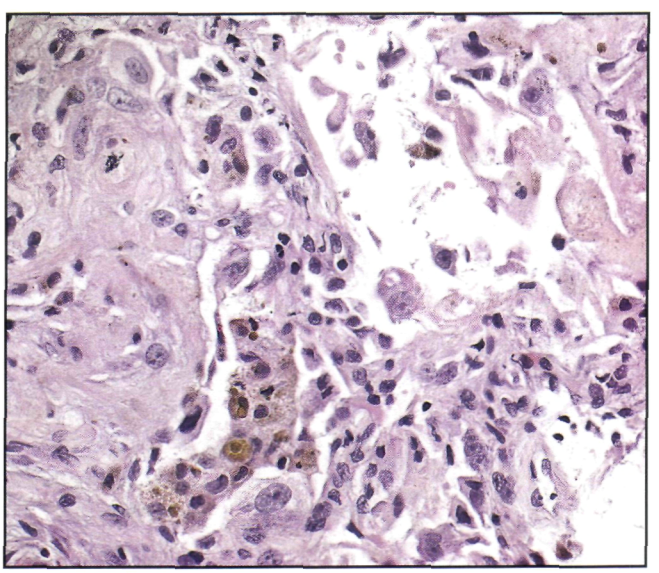

Image 5 Biopsy correlation of the case in Image 1 shows reactive atypical alveolar pneumocytes in an area with old hemorrhage. These correspond to the atypical cells seen in the bronchoalveolar lavage specimen (H&E, ×500).

changes of diffuse alveolar damage (3 cases), ACR (4 cases), and acute infection (3 cases). A common feature seen in all of these processes was interstitial inflammation with varying degrees of atypia present in the lining of alveolar epithelial cells **Image 5**.

Lavage specimens from patients with carcinoma were compared with BAL specimens from LTR. In all of the malignant cases, the cell clusters exhibited knobby contours, 3-dimensionality, and multinucleation **Image 6**. There were 3 to 10 clusters of atypical cells with 1 to 40 cells in each cluster (range 100 to 200 μm), high N/C, nuclear size 3 to 10 times that of small round lymphocytes, moderate to marked nuclear membrane irregularity, coarse chromatin, and a single prominent nucleolus or multiple nucleoli **Image 7**. No intranuclear pseudoinclusions or tenacious intercytoplasmic connection was noted in any of these malignant

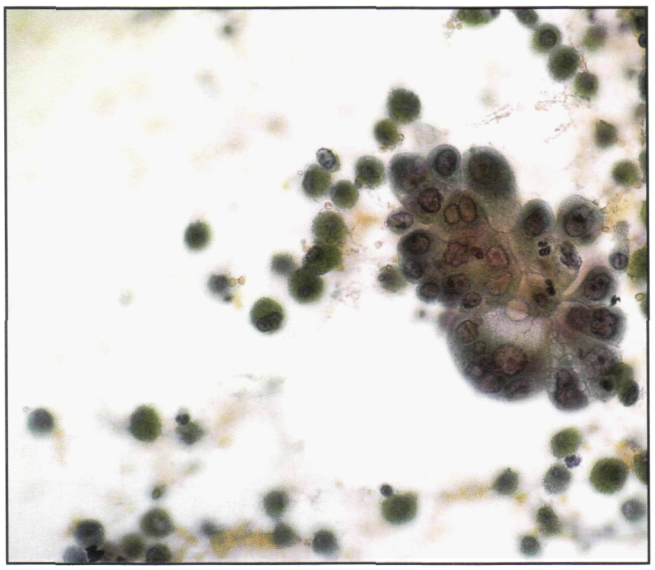

Image 6 Adenocarcinoma in bronchoalveolar lavage specimen. Note 3-dimensional cluster of cells with knobby borders. Degree of nuclear enlargement, nuclear membrane irregularity, and chromatin clumping is similar to that noted in the benign transplant cases (Papanicolaou, ×500).

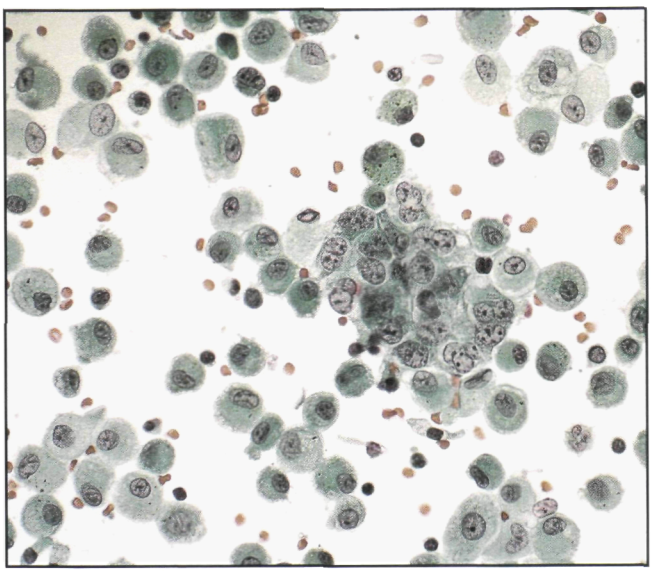

Image 7 Adenocarcinoma in bronchoalveolar lavage specimen. Note neoplastic cells with high nuclear/cytoplasmic ratio, irregular nuclear membranes, and conspicuous nucleoli. While these features are highly atypical, there was significant overlap between these neoplastic cells and the reactive cells from the lung transplant cases (Papanicolaou, ×500).

cases. While these cells were definitely recognized as atypical, there was marked overlap in the features between the transplant cases **Table 1** and **Table 2** and the carcinoma cases **Table 3** and **Table 4**.

Discussion

Previous BAL studies in LTR have focused on infectious processes[9] and immunophenotypic and functional analyses of the lymphoid cell population.[10,11] These studies did not address the issue of epithelial cell atypia. The BAL cytospin slide typically shows numerous macrophages with a few lymphocytes and bronchial epithelial cells. The vast majority of cases are negative for infectious organisms and other significant findings. However, occasional diagnostic dilemmas arise when epithelial cells worrisome for neoplastic processes are detected. The possibility of a neoplastic process must be considered because neoplasms have been reported in transplant recipients.[12] The use of BAL for the diagnosis of malignancy has been documented in NTP.[13,14] While some BAL specimens show obviously malignant features, other well-differentiated carcinomas may shed cells that are cytologically bland except for the manner by which they aggregate with depth of focus.[13,14] In a study of fine-needle aspirates, bronchial washes, and BAL specimens, Zaman et al[15] noted that the predominance of 2- and 3-dimensional tissue fragments, tenacious intercytoplasmic connections, intranuclear inclusions, and paucity of multinucleated cellular forms were more commonly associated with bronchioloalveolar carcinoma (BAC) than with hyperplastic pulmonary proliferations. Our group of malignant BAL specimens included BAC as well as other adenocarcinoma. We found that tissue fragments consisting of 2 or more cells were present in both benign transplant and malignant cases. Intranuclear inclusions in the setting of pulmonary adenocarcinoma most commonly represent accumulation of surfactant apoprotein in cells with type 2 pneumocyte differentiation.[16] This feature was not helpful in making a distinction because it was absent in all of our cases. Likewise, tenacious intercytoplasmic connection and multinucleation were not helpful in distinguishing the 2 groups. Immunostaining for carcinoembryonic antigen and tumor-associated glycoprotein B72.3 marks malignant cells in BAL specimens[4,17,18]; however, because they lack specificity these markers are not applicable to clinical specimens.

Aside from detection of malignancy, reports on BAL specimens have documented the range of cytologic atypia noted in inflammatory processes. Others[4,5] have noted that these reactive cells cluster in glandlike groups. Individually, the atypical cells may be quite large, with high N/C, prominent nucleoli, irregular nuclear membranes, and chromatin clearing. Variable cytoplasmic qualities with some cells showing vacuoles were noted. More recently, Fiorella et al[19]

Table 1
Atypical Cells From Bronchoalveolar Lavage Specimens of Lung Transplant Recipients

Specimen*/Primary	Cell Type in Background	Predominant or Clusters With Atypia	No. of Cells in Each Area Showing Atypia	No. of Cells Size of Cell Clusters (μm)	Contour of Clusters	3-Dimensionality	Tenacious Intercytoplasmic Connections	Multinucleation	Nuclear Size†
1a/ARDS	Neutrophils	4	2–3	50–100	Round and smooth	No	None	Yes	3×
1b/ARDS	Neutrophils	5	5–20	200	Knobby	Yes	None	Yes	4–8×
2/Emphysema	Neutrophils	10	2–40	150	Knobby	Yes	None	Yes	3–10×
3/Emphysema	Macrophages	10	4–20	100	Knobby	Yes	Present	Yes	4×
4/Bronchiectasis cystic fibrosis	Lymphocytes	3	1	NA	NA	No	None	Yes	4–5×
5/Hypersensitivity pneumonitis	Macrophages	3	20–50	100–300	Knobby	Yes	None	Yes	2–3×
6/Pulmonary hypertension	Macrophages	2	10	100	Knobby	Yes	None	Yes	3–6×
7/Pulmonary hypertension	Neutrophils	10	1	NA	NA	No	None	Yes	3–6×
8/Emphysema	Macrophages	7	1–10	100	Knobby	Yes	None	Yes	1–2×
9/Emphysema	Neutrophils	12	1–4	50–100	Knobby	No	None	Yes	2–5×

ARDS = adult respiratory distress syndrome; NA = not applicable (single cells).
*Specimens 1a and 1b are from the same patient.
†Nuclear size of epithelial cell measured in reference to size of a small round lymphocyte.

Table 2
Atypical Cells From Bronchoalveolar Lavage Specimens of Lung Transplant Recipients

Specimen	N/C*	Nuclear Membrane Irregularity	Nuclear Chromatin Pattern	Intranuclear Inclusions	Nucleoli	Clinical and Biopsy Correlation
1a	H	Mild	Finely granular	None	Inconspicuous	Harvest injury/DAD
1b	H	Moderate	Coarse with clumping	None	Small multiple	CMV infection
2	H	Marked	Coarse with clumping	None	Prominent multiple	*Aspergillus* infection
3	L	Moderate	Coarse with clumping	None	Prominent single	Moderate ACR
4	H	Moderate	Coarse with clumping	None	Prominent multiple	Moderate ACR
5	H	Moderate	Coarse with clumping	None	Small single	Moderate ACR
6	H	Moderate	Coarse with clumping	None	Small single	Harvest injury/DAD
7	H	Moderate	Coarse with clumping	None	Prominent single	Moderate ACR
8	H	Moderate	Coarse with clumping	None	Small single	Harvest injury/DAD
9	H	Mild	Coarse with clumping	None	Prominent single	*Nocardia* infection

ACR = acute cellular rejection; DAD = diffuse alveolar damage; CMV = cytomegalovirus.
*Nuclear/cytoplasmic (N/C) ratio determined as high (H) when more than half of cellular area occupied by nucleus, and low (L) when nuclear area occupied less than half of cell.

Table 3
Malignancy Detected in Bronchoalveolar Lavage Specimens From Non-transplant Patients

Specimen	Malignancy	Predominant Cell Type in Background	No. of Cells or Clusters With Atypia	No. of Cells in Each Area Showing Atypia	Size of Cell Clusters (μm)	Contour of Clusters	3-Dimensionality	Tenacious Intercytoplasmic Connections	Multinucleation	Nuclear Size*
10	Metastatic adenocarcinoma from breast	Macrophages	3	3–40	200	Knobby	Yes	None	Yes	5×
11	Recurrent bronchioloalveolar carcinoma	Macrophages	7	1–10	100–150	Knobby	Yes	None	Yes	3–4×
12	Poorly differentiated carcinoma	Macrophages	10	1–10	100	Knobby	Yes	None	Yes	3–4×
13	Non–small cell carcinoma	Macrophages	7	5–25	150	Knobby	Yes	None	Yes	10×

*Nuclear size of epithelial cell measured in reference to size of small round lymphocyte.

Table 4
Malignancy Detected in Bronchoalveolar Lavage Specimens From Non-Transplant Patients

Specimen	N/C*	Nuclear Membrane Irregularity	Nuclear Chromatin Pattern	Intranuclear Inclusions	Nucleoli	Clinical Follow-up
10	H	Moderate	Coarse with clumping	None	Prominent single/ multiple smaller	Metastatic disease
11	H	Marked	Coarse with clumping	None	Prominent single/ multiple smaller	Metastatic disease
12	H	Moderate	Coarse with clumping	None	Prominent single	Metastatic disease with lymphangitic carcinomatosis
13	H	Marked	Coarse with clumping	None	Prominent single	Lost to follow-up

*Nuclear/cytoplasmic ratio (N/C) determined as high (H) when more than half of cellular area occupied by nucleus, low (L) when nuclear area occupied less than half of cell.

performed cytomorphometric analysis on cytology specimens from the respiratory tract and found that the mean nuclear diameter between cells from BAC and reactive or reparative respiratory epithelium was not statistically different. We made similar cytologic observations in our LTR series. This is not surprising, because the underlying allograft syndromes result in acute alveolar damage with markedly reactive pneumocytes. Thus our study expands the clinical setting in which epithelial cell atypia is observed.

Comparing our benign transplant cases with malignant BAL specimens from other LTR would have provided a more optimal control. However, in searching our files we found that none of the 5 patients with documented non–small cell lung carcinomas that developed after lung transplantation harbored atypical cells in BAL specimens, and therefore this comparison could not be made. As stated,[4,5] careful clinicopathologic correlation is beneficial in ensuring accurate diagnosis. In lung transplantation, awareness of the characteristic clinical features of allograft syndromes and the expected range of reactive epithelial cell atypia aids in interpretation of BAL specimens.

Harvest injury typically is seen within the first month after transplantation and at histologic examination manifests as diffuse alveolar damage. BAL and biopsy specimens are taken when the distinction between ACR and infection is difficult to make clinically. Biopsy samples of harvest injury often show the organizing phase of diffuse alveolar damage with granulation tissue plugs in the air spaces and airways. One of the hallmark features of diffuse alveolar damage, hyaline membranes, was not often detected, because the recipient's first BAL and biopsy specimens typically were obtained approximately 3 to 4 weeks after transplantation, when diffuse alveolar damage is expected to be in the organizing phase.

Acute cellular rejection is seen in the vast majority of transplant recipients, commonly during the first month after transplantation, but it may occur anytime afterward. In ACR, the recipient's lymphocytes (predominantly T cells) infiltrate the donor lung and target the histocompatibility antigens. At histologic examination, changes are seen as perivascular, peribronchiolar, peribronchial, and interstitial lymphoid infiltrates with cellular injury. Acute cellular rejection is graded according to extent of the infiltrate.[20] Mild ACR is characterized by infiltrates limited to the perivascular areas. With moderate ACR, the infiltrate extends into the interstitial areas and may overflow into the air spaces. Severe ACR is a diffuse process and is further characterized by evidence of acute alveolar damage. It is not surprising that atypical epithelial cells in BAL were found in moderate ACR. With lesser degrees of rejection, reactive alveolar pneumocyte changes would not be expected, because the lymphoid infiltrate remains predominantly in the immediate perivascular areas.

Many types of infectious agents affect the allograft, with widely varying pathologic manifestations. *Pseudomonas, Staphylococcus, Enterobacter, Aspergillus, Candida, Pneumocystis*, cytomegalovirus, herpes simplex virus, and adenovirus pneumonia are the more common lung allograft infections.[21] Prophylaxis may be given for *Pneumocystis*, cytomegalovirus, and herpes simplex virus, and as a result the incidence of serious infections from these microorganisms has decreased dramatically. Nevertheless, some patients may be sensitive to the prophylactic medication, and others may be overwhelmed by the degree of immunosuppression. Generally, the risk of infection depends on 2 factors: extent of exposure to pathogens and patient susceptibility.[22] The finding of epithelial cell atypia in BAL specimens in patients with pneumonia usually indicates the presence of a serious infection. Identification of a microorganism would favor a reactive process as the cause of the epithelial atypia. Similarly, the presence of numerous neutrophils, although not specific, favors an infectious process.

In addition to clinical correlation, concurrent transbronchial biopsy is often helpful in revealing the underlying process. Atypical epithelial cells corresponding to those in the BAL specimen may be found in the biopsy specimens. On histologic sections, the tissue architecture may reveal the context in which the atypical cells are found. However, it should be noted that biopsy specimens may not include

samples of the lesion and therefore must be interpreted in the context of the entire clinicopathologic picture. In instances where biopsy specimens are not available, familiarity with the allograft syndromes provides insight into the interpretation of epithelial cell atypia. From our experience, atypical cells in BAL specimens are more likely to be derived from nonneoplastic processes. However, each case warrants careful clinical and histologic correlation, and cytologic criteria alone should not be used in the final interpretation.

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