Atypia in Pleural Effusions after Lung Transplantation

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Abstract

Background: Pleural effusion cytology is challenging due to overlap between reactive and malignant processes. Pulmonary transplant patients are immunosuppressed, and at higher risk for both malignant and infectious conditions. This study evaluates atypia in pleural effusions from lung transplantation patients.

Methods: All patients who underwent lung transplantation and had a post-transplant pleural fluid for cytologic examination were included. The initial cytologic interpretation was recorded, and the slides were reviewed for morphologic features. Follow-up clinical and pathologic information was recorded.

Results: Of 240 lung transplant patients, 36 (15%) had a total of 63 pleural effusions. The median time from lung transplant to pleural effusion was 5 months; 33 (92%) were ipsilateral to a transplanted lung. The original cytologic diagnosis was negative for malignancy in 59 (94%) effusions, suspicious for a lymphoproliferative disorder in 3 effusions and suspicious for malignancy in 1 effusion. Reactive atypia was common, with prominent nucleoli in 24 cases (38%), but clusters of mesothelial cells were uncommon (25%), and community borders were only seen in 2 cases (3%). High cellularity of mesothelial-type cells was uncommon (6%). On follow-up, 4 patients were diagnosed with malignancy (1 metastatic adenocarcinoma, 2 PTLD, 1 pleural involvement by CLL/SLL). Effusions contralateral to the transplanted lung, the presence of clusters with community borders, and high mesothelial-type cellularity were most likely to be associated with malignancy.

Conclusion: Reactive atypia is a frequent finding in the pleural effusions of patients after lung transplantation. Contralateral effusions or clusters with community borders should raise concern for malignancy.

Keywords: Effusion; Cytology; Lung transplant; Atypia

Introduction

Pleural effusion evaluation is a frequent component of non-gynecologic cytology practice. However, differentiation of reactive from malignant cells can be very challenging due to significant morphologic overlap. Many benign processes have been reported to cause significant reactive atypia in mesothelial cells, including pulmonary infarction [1], tuberculosis [2], prior chemotherapy [3], acute pancreatitis [3,4], lupus [5,6], AIDS [7] and ovarian fibroma [2].

Pleural effusions are very common in lung transplant recipients, both immediately post-transplant and during late complications. These patients are immunosuppressed, and therefore at higher risk for development of both malignant and infectious conditions. This study evaluates the range of atypia and cytopathologic features of pleural effusions from a cohort of patients who received single or double lung transplants over a period of 5 years.

Materials and Methods

This study was approved by the Institutional Review Board at the Cleveland Clinic. All patients from a major lung transplantation center who underwent unilateral or bilateral lung transplantation for a variety of disorders, and had follow-up post-transplant lung biopsies, were identified. Patients who had a post-transplant pleural fluid for cytologic examination from 2006-2010 were included in the study. A 30 cc aliquot (or less depending on total volume received) of effusion was processed using a ThinPrep processor and stained with Papanicolau stain for all cases. A cell block was made using the thrombin clot technique and stained with hematoxylin and eosin for all cases where sufficient material was available.

The initial cytologic interpretation was recorded, and all slides available on each case were reviewed by a cytotechnologist for the presence of cell clusters and cell clusters with community borders. A cytopathologist reviewed each case to confirm the findings noted by the cytotechnologist. Mesothelial cells were evaluated for the presence of prominent nucleoli, vacuoles, and signet ring morphology.

Patient data collected included reason for lung transplantation, time from transplantation to effusion, location of the effusion (ipsilateral or contralateral to the lung transplant), and follow-up pathologic specimens until 1/2011.

Statistical analysis was performed using chi square analysis.

Results

Of 240 lung transplant patients being actively followed by lung transplant biopsy from 2006-2010, 36 patients (15%) developed at least 1 pleural effusion after transplantation during the study period. Clinical demographics are summarized in Table 1. The most common reasons for lung transplant was usual interstitial pneumonia (14
patients), and severe chronic obstructive pulmonary disease (14 patients), and less commonly cystic fibrosis (4 patients), hypersensitivity pneumonitis (2 patients), desquamative interstitial pneumonia (1 patient) and hereditary hemorrhagic telangiectasia (1 patient). 27 patients (75%) had bilateral lung transplants, and 3 had right lung only and 6 had left lung only transplants. The median time from transplant to pleural fluid evaluation was 5 months (range 1-96 months).

| Reason for transplant | N (%) |
|-----------------------|-------|
| UIP                   | 14 (39%) |
| COPD                  | 14 (39%) |
| CF                    | 4 (11%) |
| Other                 | 4 (11%) |

| Time to effusion*     | N |
|-----------------------|---|
| <6 months             | 27 |
| 6-12 months           | 6 |
| >12 months            | 8 |

| Type of transplant    | N (%) |
|-----------------------|-------|
| Bilateral             | 27 (75%) |
| Unilateral            | 9 (25%) |

| Location of effusion  | N (%) |
|-----------------------|-------|
| Ipsilateral to transplanted lung | 33 (92%) |
| Contralateral to transplanted lung  | 2 (5%)  |
| Not specified          | 1 (2%) |

| Number of effusions evaluated per patient | N (%) |
|------------------------------------------|-------|
| 1                                        | 24 (67%) |
| 2-4                                      | 9 (25%)  |
| >5                                       | 3 (8%)   |

* This total is greater than 36, as several patients had multiple effusions at different time intervals.

**Table 1**: Clinical characteristics of lung transplant patients with pleural effusions (n=36).

An average of 340 mL of pleural fluid was received in the cytology laboratory (range 0.1 mL to 2000 mL). A single ThinPrep slide stained with Papanicolau stain was prepared from the material from each case, and when sufficient material was present, a cell block was prepared and a single slide stained with hematoxylin and eosin was available for review. Sufficient material was present for cell block evaluation in 55 fluids; in all 8 cases with insufficient material for a cell block, less than 10 mL of fluid was received. Review of the cytologic material demonstrated that prominent nucleoli in the mesothelial cell population was common (38%), as was the presence of mesothelial cell clusters (25%). However, cell clusters with community borders was uncommon, present in only 3 cases (5%). Cells containing vacuoles were a frequent finding (35%), but signet ring-type cells were not identified in any case. Most cases had a background of predominantly small mature lymphocytes.

| Initial cytologic interpretation | Details of follow-up, laterality of effusion to transplanted lung |
|---------------------------------|---------------------------------------------------------------|
| No                              | 52 Ipsilateral                                             |
|                                 | 1 Contralateral                                             |
| Atypical favor reactive         | Ipsilateral                                                 |
| Atypical lymphocytes            | Ipsilateral, flow cytometry negative                       |
| Yes                             | 2 patients (1 fluid each) with lung biopsy demonstrating PTLD - both ipsilateral |
|                                 | 1 patient (1 fluid) with CLL/SLL involvement of pleural space by flow cytometry - ipsilateral |
|                                 | 1 patient (2 fluids) with pleural biopsy demonstrating adenocarcinoma (3rd effusion called atypical, suspicious, see below) - both contralateral |
| Atypical suspicious for malignancy (1) | Patient found to have pleural involvement by poorly differentiated adenocarcinoma favored to be metastasis - contralateral |

**Table 2**: Correlation of follow-up with initial cytologic interpretation (n=number of effusions with this diagnosis).

The original cytologic interpretation was “negative for malignancy” in 59 cases, “atypical favor reactive” in 1 case (Figure 1), “atypical lymphoid cells” in 3 cases (all from 1 patient), and “atypical suspicious for malignancy” in 1 case (Table 2). On follow-up, 4 patients (with a combined total of 6 effusions examined) had an ultimate diagnosis of malignancy involving the lung or pleural space: 2 patients were diagnosed with post-transplant lymphoproliferative disorder on transbronchial lung biopsy, 1 patient was diagnosed with pleural fluid involvement by chronic lymphocytic leukemia/small lymphocytic lymphoma by flow cytometry, and 1 patient was diagnosed with pleural involvement by metastatic poorly differentiated adenocarcinoma of unknown primary on pleural biopsy (Figure 2). All effusions from patients diagnosed with malignancy occurred within 12 months of transplantation. All patients with a hematopoietic malignancy had bilateral lung transplants.
Epithelial malignancy was associated with the following clinical and cytopathologic features (Table 3): effusion contralateral to the transplanted lung (p=0.06) and cell clusters demonstrating community borders (p=0.001). Hematopoietic malignancy was associated with pleural effusions around a transplanted lung, but did not demonstrate other features which allowed discrimination from non-neoplastic effusions. Recurrent effusions were not statistically associated with malignancy (p=0.29).

Table 3: Correlation of follow-up malignancy with cytologic and clinical features of effusion samples (n=number of patients).

| Cytologic features                  | Patient follow-up |
|-------------------------------------|-------------------|
|                                     | No malignancy (n=32) | Epithelial malignancy (n=1) | Hematolymphoid malignancy (n=3) | P value |
| Location of effusion                |                   |                               |                             |         |
| Contralateral                       | 1 (3%)            | 1 (100%)                      | 0 (0%)                      | 0.06^   |
| Ipsilateral                         | 31 (97%)          | 0 (0%)                        | 3 (100%)                    |         |
| Prominent nucleoli                  | 15 (47%)          | 1 (100%)                      | 0 (0%)                      | 0.29*   |
| Cell clusters                       | 11 (34%)          | 1 (100%)                      | 1 (33%)                     | 0.17*   |
| Cell clusters with community borders| 1 (3%)            | 1 (100%)                      | 0 (0%)                      | 0.01*   |
| Vacuolated cells                    | 15 (47%)          | 1 (100%)                      | 0 (0%)                      | 0.29*   |
| Recurrent effusion                  | 8 (25%)           | 1 (100%)                      | 1 (33%)                     | 0.29    |

* These p values were calculated excluding hematolymphoid malignancies as these are features of epithelial malignancies.
^ This p value was calculated for patients with a unilateral lung transplant (n=9) and only for epithelial malignancies (p=0.06), as all hematopoietic malignancies developed in patients with bilateral lung transplants.

Discussion

Cytopathologic evaluation is one of the first tests performed during the workup of an unexpected or persistent serous effusion. However, significant morphologic overlap between reactive mesothelial cells and malignancy can be seen. Most studies have demonstrated that effusion cytology has high specificity (97-100%), but moderate sensitivity (50-71%) for the detection of malignancy [1-3].

Epithelial malignancy was associated with the following clinical and cytopathologic features (Figure 1): effusion contralateral to the transplanted lung (p=0.06) and cell clusters demonstrating community borders (p=0.001). Hematopoietic malignancy was associated with pleural effusions around a transplanted lung, but did not demonstrate other features which allowed discrimination from non-neoplastic effusions. Recurrent effusions were not statistically associated with malignancy (p=0.29).

Figure 1: Pleural effusion with “atypical cells, favor reactive” with community borders from patient with ipsilateral effusion but negative follow-up for malignancy (ThinPrep, 40X).

Figure 2: Pleural effusion with “atypical cells, suspicious for malignancy” from patient with contralateral effusion and diagnosis of metastatic adenocarcinoma on pleural biopsy (ThinPrep, 40X).

Pleural effusions are very common in lung transplant recipients; nearly all patients have an ipsilateral pleural effusion in the immediate post-transplant period which usually resolves within 2 weeks [10]. Approximately 20% of lung transplant patients will develop late pleural effusions [11]. The postulated causes of these effusions include rejection [12], infection, increased alveolar capillary permeability due to ischemia and reperfusion, and injury to lymphatic drainage systems.

Lung transplant patients are at increased risk for development of malignancy due to their immunosuppressive regimens. Up to 20% of...
patients who undergo a lung transplant will develop malignancy by 5 years post transplantation [13]. The most common tumors to develop are post-transplant lymphoproliferative disorders and cutaneous squamous cell carcinomas [13,14]. Post-transplant lymphoproliferative disorders typically arise earlier after transplantation; in one study, of 130 patients with a lung transplant who developed lymphoma, 84% were diagnosed within 1 year of transplant [13]. In contrast, solid malignancies occur both early and late after lung transplantation; of 203 patients who developed solid malignancies after lung transplantation, only 49% were diagnosed malignancy within 1 year [13]. In our study, all malignancies developed within 12 months after transplantation.

Although uncommon, occult malignancy in a lung donor can be transmitted to the lung transplant recipient, but almost all of these have been malignant melanomas and renal cell carcinomas [15,16]; one case of malignant melanoma transmitted in this fashion was first identified on pleural effusion cytology [17]. One lung transplant patient was reported to develop a bronchogenic carcinoma in his transplanted lung, which was proven to be donor-derived [18], while a one other lung transplant recipient has been reported to develop a new non-small cell carcinoma after transplant [13].

Given the severe injury that occurs during transplantation, and risk of infection and episodes of rejection after transplantation, it is not surprising that pleural effusions in these patients can show severe reactive atypia. The current study found that a substantial number of benign effusions from lung transplant patients demonstrated prominent nucleoli, vacuoles, and mesothelial clustering. However, large clusters of cells demonstrating community borders were distinctly uncommon. In addition, the presence of a pleural effusion contralateral to the transplanted lung was associated with a non-hematopoietic malignancy in unilateral lung transplant patients, although this did not reach statistical significance. There was also no apparent association of effusion ipsilateral to a transplanted lung and development of malignancy. In contrast, no features were predictive of a hematopoietic malignancy, particularly post-transplant lymphoproliferative disorder.

In summary, lung transplant patients frequently develop pleural effusions, and these can show significant cytomorphologic atypia concerning for neoplasia. However, the presence of an effusion contralateral to the transplanted lung and the presence of clusters with community borders were more likely to be associated with malignancy. In addition, detection of hematolymphoid neoplasms through cytologic evaluation of pleural effusions is poor. When there is a suspicion for post-transplant lymphoproliferative disorder, cytopathologists and clinicians should have a low threshold to send these specimens for additional studies (i.e. flow cytometry).

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