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Restrictive allograft syndrome post lung transplantation is characterized by pleuroparenchymal fibroelastosis

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We previously described restrictive allograft syndrome as a form of chronic lung allograft dysfunction, demonstrating restrictive pulmonary function decline. However, the histopathological correlates of restrictive allograft syndrome have yet to be satisfactorily described. We hypothesized that pulmonary pleuroparenchymal fibroelastosis, as has recently been described in bone marrow transplant recipients, may also be present in the lungs of patients with restrictive allograft syndrome. Retrospective review of 493 patients who underwent lung transplantation between 1 January 1996 and 30 June 2009, was conducted. Out of 47 patients with clinical features of restrictive allograft syndrome, 16 had wedge biopsy, re-transplant lung explant, or autopsy lung specimens available for review. All lungs showed varying degrees of pleural fibrosis. Fifteen of 16 showed parenchymal fibroelastosis, characterized by hypocellular collagen deposition with preservation and thickening of the underlying alveolar septal elastic network. The fibroelastosis was predominantly subpleural in distribution, with some cases also showing centrilobular and paraseptal distribution. A sharp demarcation was often seen between areas of fibroelastosis and unaffected lung parenchyma, with fibroblastic foci often present at this interface. Concurrent features of obliterative bronchiolitis were present in 14 cases. Another common finding was the presence of diffuse alveolar damage (13 cases), usually in specimens obtained <1 year after clinical onset of restrictive allograft syndrome. The single specimen in which fibroelastosis was not identified was obtained before the clinical onset of chronic lung allograft dysfunction, and showed features of diffuse alveolar damage. In conclusion, pleuroparenchymal fibroelastosis is a major histopathologic correlate of restrictive allograft syndrome, and was often found concurrently with diffuse alveolar damage. Our findings support a temporal sequence of diffuse alveolar damage followed by the development of pleuroparenchymal fibroelastosis in the histopathologic evolution of restrictive allograft syndrome.
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Increasing evidence suggests that chronic lung allograft dysfunction following lung transplantation is a heterogeneous condition that includes bronchiolitis obliterans syndrome as well as other types of allograft dysfunction. Although bronchiolitis obliterans syndrome, characterized clinically by irreversible obstructive deficits in pulmonary function tests,[1–4] remains the major cause of late mortality, we recently described a distinct form of chronic lung allograft dysfunction demonstrating restrictive pulmonary function decline, which we designated restrictive allograft syndrome,[5] and which accounts for 25–35% of chronic lung allograft dysfunction.[5,6] Radiologically, a significant proportion of these patients demonstrated an unusual pattern of

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interstitial fibrosis, often upper lobe-predominant, associated with traction bronchiectasis in computed tomography scans. Although initial review of restrictive allograft syndrome cases confirmed the presence of interstitial fibrosis,[5] the histopathological correlates of restrictive allograft syndrome have yet to be satisfactorily described.

Idiopathic pleuroparenchymal fibroelastosis was first proposed as a novel, distinct clinicopathological entity in 2004 by Frankel *et al*,[7] to describe cases of upper lobe-predominant pleural and subpleural fibrosis with a clinical presentation suggestive of a chronic idiopathic interstitial pneumonia. Several cases and small series with similar radiologic and pathologic features have also been reported.[8–14] Radiologically, idiopathic pleuroparenchymal fibroelastosis has been characterized by pleural thickening associated with underlying parenchymal reticular abnormalities, architectural distortion and traction bronchiectasis in a mostly upper lobe-predominant distribution.[7,10,11] Histologically, idiopathic pleuroparenchymal fibroelastosis is characterized by pronounced visceral pleural fibrosis associated with subpleural, 'intra-alveolar' fibrotic changes characterized by an admixture of elastic and fibrous tissue (fibroelastosis).

In a recent report, von der Thusen *et al*[15] described four cases of pulmonary disease following allogeneic bone marrow transplantation that presented with pneumothoraces and were found to demonstrate histopathologic features of pleuroparenchymal fibroelastosis. Histologically, chronic graft-*vs*-host-disease may present with a variety of patterns in the lung, including bronchiolitis obliterans.[16,17] In view of the fact that patients with chronic graft-*vs*-host-disease often demonstrate bronchiolitis obliterans that is reminiscent of that seen in lung transplant recipients with chronic lung allograft dysfunction, we hypothesized that pleuroparenchymal fibroelastosis might represent an important histopathologic correlate of post-lung transplant restrictive allograft syndrome. We report here evidence that pleuroparenchymal fibroelastosis is indeed a major histopathologic correlate of restrictive allograft syndrome.

Materials and methods

This study was approved by the Research Ethics Board of University Health Network. Patients with restrictive allograft syndrome were identified as previously described,[5] by retrospective review of 493 patients who underwent bilateral lung ($n=478$) or heart-lung ($n=15$) transplantation in the Toronto Lung Transplant Program between 1 January 1996 and 30 June 2009.

Restrictive allograft syndrome was defined as previously described,[5] as an irreversible decline in total lung capacity to $<90\%$ of baseline concurrent with the presence of chronic lung allograft dysfunction, which was defined as an irreversible decline in forced expiratory volume (1 s) to $<80\%$. In total, 16 specimens (5 wedge biopsies, 4 lungs explanted for retransplantation, 7 autopsies) from 16 patients with restrictive allograft syndrome were available for review. Specimens were processed according to routine surgical pathology protocols. Hematoxylin and eosin-stained sections were reviewed for all cases, with elastic trichrome or Movat stains for representative tissue blocks in selected cases. The cases were assessed for histopathological findings by two pathologists with pulmonary expertise (EO and DMH), including: degree of pleuroparenchymal fibroelastosis (0, none; 1, >0–10% of area; 2, >10–25%; 3, >25–50%; 4, $>50\%$) and distribution (subpleural, paraseptal, centrilobular or parenchymal) of pleuroparenchymal fibroelastosis; presence of bronchiolitis obliterans within and/or outside the areas of pleuroparenchymal fibroelastosis; histological features at the interface between pleuroparenchymal fibroelastosis and uninvolved lung parenchyma (whether this margin was abrupt or not, presence of fibroblastic foci); presence of honeycomb changes or other distinct histopathological patterns of chronic interstitial pneumonia; presence of diffuse alveolar damage; and presence of vascular changes.

The latest computed tomography scans before the pathology specimen for these patients were obtained. Images were acquired on different scanners ranging from 4- to 64-row detectors. All studies were blindly evaluated by two chest radiologists (UW and HCR) as previously described.[5]

Results

Clinical and demographic characteristics of the 16 patients for whom pathology material was available for review are summarized in Table 1. Computed tomography scans were previously reviewed and scored as part of our initial study of restrictive allograft syndrome.[5] These showed interstitial opacity/reticulation in all cases, with 13 showing reticulation in the upper lung zones, 12 in the middle lung zones and 14 in the lower lung zones. Upper lobe predominance was seen in eight patients. Traction bronchiectasis was reported in 13 patients, with bronchial dilatation and bronchial thickening reported in two patients each. Mosaic attenuation was seen in two and air trapping in four. Honeycombing was reported in three patients and architectural distortion in eight.

All pathology specimens reviewed showed varying degrees of pleural fibrosis (Table 2). Fifteen of 16 specimens showed areas of pleuroparenchymal fibroelastosis, characterized by confluent areas of bland, hypocellular collagen deposition with preservation and thickening of the underlying alveolar septal elastic network (Figure 1). Patients who died

Table 1 Patient characteristics

Total number	16
Recipient age at transplant, years	34.9 ± 17.7
Donor age at transplant, years	42.8 ± 19.7
Recipient sex	
Male	10
Female	6
Donor sex	
Male	7
Female	9
Original diagnosis	
Cystic fibrosis	8
Chronic obstructive pulmonary disease	2
Bronchiectasis	2
Idiopathic pulmonary fibrosis	1
Pulmonary arterial hypertension	1
Others	2
Transplant type	
Bilateral lung	14
Heart–lung	2
Cytomegalovirus mismatch	
Donor + /recipient +	7
Donor + /recipient –	5
Donor – /recipient +	2
Donor – /recipient –	2
Pulmonary function test, (% of baseline)	
Forced expiratory volume, 1 s	70.6 ± 12.5
Total lung capacity	46.4 ± 21.9

Table 2 Histologic features of pleuroparenchymal fibroelastosis in restrictive allograft syndrome patients

Pleural fibrosis	16/16 (100%)
Parenchymal fibroelastosis	15/16 (93.8%)
Subpleural	14/16 (87.5%)
Paraseptal	7/16 (43.8%)
Centrilobular	7/16 (43.8%)
Parenchymal	5/16 (31.3%)
Grade of parenchymal fibroelastosis (mean ± s.d.)	1.77 ± 1.22
Obliterative bronchiolitis	14/16 (87.5%)
Within areas of fibroelastosis	9/16 (56.3%)
Outside areas of fibroelastosis	12/16 (75%)
Diffuse alveolar damage, acute and/or organizing	13/16 (81.3%)
Findings at interface of fibroelastosis with unaffected lung tissue	
Fibroblastic foci	6/16 (37.5%)
Diffuse alveolar damage	7/16 (43.8%)
Other findings	
Thromboemboli, acute and/or organizing	6/16 (37.5%)
Acute bronchopneumonia	6/16 (37.5%)
Areas of nonspecific interstitial pneumonia-like fibrosis	4/16 (25%)
Microscopic honeycomb change	1/16 (6.3%)

or were re-transplanted showed a trend toward higher degrees of pleuroparenchymal fibroelastosis (2.27 ± 1.00; $n = 11$) than patients undergoing wedge biopsies for diagnostic purposes (1.20 ± 1.10; $n = 5$) ($P = 0.09$, t-test). The single specimen that did not show pleuroparenchymal fibroelastosis was a wedge biopsy from a patient showing acute and organizing diffuse alveolar damage, taken 2 months before the clinical onset of chronic lung allograft dysfunction.

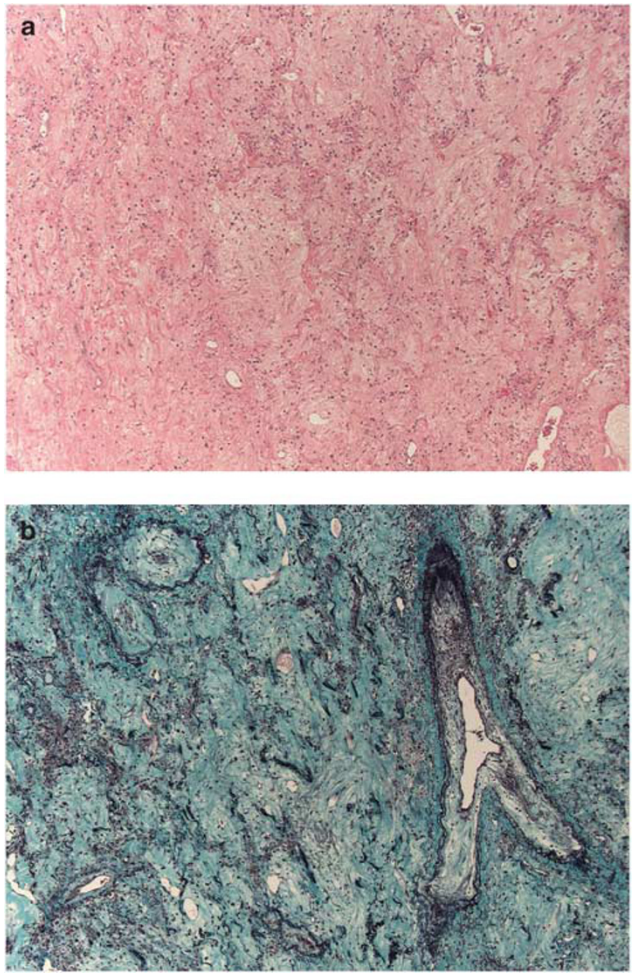

Figure 1 Pleuroparenchymal fibroelastosis: areas of pleuroparenchymal fibroelastosis characterized by confluent areas of hypocellular collagen deposition with preservation and thickening of the alveolar septal elastic framework. (**a**) Hematoxylin and eosin stain, original magnification ×50; (**b**) Elastic trichrome stain, original magnification ×50.

The areas of pleuroparenchymal fibroelastosis were present predominantly in a subpleural distribution, but in some cases were also paraseptal, centrilobular or more random (parenchymal) in distribution (Table 2, Figure 2). Areas of fibroelastosis often demonstrated a sharp demarcation with adjacent unaffected lung parenchyma (Figure 3a), with fibroblastic foci often present at this interface (Figure 3b).

Concurrent histologic features of obliterative or constrictive bronchiolitis were identified in 14 cases (Figure 4), including 10 of 11 patients who died or were re-transplanted, and 4 of 5 cases of patients undergoing wedge biopsy. Affected airways were

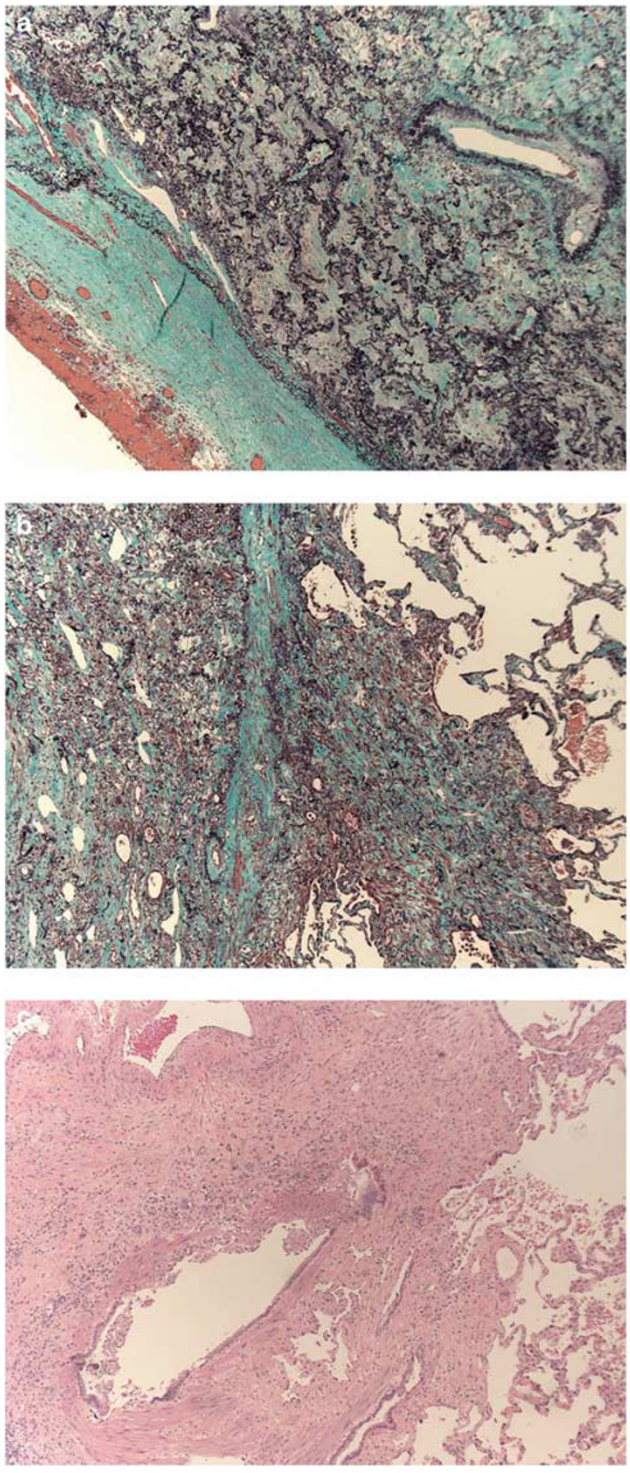

Figure 2 Distribution of pleuroparenchymal fibroelastosis: areas of pleuroparenchymal fibroelastosis were typically subpleural, with overlying pleural fibrosis (**a**), with some cases also demonstrating pleuroparenchymal fibroelastosis in a paraseptal (**b**) or centrilobular (**c**) distribution. All photomicrographs are at ×50 original magnification. Elastic trichrome stain (**a**, **b**); hematoxylin and eosin stain (**c**).

identified within areas of confluent pleuroparenchymal fibroelastosis in a majority of cases (9/16) (Figure 4a), as well as in adjacent uninvolved lung

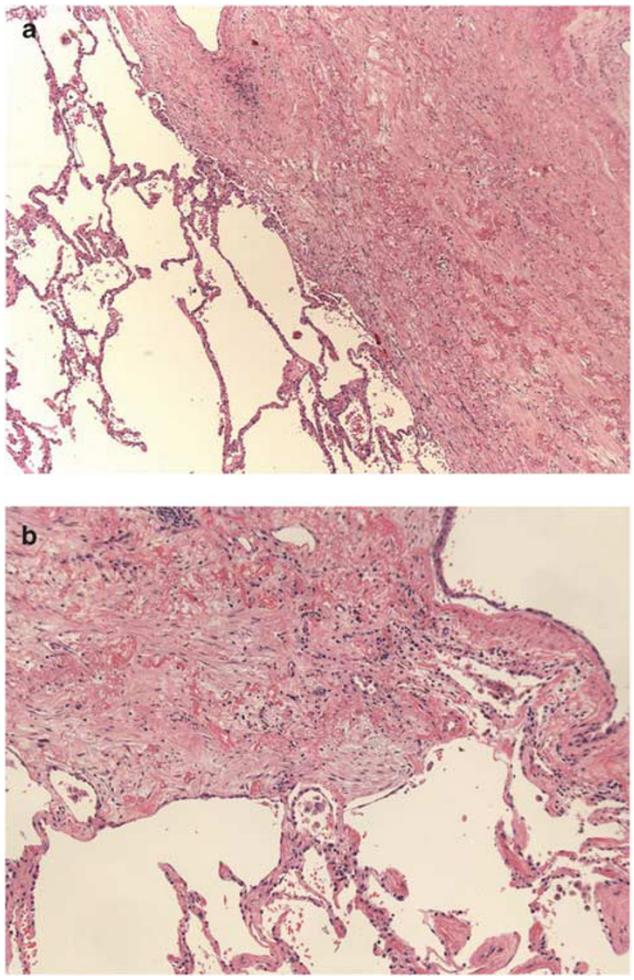

Figure 3 Interface of pleuroparenchymal fibroelastosis with unaffected lung parenchyma. (**a**) Sharp demarcation between fibroelastotic area and adjacent unaffected lung tissue (hematoxylin and eosin stain, original magnification ×50); (**b**) Fibroblastic foci at interface (hematoxylin and eosin stain, original magnification ×100).

(12/16) (Figure 4b). This was associated with postobstructive changes such as intra-alveolar foamy macrophages and cholesterol cleft formation in 12/16 cases.

Another common finding was the presence of acute and/or organizing phase diffuse alveolar damage (13/16 cases), characterized by the presence of intra-alveolar fibrinous exudates (Figure 5a) and/or areas of alveolar septal thickening associated with organizing pneumonia and reactive pneumocyte hyperplasia (Figure 5b). In seven cases, areas of diffuse alveolar damage appeared to merge into areas of pleuroparenchymal fibroelastosis (Figure 5c and d). The three specimens not showing diffuse alveolar damage were all obtained $\geq$18 months (mean 46.7 ± 38.2 months) after the clinical onset of chronic lung allograft dysfunction, whereas all 13 specimens showing diffuse alveolar damage were obtained $\leq$15 months after the onset of chronic lung allograft dysfunction (mean 4.4 ± 5.2 months, with

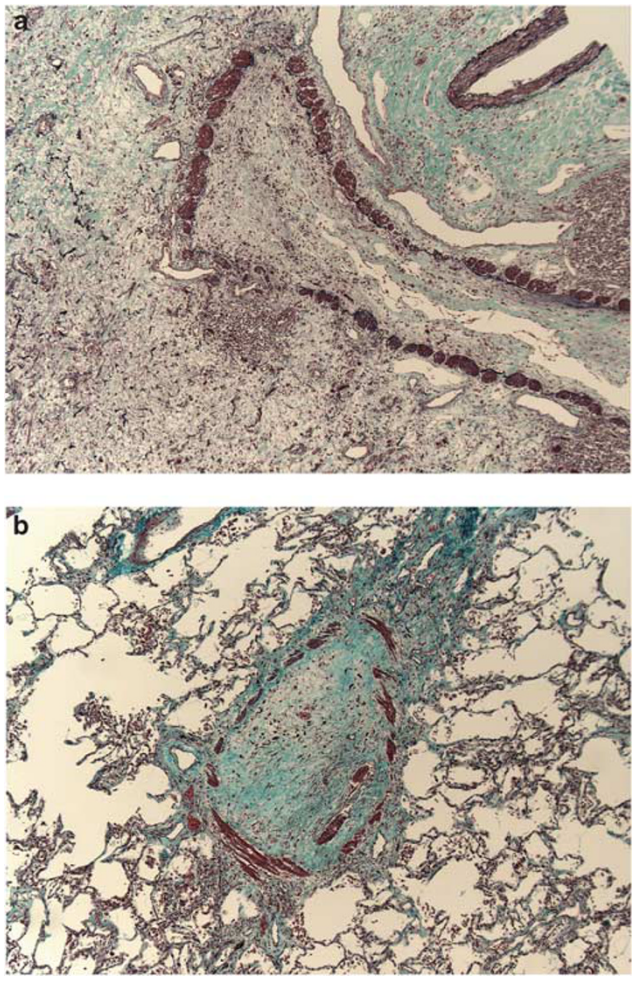

Figure 4 Obliterative bronchiolitis lesions in patients with restrictive allograft syndrome. (**a**) Obliterative bronchiolitis lesion within an area of fibroelastosis (elastic trichrome stain, original magnification $\times 50$); (**b**) Obliterative bronchiolitis lesion within area of non-fibroelastotic lung tissue (elastic trichrome stain, original magnification $\times 50$).

12 of 13 specimens <1 year after chronic lung allograft dysfunction onset).

Other findings included acute and/or organizing thromboemboli (six cases), foci of acute bronchopneumonia (six cases) and areas of nonspecific interstitial pneumonia-like fibrosis (four cases). A single case showed focal areas of microscopic honeycomb change similar to that seen in usual interstitial pneumonia, but this was not a prominent feature, and similar areas were not seen in any of the other cases.

Discussion

Although bronchiolitis obliterans syndrome had long been considered virtually synonymously with chronic lung allograft dysfunction in lung transplant recipients, recent evidence suggests that chronic lung allograft dysfunction in fact displays a range of phenotypes distinct from bronchiolitis obliterans syndrome.[5,6,18,19] We previously reported a significant subset of patients with chronic lung allograft dysfunction who displayed restrictive functional changes, which we designated as restrictive allograft syndrome.[5] Patients with restrictive allograft syndrome were found to demonstrate significantly poorer survival following the onset of chronic lung allograft dysfunction than patients with bronchiolitis obliterans syndrome (median survival: 541 *vs* 1421 days, respectively).[5]

Our present study of 16 patients with restrictive allograft syndrome is, to our knowledge, the first reporting pleuroparenchymal fibroelastosis as a major histopathologic correlate of restrictive allograft syndrome, and the largest single series of pleuroparenchymal fibroelastosis cases to date. Idiopathic pleuroparenchymal fibroelastosis as a distinct entity was first proposed by Frankel *et al*[7] in 2004. It is characterized radiologically by features suggestive of a chronic interstitial pneumonia with upper lobe predominance, and histologically by pleural fibrosis and parenchymal fibroelastosis in a predominantly subpleural distribution, with a sharp demarcation between fibroelastotic and unaffected lung parenchyma, and with the presence of fibroblastic foci at this interface. A limited number of cases with similar radiologic and pathologic features have also been reported,[8–14] including a very recent article by Reddy *et al*,[14] suggesting a broader spectrum of histopathologic findings.

In our present study, we found typical features of pleuroparenchymal fibroelastosis in all patients in whom clinical onset of restrictive allograft syndrome pre-dated the lung pathology specimen. The pleuroparenchymal fibroelastosis in these cases was predominantly subpleural; however, unlike most previous reports of pleuroparenchymal fibroelastosis, involvement in other areas (eg centrilobular, paraseptal) was also noted in a significant minority of cases.

Concurrent obliterative bronchiolitis was identified in a majority of cases, an observation that mirrors the finding by von der Thusen *et al*,[15] of obliterative bronchiolitis in 4 of 4 patients with pleuroparenchymal fibroelastosis post bone marrow transplantation. This finding suggests that although patients with restrictive allograft syndrome should not be classified as bronchiolitis obliterans syndrome due to their distinct clinical, radiologic and pathologic features, the decline in pulmonary function in patients with restrictive allograft syndrome may result from a combination of restrictive deficits secondary to pleuroparenchymal fibroelastosis and varying degrees of obstructive deficits resulting from concurrent obliterative bronchiolitis.

Consistent with our recent finding that onset of restrictive allograft syndrome is often preceded by the presence of diffuse alveolar damage in biopsies,[20] we further found that pleuroparenchymal

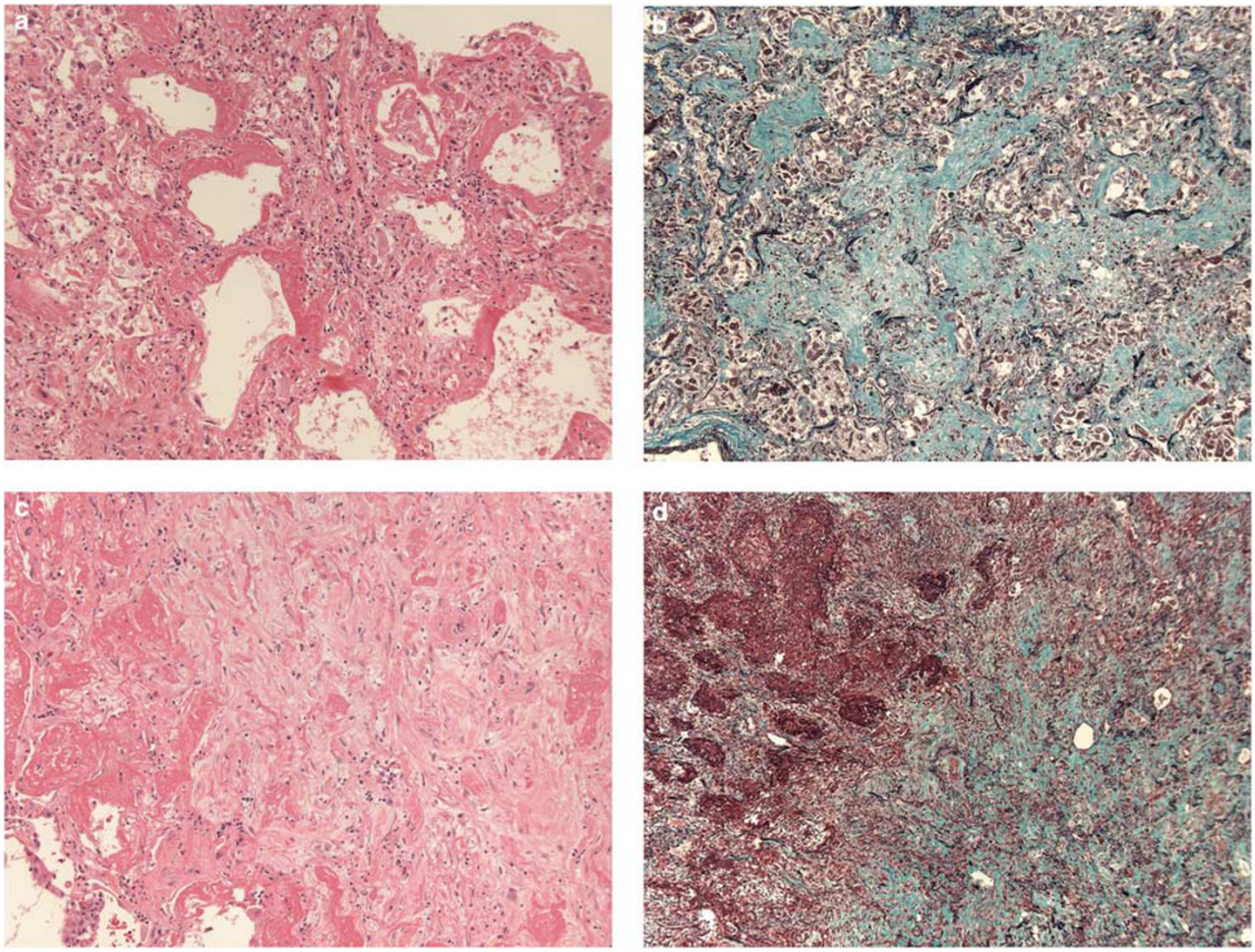

Figure 5 Diffuse alveolar damage in patients with restrictive allograft syndrome. (**a**) Diffuse alveolar damage, acute phase, characterized by intra-alveolar hyaline membrane material (hematoxylin and eosin stain, original magnification $\times 100$); (**b**) diffuse alveolar damage, organizing phase, characterized by intra-alveolar fibroblastic plugs associated with interstitial inflammation and prominent reactive pneumocyte changes (elastic trichrome stain, original magnification $\times 100$); (**c**) area of acute phase diffuse alveolar damage (left side of panel) merging into area of fibroelastosis (hematoxylin and eosin stain, original magnification $\times 100$); (**d**) area of acute phase diffuse alveolar damage (left side of panel) merging into area of fibroelastosis (elastic trichrome stain, original magnification $\times 50$).

fibroelastosis in restrictive allograft syndrome patients was very often present concurrently with features of diffuse alveolar damage. Specimens obtained <1 year after clinical onset of chronic lung allograft dysfunction typically demonstrated features of diffuse alveolar damage, whereas those obtained at intervals of a year or more after chronic lung allograft dysfunction onset showed diffuse alveolar damage less frequently. These findings, together with the finding in some cases of diffuse alveolar damage appearing to merge into areas of pleuroparenchymal fibroelastosis (Figure 5c), support a temporal sequence of diffuse alveolar damage preceding the development of pleuroparenchymal fibroelastosis in the natural history of restrictive allograft syndrome.

The etiologic factors underlying restrictive allograft syndrome and pleuroparenchymal fibroelastosis remain uncertain. Our identification of pleuroparenchymal fibroelastosis in the setting of chronic lung allograft dysfunction, taken together with the recent report of pleuroparenchymal fibroelastosis following allogeneic bone marrow transplantation,[15] as well as the finding of auto-antibodies in some patients with pleuroparenchymal fibroelastosis,[14] could suggest a contributing immunologic mechanism. On the other hand, the presence of concurrent diffuse alveolar damage in a large proportion of restrictive allograft syndrome-pleuroparenchymal fibroelastosis cases may also suggest that pleuroparenchymal fibroelastosis represents a more non-specific late sequela of diffuse alveolar damage, which would be in keeping with the suggestion made by von der Thusen *et al* that pleuroparenchymal fibroelastosis in post-bone marrow transplant patients may represent a late complication of post-bone marrow transplant idiopathic pneumonia syndrome, which has a high mortality rate and is characterized clinically and radiologically by features consistent

with diffuse alveolar damage.[15] If so, pleuroparenchymal fibroelastosis may represent a late complication of multiple and varied etiologic factors that result in acute lung injury/diffuse alveolar damage, including chemo/radiotherapy[7,10,11,15] and infections.[14] Finally, the finding of acute and/or organizing thromboemboli in our series raises the question of the role of vascular injury in the pathophysiology of pleuroparenchymal fibroelastosis. However, as thromboembolism may often be seen in the setting of diffuse alveolar damage and all instances of thromboemboli in this study were associated with diffuse alveolar damage, the significance of this finding to the development of pleuroparenchymal fibroelastosis is uncertain.

Chronic lung allograft dysfunction is the major factor today that limits long-term survival in lung transplant patients. We have previously demonstrated that chronic lung allograft dysfunction has distinct subtypes, of which restrictive allograft syndrome is a distinct form with clinical, biological and radiologic features and a more aggressive and rapidly progressive clinical course than bronchiolitis obliterans syndrome. Our novel observations in this report demonstrate that pleuroparenchymal fibroelastosis is a major histopathologic correlate of restrictive allograft syndrome in lung transplant recipients. Our findings further support a temporal connection between pleuroparenchymal fibroelastosis and antecedent diffuse alveolar damage, the nature of which needs to be further delineated.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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