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Histopathology of Explanted Lungs from Patients with a Diagnosis of Pulmonary Sarcoidosis

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Abstract

Background: Pathologic features of end stage pulmonary sarcoidosis (ESPS) are not well defined; anecdotal reports have suggested that ESPS may mimic usual interstitial pneumonia (UIP). We hypothesized that ESPS has distinct histologic features.

Methods: Twelve patients who had a diagnosis of pulmonary sarcoidosis and underwent lung transplantation were included. Controls were 10 age and sex matched lung transplant patients with UIP. H&E-stained sections were examined for the following features: extent/pattern of fibrosis; presence/quantity (per 10 high power fields) of fibroblast foci and granulomas; distribution and morphology of granulomas; presence/extent of honeycomb change. Extent of fibrosis and honeycomb change was scored as follows: 1=1-25%; 2=26-50%; 3=51-75%; 4=76-100% of lung parenchyma.

Results: Eight of 12 cases demonstrated histological findings typical of ESPS. All showed well-formed granulomas with associated fibrosis distributed in a distinct lymphangitic fashion. Granulomas were present in hilar or mediastinal lymph nodes from 6 of 6 ESPS cases and none of 8 control cases. The extent of fibrosis, honeycomb change, and fibroblast foci was significantly lower in ESPS cases compared to control cases. Two patients with remote histories of sarcoidosis showed histologic features of diseases other than ESPS (UIP and emphysema) without granulomas. Two patients with atypical clinical findings demonstrated non-necrotizing granulomas combined with either severe chronic venous hypertension or UIP.

Conclusions: ESPS and UIP have distinct histopathologic features in the lungs. Patients with a pre-transplant diagnosis of sarcoidosis may develop other lung diseases that account for their end stage fibrosis.

Introduction

Sarcoidosis is a disease of unknown etiology characterized by granuloma formation involving multiple organ sites[1]. The lungs are the most commonly involved organ; approximately 95% of sarcoidosis patients have computed tomographic (CT) evidence of lung disease [2,3]. The diagnosis depends on a combination of clinicoradiological features, non-necrotizing granulomas in a tissue biopsy, and exclusion of other etiologies, especially granulomatous infection [4]. Most cases involving the lungs follow a benign course and either resolve spontaneously or respond to steroid treatment; 10 to 30% of patients experience progressive fibrosis resulting in respiratory failure [5-9].

Little is known about the pathologic features of end stage pulmonary sarcoidosis (ESPS). Pathologic features of ESPS have been described in three studies of 17 patients in the English literature. H. Shigemitsu et al[10] described 7 patients with ESPS who underwent lung transplantation. Only four of the explanted lungs showed granulomas characteristic of ESPS; two displayed patchy interstitial fibrosis and fibroblast foci consistent with usual interstitial pneumonia (UIP). Aisner and Albin[11] reported a case of advanced pulmonary sarcoidosis in which a lung biopsy showed extensive interstitial fibrosis and honeycombing without granulomatous inflammation. Most recently Xu and colleagues reviewed their experience with 9 patients who underwent transplantation for sarcoidosis, dividing their patients into those with "active" and "fibrotic" disease based on the profusion of granulomatous inflammation in the explanted lungs. Patients with "fibrotic" disease included two in whom no granulomas were present. They concluded that late stage fibrotic disease, even when it lacks granulomatous features, is distinct from UIP but they did not include a control group[12].

We compared lung explant findings in patients with a preoperative diagnosis of sarcoidosis to age and sex matched controls with UIP to characterize histopathologic features useful in distinguishing ESPS from UIP.

Methods

Thirteen patients with a clinical diagnosis of pulmonary sarcoidosis underwent lung transplantation (5 double-lung and 7 single-lung transplantations) between 1991 and 2012 at the University of Michigan. The diagnosis of sarcoidosis was based on criteria proposed in the joint statement on sarcoidosis by the American Thoracic Society, the European Respiratory Society, and the World Association of Sarcoidosis and Other Granulomatous Diseases (2). One patient was excluded because no slides were available for review. Controls were 10 age and sex matched lung transplant recipients with a postoperative diagnosis of UIP using previously published criteria [13-15]. Patient demographic information, radiological findings and clinical diagnoses were obtained from the electronic medical record. This research was approved by the Institutional Review Board of the University of Michigan (project approval number HUM00063185) in accordance with the Institutional Committee for the Protection of Human Subjects.

Hematoxylin and eosin (H&E)-stained sections were examined by three pulmonary pathologists (CZ, LAS and JLM) with documentation of the following features: extent/pattern of fibrosis; presence/quantity (per 10 high power fields) of fibroblast foci and granulomas; distribution and morphology of granulomas; presence of granulomas in hilar/mediastinal lymph nodes; presence/extent of honeycomb change. Extent of fibrosis and honeycomb change was scored as follows: 1=1-25%; 2=26-50%; 3=51-75%; 4=76-100% of lung parenchyma. Special stains

(Gomori methenamine silver and Ziehl-Neelsen) for fungi and acid-fast bacilli were performed on selected sections.

A two-tailed Student t test was used to evaluate potential differences in continuous variables between different subgroups. A two-sided chi-square test was used to test potential differences in categorical variables of interest between different subgroups. Differences between groups were considered statistically significant if the p value was <0.05.

Results

Twelve explanted lungs from patients with a pre-transplant diagnosis of ESPS were divided into three categories based on histological findings. Group 1 (patients #1-8): ESPS; group 2 (patients #9 and 10): diseases other than ESPS; group 3 (patients # 11 and 12): overlapping features of sarcoidosis and other diseases. Clinical information for all groups is summarized in Tables 1 and 2.

The control group comprised 10 lung transplant recipients with a pathologic diagnosis of UIP. The underlying clinical condition was IPF in nine, including six men, with a mean age of 54.1 years (range 40 – 62 years). A 36-year-old woman with UIP had systemic lupus erythematosus (SLE).

Group 1: ESPS (n = 8).

Eight (66.7%) patients with a pre-transplant diagnosis of sarcoidosis had histologic findings consistent with previously reported features of ESPS. Patients included three (37.5%) women and ranged from 36 to 58 years of age (mean 45.9 years ± 8.2 years). A diagnosis of sarcoidosis had been established 4 to 26 years prior to transplant (mean 14.1 years ± 8.3 years; median 11

years). A tissue diagnosis was made in six patients while clinical- radiologic findings led to a diagnosis of sarcoidosis in two (Table 1). Radiologic changes were consistent with sarcoidosis in all eight patients. Pulmonary function tests revealed severe to very severe obstructive ventilatory defects in four patients, a moderately severe to severe restrictive defect in three, and a combined restrictive and obstructive defect in one. Six patients had pulmonary hypertension defined as a mean pulmonary artery pressure (mPAP) > 25 mmHg based on right heart catheterization.

Histologic findings are summarized in Table 3. Non-necrotizing granulomas were present in the lung sections from all 8 cases (figure 1A). The granulomas were well formed with peripheral concentric fibrosis. Granulomas were distributed in a lymphangitic pattern, involving visceral pleura and subpleural parenchyma, bronchovascular bundles, and interlobular septa. Granulomas were identified in hilar and/or mediastinal lymph nodes in all 6 patients in whom lymph nodes were sampled. No granulomas were present in any of the control cases.

Patchy fibrosis was identified in all cases of ESPS. The distribution of fibrosis followed a lymphangitic pattern, focally associated with non-necrotizing granulomas (figure 1B). In contrast, the patchy fibrosis in the control group was randomly distributed and was not associated with granulomatous inflammation (figure 1C). The fibrosis in ESPS had an average score of 2.1 ± 1.0 compared to 3.5 ± 0.7 in UIP ($p < 0.001$).

Focal honeycomb change was present in 3 of 8 (38%) ESPS cases. The extent of honeycomb change in ESPS cases ranged from 1% to 20% of lung parenchyma, with a consistent score of 1. In contrast, honeycomb change was present in all 10 control UIP cases, involving 5% to 60% of lung parenchyma, with an average score of 1.7 ± 0.8. The prevalence of honeycomb change in

ESPS was significantly lower compared to UIP (37.5% vs 100%, p = 0.012); however, the difference in the extent of honeycomb change did not reach statistical significance (p = 0.061).

Fibroblast foci were identified in 4 of 8 ESPS cases and 10 of 10 UIP cases (50% vs 100%, p = 0.048). The average number of fibroblast foci in ESPS cases was 2.0 ± 1.4/10HPF (range 1 to 4/10HPF) compared to 7.0 ± 3.5 in UIP (p = 0.002).

Group 2: diseases other than sarcoidosis (n = 2)

Two patients with a clinical diagnosis of pulmonary sarcoidosis had histological findings typical of diseases other than ESPS in their explanted lungs.

Patient 9 was a 59-year-old Caucasian female who was diagnosed with sarcoidosis by mediastinal lymph node biopsy 4 years prior to lung transplantation. Chest CT scan showed extensive interlobular septal thickening in the periphery of both lungs, greater at the bases than at the apices, associated with traction bronchiectasis and honeycomb change. Pulmonary function testing demonstrated only isolated diffusion impairment. No pulmonary hypertension was present. Multiple sections prepared from her lung explant (figure 2A and 2B) showed a combination of findings characteristic of UIP including patchy fibrosis (50%), extensive honeycomb change (> 25%) and fibroblast foci (22/HPF). No granulomas were present in either the lung or hilar lymph nodes.

Patient #10 was a 56-year old African American female whose diagnosis of sarcoidosis was established by open lung biopsy 22 years prior to transplantation. Those slides were not available for review. The patient had a remote tobacco smoking history. Chest radiograph prior to transplantation demonstrated upper and mid-zone emphysema without hilar or mediastinal lymphadenopathy. Pulmonary function tests were consistent with a very severe obstructive

ventilatory defect. No pulmonary hypertension was present. Histological examination of the lung explant showed severe emphysematous changes, consistent with the clinical impression of chronic obstructive pulmonary disease (COPD). No honeycomb change or fibroblast foci were identified. No granulomas were identified in the lung or hilar lymph nodes.

Group 3: overlap between ESPS and other diffuse lung diseases (n=2)

Patient #11 was a 49-year-old African American female who was diagnosed with sarcoidosis by transbronchial biopsy 4 years prior to lung transplantation. Chest CT prior to transplantation showed "upper lobe reticulation and traction bronchiectasis with lower lobe predominant diffuse ground glass opacification" for which diagnostic considerations included both non-specific interstitial pneumonitis (NSIP) and sarcoidosis. Pulmonary function testing revealed a severe restrictive ventilatory defect with diffusion impairment. Connective tissue disease serology was negative and her right heart catheterization revealed significant pulmonary hypertension (mPAP of 43 mmHg) with a normal right atrial pressure of 6 mmHg. An echocardiogram confirmed her pulmonary hypertension with right ventricular dilation. However, her pulmonary artery occlusion pressure was only 13 mmHg thereby eliminating left ventricular dysfunction as a cause of the pulmonary hypertension. The primary histopathologic finding from her explanted lung (Figure 3C) was fibrosis with focal honeycomb change (score 1) and fibroblast foci (3/10 HPF) but with neither the patchwork fibrosis characteristic of UIP nor a lymphangitic distribution typical of ESPS. There were rare well-formed non-necrotizing granulomas distributed mainly along interlobular septa (Figure 3B) and in the hilar lymph nodes, similar to those seen in other ESPS cases (Figure 3A). Sections also showed marked chronic venous hypertension indicated by extensive capillary hemangiomatosis-like change expanding alveolar septa (Figure 3D). Her final pathologic diagnosis was pulmonary sarcoidosis and severe chronic venous hypertension.

Patient #12 was a 42-year-old African American female who was diagnosed with sarcoidosis on the basis of a liver biopsy 16 years prior to lung transplantation. She had been continuously treated with corticosteroids. Her chief complaint was shortness of breath that had progressed over a period of several years. Chest CT showed extensive "honeycombing and cystic changes bilaterally with bilateral hilar lymphadenopathy and enlarged mediastinal lymph nodes." Pulmonary physiology was consistent with severe restrictive lung disease and diffusion impairment. No pulmonary hypertension was present. Sections from her lung explant showed extensive fibrosis distributed in a random pattern (Figure 4C), with honeycomb change (score 1) and frequent fibroblast foci (5/10HPF), consistent with UIP. In addition, there were also well-formed non-necrotizing granulomas in a lymphangitic distribution (Figure 4B), which were also present in the hilar lymph nodes (Figure 4A). Special stains of GMS and AFB were negative for microorganisms. Pathologic diagnosis was combined pulmonary sarcoidosis and UIP.

Discussion

A definite histopathologic diagnosis of ESPS was established in two thirds of our patients with a pre-transplant diagnosis of sarcoidosis. The remaining patients were equally split between those with an alternative diagnosis and those in whom sarcoidosis was combined with another diffuse lung disease.

The histologic findings in ESPS are distinctly different from end stage UIP (Table 4). The features most helpful in separating ESPS from UIP are the distribution of fibrosis and the presence or absence of granulomatous inflammation. Fibrosis in ESPS is distributed in a unique lymphangitic pattern that follows the distribution of the granulomas. In contrast, random and subpleural fibrosis and absence of granulomas are consistent features of UIP. The fibrosis in both

conditions can be associated with smooth muscle hyperplasia and scarring. The degree of architectural distortion in the forms of scarring and honeycomb change was generally milder in ESPS.

Granulomatous inflammation is a consistent finding in the lungs of patients with ESPS, and was seen in all of our patients who had other supportive clinical, radiological and histolopathologic findings. Others have suggested that granulomatous inflammation in ESPS may be obliterated by concentric fibrosis, a finding not seen in our patients[16]. It is conceivable that previously reported examples of ESPS without granulomatous inflammation may have represented patients with previous histories of sarcoidosis who, like some of ours, developed other fibrotic conditions. Caution should be exercised in using lung granulomas as the defining pathologic feature of sarcoidosis because certain infections occurring in patients with other underlying diffuse lung diseases may also cause non-necrotizing sarcoid-like granulomas. For example, UIP complicated by MAC infections may mimic the histologic findings previously attributed to ESPS although the granulomas are more likely to be situated within air spaces rather than the fibrotic interstitium. Another histologic clue more commonly seen in infection than sarcoidosis is associated organizing pneumonia (8). Non-necrotizing granuloma in the hilar or mediastinal lymph nodes is another feature that consistently differentiated ESPS from UIP in our study.

Fibroblast foci and honeycomb change are two features that are not specific, but when extensive, can be helpful in differentiating UIP from ESPS. In our current study, fibroblast foci were identified in 4 of 8 ESPS cases; however, they were quantitatively scarce. Honeycomb changes were present in 3 of 8 ESPS cases, but none of these changes were extensive in contrast to the extensive involvement characteristic of end stage UIP.

Our findings suggest that a subset of patients with an established diagnosis of sarcoidosis develop other diffuse lung diseases resulting in end stage pulmonary fibrosis. A reasonable explanation for the two patients in our series whose explanted lungs showed no histopathologic evidences of sarcoidosis is that their pulmonary sarcoidosis resolved prior to transplantation given that spontaneous remissions occur in nearly two thirds of patients[5]. Alternatively, these patients may have been misdiagnosed with pulmonary sarcoidosis. Histopathologic examination of a mediastinal lymph node in case #9 and lung tissue in case #10 revealed non-caseating granulomas. Neither patient had evidence of extra-thoracic disease. Both Mukhopadhyay[17] and Nazarullah[18] have demonstrated that such granulomas have only about a 21-27% chance of representing sarcoidosis. We believe that both of these patients developed other forms of progressive diffuse fibrotic lung disease for which transplantation was performed.

Although both sarcoidosis and IPF are relatively rare diseases, cases of combined sarcoidosis and IPF have been reported. Tachibana et al[19] reported a patient who died of acute respiratory failure 3 years after the diagnosis of sarcoidosis. The initial diagnosis was based on a mediastinoscopic biopsy of the mediastinal lymph nodes showing numerous noncaseating epithelioid granulomas. At autopsy, the lungs showed UIP with superimposed diffuse alveolar damage (DAD). It was concluded that the patient suffered from sarcoidosis and IPF during the observation period, and subsequently succumbed to an acute exacerbation of IPF. Nobata et al[20] also described a case of pulmonary sarcoidosis with UIP distributed predominantly in the lower lung fields. In our current study, 2 of 12 patients who carried a diagnosis of sarcoidosis demonstrated histologic features of UIP in the explanted lungs, with or without concurrent features of pulmonary sarcoidosis.

In summary, ESPS has characteristic histopathologic features that distinguish it from other end stage lung diseases such as UIP. Recognizing these features may be helpful in identifying coexisting UIP in open lung biopsies of patients with known sarcoidosis. This may be of clinical significance since patients with sarcoidosis listed for lung transplantation have significantly longer wait times for an allograft than do patients with IPF[21].

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CZ is the guarantor of the content of the manuscript, including the data and analysis. CZ, LAS and JLM performed microscopic examination. KMC provided patients' clinical data. CZ and LAS contributed to data analysis and interpretation. All author contributed to study design and manuscript preparation.

Table 1. Clinical and radiological information of all cases in the study group.

Patient #	Gender	Ethnicity	Age	Interval from Dx to Txplt (years)	Pre-txplt biopsy performed	Extra-thoracic sarcoid (Y/N)	Radiology	
							technique	consistent with ESPS*
1	Male	Caucasian	48	23	Yes (neck LN)	Y	HRCT	++
2	Female	African American	39	8	No	N	CXR	++
3	Male	Hispanic	42	8	Yes (open lung)	N	HRCT	++
4	Male	Caucasian	40	4	Yes (open lung)	N	CXR	++
5	Female	African American	48	22	No	N	CXR	0
6	Male	Caucasian	58	13	Yes (open lung)	N	CXR	++
7	Male	African American	56	26	Yes (TBBX)	N	HRCT	++
8	Female	African American	36	9	Yes (hilar LN)	N	CXR	++
9	Female	Caucasian	59	4	Yes (mediastinal LN)	N	CT	-
10	Female	African American	56	22	Yes (open lung)	N	CXR	-
11	Female	African American	49	4	Yes (TBBX)	N	CT	+
12	Female	African American	42	16	Yes (liver)	Y	CT	+

CXR: Chest X-Ray; CT: Computed tomography; Dx: Diagnosis; ESPS: End stage pulmonary sarcoidosis; HRCT: High resolution CT scan; LN: Lymph node; TBBX: Transbronchial biopsy; Txplt: Transplantation.

* responses: ++ highly consistent; + consistent; 0: possible; - unlikely.

Table 2. Pulmonary function test results of all patients.

Patient #	Pulmonary Function Tests						PHTN* (Y/N)
	FVC (Liter/%)	FEV1 (Liter/%)	FEV1/FVC	TLC (%)	RV (%)	DLCO (%)	
1	2.89/59	0.79/22	0.27	86	157	52	Y
2	1.7/51	1.33/51	0.78	n/a	n/a	37	Y
3	1.45/30	1.02/27	0.70	38	n/a	44	Y
4	2.34/48	0.77/21	0.33	108	240	n/a	N
5	1.84/57	0.99/40	0.54	n/a	n/a	n/a	Y
6	1.35/30	1.15/36	0.85	57	113	12	Y
7	1.52/36	0.47/15	0.31	96	215	24	Y
8	1.1/28	0.96/31	0.87	43	68	18	N
9	2.77/118	2.21/129	0.80	101	88	28	N
10	0.89/29	0.27/12	0.31	n/a	n/a	n/a	N
11	1.2/41	1.07/47	0.89	n/a	n/a	29	Y
12	1.36/35	1.08/36	0.79	36	n/a	33	N

DLCO: Diffusion capacity to carbon monoxide; FEV1: Forced expiratory volume; FVC: Forced vital capacity; n/a: not available; PHTN: Pulmonary hypertension; RV: Residual volume; TLV: Total lung capacity.

* PHTN was defined as mean pulmonary arterial pressure (mPAP) > 25 mmHg.

Table 3: Summary of histological findings of all cases in the study group.

Case #	Fibrosis		Fibroblast foci		Architectural distortion			Granulomas				
					HCC		scarring					
	distrib-ution	extent (score)	present (Y/N)	extent (#/10HPF)	present (Y/N)	extent (score)	present (Y/N)	present (Y/N)	extent (#/10HPF)	distribution	morphology	present in LN (Y/N)
1	patchy	4	N	N/A	N	N/A	Y	Y	38	lymphangitic	well-formed	Y
2	patchy	2	Y	4	Y	1	Y	Y	22	lymphangitic	well-formed	N/A
3	patchy	1	N	N/A	Y	1	N	Y	13	lymphangitic	well-formed	Y
4	patchy	2	N	N/A	N	N/A	Y	Y	45	lymphangitic	well-formed	Y
5	patchy	2	Y	1	N	N/A	Y	Y	3	lymphangitic	well-formed	N/A
6	patchy	2	N	N/A	N	N/A	Y	Y	11	lymphangitic	well-formed	Y
7	patchy	1	Y	1	N	N/A	Y	Y	3	lymphangitic	well-formed	Y
8	patchy	3	Y	2	Y	1	Y	Y	13	lymphangitic	well-formed	Y
9	patchy	3	Y	22	Y	1	Y	N	N/A	N/A	N/A	N
10	N/A	0	N	N/A	N	N/A	N	N	N/A	N/A	N/A	N
11	diffuse	4	Y	3	Y	1	Y	Y	2	lymphangitic	well-formed	Y
12	patchy	4	Y	5	1	1	Y	Y	6	lymphangitic	well-formed	Y

HCC: Honeycomb change; HPF: high power field; LN: lymph node; N/A: Not applicable.

Table 4: Comparison of major pathologic features of the ESPS cases and the UIP cases.

Pathology features	ESPS	UIP
Distribution of fibrosis	Lymphangitic distribution	Randomly distributed
Fibroblast foci	Absent or rare	Frequent
Architectural distortion	Absent or mild	Extensive
Granuloma in the lung	Present, lymphangitic distribution	Absent, unless complicated by infections
Granuloma in lymph nodes	Present	Absent

ESPS: end stage pulmonary sarcoidosis; UIP: usual interstitial pneumonia.

Figure Legends

Figure 1: All ESPS cases demonstrated well-formed granulomas within lung parenchyma; granulomas were also present in hilar or mediastinal lymph nodes in all patients for whom lymph nodes were available (A; H&E, 200x). Patchy fibrosis was also identified in all cases of ESPS (B; H&E, 20x), and this fibrosis was distributed in a lymphangitic pattern. In contrast, patchy fibrosis in the control cases was distributed in a random pattern (C; H&E, 20x).

Figure 2: Sections taken from patient 9's explant showed characteristic findings of usual interstitial pneumonia (UIP), including patchy fibrosis, fibroblast foci (A; H&E, 100x), and honeycomb change (B; H&E, 40x).

Figure 3: Sections taken from the explant from patient 11 showed rare well-formed granulomas both within hilar lymph nodes (A; H&E, 100x) and along interlobular septa (B; H&E, 100x). There was also focal honeycomb change present (C; H&E, 40x) without other changes of UIP such as patchwork fibrosis. These findings were complicated by marked chronic venous hypertension including extensive capillary hemangiomatosis-like change (D; H&E, 200x).

Figure 4: Sections from the explant of patient 12 demonstrate well-formed granulomas within hilar lymph nodes (A; H&E, 100x) and within a lymphangitic distribution (B; H&E, 100x) in pulmonary parenchyma. However, changes of UIP were also present, including fibroblast foci (arrowhead; C; H&E, 40x), randomly distributed fibrosis, and honeycomb change.

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