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Histopathology of Explanted Lungs From Patients With a Diagnosis of Pulmonary Sarcoidosis

Chen Zhang, MD, PhD; Kevin M. Chan, MD; Lindsay A. Schmidt, MD; and Jeffrey L. Myers, MD

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

RESULTS: Eight of 12 cases demonstrated histologic 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 six of six patients with ESPS and none of eight control subjects. The extent of fibrosis, honeycomb change, and fibroblast foci was significantly lower in ESPS cases compared with 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 nonnecrotizing granulomas combined with either severe chronic venous hypertension or UIP.

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

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KEY WORDS: histopathology; lung transplantation; sarcoidosis

ABBREVIATIONS: ESPS = end-stage pulmonary sarcoidosis; HPF = high-power field; IPF = idiopathic pulmonary fibrosis; mPAP = mean pulmonary artery pressure; UIP = usual interstitial pneumonia

AFFILIATIONS: From the Department of Pathology and Laboratory Medicine (Dr Zhang), Indiana University School of Medicine, Indianapolis, IN; Division of Pulmonary and Critical Care Medicine (Dr Chan), Department of Internal Medicine, University of Michigan Health Systems, Ann Arbor, MI; Marshfield Clinic (Dr Schmidt), Weston, WI; and Department of Pathology (Dr Myers), University of Michigan Health Systems, Ann Arbor, MI.

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CORRESPONDENCE TO: Chen Zhang, MD, PhD, 350 W 11th St, Rm 4084, Indianapolis, IN 46202; e-mail: chenzhan@iupui.edu

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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 patients with sarcoidosis have CT evidence of lung disease.[2,3] The diagnosis depends on a combination of clinicoradiologic 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. Shigemitsu et al[10] described seven 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 specimen showed extensive interstitial fibrosis and honeycombing without granulomatous inflammation. Xu et al[12] reviewed their experience with nine 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. The researchers concluded that late-stage fibrotic disease, even when it lacks granulomatous features, is distinct from UIP, but they did not include a control group in their study.[12] We compared lung explant findings in patients with a preoperative diagnosis of sarcoidosis to age- and sex-matched control groups with UIP to characterize histopathologic features useful in distinguishing ESPS from UIP.

Materials and Methods

Thirteen patients with a clinical diagnosis of pulmonary sarcoidosis underwent lung transplantation (five double-lung and seven 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. Control subjects were 10 age- and sex-matched lung transplant recipients with a postoperative diagnosis of UIP using previously published criteria.[13-15] Patient demographic information, radiologic 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 no. HUM00063185) in accordance with the Institutional Committee for the Protection of Human Subjects.

Tissue sections stained with hematoxylin and eosin were examined by three pulmonary pathologists (C. Z., L. A. S., and J. L. M.) with documentation of the following features: extent and pattern of fibrosis; presence and quantity (per 10 high-power fields [HPFs]) of fibroblast foci and granulomas; distribution and morphology of granulomas; presence of granulomas in hilar or mediastinal lymph nodes; and presence and extent of honeycomb change. Extent of fibrosis and honeycomb change in lung parenchyma was scored as follows: 1 = 1% to 25%; 2 = 26% to 50%; 3 = 51% to 75%; 4 = 76% to 100% of lung parenchyma. Special stains (Gomori methenamine silver and Ziehl-Neelsen) for fungi and acid-fast bacilli were performed on selected tissue sections.

A two-tailed Student *t* test was used to evaluate potential differences in continuous variables between different subgroups. A two-sided χ^2 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 $< .05$.

Results

Twelve explanted lungs from patients who received a pretransplant diagnosis of ESPS were divided into three categories based on histologic 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 idiopathic pulmonary fibrosis (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.

Group 1: ESPS (n = 8)

Eight patients (66.7%) with a pretransplant diagnosis of sarcoidosis had histologic findings consistent with previously reported features of ESPS. Patients included three women (37.5%) and ranged from 36 to 58 years of age (mean ± SD, 45.9 ± 8.2 years). A diagnosis of sarcoidosis had been established 4 to 26 years prior to transplant (mean ± SD, 14.1 ± 8.3 years; median, 11 years). A tissue diagnosis was made in six patients, while clinicoradiologic findings led to a diagnosis of

TABLE 1] Clinical and Radiologic Information of All Cases in the Study Group

Patient No.	Sex	Ethnicity	Age, y	Interval from Diagnosis to Transplant, y	Pretransplant Biopsy Performed	Extrathoracic Sarcoid, Yes/No	Radiology	
							Technique	Consistent with ESPS
1	Male	White	48	23	Yes: neck LN	Yes	HRCT scan	++
2	Female	Black	39	8	No	No	CXR	++
3	Male	Hispanic	42	8	Yes: open lung	No	HRCT scan	++
4	Male	White	40	4	Yes: open lung	No	CXR	++
5	Female	Black	48	22	No	No	CXR	0
6	Male	White	58	13	Yes: open lung	No	CXR	++
7	Male	Black	56	26	Yes: TBBX	No	HRCT scan	++
8	Female	Black	36	9	Yes: hilar LN	No	CXR	++
9	Female	White	59	4	Yes: mediastinal LN	No	CT scan	–
10	Female	Black	56	22	Yes: open lung	No	CXR	–
11	Female	Black	49	4	Yes: TBBX	No	CT scan	+
12	Female	Black	42	16	Yes: liver	Yes	CT scan	+

0 = possible; CXR = chest radiograph; ESPS = end-stage pulmonary sarcoidosis; HRCT = high-resolution CT; LN = lymph node; – = unlikely; + = consistent; ++ = highly consistent; TBBX = transbronchial biopsy.

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 mm Hg based on right-sided heart catheterization.

Histologic findings are summarized in Table 3. Non-necrotizing granulomas were present in the lung sections from all eight patients (Fig 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 alymph nodes, mediastinal lymph nodes, or both in all six patients in whom lymph nodes were sampled. No granulomas were present in any of the control subjects.

Patchy fibrosis was identified in all cases of ESPS. The distribution of fibrosis followed a lymphangitic pattern,

TABLE 2] Pulmonary Function Test Results of All Patients

Patient No.	Pulmonary Function Tests						PHTN[a]
	FVC, L (%)	FEV_1, L (%)	FEV_1/FVC	TLC, %	RV, %	D_{LCO}, %	
1	2.89 (59)	0.79 (22)	0.27	86	157	52	Yes
2	1.7 (51)	1.33 (51)	0.78	N/A	N/A	37	Yes
3	1.45 (30)	1.02 (27)	0.70	38	N/A	44	Yes
4	2.34 (48)	0.77 (21)	0.33	108	240	N/A	No
5	1.84 (57)	0.99 (40)	0.54	N/A	N/A	N/A	Yes
6	1.35 (30)	1.15 (36)	0.85	57	113	12	Yes
7	1.52 (36)	0.47 (15)	0.31	96	215	24	Yes
8	1.1 (28)	0.96 (31)	0.87	43	68	18	No
9	2.77 (118)	2.21 (129)	0.80	101	88	28	No
10	0.89 (29)	0.27 (12)	0.31	N/A	N/A	N/A	No
11	1.2 (41)	1.07 (47)	0.89	N/A	N/A	29	Yes
12	1.36 (35)	1.08 (36)	0.79	36	N/A	33	No

D_{LCO} = diffusion capacityof lung for carbon monoxide; N/A = not available; PHTN = pulmonary hypertension; RV = residual volume; TLC = total lung capacity.
[a]PHTN was defined as mean pulmonary arterial pressure > 25 mm Hg.

TABLE 3] Summary of Histologic Findings of All Cases in the Study Group

Case No.	Fibrosis		Fibroblast Foci		Architectural Distortion			Granulomas				
					HCC		Scarring					
	Distribution	Extent, Score	Present	Extent, per 10 HPFs	Present	Extent, Score	Present	Present	Extent, per 10 HPFs	Distribution	Morphology	Present in LN
1	Patchy	4	No	N/A	No	N/A	Yes	Yes	38	Lymphangitic	Well formed	Yes
2	Patchy	2	Yes	4	Yes	1	Yes	Yes	22	Lymphangitic	Well formed	N/A
3	Patchy	1	No	N/A	Yes	1	No	Yes	13	Lymphangitic	Well formed	Yes
4	Patchy	2	No	N/A	No	N/A	Yes	Yes	45	Lymphangitic	Well formed	Yes
5	Patchy	2	Yes	1	No	N/A	Yes	Yes	3	Lymphangitic	Well formed	N/A
6	Patchy	2	No	N/A	No	N/A	Yes	Yes	11	Lymphangitic	Well formed	Yes
7	Patchy	1	Yes	1	No	N/A	Yes	Yes	3	Lymphangitic	Well formed	Yes
8	Patchy	3	Yes	2	Yes	1	Yes	Yes	13	Lymphangitic	Well formed	Yes
9	Patchy	3	Yes	22	Yes	1	Yes	No	N/A	N/A	N/A	No
10	N/A	0	No	N/A	No	N/A	No	No	N/A	N/A	N/A	No
11	Diffuse	4	Yes	3	Yes	1	Yes	Yes	2	Lymphangitic	Well formed	Yes
12	Patchy	4	Yes	5	Yes	1	Yes	Yes	6	Lymphangitic	Well formed	Yes

HCC = honeycomb change; HPF = high-power field; N/A = not applicable. See Table 1 for expansion of other abbreviation.

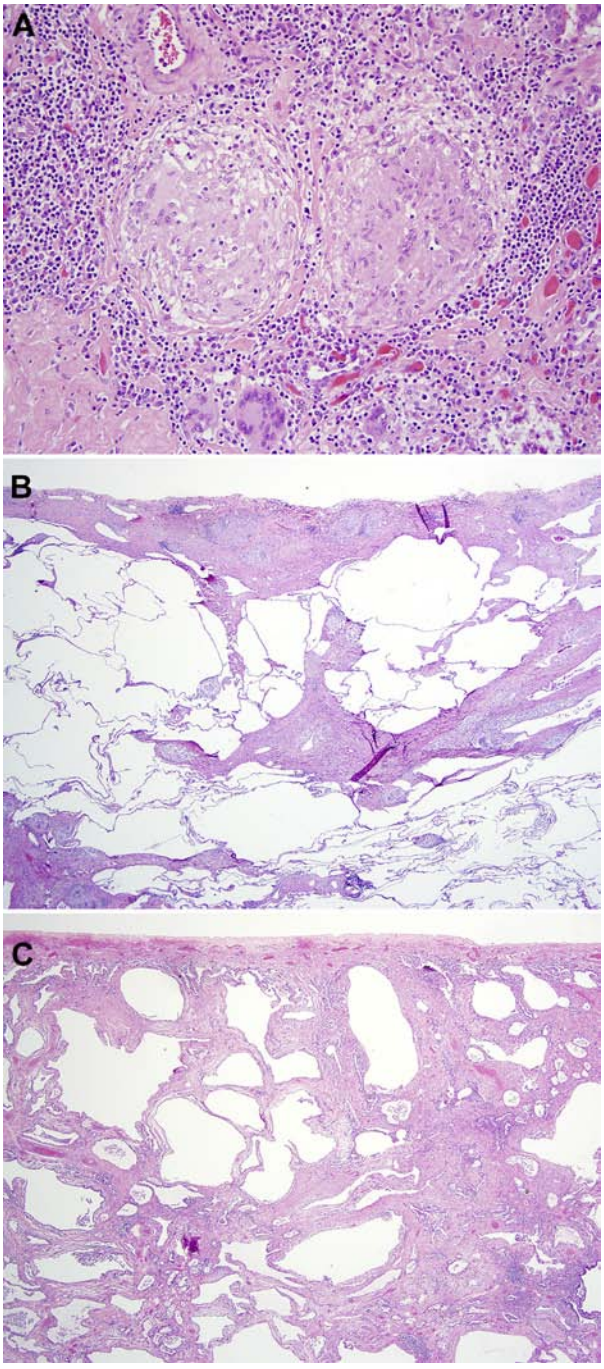

Figure 1 – *A, All end-stage pulmonary sarcoidosis (ESPS) cases demonstrated well-formed granulomas within lung parenchyma; granulomas were also present in hilar or mediastinal lymph nodes in all patients for whom lymph nodes were available (hematoxylin and eosin [H&E], original magnification × 200). B, Patchy fibrosis was also identified in all cases of ESPS (H&E, original magnification × 20), and this fibrosis was distributed in a lymphangitic pattern. C, In contrast, patchy fibrosis in the control cases was distributed in a random pattern (H&E, original magnification × 20).*

focally associated with non-necrotizing granulomas (Fig 1B). In contrast, the patchy fibrosis in the control group was randomly distributed and was not associated with granulomatous inflammation (Fig 1C). The fibrosis in ESPS had an average score of 2.1 ± 1.0 compared with 3.5 ± 0.7 in UIP ($P < .001$).

Focal honeycomb change was present in three of eight ESPS cases (38%). 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 and with an average score of 1.7 ± 0.8. The prevalence of honeycomb change in ESPS was significantly lower compared with UIP (37.5% vs 100%; $P = .012$); however, the difference in the extent of honeycomb change did not reach statistical significance ($P = .061$).

Fibroblast foci were identified in four of eight ESPS cases and 10 of 10 UIP cases (50% vs 100%; $P = .048$). The average number of fibroblast foci in ESPS cases was 2.0 ± 1.4 per 10 HPFs (range, 1-4 per 10 HPFs) compared with 7.0 ± 3.5 in UIP ($P = .002$).

Group 2: Diseases Other Than Sarcoidosis (n = 2)

Two patients with a clinical diagnosis of pulmonary sarcoidosis had histologic findings typical of diseases other than ESPS in their explanted lungs. Patient 9 was a 59-year-old white woman who was diagnosed with sarcoidosis by evaluation of mediastinal lymph node biopsy tissue 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 tissue sections prepared from her lung explant (Figs 2A, B) 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 black woman whose diagnosis of sarcoidosis was established by evaluation of a specimen obtained during an 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 test results were consistent with a very severe obstructive ventilatory

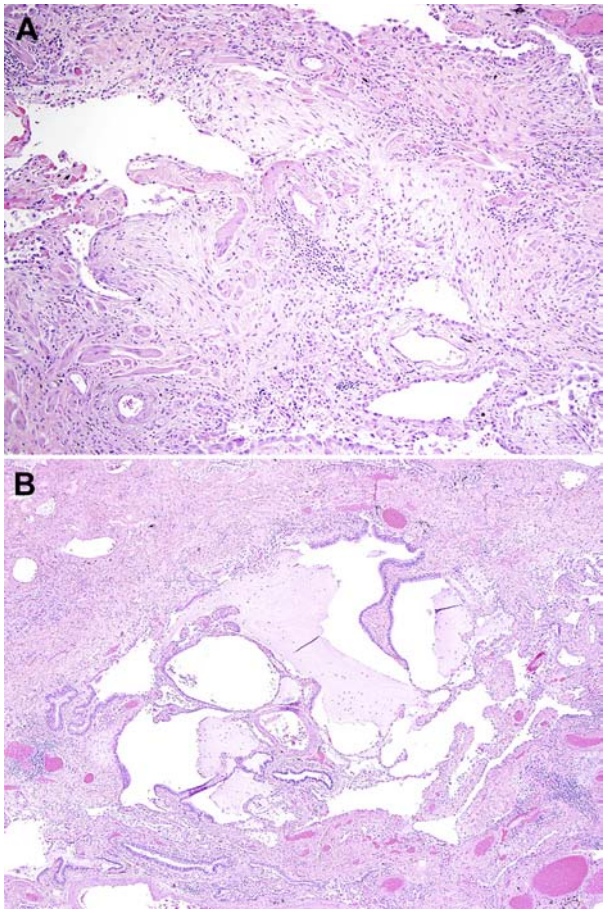

Figure 2 – *A. B. Tissue sections taken from the explanted lung of patient 9 showed characteristic findings of usual interstitial pneumonia (UIP), including patchy fibrosis, fibroblast foci, and honeycomb change. A, Micrograph showing fibroblast foci (H&E, original magnification × 100). B, Micrograph showing honeycomb changes (H&E, original magnification × 40). See Figure 1 legend for expansion of abbreviation.*

defect. No pulmonary hypertension was present. Histologic examination of the lung explant showed severe emphysematous changes consistent with the clinical impression of 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 black woman who was diagnosed with sarcoidosis after evaluation of tissue obtained by transbronchial biopsy 4 years prior to lung transplantation. According to her medical record, chest CT imaging prior to transplantation showed "upper lobe reticulation and traction bronchiectasis with lower lobe predominant diffuse ground-glass opacification," for which diagnostic considerations included both nonspecific interstitial pneumonitis and sarcoidosis. Pulmonary function testing revealed a severe restrictive ventilatory defect with diffusion impairment. Connective tissue disease serology was negative and her right-sided heart catheterization revealed significant pulmonary hypertension (mPAP, 43 mm Hg) with a normal right-sided atrial pressure of 6 mm Hg. An echocardiogram confirmed her pulmonary hypertension with right ventricular dilation. However, her pulmonary artery occlusion pressure was only 13 mm Hg, thereby eliminating left ventricular dysfunction as a cause of the pulmonary hypertension. The primary histopathologic finding from her explanted lung (Fig 3C) was fibrosis with focal honeycomb change (score, 1) and fibroblast foci (three per 10 HPFs) 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 (Fig 3B) and in the hilar lymph nodes, similar to those seen in other ESPS cases (Fig 3A). Sections also showed marked chronic venous hypertension indicated by extensive capillary hemangiomatosis-like change expanding alveolar septa (Fig 3D). The patient's final pathologic diagnosis was pulmonary sarcoidosis and severe chronic venous hypertension.

Patient 12 was a 42-year-old black woman who was diagnosed with sarcoidosis on the basis of findings in liver biopsy tissue 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. A chest CT scan showed extensive "honeycombing and cystic changes bilaterally with bilateral hilar lymphadenopathy and enlarged mediastinal lymph nodes," according to her medical record. Pulmonary physiology was consistent with severe restrictive lung disease and diffusion impairment. No pulmonary hypertension was present. Tissue sections from her lung explant showed extensive fibrosis distributed in a random pattern (Fig 4C), with honeycomb change (score, 1) and frequent fibroblast foci (5 per 10 HPFs), consistent with UIP. In addition, there were also well-formed non-necrotizing granulomas in a lymphangitic distribution (Fig 4B), which were also present in the hilar lymph nodes (Fig 4A). Special stains of Gomori methenamine silver and acid-fast bacilli 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

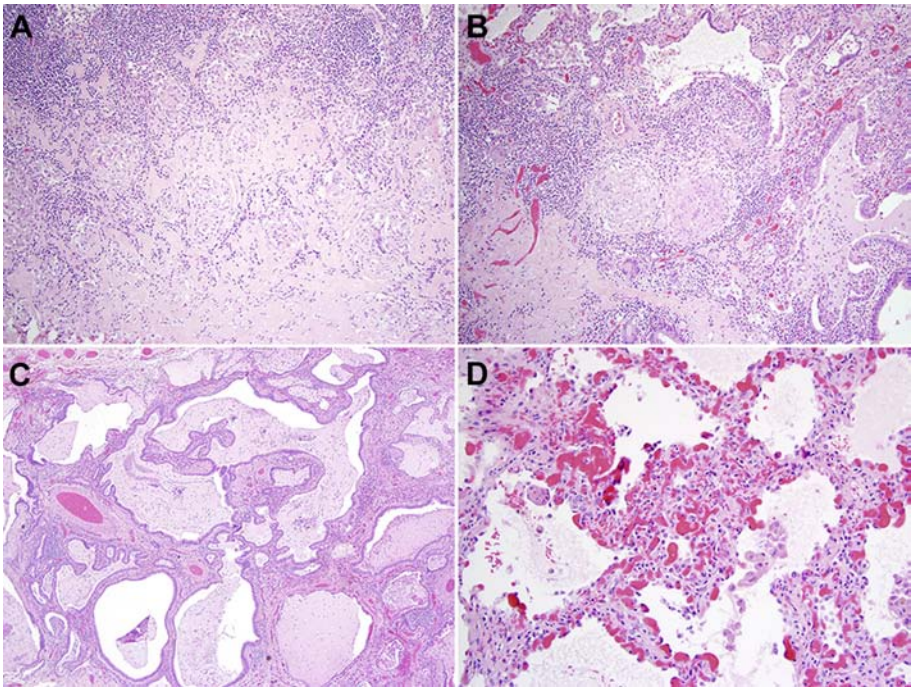

Figure 3 – *A-D, Tissue sections taken from the lung explant of patient 11 showed rare, well-formed granulomas both within hilar lymph nodes (A; H&E, original magnification × 100) and along interlobular septa (B; H&E, original magnification × 100). There was also focal honeycomb change present (C; H&E, original magnification × 40) without other changes of UIP such as patchwork fibrosis. These findings were complicated by marked chronic venous hypertension, including extensive capillary hemangiomatosis-like change (H&E, original magnification × 200). See Figure 1 legend for expansion of abbreviations.*

pretransplant 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, radiologic, and histopathologic 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 *Mycobacterium avium* complex 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 four of eight ESPS cases; however, they were quantitatively scarce. Honeycomb changes were present in three of eight ESPS cases, but none of these changes were extensive in contrast to the extensive involvement characteristic of end-stage UIP.

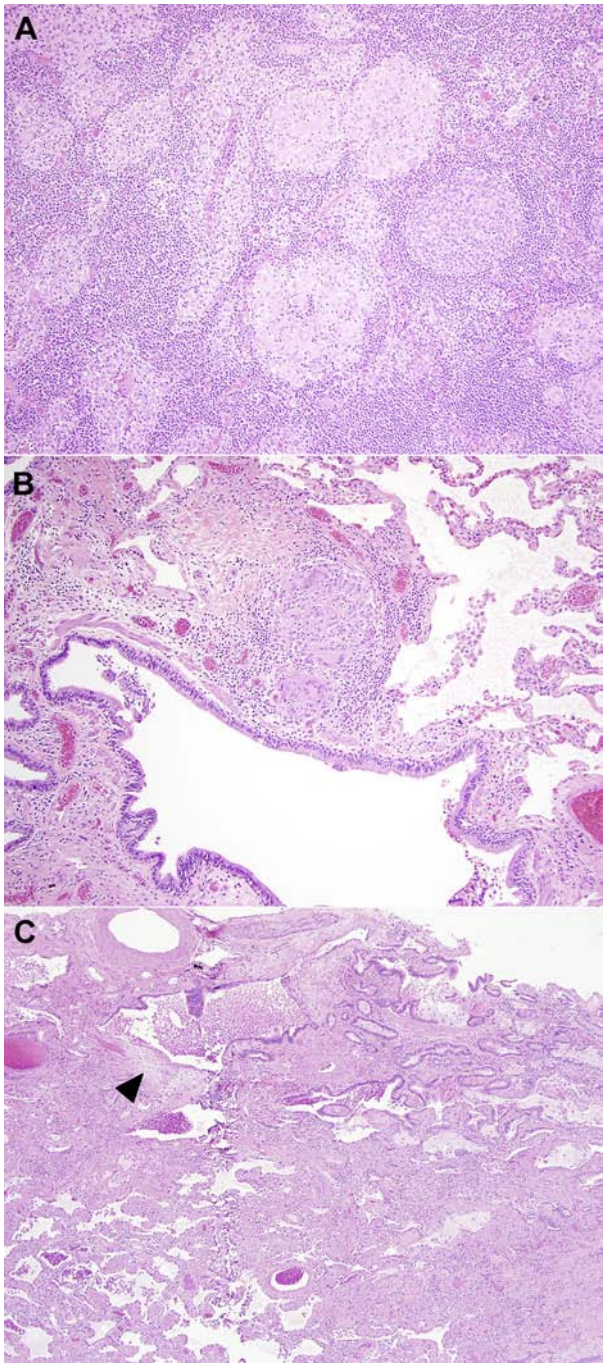

Figure 4 – *A-C, Sections from the lung explant of patient 12 demonstrate well-formed granulomas within hilar lymph nodes (A; H&E, original magnification × 100) and within a lymphangitic distribution (B; H&E, original magnification × 100) in pulmonary parenchyma. However, changes of UIP were also present, including fibroblast foci (arrowhead; C; H&E, original magnification × 40), randomly distributed fibrosis, and honeycomb change. See Figure 1 legend for expansion of abbreviations.*

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 patient 9 and lung tissue in patient 10 revealed non-caseating granulomas. Neither patient had evidence of extrathoracic disease. Both Mukhopadhyay et al[17] and Nazarullah et al[18] have demonstrated that such granulomas have only about a 21% to 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.

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

UIP = usual interstitial pneumonia. See Table 1 for expansion of other abbreviation.

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 tissue obtained during a mediastinoscopic biopsy of the mediastinal lymph nodes showing numerous noncaseating epithelioid granulomas. At autopsy, the lungs showed UIP with superimposed diffuse alveolar damage. 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, two 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 tissue collected during open lung biopsies performed in 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]

Acknowledgments

Author contributions: C. Z. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, including and especially any adverse effects. C. Z. served as principal author. C. Z., L. A. S. and J. L. M. performed microscopic examination; K. M. C. contributed to data collection; C. Z. and L. A. S. contributed to data analysis and interpretation; and C. Z., K. M. C., L. A. S., and J. L. M. contributed to the study design and manuscript preparation.

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References

1. Newman LS, Rose CS, Maier LA. Sarcoidosis. *N Engl J Med*. 1997;336(17):1224-1234.
2. Lynch JP III, Kazerooni EA, Gay SE. Pulmonary sarcoidosis. *Clin Chest Med*. 1997;18(4):755-785.
3. Lynch JP III, Sharma OP, Baughman RP. Extrapulmonary sarcoidosis. *Semin Respir Infect*. 1998;13(3):229-254.
4. Statement on sarcoidosis. Joint Statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS) and the World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) adopted by the ATS Board of Directors and by the ERS Executive Committee, February 1999. *Am J Respir Crit Care Med*. 1999;160(2):736-755.
5. Lynch JP III, Ma YL, Koss MN, White ES. Pulmonary sarcoidosis. *Semin Respir Crit Care Med*. 2007;28(1):53-74.
6. Neville E, Walker AN, James DG. Prognostic factors predicting the outcome of sarcoidosis: an analysis of 818 patients. *Q J Med*. 1983;52(208):525-533.
7. Rømer FK. Presentation of sarcoidosis and outcome of pulmonary changes. *Dan Med Bull*. 1982;29(1):27-32.
8. Scadding JG. Prognosis of intrathoracic sarcoidosis in England. A review of 136 cases after five years' observation. *BMJ*. 1961;2(5261):1165-1172.
9. Baughman RP, Winget DB, Bowen EH, Lower EE. Predicting respiratory failure in sarcoidosis patients. *Sarcoidosis Vasc Diffuse Lung Dis*. 1997;14(2):154-158.
10. Shigemitsu H, Oblad JM, Sharma OP, Koss MN. Chronic interstitial pneumonitis in end-stage sarcoidosis. *Eur Respir J*. 2010;35(3):695-697.
11. Aisner SC, Albin RJ. Diffuse interstitial pneumonitis and fibrosis in sarcoidosis. *Chest*. 1988;94(1):193-195.
12. Xu L, Kligerman S, Burke A. End-stage sarcoid lung disease is distinct from usual interstitial pneumonia. *Am J Surg Pathol*. 2013;37(4):593-600.
13. Katzenstein AL, Myers JL. Idiopathic pulmonary fibrosis: clinical relevance of pathologic classification. *Am J Respir Crit Care Med*. 1998;157(4 pt 1):1301-1315.
14. American Thoracic Society; European Respiratory Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. This joint statement of the American Thoracic Society (ATS), and the European Respiratory Society (ERS) was adopted by the ATS board of directors, June 2001 and by the ERS Executive Committee, June 2001. *Am J Respir Crit Care Med*. 2002;165(2):277-304.
15. Raghu G, Collard HR, Egan JJ, et al. ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med*. 2011;183(6):788-824.
16. Travis W, Colby T, Koss M, Rosado-de-Christenson ML, Müller NL, King TE Jr, eds. *Non-Neoplastic Disorders of the Lower Respiratory Tract (Atlas of Nontumor Pathology)*. 2nd ed. Washington, DC: Armed Forces Institute of Pathology; 2002.
17. Mukhopadhyay S, Farver CF, Vaszar LT, et al. Causes of pulmonary granulomas: a retrospective study of 500 cases from seven countries. *J Clin Pathol*. 2012;65(1):51-57.
18. Nazarullah A, Nilson R, Maselli DJ, Jagirdar J. Incidence and aetiologies of pulmonary granulomatous inflammation: a decade of experience. *Respirology*. 2015;20(1):115-121.
19. Tachibana K, Arai T, Kagawa T, et al. A case of combined sarcoidosis and usual interstitial pneumonia. *Intern Med*. 2012;51(14):1893-1897.
20. Nobata K, Kasai T, Fujimura M, et al. Pulmonary sarcoidosis with usual interstitial pneumonia distributed predominantly in the lower lung fields. *Intern Med*. 2006;45(6):359-362.
21. Shorr AF, Davies DB, Nathan SD. Outcomes for patients with sarcoidosis awaiting lung transplantation. *Chest*. 2002;122(1):233-238.