SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2015; 32; 160-166

Significance of granulomatous inflammation in usual interstitial pneumonia

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Abstract. Sarcoidosis is a systemic granulomatous disease of unclear etiology with characteristic pulmonary lesions. We describe 2 unique cases of sarcoidosis where after approximately 20 years of clinical quiescence, patients developed interstitial opacities on chest CT scan and an increase in shortness of breath. With lack of therapeutic response to a course of prednisone, both patients underwent a surgical lung biopsy that revealed a pattern consistent with Usual Interstitial Pneumonia (UIP) with honeycombing and fibroblastic foci. Postoperatively, the course of the disease was consistent with what would be expected in Idiopathic Pulmonary Fibrosis. Ultimately the disease progressed with one patient needed lung transplantation and the other requiring high-flow oxygen supplementation. In conclusion, we present two patients in whom a diagnosis of sarcoidosis preceded the diagnosis of UIP by 20 years or more. The subsequent course of disease in both patients was consistent with Idiopathic Pulmonary Fibrosis *(Sarcoidosis Vasc Diffuse Lung Dis 2015; 32: 160-166)*

Key words: UIP, IPF, sarcoidosis, granulomas

Introduction

The lungs are constantly exposed to a variety of antigens that possess the ability to elicit inflammatory and fibrotic responses. Idiopathic Pulmonary Fibrosis (IPF) is a fatal lung disease of unknown cause characterized by progressive fibrosis without inflammation (1). Patients with IPF have predominantly lower lobe involvement on chest imaging and characteristic histological pattern consistent with usual interstitial pneumonia (UIP). However, this UIP pattern of injury may also be seen in pulmonary fibrosis secondary to collagen vascular diseases, asbestosis, drug reactions, chronic hypersensitivity pneumonitis, and in some cases, sarcoidosis (2).

Received: 17 February 2014
Accepted after revision: 8 August 2014
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Unlike IPF, sarcoidosis is a systemic granulomatous disease of unknown etiology predominantly affecting the upper lobes (3). Although the disease trajectory is variable with spontaneous remission in the majority of cases, progressive, interstitial fibrosis along the bronchovascular bundles is also known to occur (4, 5). Here we present 2 cases with initial diagnoses of sarcoidosis. After a clinical quiescence for 20 years, both cases developed progressive dyspnea, radiographic changes suggesting fibrotic disease, and histologic findings revealing both non-necrotizing granulomas and UIP. Despite evidence of granulomatous inflammation, the clinical course was consistent with IPF.

Case Reports

Case I

A 64 year-old woman with a diagnosis of IPF presented for lung transplant evaluation. Approxi-

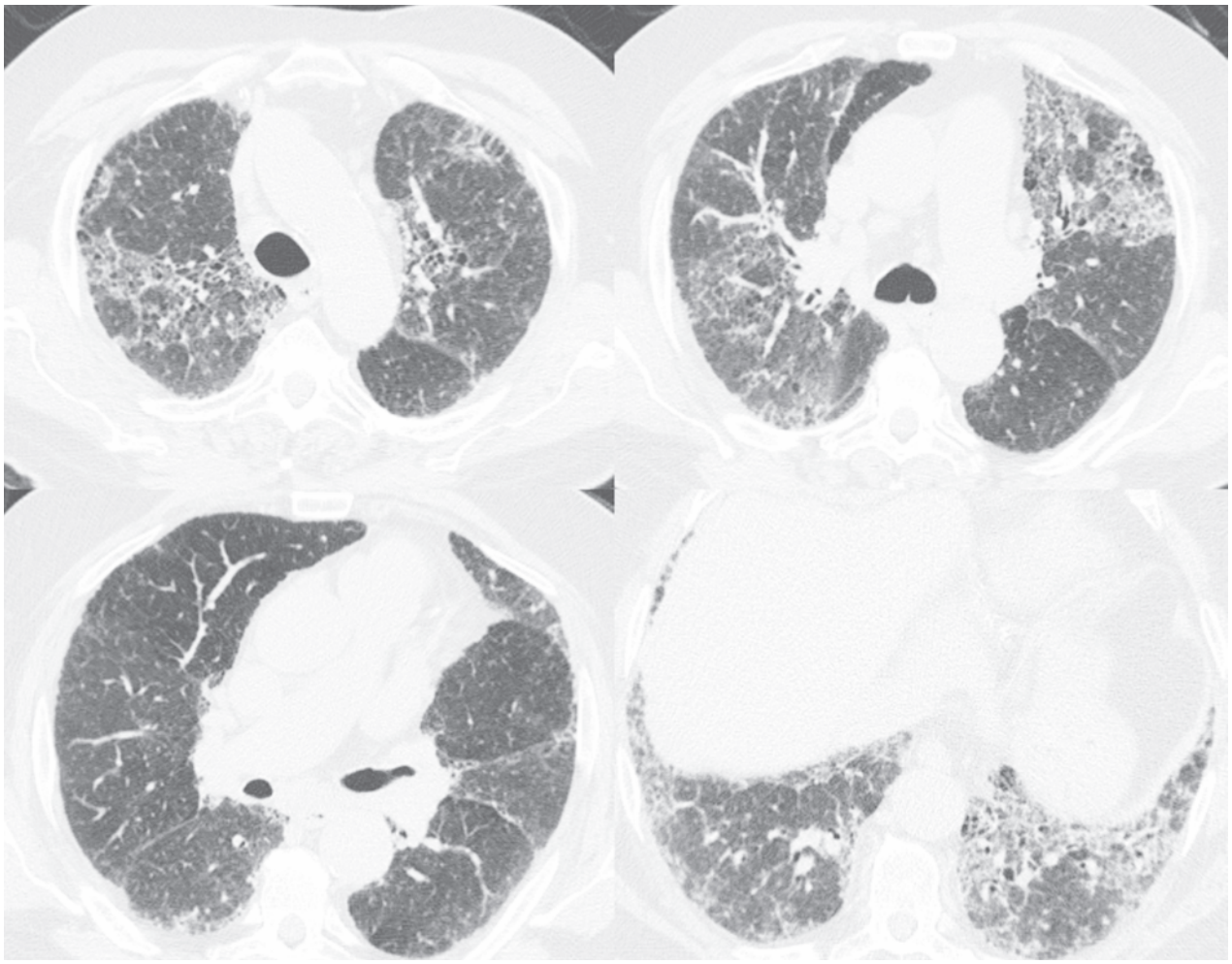

Fig. 1. High Resolution chest CT for case 1. Chest CT scan demonstrating diffuse fibrotic changes with some ground glass opacity and traction bronchiectasis. Areas of possible honeycombing are seen as well.

mately 20 years prior to this presentation, a diagnosis of sarcoidosis was made via trans-bronchial lung biopsy and remission was achieved with six months of prednisone therapy. No clinical manifestations of extra-pulmonary sarcoidosis were seen at initial diagnosis. The patient was a life-long non-smoker and had no known toxic exposures. Her other health history was positive for a pituitary adenoma that was resected and thyroid disease. Her father had pulmonary fibrosis.

Now she presented with progressive dyspnea and cough. Her physical exam demonstrated digital clubbing and bilateral crackles on auscultation of the chest. Subsequently she was admitted to the hospital with progressive hypoxia. Work up did not reveal infectious etiology. Despite having a mildly positive anti-citrullinated protein (anti-ccp), no other manifestations of inflammatory disease were present and she had minimal response to corticosteroids. A repeat chest CT scan demonstrated persistence of bilateral interstitial infiltrates (Figure 1). An open lung biopsy performed to evaluate the etiology of the fibrotic lung disease showed a UIP pattern (figure 2, panel A and C), though the lymph nodes that were sampled demonstrated non-necrotizing granulomas (figure 2, panel B). Genetic testing for novel mutations (TERT/TERC/SFTPC) was not pursued. Over the next few months her condition gradually deteriorated and she required lung transplantation. The pathology of the explant lung showed UIP.

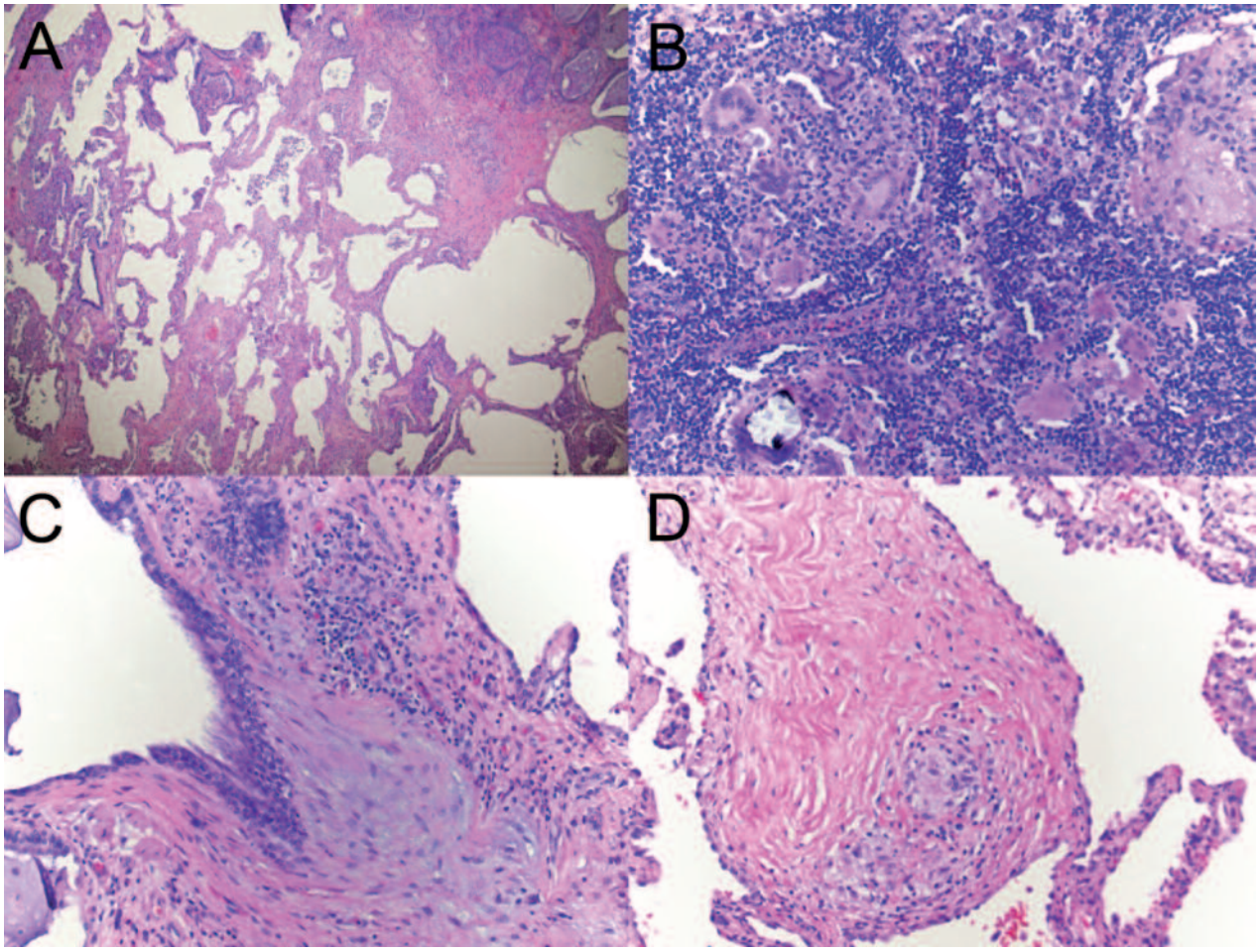

Fig. 2. Histopathology for case 1(all H&E). Low power view of active fibrosis adjacent to areas of honeycombing (A). High power views showing granuloma in lymph node (B), fibroblastic focus (C), and granuloma in lung parenchyma (D).

Case II

A 74-year-old man, ex-smoker, presented for management of sarcoidosis. He was diagnosed in 1987 via trans-bronchial biopsy but did not require any treatment. No extra-pulmonary manifestation of sarcoidosis was present at that time. Approximately 20 years later, he had dyspnea and biopsies showed non-necrotizing granulomas in the lymph nodes and lung parenchyma. He was treated for one year with stabilization of symptoms and PFT's. Two years later he presented with worsening dyspnea and progressive decline in lung capacity that did not improve with prednisone therapy. Chest CT scan showed diffuse fibrotic changes (figure 3). His interstitial lung disease serological work up was unrevealing and a surgical lung biopsy showed a UIP pattern (figure 4, panel A, B and C) leading to discontinuation of his prednisone. Further evaluation identified pulmonary hypertension for which he was started on sildenafil. He is currently also on a proton pump inhibitor, n-acetyl cysteine pirfenidone and 6-8 L/min oxygen supplementation.

Discussion

We present two cases of fibrotic lung disease with histological and clinical features consistent with UIP/IPF in the setting of remote history of active

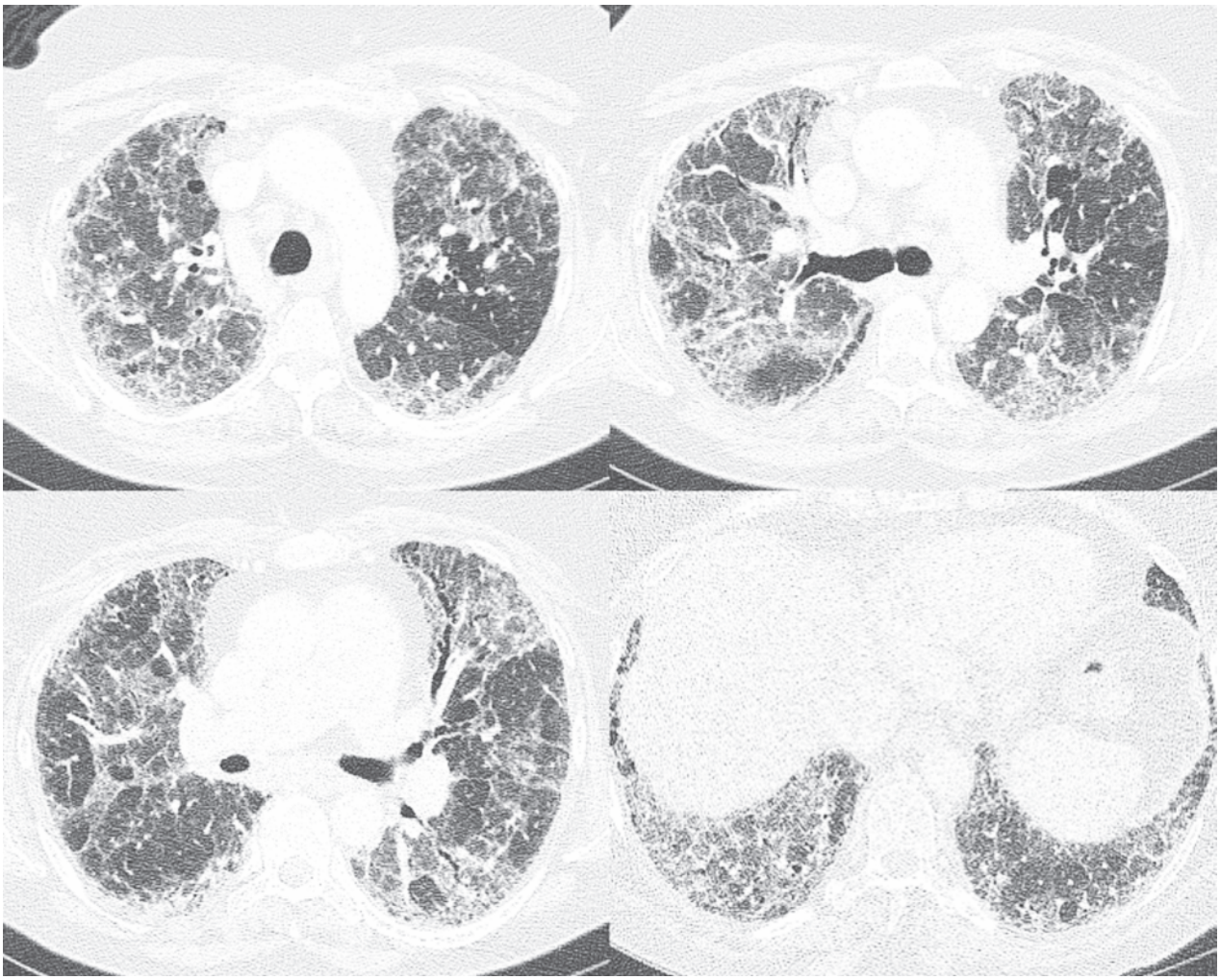

Fig. 3. High Resolution chest CT for case 2. Chest CT scan demonstrating diffuse interstitial infiltrates and traction bronchiectasis. Extensive ground glass opacities, mosaic attenuation and subpleural honeycombing is also present.

sarcoidosis. Both cases had a prolonged period of inactive disease before developing fibrotic lung disease. Though the chest CT scans and lung biopsy were not classic for IPF, both patients presented in the typical age range for IPF and followed a clinical course similar to IPF with a lack of response to steroids. These cases seem to show a process distinct from progressive relentless sarcoidosis culminating into pulmonary fibrosis and highlight what can be a difficult problem: determining the primary cause of pulmonary fibrosis in patients with a past history of sarcoidosis. The incidence of this clinical presentation is not known and is seen infrequently in our sarcoidosis/ILD clinic but concomitant UIP and sarcoidosis have been previously been reported (6, 7). Several clinical, radiologic and histological features that could be useful in differentiating fibrotic sarcoid and IPF are outlined in the discussion.

Differences in the clinical presentation of IPF and sarcoidosis: IPF is seen after 50 years of age and can be associated with a history of cigarette smoking. It presents with a 1-2 year history of an insidious onset of exertional dyspnea, cough, bilateral lower lung crackles and clubbing. In contrast, sarcoidosis patients with progressive fibrosis are typically symptomatic for a much longer duration and can have extra-pulmonary manifestations. In a series of patients

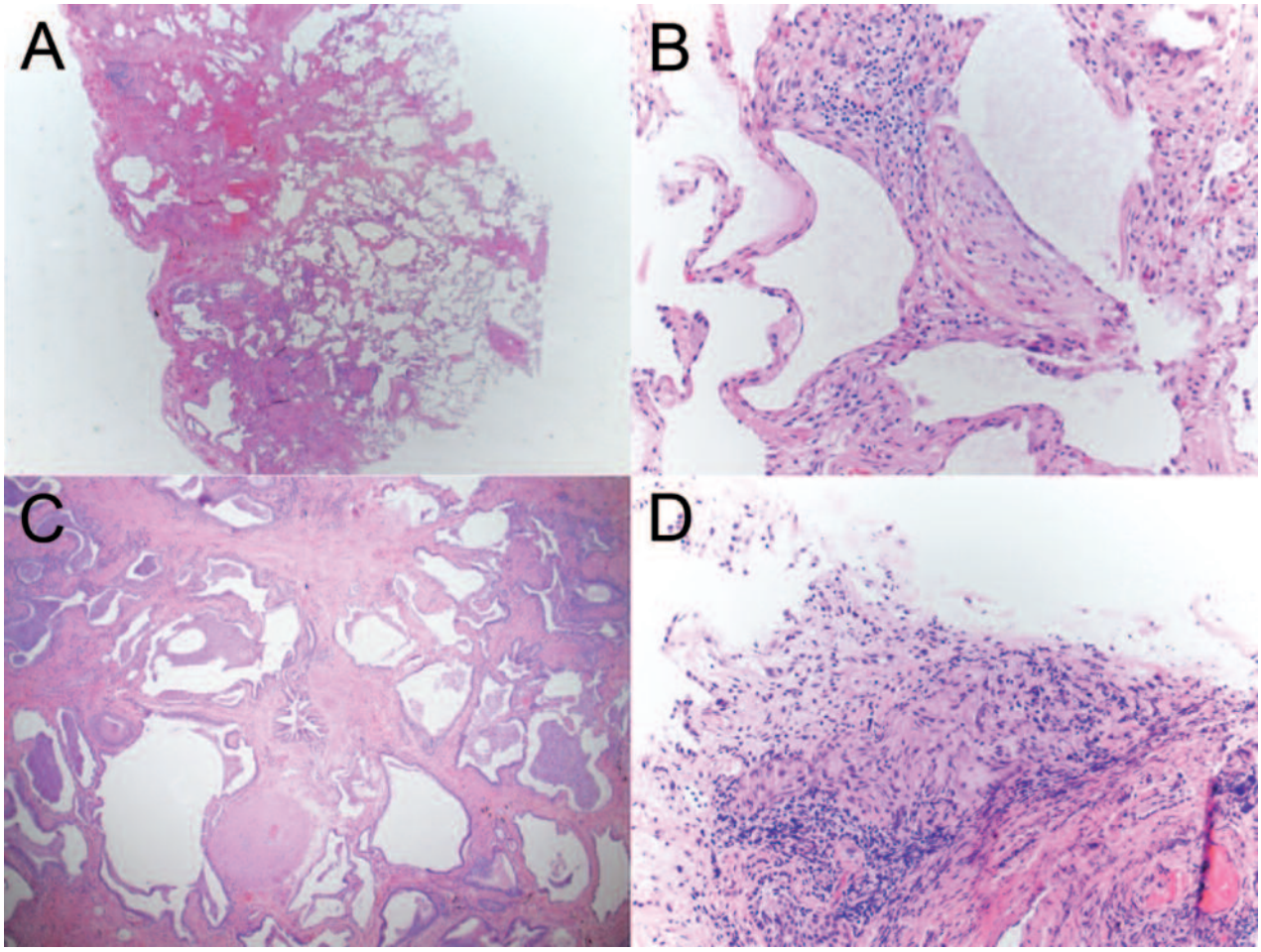

Fig. 4. Histopathology for case 2 (all H&E). Low power views showing temporal heterogeneity with subpleural fibrosis with adjacent normal appearing lungs (A), and areas of honeycombing (C). High power views showing fibroblastic focus (B) and granuloma from aspiration of a lymph node (D).

who underwent lung transplantation, those with histology showing sarcoidosis were younger (age 43-66 years) and had symptoms ranging from 17-33 years (mean 23.3) compared to 3-7 years (mean 4.8) for those with interstitial pneumonitis (2, 8).

Histologic features differentiating IPF and fibrotic lung disease from sarcoidosis: In contrast to the subpleural lower lobe predominant fibrosis that is typical for UIP/IPF, patients with fibrotic sarcoidosis have an upper lobe predominant central and peribronchial pattern of scarring and honeycombing (9, 10), with bronchial distortion (5), bronchiectasis or bronchioloectasis with occasional residual granulomas. Granulomas in the lymph nodes could be seen in fibrotic forms of the disease (8). In contrast to the granulomas occurring in perilymphatic distribution in active pulmonary sarcoidosis, in fibrotic sarcoidosis the granulomas are small and may appear as areas of hyaline fibrosis (9). Fibroblastic foci that are commonly seen in UIP are rarely present in sarcoidosis even in cases with rapidly progressing disease (5). The statement issued by the ATS/ERS/JRS/LATS provides guidance about histological patterns of UIP (Table 1) (11). The key differences between UIP and Sarcoidosis are outlined in Table 2. Based on ATS guidelines prominent airway centered changes, similar to ones seen in fibrotic sarcoidosis, rule out UIP. Although the presence of granulomatous inflammation inherently rules out IPF, an isolated or occasional granuloma may not be completely atypical in UIP. The diagnostic implication of the non-

Table 1. ATS/ERS/JRS/LATS Histologic criterion for probable or possible UIP

Probable UIP	Possible UIP (all three needed)
Evidence of marked fibrosis /architectural distortion ± honeycombing	Patchy or diffuse involvement of the lung parenchyma by fibrosis, with or without interstitial inflammation
Absence of either patchy involvement or fibroblastic foci but not both	Absence of other criterion of UIP on Table 1
Honeycomb changes only	Absence of features of 'not UIP pattern'

Table 2. Histologic features of IPF and Sarcoidosis

	Usual Interstitial Pneumonia	Sarcoidosis
Main histopathology finding in fibrotic disease	Evidence of marked fibrosis/architectural distortion, ± honeycombing in a predominantly subpleural/paraseptal distribution.	Peribronchial fibrosis with associated bronchiectasis and bronchiloectasis
Distribution	Patchy involvement of the lung parenchyma by fibrosis	Upper lob predominant
Classical Lesion	Fibroblastic focus	Non-necrotizing granuloma

Table 3. Radiologic Features of UIP and fibrosing sarcoidosis

	UIP*	Sarcoidosis
Distribution	Subpleural, basal predominance	Peribonchial, upper and middle lobe predominance
Parenchymal abnormality	Reticular abnormality Honeycombing Traction Bronchiacactasis	Reticular of micronodules No honeycombing Bronchiactasis, central

* Absence of (all of these seven features): upper or mid-lung predominance, perbonchial prominence, extensive ground glass abnormality, profuse micronodules, discrete cysts, mosaic attenuation and consolidation in bronchopulmonary segment

necrotizing granulomas seen in the lymph nodes and occasionally in the lungs of our two cases remains unclear.

Radiologic features of IPF and fibrotic disease from sarcoidosis: According to the ATS 2011 statement (Table 3) (9), many of the radiographic features of sarcoidosis render a diagnosis of IPF unlikely. These features include an upper, mid-lung, or peribronchovascular predominance, and the presence of nodular opacities. While mediastinal lymph node enlargement may be seen in both IPF and Sarcoidosis, it is usually minimal (< 1.5 cm) in IPF and much more pronounced in acute and chronic sarcoidosis.

Twenty to fifty percent of patients with Sarcoidosis progress to develop stage IV (fibrotic) disease (12). Three different patterns have been described in chronic fibrosing sarcoidosis (13); 1) The most common is a *bronchial distortion pattern* (49%) with or without co-existent masses (due to confluent fibrosis); 2) A *honeycombing pattern* (29%); and 3) A *linear pattern of opacities* (24%). In addition, distortion of the airways, displacement of the hila, fissures and bronchovascular bundles is also frequently seen in stage IV sarcoidosis. While our cases do not meet criteria for definite UIP, they do show a diffuse fibrotic pattern as opposed to the more central pattern of bronchial distortion more commonly seen in Sarcoidosis. However lower lobe fibrotic disease has been reported in sarcoidosis (6).

Biomarkers to differentiate IPF and fibrosing Sarcoidosis: Biological mechanisms and biomarkers that could discriminate UIP (IPF) from fibrosing sarcoidosis have been investigated. The plasma levels of IL-18, a pro-inflammatory cytokine that induces Th-1 cells to synthesize interferon-γ (INF- γ), has been reported to be elevated in plasma and bronchoalveolar lavage fluid from subjects with Sarcoidosis (n-15) in comparison to subjects with IPF (n=10). IL-18 could be a candidate biomarker to distinguish UIP/IPF from fibrotic sarcoidosis (14).

Angiotensin converting enzyme (ACE) single nucleotide polymorphisms or serum ACE levels are neither diagnostic nor do they differentiate IPF from sarcoidosis (15, 16). In an innovative microarray study Leng et al identified similar activated pathways- mapping to cell proliferation, differentiation, and migration- when IPF and stage IV sarcoidosis where compared to normal lung tissue. This suggested that the pathways for extracellular matrix and collagen deposition could be similar. However when transcription networks in IPF and sarcoidosis were directly compared, remarkable differences were found in regulation of myeloblastosis viral oncogene (MYB) and bone morphogenetic protein receptor-2, suggesting that the two diseases are regulated by overlapping, but distinct, transcription networks (17). Though specific biomarkers that differentiate progressive fibrosis from diverse etiologies do not currently exist, progress is being made to discover markers of disease that will become clinically available in the future.

Conclusion

We present two unusual cases of pulmonary fibrosis with a distant history of sarcoidosis, who subsequently developed a fibrotic process and biopsy suggestive of UIP. Prolonged duration of inactive sarcoidosis and the subsequent clinical course in both of these cases was consistent with IPF, suggesting that the prior granulomatous inflammation did not contribute to development of the newly diagnosed fibrotic lung disease. This late-onset progressive fibrosis appears to be distinct from fibrosis due to chronic sarcoidosis and raises the possibility of a separate UIP/IPF-like process in these patients. This unique phenomenon should be further studied in larger cohorts of subjects with fibrotic lung disease.

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