Chapter 3
Diseases that Mimic Idiopathic Pulmonary Fibrosis

There are number of conditions that may commonly be confused and difficult to differentiate from idiopathic pulmonary fibrosis (IPF). This chapter discusses these conditions in more detail.

3.1 Non-specific Interstitial Pneumonia

Non-specific interstitial pneumonia (NSIP) is a pathologic entity that was first described in 1994 [1]. It is the second most common of the idiopathic interstitial pneumonias (IIPs) and can be difficult to differentiate from IPF [2]. The diagnosis of NSIP should only be made pathologically and, unlike IPF, is never a diagnosis that can be made based upon radiography alone. Pathologically, NSIP is characterized by diffuse homogenous fibrotic and/or cellular infiltrates, and therefore, can be further subcategorized into fibrotic NSIP, cellular NSIP, or mixed cellular fibrotic NSIP [3]. This pathologic pattern of injury may be idiopathic in nature or result from other causes of interstitial lung disease (ILD) including chronic hypersensitivity pneumonitis (HP), connective tissue diseases (CTDs), or autoimmune featured ILD. NSIP is the pathologic entity that is most commonly seen in all of the CTDs [4], not including rheumatoid arthritis where usual interstitial pneumonia (UIP) is the most

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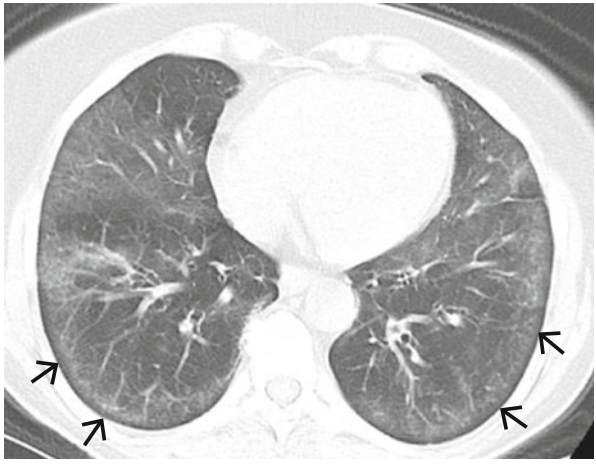

FIGURE 3.1 The radiographic appearance of non-specific interstitial pneumonia with characteristic rim of subpleural sparing, as indicated by the arrows

common [5]. Therefore, when the diagnosis of NSIP is made pathologically, it is incumbent on the clinician to make sure that there is no identifiable cause before the diagnosis of idiopathic NSIP can be made. It is a condition that has a distinctly better course than IPF, with a 5-year survival of approximately 80 % of patients [6]. However, patients with severe functional impairment have a grim prognosis similar to those with IPF [7]. Given the prognostic implications, it is important to differentiate NSIP from IPF. Idiopathic NSIP tends to occur in younger patients and tends to be more predominant in females, in contrast to IPF, which has a male predominance [8]. The clinical presentation is very similar to that of IPF, with insidious onset of shortness of breath, and sometimes associated with a chronic non-productive cough [8]. Unlike IPF, there is no characteristic radiographic appearance, hence why this diagnosis always requires the pathologic specimen [3]. One radiographic finding that has some measure of specificity for NSIP is a rim of subpleural sparing (unaffected lung in the subpleural space), a finding reported in 21–64 % of cases [6, 9] (Fig. 3.1).

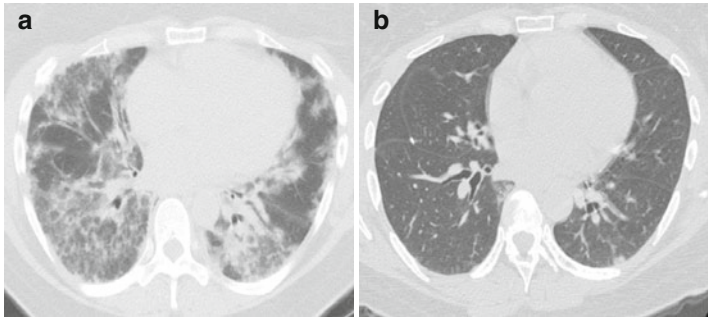

FIGURE 3.2 High resolution computed tomographic images showing the cellular variant of non-specific interstitial pneumonia. (**a**) Before treatment, and (**b**) improvement in infiltrates after treatment with corticosteroids

The treatment approach for NSIP is also quite different to that of IPF, with immunosuppressive therapy commonly regarded as standard of care, although studies attesting to this are lacking [8]. The cellular variant of NSIP (less common) is felt to be more responsive to immunosuppressive therapy (Fig. 3.2). Whether fibrotic NSIP is a disease that may be responsive to anti-fibrotic therapy is unknown and requires independent studies.

3.2 Connective Tissue Disease-Associated Interstitial Lung Disease

ILD is commonly present in many of the CTDs. The prevalence of connective tissue disease-associated interstitial lung disease (CTD-ILD) for the various CTDs is estimated to be [10]:

- scleroderma 40–100 %;
- rheumatoid arthritis 20–30 %;
- polymyositis/dermatomyositis 20–50 %;
- systemic lupus erythematosus 2–8 %; and
- Sjogren's syndrome up to 25 %.

CTD-ILD is a relatively easy diagnosis to make in the context of a patient with pre-existing CTD. In such situations a diagnosis of idiopathic interstitial pneumonitis (such as IPF or idiopathic NSIP) cannot be made being that there is a pre-existing identifiable etiology for the ILD. A thorough patient history and physical examination may provide important clues to an underlying CTD since, in many cases, the onset of respiratory symptoms and ILD may herald the onset of the underlying CTD. In rarer instances, patients may present without any CTD features, which might only manifest months to years after the diagnosis of the underlying ILD [11]. Therefore, patients who are initially diagnosed with an IIP can have their diagnosis evolve over time if an underlying CTD subsequently manifests. The radiographic features of CTD-ILD tend to be non-specific and, in many cases, a UIP pattern occurs [11]. Various radiographic examples are shown in Fig. 3.3. Table 2.1 (see Chap. 2) summarizes the major pathologic entities and presenting signs and symptoms of the more common CTDs.

3.3 Chronic Hypersensitivity Pneumonitis

Chronic HP is perhaps the one disease that is most difficult to differentiate from IPF. HP can present acutely, subacutely, or chronically. Patients who develop chronic HP do not necessarily have a history of either acute or subacute HP or a documented history to a known allergen. Chronic HP can occur as a result of exposure in either an occupational or home setting following long-term inhalation of a wide spectrum of organic antigens from mammalian and avian proteins, fungi, thermophilic bacteria, and certain chemical compounds [12]. Chronic HP occurs most commonly in those with some type of exposure to birds, especially bird droppings (Bird fancier's lung), among farmers (Farmer's lung), or after exposure to moldy hay grain or silage, or contaminated forced-air systems and water reservoirs [12]. There are many other potential exposures that can result in chronic HP, underscoring the need for

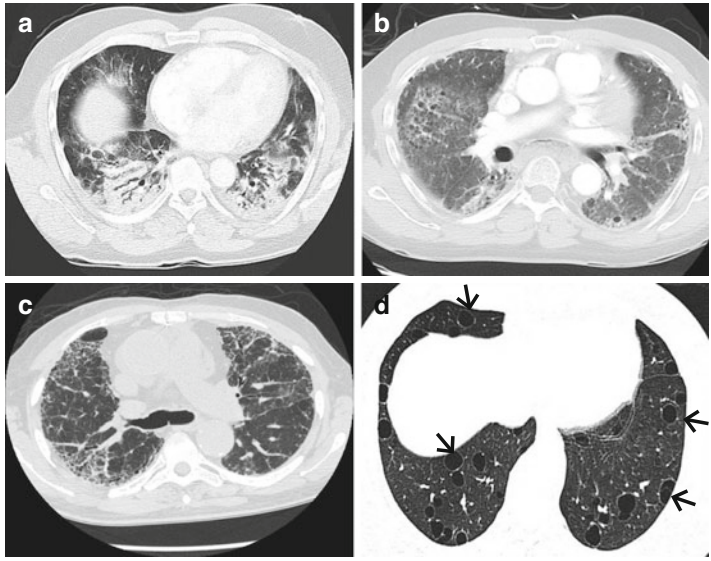

FIGURE 3.3 High resolution computed tomographic images demonstrating the heterogeneous radiographic appearance of connective tissue disease-interstitial lung disease. (**a**) Organizing pneumonia (rheumatoid arthritis), (**b**) fibrotic non-specific interstitial pneumonia (mixed connective tissue disease), (**c**) usual interstitial pneumonia (systemic lupus erythematosus), and (**d**) lymphocytic interstitial pneumonia (Sjögren's) with characteristic cystic changes as indicated by the arrows

a thorough social and occupational history in anyone presenting with ILD. Patients can present very similarly to those with IPF with chronic insidious onset of shortness of breath. An important clinical clue is if shortness of breath and cough worsen in any specific environment, either at work or at home. However, this is more likely to indicate acute or subacute HP and is not very sensitive for chronic HP. Chest imaging may demonstrate distinct changes, including poorly formed small nodules, ground-glass attenuation (either patchy or diffuse), peribronchiolar infiltrates, or areas of air trapping that are best seen on expiratory computed tomography (CT) imaging (Fig. 3.4) [13]. Pathologically, the presence of poorly formed

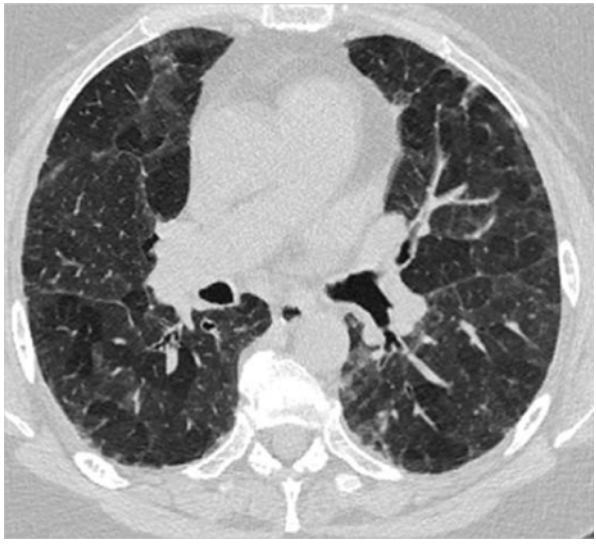

FIGURE 3.4 The typical radiographic appearance of chronic hypersensitivity pneumonitis with peribronchiolar infiltrates and mosaic appearance from air trapping

granulomas, especially in a peribronchiolar distribution, are suggestive of HP. Peribronchiolar fibrosis should also raise the index of suspicion for chronic HP. Treatment includes identification and avoidance of the offending antigen and in some cases immunosuppressive therapy with steroids ± a cytotoxic agent [12]. At present there are no firm guidelines for the diagnosis or treatment of chronic HP.

3.4 Unclassifiable Interstitial Lung Disease

Even in the best hands, under the best circumstances, and despite everyone's best efforts, there are number of patients with ILD that remains unclassifiable. This represents approximately 10 % of patients with ILD [14]. Patients with unclassifiable disease likely represent a mix of ILDs, including IPF, NSIP, and chronic HP. It makes sense therefore, that these

patients tend to have an unpredictable disease course [14, 15]. One of the main reasons patients remain unclassifiable is due to the lack of a surgical lung biopsy, which may be contraindicated because of patient comorbidities or severity of illness. However, there are some patients who remain unclassifiable despite a surgical lung biopsy that may show changes that are non-specific or unclassifiable, including 'end-stage fibrotic lung disease.' There are also patients who have conflicting clinical, radiographic, and pathologic changes and therefore a specific clinical diagnosis is unattainable.

Key Points

- **NSIP:**
  - Can be idiopathic or more commonly secondary to CTD.
  - Diagnosis requires lung biopsy.
  - Treatment is with immunosuppressive therapy in most cases.
- **CTD-ILD**
  - ILD can be the presenting symptom in some cases.
  - Diagnosis can be made on clinical history and positive serologies.
  - If lung biopsy is obtained, it can show NSIP, UIP, OP, pleuritis, or any combination thereof.
  - Treatment is with immunosuppressive therapy in most cases.
- **Chronic HP**
  - Can occur in the absence of an identifiable exposure.
  - Chest imaging may show poorly formed small nodules, ground-glass attenuation, peribronchiolar infiltrates, or areas of air trapping.

- Histopathologic findings include granulomas, NSIP, and/or UIP pattern in peribronchiolar distribution.
- Treatment is withdrawal of exposure (if known) and immunosuppression in some cases.

- **Unclassifiable ILD**
  - Specific diagnosis may not be possible in a minority of ILD cases.
  - Frequently results from inability to safely perform lung biopsy or non-specific findings on lung biopsy.

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