Nonspecific Interstitial Pneumonia: Radiologic, Clinical, and Pathologic Considerations[1]

LEARNING OBJECTIVES FOR TEST 2

After reading this article and taking the test, the reader will be able to:

■ Describe the common clinical, pathologic, and radiologic features of idiopathic and secondary NSIP.

■ List imaging findings that are uncommon in NSIP and are suggestive of alternate diagnoses.

■ Discuss challenges in diagnosis of NSIP and how a multidisciplinary approach can lead to improved patient care.

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Nonspecific interstitial pneumonia (NSIP) has variable clinical, pathologic, and radiologic manifestations. Cellular and fibrotic NSIP are the two main histologic subtypes and differ from one another in the degree of inflammation and fibrosis. It is important to differentiate NSIP from other diffuse lung diseases, especially usual interstitial pneumonia and hypersensitivity pneumonitis, owing to differences in prognosis and treatment. At high-resolution computed tomography, the most common findings suggestive of NSIP are lower lobe peripherally predominant ground-glass opacity with reticular abnormality, traction bronchiectasis, and lower lobe volume loss. Nodules, cysts, and areas of low attenuation are uncommon and should point one toward other diagnoses. Because many cases of NSIP are associated with collagen vascular diseases, it is important to look for associated findings that may suggest an underlying collagen vascular disease. Given the difficulty clinicians, pathologists, and radiologists experience in making the diagnosis of NSIP, a group approach in which these specialists work together to reach a consensus diagnosis has the highest likelihood of achieving the correct diagnosis.

TEACHING POINTS
See last page

Introduction

The idiopathic interstitial pneumonias (IIPs) are a heterogeneous group of disorders that include usual interstitial pneumonia (UIP), nonspecific interstitial pneumonia (NSIP), respiratory bronchiolitis–interstitial lung disease (RB-ILD), acute interstitial pneumonia (AIP), cryptogenic organizing pneumonia (COP), desquamative interstitial pneumonia (DIP), and lymphoid interstitial pneumonia (LIP). Although 50%–60% of patients with IIP receive a diagnosis of UIP, NSIP is the second most common cause of IIP, accounting for 14%–36% of cases (1).

Although many of the IIPs have clinical, radiologic, and pathologic similarities, definitive diagnosis is essential because these diseases have different prognoses and treatment. The ability to diagnose UIP with high-resolution computed tomography (CT) has been well established, but the ability to diagnose NSIP with high-resolution CT has consistently proved more difficult (2–9). Reasons for the difficulty in diagnosing NSIP include varying histologic criteria for making this diagnosis and substantial overlap of histologic and radiologic findings with those of other conditions, including UIP, COP, hypersensitivity pneumonitis, and DIP.

The goal of this article is to review the common clinical, pathologic, and radiologic findings seen in NSIP. In addition, we present many findings that are very rare in NSIP and should point one toward another diagnosis. No single radiologic finding is diagnostic of NSIP, but a constellation of findings can help one make the correct diagnosis. Nonetheless, the best chance for a correct diagnosis lies in the integration of clinical, pathologic, and radiologic findings.

Clinical Features

As the name suggests, the clinical findings in NSIP are often nonspecific. Most patients with NSIP are in the age range of 40–50 years and have a gradual onset of symptoms. Although the overall prevalence is higher in women due to its association with collagen vascular disease, the prevalence of idiopathic NSIP is equal between the sexes. Unlike DIP, RB-ILD, and respiratory bronchiolitis, there is no known association with smoking (10). Smoking is not thought to be protective, as in hypersensitivity pneumonitis (11).

Although many cases of NSIP are idiopathic, there is a very high association with underlying collagen vascular diseases, and NSIP is the most common histologic abnormality in those with a collagen vascular disease and coexistent lung abnormalities (12). Various collagen vascular dis-
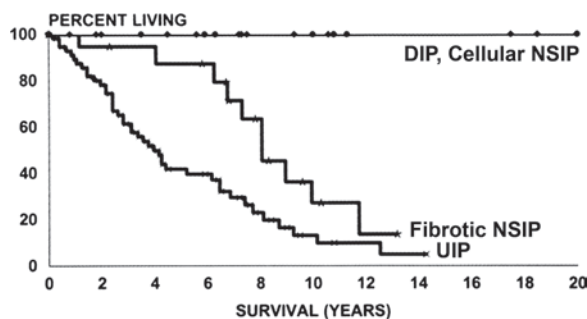

Figure 1.   Kaplan-Meier survival curves in patients with cellular NSIP, DIP, fibrotic NSIP, and UIP. Those with DIP and cellular NSIP have excellent survival rates, whereas those with UIP have the lowest survival rates. Those with fibrotic NSIP fare worse than those with cellular NSIP but better than those with UIP.
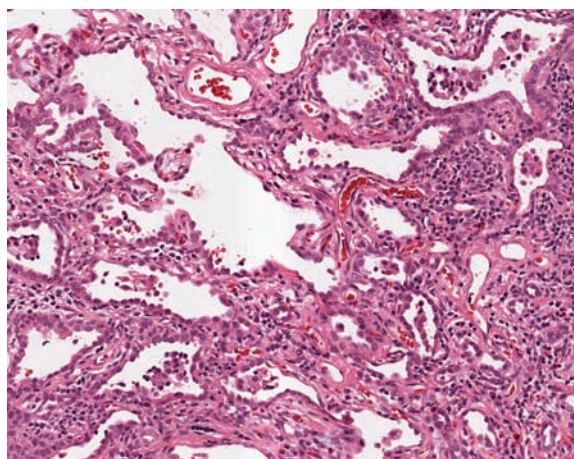

Figure 2.   Cellular NSIP. High-power photomicrograph (original magnification, ×20; hematoxylin-eosin [H-E] stain) of a section of lung tissue shows the homogeneous septal thickening characteristic of NSIP. Alveolar septa are expanded by both chronic inflammation and a small amount of collagen. The cells lining the septa (pneumocytes) show mild reactive changes.

eases can be associated with NSIP, including systemic sclerosis (scleroderma), polymyositis and dermatomyositis, Sjögren syndrome, and rheumatoid arthritis. Therefore, it is always important to look for associated findings in radiologic studies, which may aid in diagnosis of an unknown collagen vascular disease.

In addition to collagen vascular disease, NSIP can be associated with toxic effects of drugs, occupational exposure, and hypersensitivity pneumonitis. This is important to remember because the removal of the offending agent can reverse disease before fibrosis begins (13).

One of the important reasons for making an accurate diagnosis of NSIP lies in its survival rate compared with that of other interstitial lung diseases, especially UIP. Even with advances in medicine, the survival rate of UIP is dismal. The 5-year

Histologic Criteria for Diagnosis of Idiopathic NSIP		
Subtype of NSIP	Key Features	Pertinent Negative Factors
Cellular	Mild to moderate chronic interstitial inflammation	Absence of dense interstitial fibrosis
	Type II pneumocyte hyperplasia	Absence of diffuse severe alveolar septal inflammation
	Lung architecture is preserved	Organizing pneumonia involves <20% of the biopsy specimen
		Absence of the following features: hyaline membranes and other findings of acute lung injury, granulomas, organisms or viral inclusions, dominant airways disease
		Eosinophils are inconspicuous or absent
Fibrotic	Dense or loose interstitial fibrosis with a uniform appearance	Fibroblastic foci with dense fibrosis are inconspicuous or absent
	Mild to moderate chronic interstitial inflammation	Absence of a temporally heterogeneous pattern
	Lung architecture is frequently preserved (enlarged fibrotic airspaces may be present)	Honeycombing is inconspicuous or absent
		Absence of the following features: hyaline membranes and other findings of acute lung injury, granulomas, organisms or viral inclusions, dominant airways disease
		Eosinophils are inconspicuous or absent

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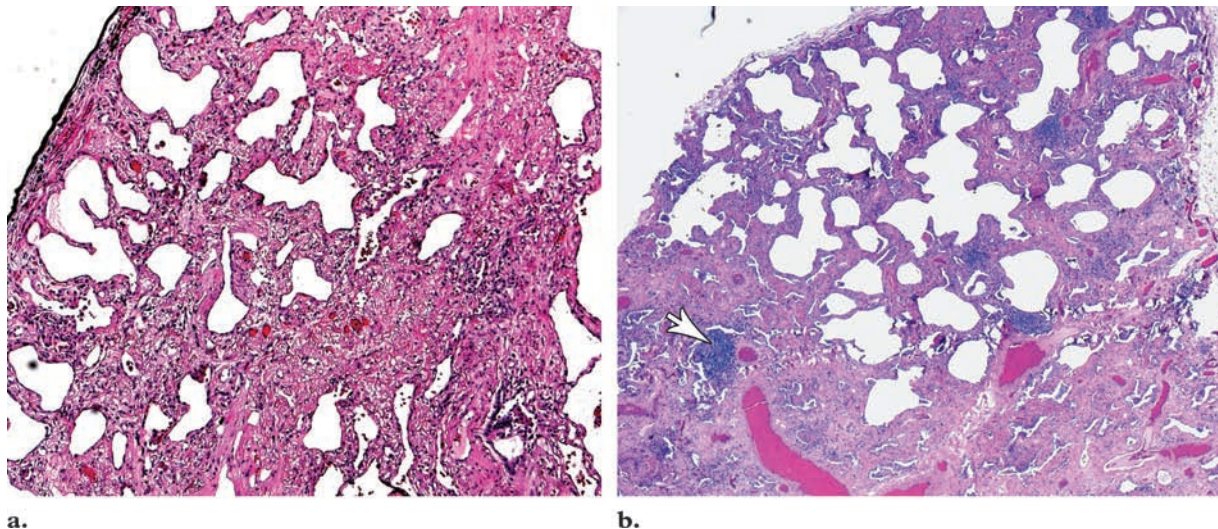

a.   b.

Figure 3. Fibrotic NSIP. **(a)** Photomicrograph (original magnification, ×5; H-E stain) from a patient with idiopathic fibrotic NSIP shows diffuse interstitial thickening by mature collagen, a finding consistent with fibrotic NSIP. Note the absence of honeycombing, fibroblastic foci, and significant inflammation. **(b)** Photomicrograph (original magnification, ×5; H-E stain) from a patient with fibrotic NSIP related to collagen vascular disease shows mixed cellular and fibrotic changes with associated lymphoid aggregates (arrow).

and 10-year survival rates for idiopathic UIP are 43% and 15%, respectively (14). At the other end of the spectrum, idiopathic cellular NSIP and DIP have a survival rate of nearly 100% (14,15). However, the survival rate of idiopathic fibrotic NSIP is far worse than that of cellular NSIP but better than that of UIP: 5-year survival rates range from 45% to 90% and 10-year survival rates are only 35% (Fig 1) (14,16–18).

Pathologic Features

Pathologically, NSIP is characterized by spatially and temporally uniform interstitial inflammation with varying degrees of fibrosis (11,15). Initially, NSIP was pathologically divided into three categories based on the level of fibrosis. Cellular NSIP (group I) demonstrated prominent inflammation without significant fibrosis (Table) (Fig 2). Mixed cellular and fibrotic NSIP (group II) demonstrated both inflammation and fibrosis, while fibrotic NSIP (group III) had significant fibrosis with little or no inflammation. However, because of similar survival characteristics in the mixed and fibrotic NSIP groups, groups II and III are now generally combined into a single group called "fibrotic NSIP" (Table) (Fig 3) (18).
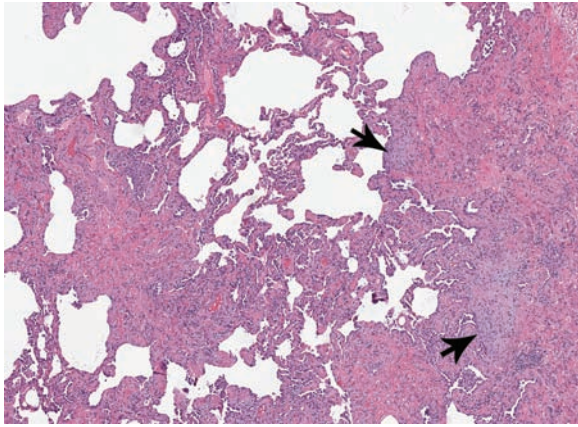
Figure 4. UIP. Photomicrograph (original magnification, ×5; H-E stain) of a section of lung tissue shows a heterogeneous pathologic process, with fibrotic regions and uninvolved lung within the same field. Multiple fibroblastic foci (arrows) are present in the interstitium. Fibroblastic foci have a pale blue or myxoid appearance reminiscent of organizing pneumonia; however, fibroblastic foci are found in the interstitium, whereas plugs of organizing pneumonia exist in the airspaces.

Figure 5. Hypersensitivity pneumonitis. Photomicrograph (original magnification, ×5; H-E stain) of a section of lung tissue shows granulomas with multinucleated giant cells (arrows). The alveolar septa on the left side of the image show expansion by both collagen (fibrosis) and chronic inflammatory cells.

Figure 6. COP. Photomicrograph (original magnification, ×5; H-E stain) of a section of lung tissue shows organizing pneumonia (arrows) filling the alveolar spaces and small airways. Typically, organizing pneumonia has a pale blue or myxoid appearance with a streaming quality and a round or serpentine shape. The surrounding alveolar septa are mildly thickened by chronic inflammation composed of lymphocytes.

The pathologic differential diagnosis for NSIP is extensive. UIP is often the main differential consideration. However, UIP classically demonstrates temporal heterogeneity, which represents pathologic processes at different stages of development. The lung appears heterogeneous with alternating areas of normal lung, interstitial inflammation, fibrosis, and honeycombing, often within the same microscopic field (Fig 4). These changes are often most severe in the subpleural region of the lung. Fibroblastic foci, foci of proliferating fibroblasts, are a hallmark of the diagnosis.

The histologic differential diagnosis of NSIP also includes hypersensitivity pneumonitis, COP, LIP, respiratory bronchiolitis, and DIP. Differentiation of these entities from NSIP relies on identification of additional histologic features. Chronic hypersensitivity pneumonitis, while sometimes manifesting as an NSIP-pattern process, most commonly includes scattered poorly formed granulomas (Fig 5), a feature not typical of NSIP. It is often difficult to distinguish COP (Fig 6) from NSIP because up to 50% of NSIP cases also include areas of organizing pneumonia. However, in NSIP, the areas of organizing pneumonia should involve less than 20% of the biopsy specimen (15). In addition, the presence of temporally uniform fibrosis in areas that do not contain organizing pneumonia is often helpful in distinguishing between these two entities.
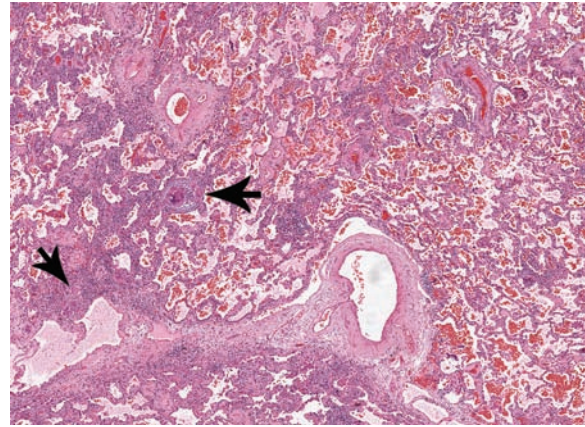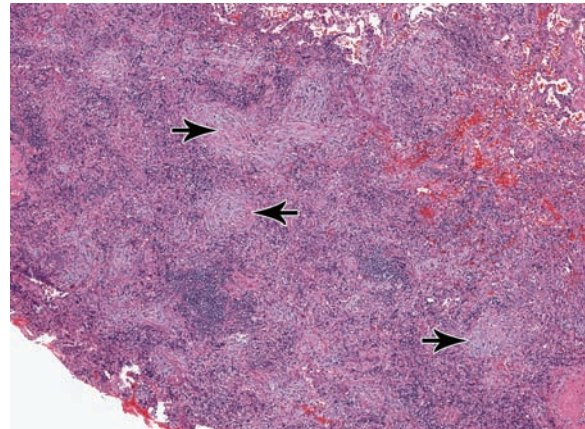
LIP can have considerable histologic overlap with the cellular form of NSIP, particularly in cases associated with a collagen vascular disease or immunodeficiency. However, LIP demonstrates significant expansion of the pulmonary interstitium with a mononuclear cell infiltrate (Fig 7), which is less pronounced in cellular NSIP (19). The presence of brown pigmented macrophages in airspaces in the smoking-related lung diseases helps differentiate respiratory bronchiolitis (Fig 8) and DIP (Fig 9) from NSIP at pathologic analysis. RB-ILD is the clinical manifestation of interstitial
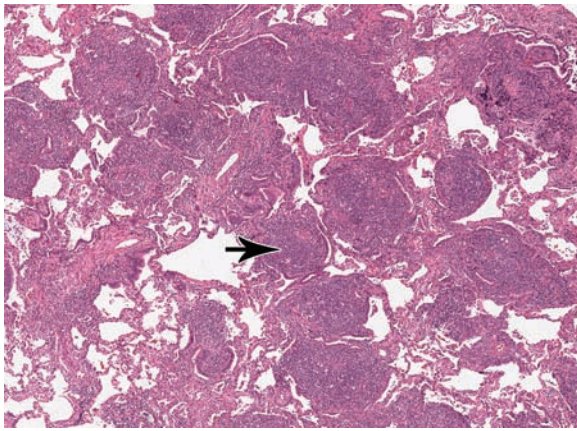
Figure 7. LIP. Photomicrograph (original magnification, ×5; H-E stain) of a section of lung tissue shows lymphocytes that mildly expand the alveolar septa and that form large lymphoid aggregates. Many lymphoid aggregates show a germinal center (arrow), which is characterized by a round central collection of larger active B lymphocytes.
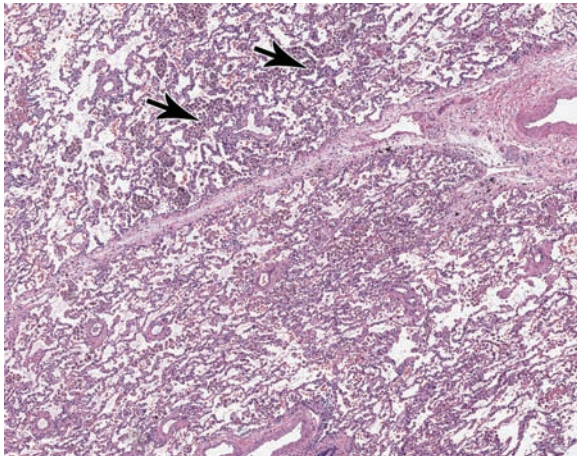
Figure 8. Respiratory bronchiolitis. Photomicrograph (original magnification, ×5; H-E stain) of a section of lung tissue shows dense collections of light brown pigmented macrophages (arrow) in the small bronchioles and adjacent alveolar spaces. Unlike DIP, this process is patchy rather than diffuse. In a patient with these histologic findings and restrictive physiologic impairment, the diagnosis of RB-ILD may be made.

Figure 9. DIP. Photomicrograph (original magnification, ×5; H-E stain) of a section of lung tissue shows loose collections of light brown pigmented macrophages (arrows) in virtually all the airspaces of the lung. The adjacent alveolar septa remain thin and free of significant inflammation or fibrosis.

lung disease associated with the pathologic findings of respiratory bronchiolitis (11).

Radiologic Findings Suggesting the Diagnosis of NSIP

Initially, the high-resolution CT appearance of NSIP was thought to be rather uniform. Cottin et al (20), Kim et al (21), and Park et al (22,23) all described a lower lobe predominant process with patchy areas of ground-glass opacity and varying degrees of reticular abnormality and consolidation. Honeycombing was thought to be a rare
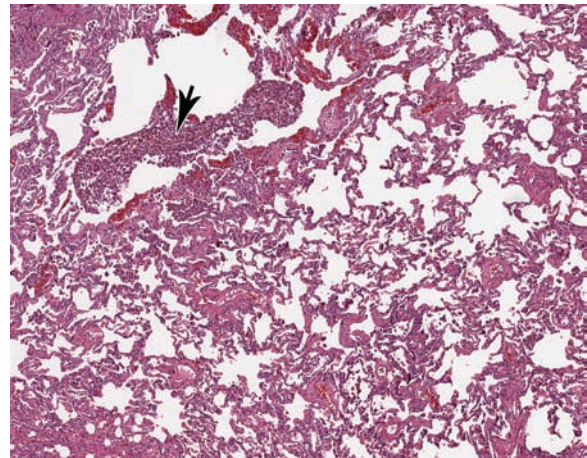
occurrence. However, given the histologic variability of NSIP, it is no surprise that its radiologic appearance at high-resolution CT proved to be more heterogeneous than originally thought. In 2000, Hartman et al (24) showed that the previously described high-resolution CT findings of NSIP were found in only 22% of patients with NSIP in their study. More important, honeycombing, which was thought to be exceedingly rare in patients with NSIP, was found to varying degrees in 30% of the patients in their study. Soon after, MacDonald et al (5) confirmed that the high-resolution CT findings of UIP and NSIP can significantly overlap.

Given the clinical, pathologic, and radiologic heterogeneity of NSIP, it is often difficult to make an accurate diagnosis of NSIP. Although no single high-resolution CT finding is diagnostic, the presence of multiple findings can help suggest the diagnosis in the right clinical setting.

Symmetric Lower Lobe Distribution

Location is one of the key factors in helping one make the diagnosis of NSIP. Like UIP, NSIP most often demonstrates a lower lobe distribution. In 2005, Elliot et al (2) found that 90% of those with NSIP had lower zone predominance, whereas 6% had a diffuse pattern. Similarly, Johkoh et al (25) and Jeong et al (3) described lower lung predominance in 95% and 84% of those with NSIP,
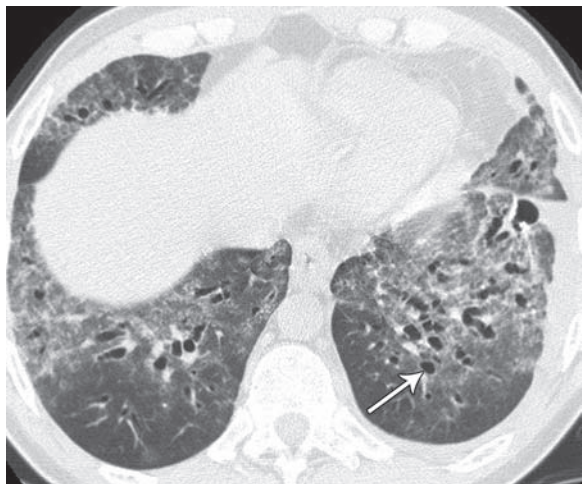
Figure 10.   Subpleural sparing in a 39-year-old woman with fibrotic NSIP. High-resolution CT image shows lower lobe predominant ground-glass opacity with peribronchovascular predominant fibrosis, mild reticular abnormality, traction bronchiectasis (arrow), and relative sparing of the immediate subpleural lung. Subpleural sparing can be suggestive of NSIP; however, its absence does not allow exclusion of the diagnosis.

Figure 11.   Lower lobe distribution in a 52-year-old woman with fibrotic NSIP. High-resolution CT image shows symmetric lower lung predominant ground-glass opacity, reticular abnormality, and traction bronchiectasis (arrow). The distribution of NSIP is almost always lower lung predominant and is usually symmetric.
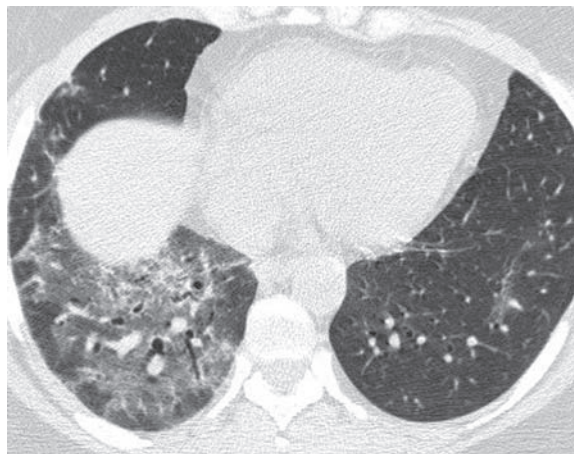

Figure 12.   Lower lobe asymmetric pattern in a 57-year-old woman with fibrotic NSIP. High-resolution CT image shows right lower lobe predominant ground-glass opacity, traction bronchiectasis, and subpleural sparing. Although symmetric disease is most common, asymmetric disease can occur in a minority of cases. Unilateral findings are exceedingly rare in NSIP and should suggest an alternate diagnosis.

respectively, and a diffuse distribution in 5% and 16%, respectively. Primarily upper lobe disease is very rare in NSIP and should make one consider other diagnoses, such as chronic hypersensitivity pneumonitis or sarcoidosis.

NSIP was initially thought to involve primarily the lung periphery. However, as with many of the initial beliefs about the disease, many studies have shown significant variability in its axial distribution. Hartman et al (2), Elliot et al (5), Mac-Donald et al (24), and Johkoh et al (25) found that only 68%, 74%, 60%, and 38% of patients with NSIP, respectively, had a peripherally predominant pattern, whereas the remainder most often had a diffuse or random distribution of disease. In our experience, lower lobe peribronchovascular predominance, with subpleural sparing, is quite common in NSIP (Fig 10).

Symmetry is another high-resolution CT finding that can help one in making the diagnosis of NSIP. Almost all patients have bilateral disease. In addition, in the vast majority of patients, the disease is bilateral and symmetric (Fig 11). However, certain imaging findings, such as ground-glass abnormality and honeycombing, can be asymmetric or occasionally even unilateral (Fig 12). Nonetheless, entirely unilateral disease in NSIP has not been described in the literature or seen in our practice. If unilateral disease is present, this should steer one away from the diagnosis of NSIP. Chronic focal ground-glass opacity can be seen with chronic infection, organizing

pneumonia, bronchioloalveolar cell carcinoma, or even lymphoma (26).

Ground-Glass Abnormality

Ground-glass opacity is the salient CT feature of NSIP and is found in nearly all cases. Areas of ground-glass abnormality have been widely reported in the literature, and ground-glass abnormality has been reported to be present in 76%–100% of cases (2,3,5,8,14,16,18,20,27). In some cases of cellular NSIP, ground-glass opacity is present in the absence of traction bronchiectasis and thus it likely represents areas of inflammation.
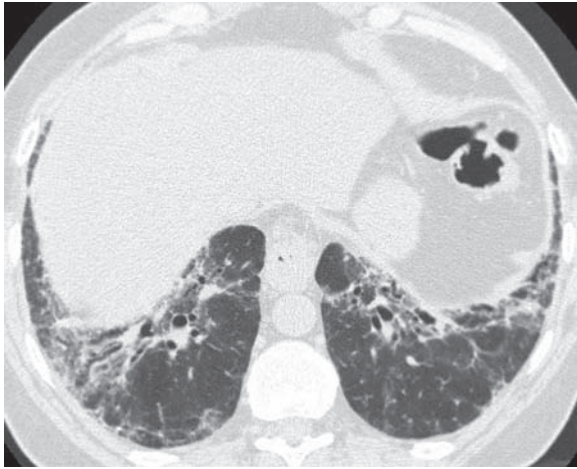
Teaching Point

Figure 13. Ground-glass opacity in a 43-year-old woman with fibrotic NSIP. High-resolution CT image shows lower lobe ground-glass opacity with traction bronchiectasis. In cellular NSIP, ground-glass abnormality represents inflammation. However, in fibrotic NSIP, ground-glass abnormality often represents fine fibrosis, which explains the presence of traction bronchiectasis in this case, given the paucity of reticular abnormality. Ground-glass opacity is a major CT feature of NSIP and is found in nearly all cases.
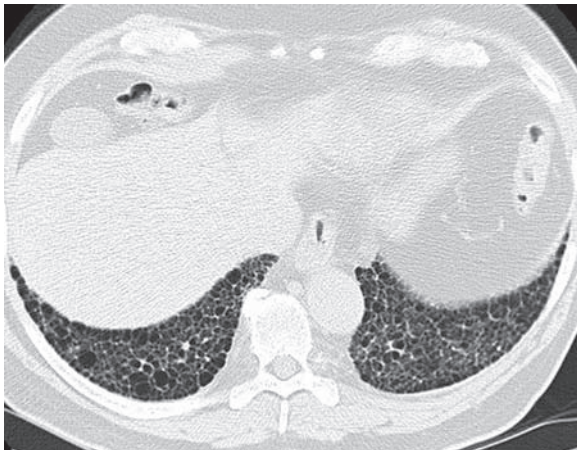

Figure 14. Ground-glass opacity in a 32-year-old man with DIP. High-resolution CT image shows diffuse ground-glass opacity with superimposed cysts (arrow), findings best seen in the anterior left lung. The additional history of heavy smoking helped further differentiate DIP from NSIP. Ground-glass opacity is seen in a wide variety of lung diseases, and the presence of ground-glass abnormality alone does not help one make the diagnosis of NSIP.

Figure 15. Absence of ground-glass opacity in a 71-year-old man with UIP. CT image shows lower lobe predominant honeycombing without any appreciable ground-glass opacity. The absence of ground-glass opacity, in addition to the extensive honeycombing, helps eliminate NSIP from the differential diagnosis.

Figure 16. Reticular abnormality in a 56-year-old man with fibrotic NSIP. High-resolution CT image shows bilateral lower lobe predominant reticular abnormality with traction bronchiectasis and mild ground-glass opacity. Reticular abnormality represents lung fibrosis and is found in nearly all patients with fibrotic NSIP.

However, in fibrotic NSIP, it is almost always associated with traction bronchiectasis and reticular abnormality; thus, it likely represents fine fibrosis rather than inflammation (Fig 13) (21,28).

However, prominent ground-glass abnormality is a common finding in many diffuse lung diseases, including all of the IIPs except UIP (Fig 14). Therefore, although its presence cannot help one make the diagnosis of NSIP, the absence of ground-glass abnormality can steer one toward

a diagnosis of UIP, even if no honeycombing is present (Fig 15).

Reticular Abnormality

Fine reticular abnormality is seen in almost all patients with fibrotic NSIP and represents areas of fine fibrosis (Fig 16). Recent studies since 2000 have found reticular abnormality in 80%–94% of

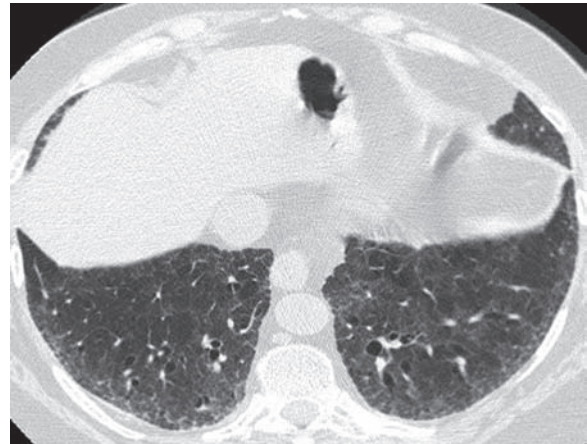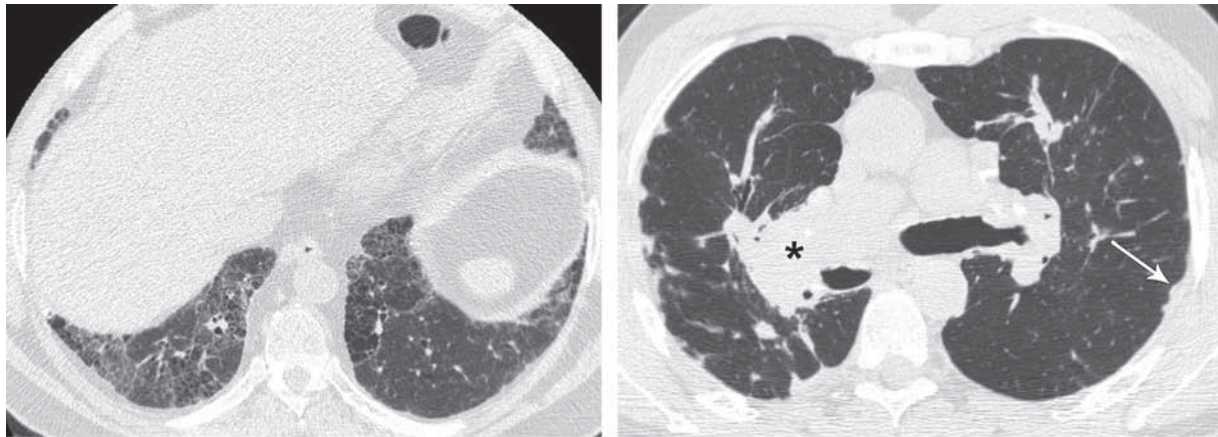a.   b.

Figure 17.   Reticular abnormality in a 47-year-old man with sarcoidosis. **(a)** High-resolution CT image shows bilateral lower lobe reticular abnormality. This case of sarcoidosis would be difficult to differentiate from NSIP on the basis of this single section. **(b)** CT image obtained at a superior level shows subpleural nodules (arrow) and a central conglomerate mass on the right (∗), findings suggestive of the correct diagnosis. Reticular abnormality can be seen in many other fibrotic lung diseases including UIP, hypersensitivity pneumonitis, and sarcoidosis.

Figure 18.   Absence of reticulation in a 46-year-old woman with Sjögren syndrome and LIP. High-resolution CT image shows midlung predominant ground-glass abnormality with some poorly defined centrilobular nodules (black arrow) and cysts of varying sizes (white arrow). The cysts are both within and separate from the ground-glass opacity. The absence of reticulation and the presence of cysts and centrilobular nodules help differentiate this case of LIP from NSIP.

Figure 19.   Traction bronchiectasis in a 59-year-old man with fibrotic NSIP. Coronal high-resolution CT image shows prominent lower lung traction bronchiectasis (arrow) with associated reticular abnormality and lower lobe volume loss.

patients with NSIP (2,5,8,9,27). Although reticulation may help guide one toward the diagnosis of NSIP, its presence alone should not be considered indicative of the diagnosis, since it can be found in various other conditions such as UIP, hypersensitivity pneumonitis, or sarcoidosis (Fig 17). Nonetheless, reticulation is uncommon in DIP, RB-ILD, COP, and LIP (Fig 18). Reticulation is uncommon in early acute interstitial pneumonia, but a significant percentage of patients with this

disease can progress to a fibrotic pattern with associated reticular abnormality.

Traction Bronchiectasis

Traction bronchiectasis or bronchiolectasis is almost universal in patients with fibrotic NSIP and is related to underlying fibrotic changes. In the vast majority of patients with NSIP, traction bronchiectasis is most prominent in the lower lung zones (Fig 19), since that is where the fibrotic changes are most prominent. Even though reticulation may not be evident, traction

Figure 20. Traction bronchiectasis in a 44-year-old man with chronic hypersensitivity pneumonitis. High-resolution CT image shows lower lung ground-glass opacity, reticulation, and traction bronchiectasis. Areas of lobular low attenuation (arrow) help differentiate this case of hypersensitivity pneumonitis in a hot tub owner from NSIP.

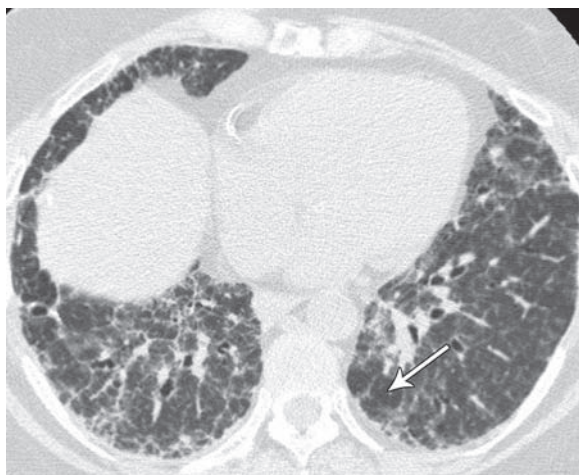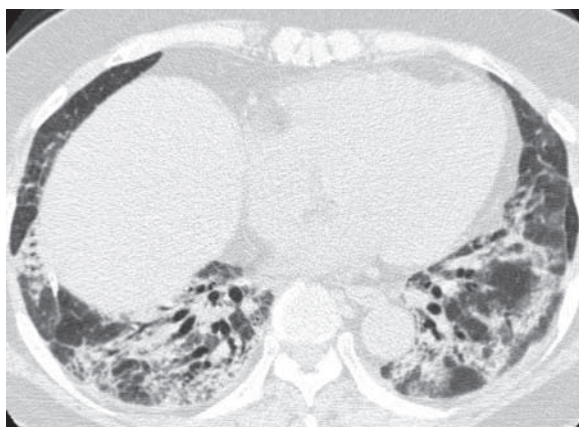**Figure 21.** Lower lobe volume loss in a 55-year-old woman with fibrotic NSIP. Coronal high-resolution CT image shows prominent lower lobe volume loss with associated traction bronchiectasis and reticular abnormality. The lower lobe volume loss appears as inferior displacement of the fissures and crowding of lower lobe bronchi and vessels. Although this finding is common in fibrotic NSIP, any disease causing lower lobe fibrosis can demonstrate lower lobe volume loss.

brotic lung disease, so its diagnostic value in isolation is limited (Fig 20).

Lower Lobe Volume Loss

Lower lobe volume loss is often seen in patients with fibrotic NSIP and is usually seen in conjunction with other signs of lung fibrosis, including traction bronchiectasis and reticular abnormality (Fig 21). The presence of lower lobe volume loss is not specifically described in most articles, but Johkoh et al (25) found lower lobe volume loss in 91% of patients with NSIP.

Radiologic Findings That May Be Associated with NSIP

Consolidation

With regard to consolidation, the literature once again details a wide range of prevalence, ranging from 0% to 98% (2–5,8,9,20–25,28). It is not clear why such a discrepancy exists between various studies. Nonetheless, it is uncommon for consolidation to be the primary abnormality in NSIP. If consolidation in NSIP is a chronic finding, it is often related to a component of associated organizing pneumonia and underlying fibrosis and often associated with traction bronchiectasis (Fig 22). This

Figure 22. Airspace consolidation in a 41-year-old man with fibrotic NSIP. High-resolution CT image shows lower lobe ground-glass opacity and airspace consolidation with associated reticular abnormality and traction bronchiectasis. Airspace consolidation can be seen in NSIP but should not be the primary abnormality. In addition, areas of airspace consolidation often improve over the course of the disease. If present in NSIP, airspace consolidation is thought to be due to a combination of organizing pneumonia and underlying fibrosis.

bronchiectasis points toward underlying fibrotic changes. Earlier studies demonstrated a wide range in the presence of traction bronchiectasis (4,5,20,22,24,27,28), but more recent studies by Johkoh et al (25), Nishiyama et al (7), and Tsubamoto et al (9) demonstrated traction bronchiectasis in 95%, 93%, and 100% of patients with NSIP, respectively. Traction bronchiectasis can be seen in any patient with underlying fi-
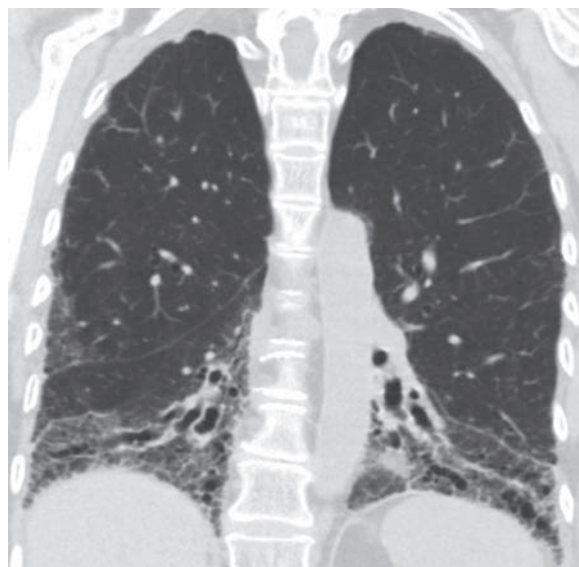
Figure 23. Airspace consolidation in a 29-year-old man with chronic eosinophilic pneumonia. CT image shows bilateral peripherally predominant airspace consolidation. An airspace predominant process should point one away from the diagnosis of NSIP.
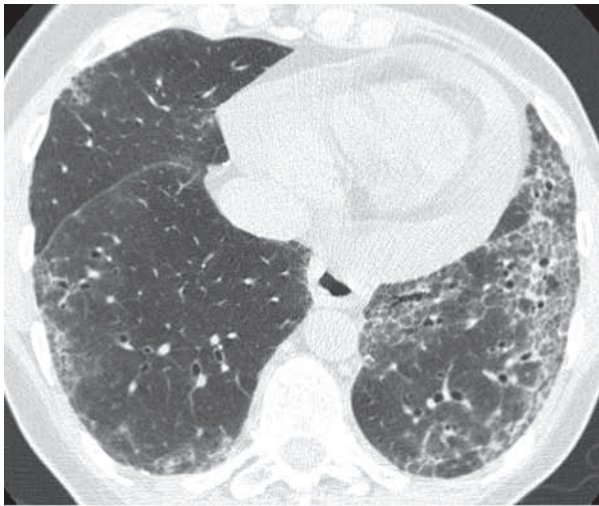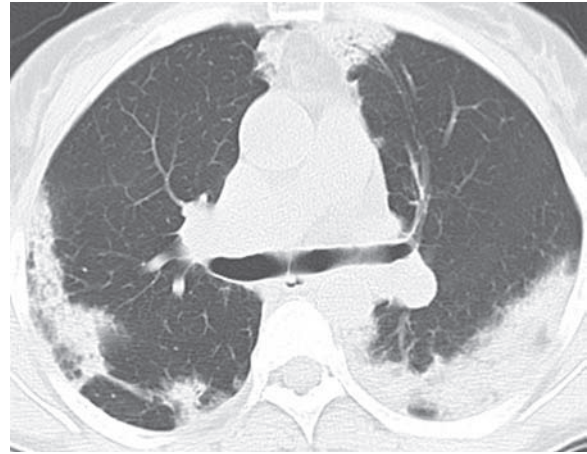
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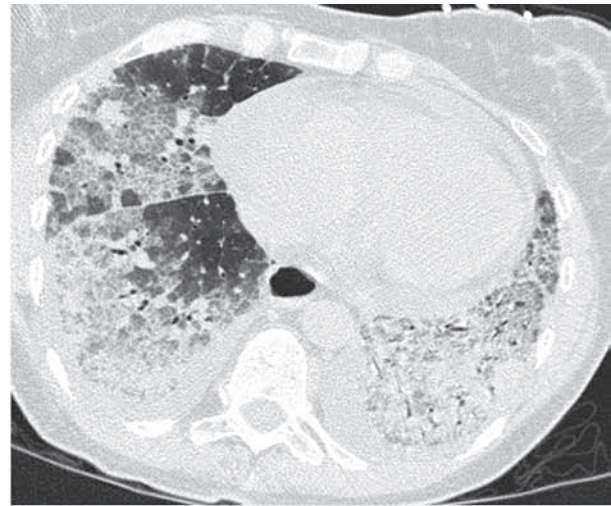
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Figure 24. Acute exacerbation in a 58-year-old woman with NSIP related to scleroderma. **(a)** Baseline high-resolution CT image shows moderate ground-glass and reticular abnormality with traction bronchiectasis. A moderate pericardial effusion is present. **(b)** High-resolution CT image obtained 3 weeks later, after development of acute symptoms with hypoxia, shows extensive new superimposed consolidation and ground-glass abnormality with bilateral pleural effusions.

combination of findings may be seen in patients with underlying dermatomyositis or polymyositis. If chronic consolidation is the primary finding, one should think of other disorders such as organizing pneumonia, diffuse alveolar damage, eosinophilic pneumonia (Fig 23), chronic infection, or bronchioloalveolar cell carcinoma.

If rapidly developing airspace consolidation or ground-glass abnormality is seen in an acutely ill patient with NSIP, one should consider the possibility of an acute exacerbation (29). Although well known in patients with UIP, acute exacerbations can also occur in patients with other interstitial pneumonias, including NSIP. As with acute exacerbations of UIP, biopsy often shows

diffuse alveolar damage. Radiologic studies demonstrate new areas of consolidation and ground-glass opacity superimposed on more chronic background changes of NSIP (Fig 24). Although acute exacerbation occurs less frequently than in patients with UIP, Park et al (29) found that the yearly likelihood of an acute exacerbation in a patient with NSIP was 4.2%.

Honeycombing

The presence of honeycombing, once thought to exclude the diagnosis of NSIP, can occasionally be seen in fibrotic NSIP (Fig 25). The literature reports a prevalence of honeycombing ranging from 0% to 44% (2,3,5,8,9,20–22,25,28,30). The presence of honeycombing in patients with NSIP may reflect foci of UIP at sites where biopsy samples revealed NSIP, since histologic
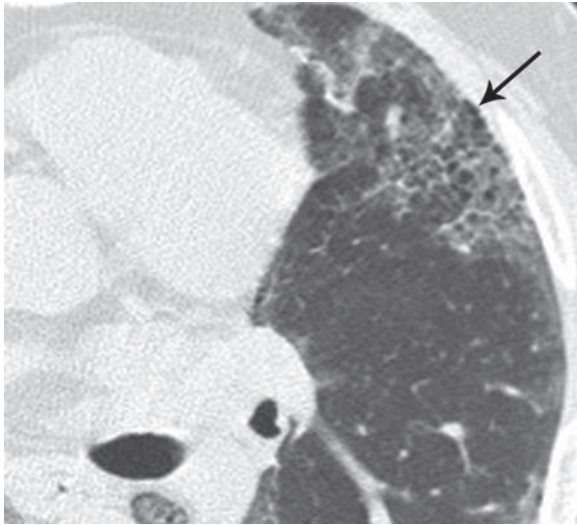
Figure 25. Honeycombing in a 64-year-old man with fibrotic NSIP. High-resolution CT image (detail view) shows reticular abnormality with a small focus of honeycombing (arrow). Although honeycombing can occasionally be seen in NSIP, it should not be a predominant feature.
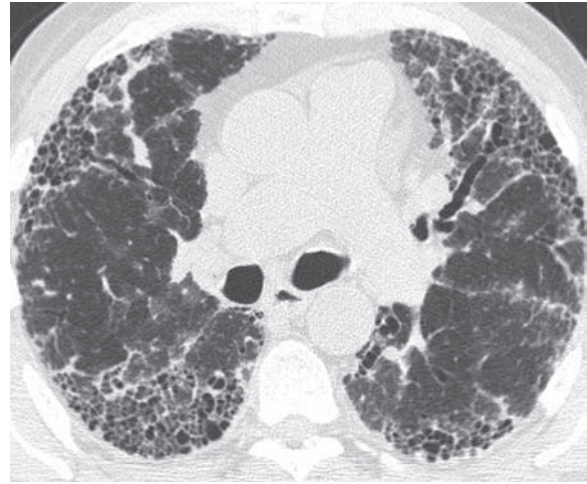

Figure 26. Honeycombing in a 57-year-old man with UIP. High-resolution CT image shows peripheral reticular abnormality, traction bronchiectasis, and classic subpleural honeycombing. The degree of honeycombing and the absence of ground-glass abnormality should suggest the diagnosis of UIP instead of NSIP.

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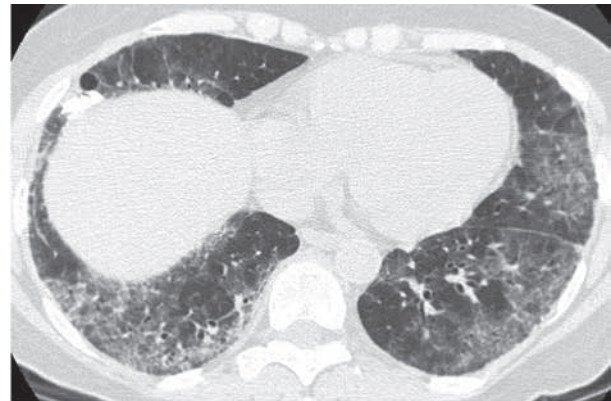
28.

Figures 27, 28. **(27)** Cellular NSIP in a 40-year-old man. High-resolution CT image shows mild ground-glass attenuation without underlying fibrotic change, findings that may suggest cellular NSIP. **(28)** Cellular NSIP in a 57-year-old woman. High-resolution CT image shows peripheral ground-glass opacity with reticular abnormality and traction bronchiectasis, findings that may suggest fibrotic NSIP; however, cellular NSIP was demonstrated at biopsy. There is no reliable way to differentiate cellular and fibrotic NSIP on the basis of radiologic features.

heterogeneity is known to exist among biopsy samples (31,32). In general, however, the presence of honeycombing at CT is a strong predictor of histologic UIP (Fig 26) (33).

Differentiation between Cellular and Fibrotic NSIP

Cellular NSIP is much less common than fibrotic NSIP (14,31). It is often characterized by the absence of severe fibrotic changes or honeycombing. Sumikawa et al (8) and Tsubamoto et al (9) evaluated the extent of parenchymal abnormalities in both cellular and fibrotic NSIP. Although there was a greater degree of reticulation in fibrotic NSIP, reticulation could be seen in cellular NSIP as well. In addition, there was no difference in the extent of ground-glass abnormality, airspace consolidation, and traction bronchiectasis between the two groups. MacDonald et al (5) compared the CT features of fibrotic and cellular NSIP; they found that cellular NSIP was associated with a finer pattern of reticular abnormality and was less often subpleural in distribution (Fig 27). However, the imaging features of cellular and fibrotic NSIP often overlap, and there is no reliable way to differentiate between the two subtypes (Fig 28).

Teaching Point

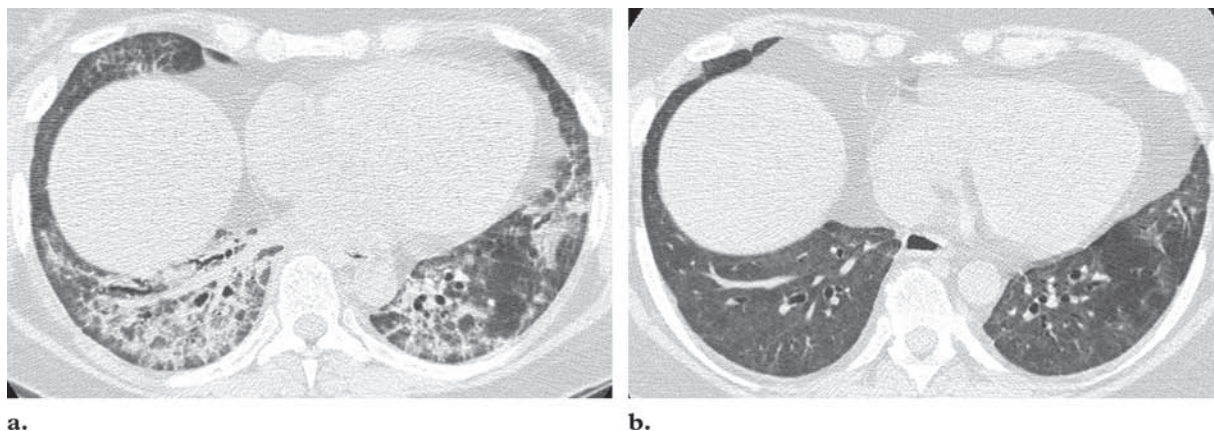**Figure 29.**   Changes over time in a 48-year-old woman with NSIP. **(a)** Initial high-resolution CT image shows lower lobe predominant ground-glass opacity, areas of airspace consolidation, reticular abnormality, and traction bronchiectasis. Note the subpleural sparing. **(b)** Follow-up image obtained 1 year later shows a dramatic reduction in the amount of ground-glass opacity and consolidation. Reticular abnormality and traction bronchiectasis persist. It is common for ground-glass opacity and airspace consolidation to show improvement at subsequent imaging, although underlying fibrosis often persists.
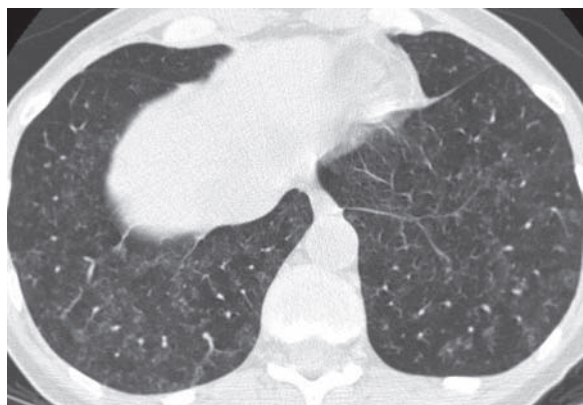
Figure 30.   Nodules in a 64-year-old woman with hypersensitivity pneumonitis. High-resolution CT image shows diffuse ill-defined centrilobular nodules. In our experience, nodules are very uncommon in NSIP and should point one away from that diagnosis.

Figure 31.   Low attenuation in a 55-year-old woman with hypersensitivity pneumonitis. High-resolution CT image shows areas of normal lung (black arrow) interspersed with areas of low attenuation (straight white arrow) and areas of increased attenuation (curved white arrow). These findings in conjunction with diffuse centrilobular nodules (arrowhead) help one make the diagnosis.

Radiologic Changes over Time

As with UIP, the imaging characteristics of NSIP often change over time. Kim et al (28), Screaton et al (34), and Silva et al (35) each demonstrated a statistically significant decrease in the amount of ground-glass opacity and consolidation in patients with NSIP at follow-up imaging (Fig 29). In the study by Screaton et al (34), all six patients who had an initial high-resolution CT pattern consistent with a predominantly inflammatory process (consolidation, ground-glass abnormality, nodules) demonstrated improvement at follow-up imaging. However, in those with a more pronounced fibrotic pattern (reticulation, honeycombing, mixed ground-glass and reticular pattern) at initial high-resolution CT, only

22% (seven of 32) had significant improvement at subsequent imaging, whereas 59% (19 of 32) demonstrated no significant change and 19% (six of 32) showed progression of disease.

In a recent article by Silva et al (35), 35% of patients with NSIP (eight of 23) demonstrated no significant change in the underlying pattern of disease over time, whereas 65% (15 of 23) showed a marked increase in the degree of fibrosis. In five patients, the level of fibrosis progressed to such a degree that although these patients had initial high-resolution CT findings highly sug-

Figure 32. Cystic change in a 42-year-old male smoker with DIP. High-resolution CT image shows multiple small cysts within areas of ground-glass abnormality, a common finding in DIP. In the setting of diffuse lung disease, cystic change associated with ground-glass abnormality should make one think of DIP or LIP.
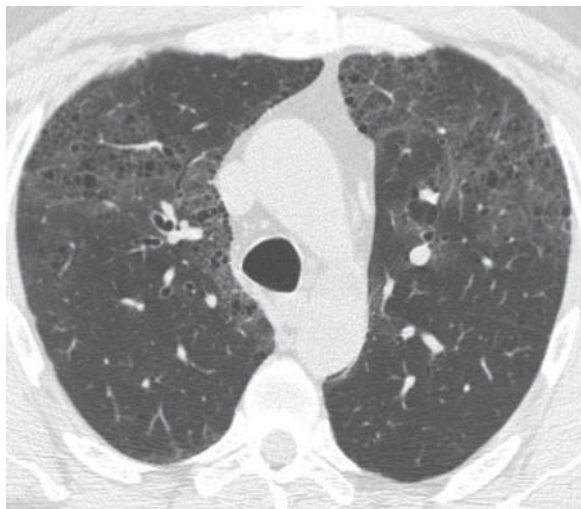
gestive of NSIP, the results of follow-up imaging after 3 years were more suggestive of UIP than NSIP. However, few long-term studies have been performed to evaluate the natural progression of disease in NSIP, and further study is necessary.

Radiologic Findings That Should Suggest an Alternate Diagnosis

Nodules

The prevalence of nodules in NSIP has varied extensively in different studies, ranging from 0% to 96% (4,9,25,30). As with airspace consolidation, it is not clear why such a discrepancy exists; it may reflect a difference in the definition of nodules. However, in our experience, diffuse nodules are very infrequent in NSIP. If centrilobular nodules are present, one should think of other forms of diffuse lung disease such as RB-ILD or hypersensitivity pneumonitis (Fig 30). In addition, chronic bronchiolar infections (bacterial, viral, fungal), pneumoconioses, sarcoidosis, asthma, autoimmune and immunodeficiency diseases, and constrictive bronchiolitis can all demonstrate diffuse centrilobular nodules.

Low Attenuation

Areas of low attenuation or mosaic attenuation may reflect vascular disease but more commonly indicate small airways obstruction. The presence of areas of low attenuation interspersed with areas of interstitial abnormality should make one think of hypersensitivity pneumonitis (Fig 31). In a study
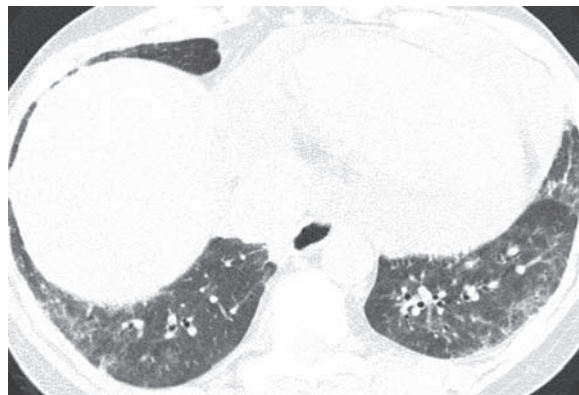
Figure 33. NSIP in a 41-year-old woman with scleroderma. High-resolution CT image shows the typical findings of fibrotic NSIP in addition to esophageal dilatation. Given the association of NSIP with collagen vascular diseases, it is important to look for associated findings.

by Silva et al (30), 81% of patients with chronic hypersensitivity pneumonitis had this finding, compared with 34% of patients with NSIP.

Cystic Change

Cystic changes, other than honeycombing, are very rare in NSIP. If multiple cysts are present, other forms of diffuse lung disease should be considered, such as LIP, DIP, lymphangioleiomyomatosis, and pulmonary Langerhans cell histiocytosis. Thin-walled cysts up to 3 cm in size, often associated with ground-glass abnormality, can be seen in up to 82% of those with LIP (Fig 18) (36). However, most often the cysts involve only a small percentage of the total lung parenchyma. In DIP, which is most commonly related to cigarette smoking, the thin-walled cysts are usually less than a centimeter in size and identified in areas of ground-glass opacity (Fig 32). The ground-glass opacity in DIP tends to be basal and peripherally predominant (37).

Associated Findings Suggesting Underlying Collagen Vascular Diseases

Although many cases of NSIP are idiopathic, NSIP is commonly associated with underlying collagen vascular diseases. Various collagen vascular diseases can be associated with NSIP, including scleroderma, polymyositis or dermatomyositis, Sjögren syndrome, and rheumatoid arthritis. Given this association, it is important to look for additional abnormalities that may aid in diagnosis.

Findings that can suggest an underlying collagen vascular disease include esophageal abnormalities (Fig 33), pleural or pericardial effusions

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or thickening (Fig 34) (33), pulmonary arterial enlargement, and bone and joint disease. Although pleural disease is very common in systemic lupus erythematosus, fibrotic interstitial disease is relatively uncommon in this disease in comparison with the other collagen vascular diseases (11). Lymphadenopathy can be seen in both idiopathic and secondary NSIP.

Challenges in Diagnosis

Diagnosis of NSIP with high-resolution CT can be difficult even for expert pulmonary radiologists. Flaherty et al (16) found that only 18 of 44 patients (41%) thought to have definite or probable NSIP at high-resolution CT actually had NSIP at histopathologic analysis. In 2005, Tsubamoto et al (9) and Elliot et al (2) found that the correct diagnosis of NSIP was made by radiologists in 65% and 68% of cases, respectively. Most recently, Sumikawa et al (8) accurately diagnosed NSIP in 55 of 64 patients (86%), by far the highest rate. Curiously, only 25 of 40 cases of UIP (62%) were accurately diagnosed.

However, radiologists are not the only ones who have difficulty making the correct diagnosis of NSIP. Pathologists also have difficulty in making this diagnosis. Multiple pathology articles have shown high interobserver variation and low levels of agreement in the diagnosis of NSIP. This problem is compounded by sampling error and high levels of intrapatient variability, as biopsy samples from different parts of the lung may demonstrate different diseases (31,32).

Because of the overlap in clinical, imaging, and pathologic features of NSIP, the American Thoracic Society and European Respiratory Society have recommended that clinicians, pathologists, and radiologists work together to reach a consensus diagnosis. In 2004, Flaherty et al (38) found that use of a consensus-based approach resulted in alteration of clinical, radiologic, and pathologic diagnoses in 34%, 53%, and 19% of cases, respectively. Similarly, a recent study by Travis et al (15) found that a definite pathologic diagnosis of NSIP changed in 19% of instances when a consensus approach was used.

Conclusions

A lower lobe, peripherally predominant pattern with ground-glass opacity and superimposed reticular abnormality, traction bronchiectasis, and lower lobe volume loss is seen in the majority of patients with NSIP. Although not specific, these findings should suggest the diagnosis of NSIP in the presence of consistent clinical and histologic findings. Integration of clinical, radiologic, and

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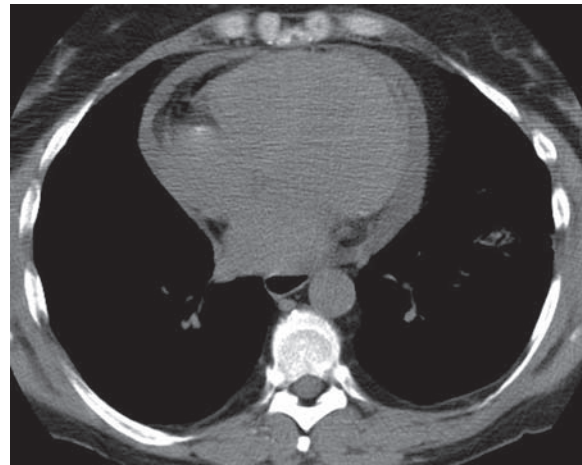
Figure 34.   NSIP in a 65-year-old woman with rheumatoid arthritis. High-resolution CT image shows a pericardial effusion. CT images obtained with lung windows showed an NSIP pattern. Pericardial or pleural disease is uncommon in idiopathic NSIP.

pathologic features frequently results in alteration of initial single-discipline diagnoses. Therefore, radiologists, pathologists, and clinicians should jointly discuss each case to achieve the highest likelihood of a correct diagnosis to assist in disease management.

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Nonspecific Interstitial Pneumonia: Radiologic, Clinical, and Pathologic Considerations

Seth J. Kligerman, MD, et al

Page 78

Ground-glass opacity is the salient CT feature of NSIP and is found in nearly all cases.

Page 83

However, the imaging features of cellular and fibrotic NSIP often overlap, and there is no reliable way to differentiate between the two subtypes (Fig 28).

Page 85

The presence of areas of low attenuation interspersed with areas of interstitial abnormality should make one think of hypersensitivity pneumonitis (Fig 31).

Page 85

Although many cases of NSIP are idiopathic, NSIP is commonly associated with underlying collagen vascular diseases. Various collagen vascular diseases can be associated with NSIP, including scleroderma, polymyositis or dermatomyositis, Sjögren syndrome, and rheumatoid arthritis. Given this association, it is important to look for additional abnormalities that may aid in diagnosis.

Page 86

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