Nonspecific Interstitial Pneumonia: Radiologic, Clinical, and Pathologic Considerations

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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.
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 diseases 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
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).
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
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.

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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.

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,
respective, 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 pneumonia 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), MacDonald 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.
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 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).
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...
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).

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.

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.
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

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%.
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).
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-
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).

**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 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.

**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...
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 rela-
tively 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 radiolo-
gists. Flaherty et al (16) found that only 18 of 44
patients (41%) thought to have definite or prob-
able NSIP at high-resolution CT actually had
NSIP at histopathologic analysis. In 2005, Tsu-
bamoto et al (9) and Elliot et al (2) found that
the correct diagnosis of NSIP was made by radi-
ologists in 65% and 68% of cases, respectively.
Most recently, Sumikawa et al (8) accurately di-
gnosed 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 mak-
ing 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 Tho-
racic Society and European Respiratory Society
have recommended that clinicians, pathologists,
and radiologists work together to reach a consen-
sus 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, re-
spectively. Similarly, a recent study by Travis et al
(15) found that a definite pathologic diagnosis of
NSIP changed in 19% of instances when a consen-
sus approach was used.

Conclusions
A lower lobe, peripherally predominant pattern
with ground-glass opacity and superimposed retic-
ticular 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
pathologic features frequently results in altera-
tion 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 dis-
ease management.

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

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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.
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