Nonspecific Interstitial Pneumonia: What Is the Optimal Approach to Management?

Sara Tomassetti, MD[1] Jay H. Ryu, MD[2] Sara Piciucchi, MD[3] Marco Chilosi, MD[4] Venerino Poletti, MD[1]

[1] Department of Diseases of the Thorax, GB Morgagni Hospital, Forlì, Italy
[2] Division of Pulmonary and Critical Care Medicine, Mayo Clinic, Rochester, Minnesota
[3] Department of Radiology, GB Morgagni Hospital, Forlì, Italy
[4] Department of Pathology, University of Verona, Verona, Italy

Address for correspondence Sara Tomassetti, MD, Department of Diseases of the Thorax, GB Morgagni Hospital, via C Forlanini 34, 47121 Forlì (FC), Italy (e-mail: s.tomassetti@gmail.com).

Semin Respir Crit Care Med 2016;37:378–394.

Abstract

We reviewed current aspects of the clinical and pathogenic profile of nonspecific interstitial pneumonia (NSIP), to better elucidate the complex issue of management and treatment options for NSIP patients. Recent findings suggest that idiopathic NSIP is a complex clinical entity with a disease spectrum that includes at least three different phenotypes: NSIP associated with autoimmune features, emphysema, and familial interstitial lung disease. This distinction, based mainly on clinical findings, may be of critical importance when it comes to making a decision on patients' management. This hypothesis warrants further studies. Currently, two major radiologic–pathologic different profiles have been well established. First, the "inflammatory type" characterized by prominent lymphocytic inflammation both on biopsy and bronchoalveolar lavage (BAL), and high-resolution computed tomography (HRCT) with mixed NSIP/organizing pneumonia pattern that tends to have a better response to corticosteroid and immunosuppressive treatment. Second, the "highly fibrotic" subgroup that shows prominent reticular changes and traction bronchiectasis by HRCT, high fibrotic background on biopsy, and no lymphocytosis on BAL. The latter fibrotic NSIP is the subgroup with less potential to respond to immunosuppressive treatment and a marginal risk to evolve into "full-blown idiopathic pulmonary fibrosis." The management of patients with fibrotic, progressive, and immunosuppressive treatment, refractory NSIP remains uncertain, and further studies are needed to address the role of antifibrotic drug in this settings. Oxygen therapy, pulmonary rehabilitation, and lung transplantation are of importance in the current management of severe, progressive, and refractory NSIP patients.

Keywords
- interstitial lung diseases
- idiopathic nonspecific interstitial pneumonia
- cyclophosphamide
- rituximab

The term nonspecific interstitial pneumonia (NSIP) refers to a histopathologic pattern seen on lung biopsy. The NSIP pattern can be associated with many systemic nonneoplastic conditions, such as connective tissue disorders (CTDs), drug-induced lung diseases, hypersensitivity pneumonitis (HP), occupational and environmental exposure, smoking-related interstitial lung disease (ILD), viral infections (mainly human immunodeficiency virus [HIV]), graft versus host disease (GVHD), prior acute lung injury (particularly slowly healing diffuse alveolar damage [DAD]), recurrent organizing pneumonia (OP), and more rare conditions (familial pulmonary fibrosis, immunoglobulin G4 [IgG4]-related disease, Rosai–Dorfman disease, Castleman disease, and other myelodysplastic syndromes).[1,2] A diagnosis of idiopathic NSIP is made when none of the mentioned conditions can be identified. Thus, idiopathic NSIP is the term currently used to define a distinct entity among chronic fibrosing idiopathic interstitial pneumonias (IIP).[3]

Issue Theme Orphan Lung Diseases; Guest Editors: Jay H. Ryu, MD, and Luca Richeldi, MD

DOI http://dx.doi.org/10.1055/s-0036-1583176.
ISSN 1069-3424.

Historical Perspective

The term NSIP first appeared in the medical literature in 1987 when Suffredini et al[4] described a pattern of nonspecific interstitial lung inflammation seen in association with HIV infection. In 1994, Katzenstein and Fiorelli[5] described 95 cases of lung biopsies whose morphology did not fit the traditional Liebow classification of interstitial pneumonias.[6] Among these cases of "chronic interstitial pneumonia not otherwise specified," 64 shared similar features and referred to as the NSIP pattern with the key histopathologic feature being that the process was temporally uniform, with inflammation and fibrosis that appeared to be occurring over a single time span. These authors reported a low mortality rate (11%) overall and no death in the subgroup of "pure inflammation and no fibrosis." However, given both the association with a broad spectrum of systemic disorders (CTD, organic dust exposure, prior lung injury) and the fact that NSIP might reflect a nonrepresentative biopsy of another disorder, these authors concluded that NSIP should not be considered a specific disease. In subsequent publications, the term NSIP has evolved from its original use, which was intended to indicate a histologic pattern related to a variety of etiologies, to identify almost exclusively a form of IIP.[7–11] This and subsequent investigations led to the recognition of NSIP as a "provisional" type of IIP in the 2002 American Thoracic Society/European Respiratory Society (ATS/ERS) consensus statement. The recognition of the provisional status was mainly related to the uncertainty surrounding the clinical profile, etiology, and pathogenesis of this entity.[12] NSIP became "officially" a "wastebasket category," and concern was expressed that this provisional entity might generate confusion, being difficult to distinguish from other IIP.

In 2008, Travis et al[13] reviewed 67 cases of idiopathic NSIP in a series of ATS workshops, delineating the clinical profile of NSIP, a disease that occurs mostly in middle-aged women who are never-smokers and characterized by a very good prognosis. Idiopathic NSIP was subsequently recognized to be a distinct clinical entity in the ATS/ERS international consensus classification update recently published.[3]

Epidemiology

Idiopathic NSIP is a relatively rare entity with limited case series reported in the literature to date. In a recent cohort study conducted in central Denmark at Aarhus University Hospital, between 2003 and 2009, among 431 incident cases of ILD, 7% of NSIP were observed. NSIP was the fourth most frequent ILD observed after idiopathic pulmonary fibrosis (IPF) (28%), CTD-ILD (14%), and HP (7%). The overall ILD incidence was 4.1 per 100,000 inhabitants/year, with NSIP incidence being estimated at 3.0 cases per million inhabitants/year.[14]

NSIP occurs mostly in middle-aged women; median age has been reported to be 52 years with a wide range from 26 to 73 years.[13] The predominance of this disease in females compared with males has been consistently reported in almost all series published to date, with a female predominance of 67% in 2008 ATS report.[13] A prevalence of never-smokers has been reported in numerous case series, including the ATS report in which the prevalence of never-smokers was 69%.[13] However, some case series showed a prevalence of current/previous smokers, with the highest prevalence of smokers reported as 71%.[15]

Survival for patients with idiopathic NSIP is much better than that of IPF, with early studies suggesting a survival at 5 years of 82.3% and at 10 years of 73.2%.[13] In the recent Danish study, 5-year survival was 73.6%, exceeded only by HP (93%) and followed by CTD-ILD (48.2%) and IPF (ranging between 46 and 9% depending on disease severity and GAP [gender, age, physiology] I and III stages, respectively).[14]

Etiology and Pathogenesis

Numerous series have associated the histopathologic pattern of NSIP with CTD, HP, infections (e.g., *Pneumocystis*), immunosuppression including HIV, and other more rare entities, such as lymphoproliferative lung disorders (low grade), IgG4-related disease, and human T-lymphotropic virus-1 (HTLV-1) carriers.[2] NSIP has been recently recognized also as one of the histologic features in the complex spectrum of familial pulmonary fibrosis.[16–21] The most important distinction to decipher in understanding the clinical relevance of NSIP is whether it is idiopathic or secondary (identifiable cause or underlying disease). Therefore, it has been suggested that the identification of NSIP should prompt the physician to redouble efforts to find potential etiologies.

Concepts about pathogenesis of NSIP are evolving. The understanding of NSIP pathogenesis has been hampered by the confusion generated by the relationship with other IIP, particularly IPF. Usual interstitial pneumonia (UIP) and NSIP histology patterns share a similar genetic background and causative agents (e.g., CTD, hypersensitivity) and similar demographic characteristics, and some authors in the past have hypothesized that UIP may represent the late stage of NSIP.[22] Recently, Schneider et al[23] reported a subset of fibrotic NSIP patients who developed radiological and histopathologic features of UIP-like fibrosis, bringing back up the hypothesis that, in some cases, a UIP pattern may be the result of chronic inflammation. However, IPF and NSIP appear to be divergent in terms of pathogenetic events. In IPF, the cumulative action of an accelerated parenchymal senescence determined by either telomere dysfunction and/or an array of genetic predisposing factors, together with the concurrent noxious effects of tobacco smoking, compromises the regenerative potential of parenchymal epithelial progenitor cells, triggering a cascade of molecular signals (transforming growth factor-β, Wnt pathway, Caveolin-1, etc.) and events (scarring, bronchiolar proliferation, abnormal remodeling), eventually leading to severe and irreversible fibrosis and associated functional impairment.[24,25] In idiopathic NSIP, inflammatory and autoimmune pathways are the dominant events. Increased expression of 5-hydroxytryptamine 2A/B receptors was observed in IPF but not in NSIP.[26] Free DNA in serum was increased in IPF but not in idiopathic NSIP.[27] The expression of p53 and p21 on epithelial cells is significantly increased in UIP lesions compared with fibrotic NSIP lesions,

confirming that augmented epithelial apoptosis is more prominent in IPF.[28] Autoantibodies to aminoacyl-tRNA synthetases are detected in ~7% of subjects with idiopathic NSIP,[29] and other autoantibodies are not infrequently found in this cohort of patients.[30] These findings draw attention to B lymphocytes as culprits and, along with the increased number of CD3/CD8 lymphocytes in bronchoalveolar lavage (BAL) fluid, underpin the hypothesis that most cases of idiopathic NSIP may be a specific form of autoimmune pneumonitis.

Periostin, a matrix protein, is overexpressed in IPF and fibrosing NSIP (fNSIP) in comparison with the low expression observed in cellular NSIP and OP.[31] Fibroblasts from NSIP demonstrate characteristics similar to controls, whereas fibroblasts from UIP show an increased contractility.[32] A recent proteomic study on lung tissue[33] documented a different profile of vimentin expression in 8 NSIP compared with 8 IPF and 30 controls. Vimentin is expressed in alveolar walls of NSIP compared with fibroblastic foci in UIP, and different vimentin subtypes are expressed in the two diseases. Moreover, Korfei et al[34] compared the proteome profile of 14 IPF to 8 fNSIP and observed the oxidative stress is a key factor in both IPF and fNSIP pathogenesis, but found a distinctive signature of an increased alveolar epithelial protection against oxidative and endoplasmic reticulum (ER) stress in fNSIP. Takahashi et al[35] showed that the greater expression of matrix metalloproteinase-2 (MMP-2) and vascular endothelial growth factor A in NSIP compared with IPF may play a role in the pathogenesis of neovascularization of early intra-alveolar fibrotic lesions. Recently, Bargagli et al[36] observed a procoagulant status in IPF (35 patients), probably related to endothelial activation and microvascular injury, that was not present in NSIP (7 patients) and controls (44 patients).

Abnormal oxidative stress might have a role in sustaining the alveolar damage because this phenomenon has been documented in scleroderma, a CTD that may present with NSIP. Baroni et al[37] showed that autoantibodies against platelet-derived growth factor receptor in scleroderma patients selectively induce reactive oxygen species cascade and stimulate type I collagen gene expression and myofibroblast phenotype conversion in normal human primary fibroblasts. Complex interplay between epithelial injury, cytokines, gene expression, and immune dysregulation is present in NSIP. Numerous pathways have been implicated in the pathobiology of NSIP, including MMPs, heat shock protein 47, surfactant protein C, adhesion molecules, intercellular adhesion molecule 1, interleukin 4 (IL-4), IL-13, IL-18, interferon gamma, and profibrotic chemokines (CCL7, CCL5).[1]

These pathogenetic differences fit well with the differing clinical profile of these two entities, IPF and NSIP, strikingly divergent in terms of clinical features, prognosis, and response to treatment.

The Multidisciplinary Approach to Idiopathic NSIP Diagnosis

The diagnosis of idiopathic NSIP requires a multidisciplinary discussion (MDD) that includes pulmonologists, radiologists, and pathologists. Compared with other IIPs, particularly IPF, in which the diagnosis can be reached with high confidence by radiologists and clinicians without the need for lung biopsy in a considerable proportion of patients,[38,39] the diagnosis of NSIP requires histopathologic information in the vast majority of cases.[3,13] Differentiating NSIP from IPF and HP is particularly difficult. When high-resolution computed tomography (HRCT) does not show the typical bibasal subpleural honeycombing of UIP and the clinical-radiologic features do not allow a confident diagnosis of HP, lung biopsy carries the most important piece of diagnostic information.[3,13] In this scenario, the pathologic features influence more than any other information both interobserver agreement and diagnostic confidence level.[40–42] However, pathology itself is insufficient to warrant a diagnosis of idiopathic NSIP, and pathology findings need to be integrated with clinical and radiologic information in a dynamic scenario in which pathologists, clinicians, and radiologists interact. Moreover, when coexisting patterns are observed, MDD may determine the significance of individual patterns.[3] An important role for clinicians in the MDD is to collect a thorough exposure history, family history, and assessment for underlying CTD. Findings strongly suggestive of CTD would likely denote a case of secondary NSIP rather than idiopathic NSIP. Differential diagnosis with autoimmune disorders may be difficult in some cases, requiring an integrated approach with rheumatologists involved in the MDD.[3,43–46]

Clinical Features of Idiopathic NSIP

The clinical profile of NSIP is complex. Idiopathic NSIP patients typically present cough and dyspnea with acute, subacute, or chronic onset of symptoms, with a duration that varies from few days to years.[1,3,13] Pulmonary function tests show a restrictive ventilatory defect with a decrease in gas transfer. Hypoxemia is present in more advanced disease. Measurement of lung function (i.e., forced vital capacity [FVC] and diffusing capacity of lung for carbon monoxide [DLCO]) is recommended not only to initially assess the severity of pulmonary impairment but also to evaluate disease progression, response to treatment, and prognosis.[47,48] Despite idiopathic NSIP being currently classified with IPF as a major form of chronic fibrosing IIP,[3] many clinical features differentiate these two entities. Idiopathic NSIP occurs predominantly in never-smoker women,[13] whereas IPF tends to be a disease of elderly smoker men.[38] Idiopathic NSIP patients are generally younger than those with IPF; the median age of NSIP is 52 years compared with IPF which typically occurs in the sixth to seventh decade.[13,38] Most notably, a low, but considerable proportion of idiopathic NSIP patients have systemic signs or symptoms such as weight loss (25%), fever (22%), arthralgias (14%), Raynaud phenomenon (8%), myalgias (7%), skin rash (5%), and arthritis (3%).[13] Inspiratory crackles are common, similar to IPF, but clubbing has been reported in less than 10% of cases[13]; in contrast, one-half of IPF patients have finger clubbing.

Autoimmune Features of Idiopathic NSIP

It is not uncommon for NSIP to be the first, and possibly the sole, manifestation of an otherwise occult CTD. Clinical

features of idiopathic NSIP and CTD-NSIP may overlap, and identifying an underlying CTD in NSIP patients can be challenging, as boundaries between idiopathic NSIP and CTD-NSIP are not clearly defined. Several observations raise the possibility that idiopathic NSIP may be an early manifestation or a forme fruste of CTD. First, histologically, NSIP is the most common pattern in all CTD-associated ILDs, except for rheumatoid arthritis (RA) which is characterized by a higher frequency of UIP.[49] Second, the clinical profile of idiopathic NSIP and CTD-NSIP may overlap in terms of age, gender, smoking history, and symptoms. Laboratory findings may also overlap with the presence of elevated inflammatory markers, such as sedimentation rate and C-reactive protein, and autoimmune markers in both diseases (e.g., antinuclear antibodies, rheumatoid factor). Recent studies suggest a likely association between NSIP and an autoimmune background.

The hypothesis that NSIP might represent the first clinical presentation of CTD was raised by Sato et al,[50] who retrospectively reviewed six patients with histologically proven NSIP who later developed typical CTD. Kinder et al found that more than 80% of 28 patients with idiopathic NSIP presented with an undifferentiated CTD (UCTD) from the beginning.[51] In an Asian cohort of 83 patients with idiopathic NSIP, 10% developed CTD during follow-up (scleroderma, polymyositis/dermatomyositis, RA, mixed CTD).[52] In our Italian cohort of 27 patients with idiopathic NSIP, 50% developed an autoimmune disease (i.e., autoimmune thyroiditis in 26%; UCTD in 22%; CTD in 11% of cases: scleroderma, polymyositis/dermatomyositis, RA).[30]

Unfortunately, the criteria for UCTD remain controversial. Corte et al[53] applied the classification criteria proposed by Mosca et al[54] to investigate the clinical significance of a diagnosis of UCTD in a large cohort of IIP patients (i.e., 45 NSIP and 56 IPF, all proven by surgical lung biopsy). They found that UCTD was present in 21% of cases, more prevalent in NSIP compared with IPF (31 and 13%, respectively). Patients with NSIP compared with IPF showed a higher frequency of Raynaud phenomenon (27 and 4%, respectively; $p = 0.0001$) and positive autoimmune serology ($p = 0.007$). The diagnosis of UCTD was associated with a threefold increase in the likelihood of NSIP (odds ratio [OR], 3.16; 95% confidence interval [CI], 1.14–8.7; $p = 0.03$), and had a sensitivity of 31% and a specificity of 88% for NSIP histology. Using the broader spectrum criteria for UCTD previously published by Kinder et al,[51] the prevalence of UCTD in NSIP increased up to 71%, with an OR of 4.43, 95% CI of 1.9 to 10.3 ($p = 0.001$), and a sensitivity of 71% and a specificity of 64% for NSIP histology. Above all, both mentioned criteria (i.e., Mosca and Kinder) cannot be used as a substitute for a diagnostic biopsy in distinguishing between IPF and NSIP.

Many IIP patients, and the vast majority of NSIP, do not fulfill CTD diagnostic criteria, but clearly have a significant autoimmune disease. In some patients, these features may occur in the absence of serologic abnormalities, while in others a highly specific serum antibody may be present without typical systemic or extrapulmonary findings. Researchers have proposed different criteria and terms to define those patients, including "UCTD-ILD,"[51] "lung-dominant CTD,"[55,56] and "autoimmune featured ILD."[57] Although studies published to date used those heterogeneous definitions, evidence clearly shows that a diagnosis of CTD should be considered for ILD occurring particularly in women and subjects younger than 50 years, and in those with radiologic or pathologic features of NSIP.[58]

Another observation is that CTD features are relevant in regard to clinical and radiologic features, pathological patterns, and possibly natural history, but this needs confirmations.[58] However, the lack of consensus as to how to categorize these patients has been hindering progress in research efforts. In this view, the ATS/ERS task force[59] recently replaced these heterogeneous terms with "interstitial pneumonia with autoimmune features (IPAF)." The term IPAF describes individuals with both ILD and combination of other clinical, serologic, and/or pulmonary morphologic features which putatively stem from an underlying systemic autoimmune syndrome, but do not meet current rheumatologic criteria for a specific CTD. The statement provides a platform for future studies in this field, and is not intended as clinical care guidelines. Classification criteria for IPAF are proposed by ATS/ERS research statement.[59]

NSIP and Cigarette Smoke

The pathogenic relationship between cigarette smoking and respiratory diseases such as emphysema, chronic obstructive pulmonary disease (COPD), and lung cancer is well established, and in regard to IIP, smoking has been identified as causative agent of respiratory bronchiolitis–ILD and desquamative interstitial pneumonia, diseases having a fairly good prognosis and good response to smoking cessation.[3] Among major chronic fibrosing IIP[3] (i.e., IPF and NSIP), the relationship between smoking, IPF, and lung cancer has been thoroughly investigated,[60–63] whereas the links between idiopathic NSIP and cigarette smoke remains unclear. Pathogenic links between cigarette smoke and IPF, a disease occurring in elderly smokers, underlined by a process of accelerated parenchymal senescence and with a behavior similar to many neoplastic disorders, are also quite intuitive. However, for NSIP, a disease occurring mostly in younger never-smokers women, the link with cigarette smoke appears less intuitive and have been less intensively investigated.[64] A case of fibrotic NSIP in a former smoker is shown in ►**Fig. 1**.

In a retrospective HRCT study, Marten et al[65] compared the prevalence and extent of emphysema in smokers with NSIP to both smokers with COPD and to "healthy" smokers (with normal forced expiratory volume 1 (FEV1)). The results revealed emphysema in a striking majority of NSIP cases (77.8%), similar to COPD cases (73.5%). Both NSIP and COPD showed a higher prevalence of emphysema when compared with "healthy smokers" (17.5%; $p = 0.0005$). The high prevalence of emphysema in the NSIP patients, which did not differ from the COPD controls, provided, according to the authors, an indirect support for a smoking-related pathogenesis in some NSIP patients. Interestingly, NSIP patient cohort was enriched of smokers and men (18 smokers and former smokers compared with 11 never-smokers; 13 men compared with 5 women; $p = 0.03$). The strikingly divergent clinical profile of this study population, compared with

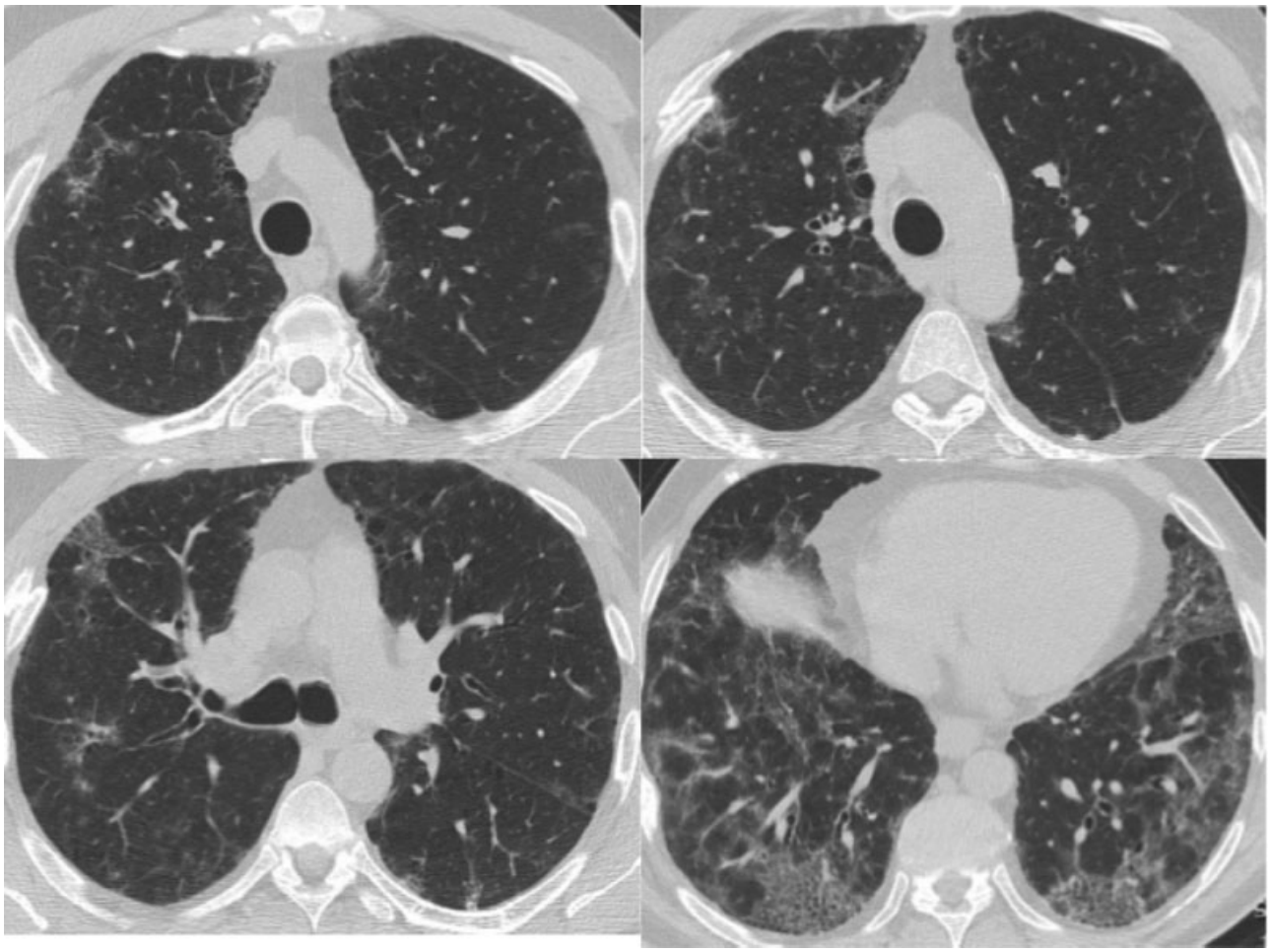

Fig. 1 HRCT findings of fibrotic NSIP in a former smoker. A moderate ground-glass attenuation associated with a mild reticulation is visible in both lower lobes with a prevalent peripheral distribution. Traction bronchiectasis is also present. Paraseptal emphysema is present in both upper lobes.

previously published studies on NSIP, leaves us wondering whether there might be a subgroup of NSIP patients, mostly male smokers, in which cigarette smoke is more relevant than other pathogenic factors.

Cottin et al[60] have extensively described the coexistence of fibrosis and emphysema (combined pulmonary fibrosis and emphysema [CPFE]), but the histology of these patients remains to be further elucidated, and whether a significant subgroup of these CPFE cases might represent a cohort of smoking-related NSIP associated with emphysema is currently unknown. Recently, a common pathogenic pathway has been proposed for emphysema and NSIP, consisting in an increased ectodomain shedding of cell adhesion molecules 1 (CADM1 α-shedding) that cause apoptosis in type II lung alveolar epithelial cells, an early pathogenic event of both emphysema and NSIP.[66] Shinohara et al[67] reported a case of an elderly male patients with normal pulmonary function, whose symptoms, serum KL-6 levels, and HRCT findings improved without treatment after smoking cessation, thus hypothesizing that smoking cessation at an early stage may be of critical importance. The natural history of patients with NSIP and emphysema remains to be elucidated, and the possible association with pulmonary arterial hypertension may identify a subgroup of patients with dismal prognosis.[49,68,69] Further studies are needed to define the clinical profile of idiopathic NSIP in smokers, a subgroup of patients that seems different from the majority of idiopathic NSIP patients and may benefit from a different approach to management.

Familial NSIP

Familial NSIP can be indistinguishable from nonfamilial cases based on HRCT and lung biopsy features. Different subtypes of IIP can exist in the same family.[18] All patients with suspected NSIP should therefore be questioned about relevant family history, as this may guide gene mutation search and evaluation or management of other family members.[3]

Heterozygous mutations in surfactant proteins, telomerase mutations, ELMOD 2, and MUC5B, the majority with autosomal dominant transmission, are responsible for ~20% of all familial interstitial pneumonias.[3,70] Genetic studies may help to identify the underlying pathogenic mechanisms of familial NSIP in the future. The clinical utility of genetic testing is for the screening of family members, prevention of drug toxicity, and, particularly

during screening for lung transplant, identification of occult myelodysplastic syndromes.[70–72]

Familial NSIP may present with clinical and radiographic findings that overlap with those observed in IPF. Furthermore, Lee et al[73] have shown that in the vast majority of familial IIP cases the HRCT features do not conform with classic UIP and NSIP patterns. Given this scenario, the distinction between cases of familial NSIP or familial IPF rests in pathologists' hand. Apparently, as for idiopathic NSIP and IPF, the pathologists add to the MDD of these cases the most important piece of information to differentiate those entities. However, in familial IIP there are two important caveats: first, the biopsy findings are confusing even for expert pathologists[21] and, second, the prognostic impact of biopsy information in this subgroup of patients has never been evaluated.

Some reports underscore that familial NSIP might be associated with a dismal prognosis, more similar to IPF than to idiopathic NSIP.[18,74] However, it is currently unclear what is the difference between familial and idiopathic NSIP in terms of prognosis and optimal treatment. Despite multiple attempts, currently no formal definition has been proposed for familial forms of pulmonary fibrosis. Familial NSIP is currently considered as part of the complex clinical spectrum of idiopathic NSIP, and recommended approach for familial NSIP does not diverge from idiopathic NSIP.[3]

Bronchoalveolar Lavage and Transbronchial Biopsy

For patients with suspected NSIP, typical diagnostic studies performed on BAL are microbiological studies (to exclude infections) and cellular analysis with cytopathology (to exclude malignancy) and differential cell count.[75] The reason for cellular analysis with cell count when NSIP is suspected is that identification or exclusion of a predominantly inflammatory cellular pattern (lymphocytosis) may help narrow the differential diagnosis with other distinct types of ILD and potentially identify particular subgroups of idiopathic NSIP patients. The notion that lymphocytosis in the BAL correlates with an increased likelihood of NSIP is supported by numerous studies, but all have limitations. Current ATS guidelines[75] classify NSIP in the group of ILD with a BAL lymphocytic cellular pattern, with more than 15% lymphocytes. BAL lymphocytosis is observed in cellular NSIP and in mixed patterns of NSIP-OP.[76] BAL profile in cellular NSIP resembles that of cryptogenic OP and HP, with similar percentage of lymphocytes, but with lower total cell count; scattered mast cells and eosinophils are also being detected. The absence of BAL lymphocytosis suggests a diagnosis of IPF rather than NSIP (OR, 12.7; $p < 0.001$).[77] Ohshimo et al[78] showed that a cutoff level of 30% for lymphocytes in BAL demonstrated a favorable discriminative power for the diagnosis of IPF. Out of 74 patients, 6 (8%) showed a lymphocytosis greater than 30% and the final diagnosis were NSIP in three cases and HP in three cases.[78]

The BAL profile of fibrotic NSIP diverges from that of cellular NSIP and shows a cellularity similar to that of IPF, without significant lymphocytosis. Veeraraghavan et al[79] compared BAL of 19 fNSIP patients, all presenting clinically as IPF (i.e., no difference between UIP and NSIP in gender, age, and smoking status), to 35 UIP patients. There was no difference in the cellular profile of BAL between fibrotic NSIP and UIP, with neutrophils 9% in both groups, lymphocytes 5 and 4%, respectively, and eosinophils 7% in both groups.

We can conclude that BAL seems helpful to differentiate cellular NSIP from IPF, but in the subgroup of fNSIP patients both clinical profile and BAL cellularity seem indistinguishable from IPF. Whether specific combinations of clinical-radiologic and BAL features may identify specific subgroups of NSIP patients with a predominantly inflammatory cellular pattern and better prognosis remain an open issue that needs further evaluation.

The accuracy of transbronchial lung biopsy in the diagnosis of NSIP has never been evaluated in controlled studies. However, looking at the data from our study designed to assess transbronchial biopsy (TBB) accuracy in UIP, we can conclude that the sensitivity for NSIP is very low (i.e., ranging between 16 and 33%)[80]; thus, TBB does not seem informative in the vast majority of NSIP cases. A novel biopsy method, bronchoscopic lung cryobiopsy, has been recently proposed in IIP diagnosis, and promising preliminary results show that NSIP pattern can be detected by this method.[42,81] Diagnostic accuracy of bronchoscopic lung cryobiopsy needs to be further evaluated in prospective controlled studies, and surgical lung biopsy remains the gold standard for a confident multidisciplinary diagnosis of NSIP.[3]

Radiographic Characteristics

The ATS project[13] provided a characterization of HRCT features from 61 idiopathic NSIP patients. The abnormalities involved the lower lungs in 92% of cases, with only 8% equally severe in both upper and lower lungs. In the axial dimension, they were diffuse in 58% or predominantly peripheral in 35%. Ground-glass opacities have been reported in the majority of idiopathic NSIP cases published thus far.[52,82–86] The most common features observed in the ATS project[13] were reticular pattern (87%), traction bronchiectasis (82%), and lobar volume loss (77%), while ground-glass attenuation was seen in 44%. Although useful to differentiate NSIP from IPF,[87] the subpleural sparing was present only in 21% of NSIP cases.[13] The HRCT features most predictive of NSIP are ground-glass opacities and subpleural sparing, with an OR of 1.04 for each 1% increase in the proportion of ground-glass attenuation.[83] In the differential diagnosis with HP and IPF, the relative absence of lobular areas of decreased attenuations and the lack of honeycombing are the other two most relevant findings.[87]

It is interesting to note that HRCT profile of NSIP is often mixed, with ground-glass opacities associated with consolidations and/or fibrotic features such as reticular distortion of secondary lobule architecture and traction bronchiectasis. The correlation between these complex radiographic patterns and clinical-pathologic features of NSIP remains unclear. Sumikawa et al[88,89] have studied radiologic–pathologic correlation in NSIP, but failed to identify a statistically significant correlation between HRCT pattern and histological subgroups. The typical HRCT features that we observe in NSIP-OP

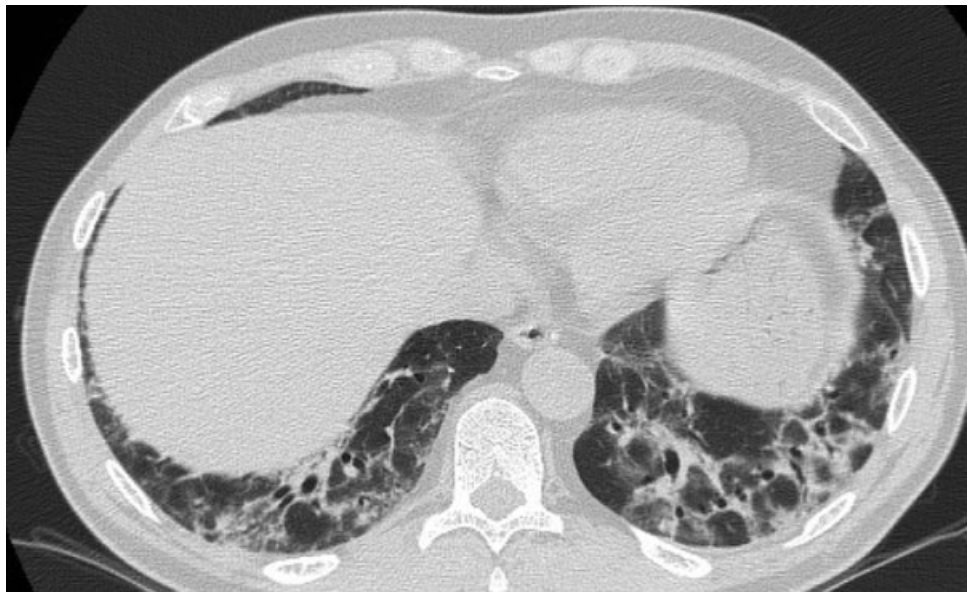

Fig. 2 Typical HRCT findings of a mixed case of NSIP-OP confirmed by lung cryobiopsy. In the posterobasal segments of both lower lobes, a moderate ground-glass attenuation is visible, with the typical perilobular distribution.

cases confirmed histologically by cryobiopsy (Venerino Poletti, MD, 2015, unpublished data) is shown in ►**Fig. 2**.

Given the implication for patient management and the divergent treatment approaches, the most difficult diagnostic challenge for radiologist is differentiating idiopathic NSIP from IPF. The differential HRCT characteristics of IPF/UIP and idiopathic NSIP have been recently evaluated by Sumikawa et al.[90] These authors found in cases with histologic diagnosis of idiopathic NSIP, compared with IPF/UIP, a higher prevalence of ground-glass attenuation without traction bronchiectasis ($p = 0.003$), subpleural sparing ($p = 0.007$), and peribronchovascular predominance ($p = 0.003$). However, honeycombing, intralobular opacity, and peripheral predominance were more prevalent in IPF/UIP. A total of 89% (35/39) of idiopathic NSIP cases were correctly classified as NSIP, but only 21% (16/75) IPF/UIP were correctly classified as definite UIP. The diagnostic accuracy of HRCT for UIP and NSIP has been reported to be ~70% in various studies.[39,83,87,91] Discordance between HRCT and histology findings occurs in approximately one-third of cases. The presence of bibasal subpleural honeycombing in the absence of other features has a sensitivity of 40% and a specificity of 95% in the diagnosis of UIP. In contrast, the predominant features of ground-glass opacities have a sensitivity of 95% but a specificity of 40% for the diagnosis of NSIP.[91] The presence of emphysema makes the distinction between UIP and NSIP even more difficult.[92] Thus, in the absence of typical radiologic features of UIP (i.e., predominant honeycombing with bibasal subpleural distribution), lung biopsy should be performed to discriminate UIP from NSIP.

Similar to pathologic and clinical evaluation, the interpretation of HRCT suffers from a significant interobserver variability. The kappa statistic for agreement for NSIP has been reported to be from moderate (0.51), in older studies,[93] to very good (0.95), in more recent studies,[86] probably reflecting the current better understanding of HRCT features of NSIP.

HRCT findings in NSIP have significant prognostic implications. Hozumi et al[94] showed that the extent of areas with ground-glass attenuation without traction bronchiectasis and areas of air-space consolidations are associated with a favorable outcome, whereas reticular opacities carry a worse prognosis (►**Figs. 3** and **4**). Subpleural sparing predicts a better outcome (mortality hazard ratio [HR], 0.25; 95% CI, 0.06–1.06).[90] Coarseness of fibrosis is significantly associated with worse prognosis (HR, 1.48; 95% CI, 1.1–1.99).[95] Various studies have evaluated follow-up HRCT, showing a variable evolution of the HRCT features over time with improvement in the extent of ground-glass opacities and consolidations in the majority of cases, and fibrotic progression, with or without recurrence, in approximately one-third of patients.[82,95–98] In a small minority (<5%), the evolution to UIP has been reported.[97]

Pathologic Findings

The two key findings used by Katzenstein and Fiorelli[5] to describe NSIP histologic features were homogeneity (spatial and temporal) of the lesions and absence of typical aspects observed in other interstitial pneumonias (►**Fig. 5A**). At higher power, an expansion of the interstitium and a variable extent of chronic inflammation and fibrosis are evident. The inflammatory cell infiltrate comprises mainly small lymphocytes with a variable quantity of plasma cells and macrophages; the fibrosis can be collagenous or fibroblastic in nature, or even both. A cuboidal hyperplasia/metaplasia of alveolar epithelium is also evident (►**Fig. 5B**). The other main feature in the diagnosis of fibrotic NSIP is the lack or scarcity

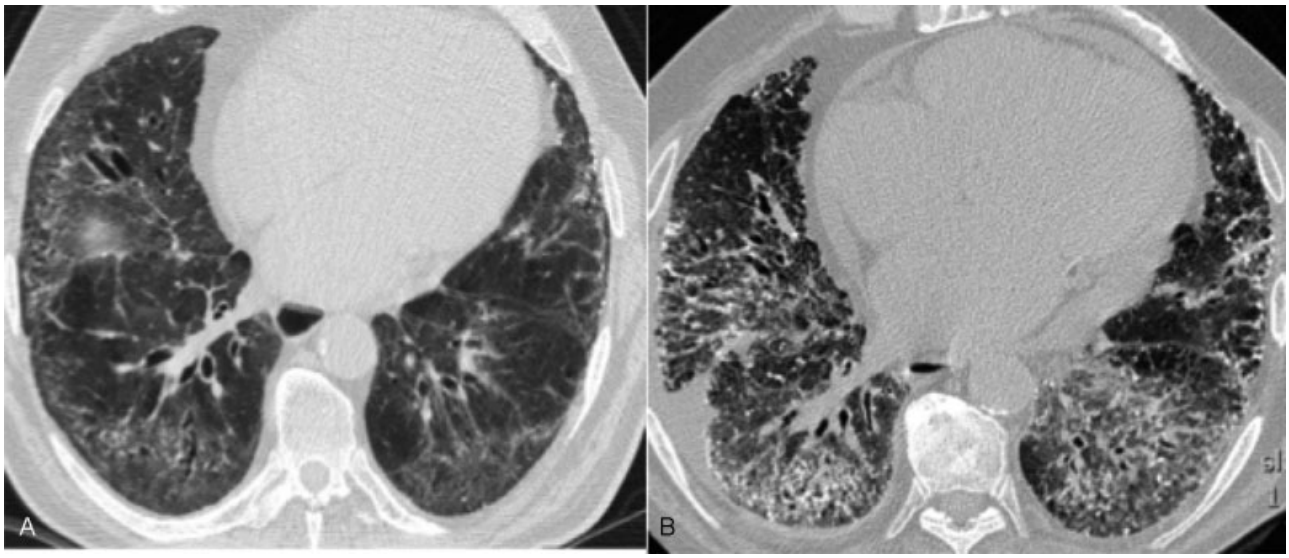

Fig. 3 Evolution of a case of fibrotic NSIP related to scleroderma, confirmed by surgical lung biopsy. (**A**) Baseline HRCT. Mild peripheral reticulation, with traction bronchiectasis and subpleural sparing, is present. (**B**) Follow-up HRCT, after 4 years. Severe thickening of interlobular septa with associated multiple dendriform calcification in middle lobe, lingula, and both lower lobes. Multiple traction bronchiectasis and a relative subpleural sparing are visible as well. A moderate pericardial effusion associated with pleural bilateral is evident. Significant esophageal dilation is present in both exams.

of any of the following features: fibroblastic foci, intra-alveolar buds of granulation tissue, intra-alveolar accumulation of pigmented macrophages, granulomas, and honeycombing. Depending on the proportion between inflammation and fibrosis, three different groups were initially described: group I primarily with interstitial inflammation, group II with both inflammation and fibrosis, and group III with a predominance of fibrosis. Subsequent studies[99] kept separate the cellular NSIP (►**Fig. 6A**), previous group I, from the fibrotic NSIP (►**Fig. 6B**), the latter derived from the unification of previous group II and III. Histologic features of NSIP are proposed by the 2008 ATS project.[13]

Immunohistochemistry using specific monoclonal antibodies may be useful (e.g., against cathepsin K to identify small and not well-formed granulomas[100]; against truncated p63, gamma laminin, or 27 heat shock protein to identify

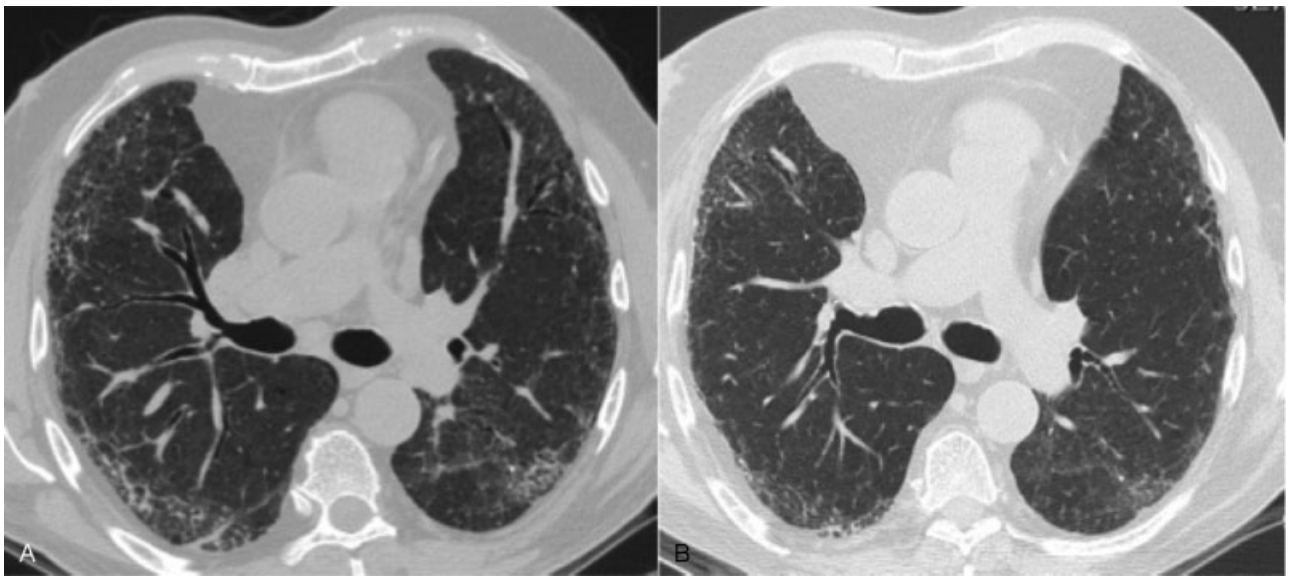

Fig. 4 Evolution of a case idiopathic fibrotic NSIP, confirmed by lung cryobiopsy. (**A**) Baseline HRCT. Mild peripheral ground-glass attenuation is present in both lungs, with lower lobes prevalence. Subpleural sparing and bilateral dendriform calcifications are present as well. (**B**) Follow-up HRCT, after 4 years. Moderate reduction of ground-glass attenuation. Reticulation and traction bronchiectasis are substantially stable.

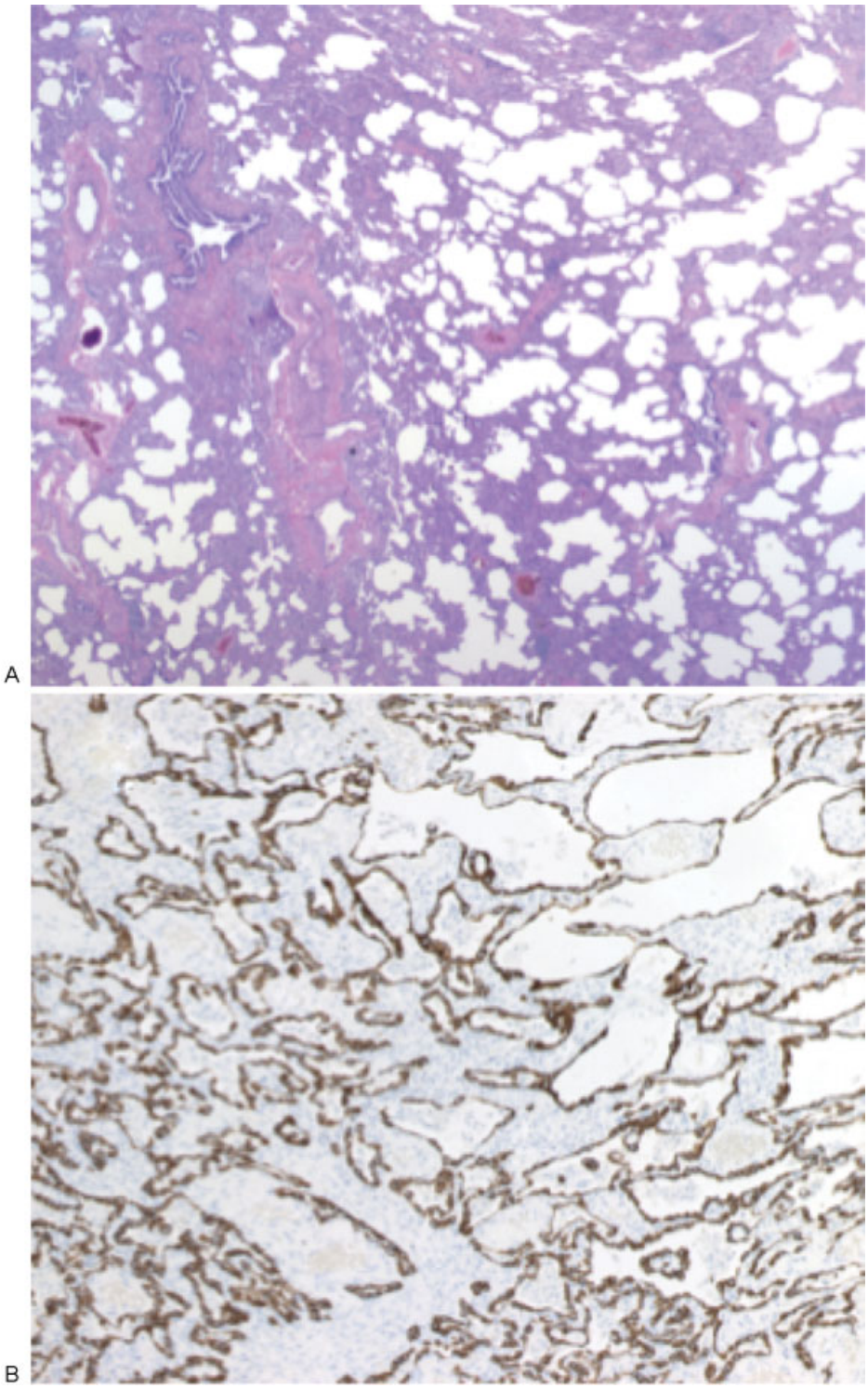

Fig. 5 Surgical lung biopsy of NSIP. (**A**) Hematoxylin and eosin (H&E) midpower magnification. A temporally homogeneous alveolar septal infiltrate is evident. (**B**) Cytokeratin B immunostaining. Uniform cuboidal metaplasia of the epithelium is evident.

fibroblastic foci[101]; against IgG4 to identify cases related to IgG4-related sclerosing disease[102]). Molecular biology is rarely necessary to identify a lymphoid neoplasm, viral-associated infections (i.e., HIV, human herpesvirus-8, Epstein–Barr virus), or *Pneumocystis jirovecii* cysts.[103]

Others have suggested that some additional "ancillary findings" may be suggestive of a nonidiopathic NSIP, such as: follicular bronchiolitis, lymphoid follicles, pleural plasmacytic infiltration in CTD[104]; a combination of different patterns (NSIP associated with patchy DAD or OP) in polymyositis/dermatomyositis; and NSIP changes distributed along bronchioles in GVHD-related pneumonitis.[105] Among 13 NSIP patients with clinically "lung-dominant CTD," Omote et al[56] reported 84% (11/13) of case presenting

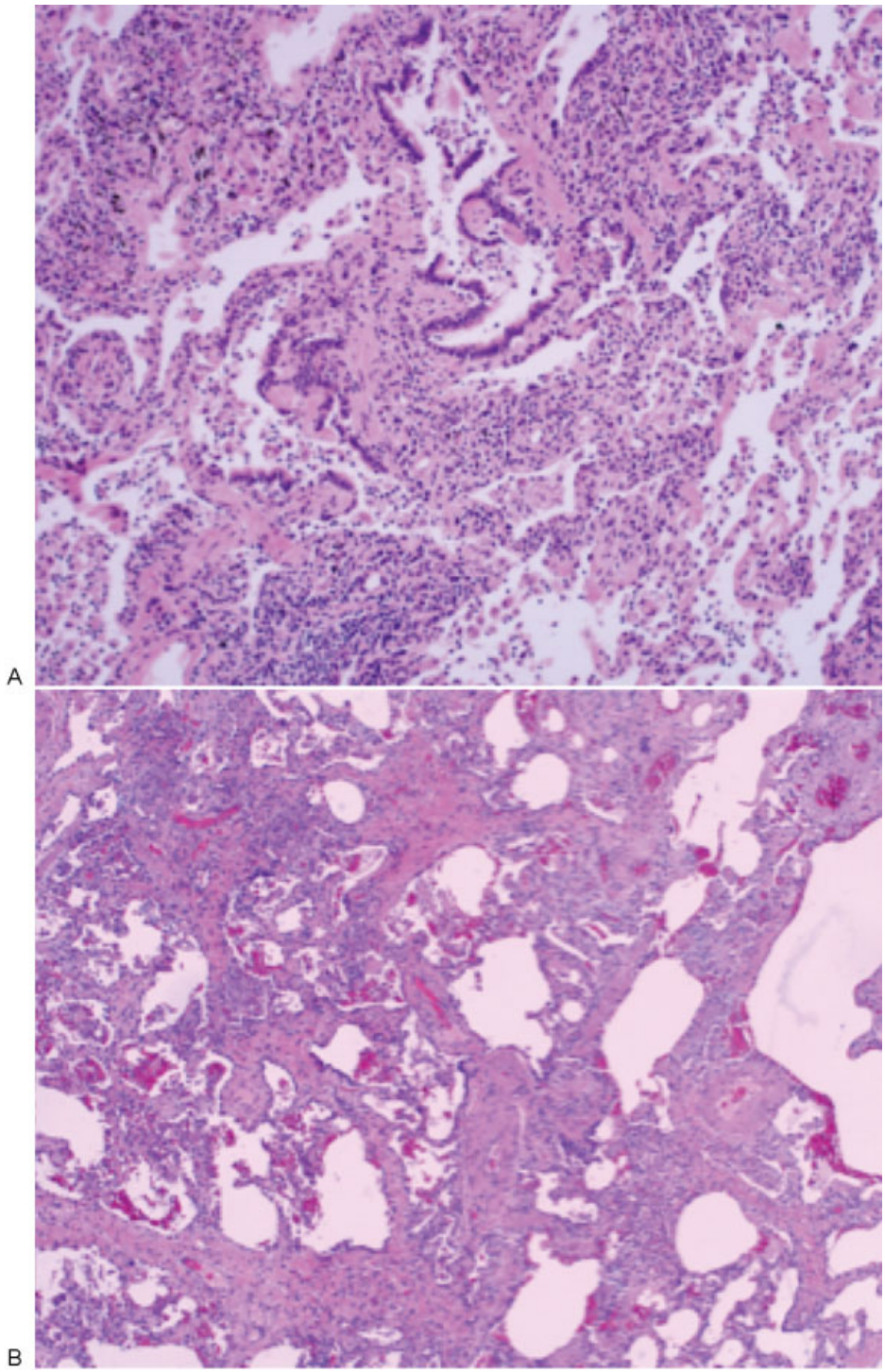

Fig. 6 Surgical lung biopsy of cellular and fibrotic NSIP. H&E midpower magnification. (**A**) Cellular nonspecific interstitial pneumonia: the alveolar septa are infiltrated by mononuclear cells, whereas fibrosis is scanty. (**B**) Fibrotic nonspecific interstitial pneumonia: the alveolar septa are thickened by the accumulation of collagen, the architecture is "preserved," and cellular infiltrate is mild.

histopathologic features characteristics for "lung-dominant CTD" (i.e., prominent plasmacytic infiltration and lymphoid aggregates with germinal centers).

Differential diagnosis between NSIP and other entity may be challenging, particularly with UIP, but also with other inflammatory ILD such as HP and lymphocytic interstitial pneumonia (LIP). The histologic classification of NSIP is further complicated by the fact that areas of NSIP and other IIP may overlap in the same patient. "Discordant cases" of UIP (i.e., UIP in one lobe and NSIP in the other lobe biopsied) have a prognosis similar to that of IPF with "concordant" histologic findings (i.e., UIP in all biopsied lobes); therefore, management approach is the same.[106]

A recent study aimed to characterize OP component in NSIP and found a prevalence of coexistent OP in 79% of NSIP cases (26/33), with no significant impact on prognosis.[76] Takeuchi et al[107] recently reported the association between pleuroparenchymal fibroelastosis and NSIP after hematopoietic stem cell transplantation, possible causes being reactions to drugs or radiation, or chronic GVHD. All these diagnostic challenges are reflected in the low level of agreement between pathologists in the diagnosis of NSIP, with a reported kappa statistic of only 0.32 (fair), in old studies,[108] increased to 0.73 (good), in more recent studies.[90]

Similar to radiology, pathologic features of NSIP have relevant prognostic implications. First, pathology is the sole method to discriminate between IPF/UIP and NSIP in cases presenting with NSIP HRCT features in a nonspecific clinical scenario, and this information carries a relevant prognostic impact.[90] Second, prognosis of cellular NSIP is better than fibrotic NSIP.[99,109] Recently, Kambouchner et al[110] showed the prognostic relevance of histologic variants of NSIP, defined as overlaps with other "minor" histological features and classified in seven subgroups: essential NSIP (36%), UIP overlap (26%), chronic HP (cHP) overlap (10%), OP overlap (6%), organizing DAD overlap (10%), desquamative interstitial pneumonia overlap (7%), and LIP overlap (2%). The overlaps with OP and HP were associated with the respective clinical diagnosis of CTD and HP ($p = 0.04$ and 0.02, respectively). Survival was different between subgroups ($p = 0.0002$), with organizing DAD overlap exhibiting the poorest survival at 5 years (32%), followed by UIP overlap (57%). Independent predictors of mortality were organizing DAD overlap (HR, 4.99; 95% CI, 2.15–11.58; $p = 0.0002$), UIP overlap (HR, 2.11; 95% CI, 1.12–3.99; $p = 0.02$), and a clinical diagnosis of cHP (HR, 2.17; 95% CI, 1.05–4.47; $p = 0.035$). It is interesting to note that in the context of UCTD, histology seems to carry relevant information, with survival for UCTD-UIP being shorter than that of the UCTD-NSIP group ($p = 0.021$), but significantly better than that of the IPF group ($p = 0.042$).[111]

Prognosis

Since initial studies, NSIP has consistently been described as a disease with a good prognosis. In 1994, Katzenstein and Fiorelli[5] reported a low mortality rate (11%) and no death in the subgroup of "pure inflammation and no fibrosis." The ATS report[112] published in 2008 noted 20% mortality at 5 years and 27% at 10 years.

Recent studies investigated the prognosis of idiopathic NSIP compared with NSIP related to autoimmune diseases. Two studies showed that UCTD-NSIP had a significantly better survival than idiopathic NSIP.[113,114] However, the prognostic significance of UCTD in IIPs (including NSIP) remains unclear because other recent studies of UCTD and CTD failed to prove a survival benefit.[53,115] This is mainly related to study biases and small number of subjects in these case series with differences in UCTD definitions.

At baseline, a mild impairment in lung function and several radiographic and pathologic features have been shown to correlate with a better prognosis, including ground-glass opacities without bronchiectasis, subpleural sparing, and a cellular histology type. During follow-up, HRCT may be informative showing a decrease in ground-glass opacities in cases that respond to treatment and worsening of the coarse fibrosis in nonresponders.

However, in clinical practice changes of lung function over time and clinical monitoring for lung and systemic symptoms are of great importance. Serial lung function measurements are crucial for the clinical follow-up of NSIP patients and have shown to be predictive of patients' outcome.[47] Latsi et al[116] showed that at 12 months, serial pulmonary function trends have considerable prognostic value in UIP and NSIP, with histology not giving any additional prognostic information when functional impairment is severe. Flaherty and Martinez[117] found that a 6-month change in FVC gave additional prognostic information to baseline values for patients with IIPs, including 29 patients with NSIP. A follow-up study of 48 idiopathic NSIP cases demonstrated that at the time of presentation the pathological pattern, age, and DLCO had important prognostic implications, but after 6 months of follow-up, changes in FVC, initial DLCO, and sex were the only independent prognostic factors.[85] Recently, the GAP model derived from IPF patients has been successfully applied to different subgroups of fibrotic ILD (ILD-GAP) in a study that included 45 idiopathic NSIP.[48]

The natural history of NSIP is extremely variable. Some patients improve, others remain stable or improve on treatment, while others evolve to end-stage fibrosis and may die of the disease.[13,52,95] Acute exacerbation, typically described in subjects with IPF, may also occur in idiopathic NSIP.[118] This heterogeneous profile makes it particularly difficult to classify idiopathic NSIP based on disease behavior. However, idiopathic NSIP is a clinical entity in which we can recognize different clinical, radiological, and histological subgroups. These subgroups show a different disease behavior and this is of great importance when it comes to choosing what the optimal approach to management would be. The vast majority of cellular NSIP and some fibrotic NSIP can be classified in the group of "reversible disease with a risk of progression"; some fibrotic NSIP can remain "stable with residual disease"; some fibrotic NSIP can "irreversibly progress" with or without "potential for stabilization."[3] The main features of idiopathic NSIP classified according to disease behavior, goal for treatment, and monitoring strategies are reported in ►**Table 1**.

Treatment and Other Aspects of Management

Treatment of NSIP has always been based on steroids and immunosuppressive agents, but for mild and stable cases it is sometimes possible to adopt a policy of careful observation without pharmacologic therapy.[119] There are no randomized controlled trials validating the current approach, but several retrospective studies have reported treatment with corticosteroids, immunosuppressive agents, and, recently, rituximab for severe treatment refractory disease. Treatment regimens and duration of treatment were variable in the published

Table 1 NSIP classification according to disease behavior

NSIP subtype	Clinical behavior	Treatment goal	Monitoring strategy
Cellular NSIP and some fibrotic NSIP	Reversible disease with risk of progression	Initially achieve response and then formulate longer-term therapy	Short-term observation to confirm treatment response. Long-term observation to ensure that gains are preserved
Fibrotic NSIP	Stable with residual disease	Maintain status	Long-term observation to assess disease course
	Progressive, irreversible disease with potential for stabilization	Stabilize	Long-term observation to assess disease course
	Progressive, irreversible disease despite therapy	Slow progression	Long-term observation to assess disease course and need for transplant or effective palliation

Source: Adapted from Travis et al.[13]

studies. Adverse events can be substantial, even for the use of only steroids,[120] and careful assessment of risks and benefits needs to be discussed prior and during the treatment.

The assessment of response is not standardized, but broadly accepted to monitor symptoms and pulmonary function tests (FVC, DLCO, and 6-minute walking test). HRCT is useful in selected cases, particularly in the assessment of treatment response or pulmonary complications. Cases in which an HRCT improvement after treatment is more likely are cases with extensive ground-glass opacities, subpleural sparing, and NSIP/OP radiologic pattern. Initial follow-up is usually at 3 months, particularly for severe and progressive cases, and subsequent follow-up is 6 months to 1 year depending on disease severity and treatment response. HRCT is not always required, with the decision on whether to perform HRCT being made on a case-by-case basis.

The treatment approach employing steroids and immunosuppressive agents seems more successful in the subgroup of NSIP presenting with an inflammatory background (i.e., NSIP-OP cases, NSIP with prominent lymphocytic infiltration). For the majority of NSIP presenting with an "inflammatory background" or with an "autoimmune flavor," the "inflammatory/immune-dysregulation" model is broadly appropriate for treatment purpose. However, given the overlapping disease mechanisms, this approach is overly simplistic and it is likely that selected fNSIP patients with progressive fibrosis resistant to immunomodulation (i.e., group "progressive, irreversible disease despite therapy" as shown in ►**Table 1**) may benefit from antifibrotic treatments used in IPF.[119] For fNSIP without autoimmune features, and particularly for patients with a family history of fibrotic progressive ILD or NSIP with emphysema, it is yet to be established whether the current approach is the most appropriate. For relentlessly progressive cases, it would be crucial to know whether an antifibrotic treatment may be of any benefit. With recent treatment advances in IPF, it appears necessary to reappraise the way in which clinicians should formulate treatment strategies in non-IPF IIPs.[119] However, until this is explored by controlled trials, the accurate deployment of currently available treatment depends on the confirmation or exclusion of IPF.[119] Lung transplantation is currently the only available option for some selected patients with progressive idiopathic NSIP. Rehabilitation and oxygen therapy are other important interventions.[119]

Systemic Corticosteroids

The optimal dose and duration of corticosteroid treatment is not known.[1] Pulse intravenous methylprednisolone is used for patients with severe disease (1 g/day for 3 days, followed by oral prednisone once daily 1 mg/kg ideal body weight, gradually tapered).[120,121] Patients responding or stabilizing with steroid treatment only are tapered, and then, generally after 1 year, treatment is discontinued.[1] For patients with progressive or relapsing disease or with corticosteroids intolerance, cytotoxic agents are initiated.

Lee at al[122] have recently reported the use of corticosteroid in 35 NSIP patients. All received corticosteroid alone as initial treatment, dose ranging between 0.4 and 1.1 mg/kg/day (only in two cases the dose exceeded 1.5 mg/kg/day), slowly tapered after 4 to 6 weeks. These authors observed a steroid response in 86% of cases (30/35), and no relapse in 51% (18/35). Among 30 steroid responders, 6 (20%) required long-term steroid use due to "disease worsening" when steroids were reduced. Maintenance dose in this subgroup was 5 mg in five patients and 15 mg in one patient. Cytotoxic agents were added in seven patients (four cyclophosphamide [CYC] and three azathioprine [AZA]) who showed disease progression or steroid dependency. Interestingly, there was a significant correlation between the initial dose of steroid used and the risk of relapse (i.e., median initial dose of prednisolone 0.6 and 0.5 mg/kg/day in the group without and with relapse, respectively; $p = 0.02$). Although not statistically significant, also the total treatment duration was longer in the group without relapse (i.e., median duration of 7.7 and 4.7 months in the group without and with relapse, respectively; $p = 0.18$).

Immunosuppressive Agents

Retrospective studies, limited by small number of patients, have reported the use of CYC and, recently, rituximab in refractory cases of NSIP.[7,120,121,123–126] The use of AZA,

cyclosporine, and, recently, mycophenolate mofetil has been reported anecdotally and borrowed from experience in CTD-ILD.[2,127] Immunosuppressive agents are used in refractory or relapsing NSIP or in cases of intolerance to corticosteroids.

Kondoh et al[123] reported the use of combined CYC and low-dose prednisone in 12 cases of biopsy-proven fibrotic NSIP. Patients were initially treated with intermittent pulse dose of methylprednisolone for 4 weeks (i.e., 1,000 mg/day for 3 days at 1-week intervals), followed by CYC (1–2 mg/kg/day) and low-dose prednisone (20 mg on alternate days). A total of 33% (4/12) of patients improved and the remaining 67% were stable. No adverse events were reported during high-dose corticosteroid, whereas 21% of patients had CYC-related adverse events (i.e., one hemorrhagic cystitis, two leukopenia, one myelodysplastic syndrome, two herpes zoster, one alopecia, and one aspergilloma).

Corte et al[124] reported that in the empirical treatment of advanced, rapidly progressive known or suspected NSIP, intravenous CYC is well tolerated as a rapidly acting immunosuppressant and was associated with improvement or stability in most cases. NSIP was suspected in 47 cases and confirmed by biopsy only in 7 patients; scleroderma was excluded. Intravenous CYC was given at 600 mg/m^2, diluted in 100 mL normal saline solution, and given as a 30-minute infusion. Full blood count, renal function tests, hepatic function tests, and urinalysis were performed before each CYC dose. Mesna was given to prevent urothelial toxicity when individual doses exceeded 1 g ($n = 44$). Treatment was well tolerated, with 70% having no adverse events. Adverse event were infection in six cases, alopecia and elevated liver enzymes in one (both resolved following cessation of therapy), and transient hematuria in one (resolved spontaneously). In the 6 months prior to treatment, 94% patients had declined (decline in symptoms [World Health Organization functional class], $n = 46$; imaging data, $n = 12$; pulmonary function, $n = 17$). During treatment, there was stability in 25 (46%), improvement in 22 (41%), and progression in 6 patients (11%). Four patients died within 12 months of treatment from progressive disease ($n = 3$) and acute coronary syndrome ($n = 1$). Interestingly, patients with HRCT features of NSIP/OP (i.e., radiological evidence of NSIP with consolidation overlap) had a greater improvement in DLCO at 6 months compared with patients without consolidation on HRCT scan ($p = 0.005$).

Keir et al[128] reported the use of rituximab in 50 patients with non-IPF (CTD-ILD, $n = 33$; HP, $n = 6$; miscellaneous IIP, $n = 11$) severe ILD (median FVC 44%, range 24–99%, and median DLCO 24.5%, range 11–64%), progressing despite conventional immunosuppression. The study showed a median improvement in FVC of 6.7% ($p < 0.01$) and stability in DLCO (0% change, $p < 0.001$). In total, 2 patients developed severe pneumonia and 10 patients died of disease progression, a median of 5 months after treatment. Idiopathic NSIP was not included in this study and further studies are needed to address a possible role for rituximab in idiopathic NSIP.

Treatment of Pulmonary Hypertension Associated with Fibrotic NSIP

Corte et al[129] have recently investigated in a randomized, double-blind, placebo-controlled study the efficacy and safety of endothelin-1 receptor antagonist (bosentan) in a group of 60 fibrotic IIP; among them 14 were NSIP. The primary study end point was a fall from baseline pulmonary vascular resistance index (PVRi) of 20% or more over 16 weeks. Paired right heart catheter data were available in 25 bosentan and 14 placebo cases. No difference was detected between treatment and placebo arms, neither in term of primary end point (PVRi change), functional capacity, and symptoms, nor in adverse events. In addition, 26.7% of patients in the IPF group reached the primary PVRi end point versus 33.3% in the NSIP group ($p = 0.69$). The results of the current study imply that patients with IIP and pulmonary hypertension do not benefit from treatment with bosentan and that an "off-label therapeutic trial" is not warranted.

Conclusion

Idiopathic NSIP is a complex clinical entity with a disease spectrum that includes different phenotypes. Clinically, we can recognize three different phenotypes: NSIP associated with IPAF, emphysema, and familial ILD. Based on current data, we can speculate that the majority of NSIP patients will be reclassified as IPAF according to recent guidelines,[59] whereas NSIP associated with emphysema and familial forms will represent a minority of idiopathic cases. Whether this clinical distinction carries prognostic and therapeutic significance remains to be elucidated.

Radiologic–pathologic correlations have shown that we have two major different profiles: (1) the "inflammatory type" characterized by prominent lymphocytic inflammation both on biopsy and BAL, and HRCT with mixed NSIP/OP pattern that tends to have a better treatment response, and (2) a "highly fibrotic" subgroup that shows prominent reticular changes and traction bronchiectasis by HRCT, high fibrotic background on biopsy, and no lymphocytosis on BAL. The latter fibrotic NSIP is the subgroup with less potential to respond to immunosuppressive treatment and a marginal risk to evolve in "full-blown IPF."[2] The management of patients with fibrotic, progressive, and immunosuppressive treatment refractory NSIP remains uncertain and further studies are needed to address the role of antifibrotic drug in this settings.

Funding
This work was supported by the AMMP (Associazione Morgagni Malattie Polmonari), Forlì, Italy.

Conflicts of Interest
S. T. and V. P. have received steering committee consultancy fees from InterMune and speaker's fees from Boehringer Ingelheim, InterMune, and Chiesi, but they have nothing to disclose in relation to this publication. J. H. R., S. P., and M. C. have nothing to disclose.

References

1 Martinez FJ, Flaherty KR. Nonspecific interstitial pneumonia. In: Schwartz MI, King TE, eds. Interstitial Lung Diseases. 5th ed. Shelton, CT: People's Medical Publishing House-USA; 2010: 945–959

2 Poletti V, Romagnoli M, Piciucchi S, Chilosi M. Current status of idiopathic nonspecific interstitial pneumonia. Semin Respir Crit Care Med 2012;33(5):440–449

3 Travis WD, Costabel U, Hansell DM, et al; ATS/ERS Committee on Idiopathic Interstitial Pneumonias. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med 2013; 188(6):733–748

4 Suffredini AF, Ognibene FP, Lack EE, et al. Nonspecific interstitial pneumonitis: a common cause of pulmonary disease in the acquired immunodeficiency syndrome. Ann Intern Med 1987; 107(1):7–13

5 Katzenstein AL, Fiorelli RF. Nonspecific interstitial pneumonia/ fibrosis. Histologic features and clinical significance. Am J Surg Pathol 1994;18(2):136–147

6 Liebow AA, Carrington CB. The interstitial pneumonias. In: Simon M, Potchen EJ, LeMay M, eds. Frontiers of Pulmonary Radiology: Pathophysiologic, Roentgenographic and Radioisotopic Considerations. New York, NY: Grune Stratton; 1969:102–141

7 Cottin V, Donsbeck AV, Revel D, Loire R, Cordier JF. Nonspecific interstitial pneumonia. Individualization of a clinicopathologic entity in a series of 12 patients. Am J Respir Crit Care Med 1998; 158(4):1286–1293

8 Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 1998;157(1):199–203

9 Nagai S, Kitaichi M, Itoh H, Nishimura K, Izumi T, Colby TV. Idiopathic nonspecific interstitial pneumonia/fibrosis: comparison with idiopathic pulmonary fibrosis and BOOP. Eur Respir J 1998;12(5):1010–1019

10 Daniil ZD, Gilchrist FC, Nicholson AG, et al. A histologic pattern of nonspecific interstitial pneumonia is associated with a better prognosis than usual interstitial pneumonia in patients with cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 1999;160(3):899–905

11 Park JS, Lee KS, Kim JS, et al. Nonspecific interstitial pneumonia with fibrosis: radiographic and CT findings in seven patients. Radiology 1995;195(3):645–648

12 American Thoracic Society, European Respiratory Society. ATS/ ERS International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. Am J Respir Crit Care Med 2002;162:27

13 Travis WD, Hunninghake G, King TE Jr, et al. Idiopathic nonspecific interstitial pneumonia: report of an American Thoracic Society project. Am J Respir Crit Care Med 2008;177(12): 1338–1347

14 Hyldgaard C, Hilberg O, Muller A, Bendstrup E. A cohort study of interstitial lung diseases in central Denmark. Respir Med 2014; 108(5):793–799

15 Flaherty KR, Toews GB, Travis WD, et al. Clinical significance of histological classification of idiopathic interstitial pneumonia. Eur Respir J 2002;19(2):275–283

16 Rosas IO, Ren P, Avila NA, et al. Early interstitial lung disease in familial pulmonary fibrosis. Am J Respir Crit Care Med 2007; 176(7):698–705

17 Selman M, Pardo A, Barrera L, et al. Gene expression profiles distinguish idiopathic pulmonary fibrosis from hypersensitivity pneumonitis. Am J Respir Crit Care Med 2006;173(2): 188–198

18 Steele MP, Speer MC, Loyd JE, et al. Clinical and pathologic features of familial interstitial pneumonia. Am J Respir Crit Care Med 2005;172(9):1146–1152

19 Kumar A, Dougherty M, Findlay GM, et al. Genome sequencing of idiopathic pulmonary fibrosis in conjunction with a medical school human anatomy course. PLoS ONE 2014;9(9):e106744

20 Ravaglia C, Tomassetti S, Gurioli C, et al. Features and outcome of familial idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis 2014;31(1):28–36

21 Leslie KO, Cool CD, Sporn TA, et al. Familial idiopathic interstitial pneumonia: histopathology and survival in 30 patients. Arch Pathol Lab Med 2012;136(11):1366–1376

22 du Bois R, King TE Jr. Challenges in pulmonary fibrosis x 5: the NSIP/UIP debate. Thorax 2007;62(11):1008–1012

23 Schneider F, Hwang DM, Gibson K, Yousem SA. Nonspecific interstitial pneumonia: a study of 6 patients with progressive disease. Am J Surg Pathol 2012;36(1):89–93

24 Chilosi M, Carloni A, Rossi A, Poletti V. Premature lung aging and cellular senescence in the pathogenesis of idiopathic pulmonary fibrosis and COPD/emphysema. Transl Res 2013;162(3):156–173

25 Chilosi M, Doglioni C, Murer B, Poletti V. Epithelial stem cell exhaustion in the pathogenesis of idiopathic pulmonary fibrosis. Sarcoidosis Vasc Diffuse Lung Dis 2010;27(1):7–18

26 Königshoff M, Dumitrascu R, Udalov S, et al. Increased expression of 5-hydroxytryptamine2A/B receptors in idiopathic pulmonary fibrosis: a rationale for therapeutic intervention. Thorax 2010; 65(11):949–955

27 Casoni GL, Ulivi P, Mercatali L, et al. Increased levels of free circulating DNA in patients with idiopathic pulmonary fibrosis. Int J Biol Markers 2010;25(4):229–235

28 Jinta T, Miyazaki Y, Kishi M, et al. The pathogenesis of chronic hypersensitivity pneumonitis in common with idiopathic pulmonary fibrosis: expression of apoptotic markers. Am J Clin Pathol 2010;134(4):613–620

29 Watanabe K, Handa T, Tanizawa K, et al. Detection of antisynthetase syndrome in patients with idiopathic interstitial pneumonias. Respir Med 2011;105(8):1238–1247

30 Romagnoli M, Nannini C, Piciucchi S, et al. Idiopathic nonspecific interstitial pneumonia: an interstitial lung disease associated with autoimmune disorders? Eur Respir J 2011;38(2):384–391

31 Okamoto M, Hoshino T, Kitasato Y, et al. Periostin, a matrix protein, is a novel biomarker for idiopathic interstitial pneumonias. Eur Respir J 2011;37(5):1119–1127

32 Miki H, Mio T, Nagai S, et al. Fibroblast contractility: usual interstitial pneumonia and nonspecific interstitial pneumonia. Am J Respir Crit Care Med 2000;162(6):2259–2264

33 Ohara I, Aida S, Shimazaki H, et al. Proteomic analysis in usual and nonspecific interstitial pneumonia. Histol Histopathol 2014; 29(3):377–386

34 Korfei M, von der Beck D, Henneke I, et al. Comparative proteome analysis of lung tissue from patients with idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP) and organ donors. J Proteomics 2013;85:109–128

35 Takahashi M, Kunugi S, Terasaki Y, et al. The difference of neovascularization in early intra-alveolar fibrosis between nonspecific interstitial pneumonia and usual interstitial pneumonia. Pathol Int 2013;63(5):237–244

36 Bargagli E, Madioni C, Bianchi N, Refini RM, Cappelli R, Rottoli P. Serum analysis of coagulation factors in IPF and NSIP. Inflammation 2014;37(1):10–16

37 Baroni SS, Santillo M, Bevilacqua F, et al. Stimulatory autoantibodies to the PDGF receptor in systemic sclerosis. N Engl J Med 2006;354(25):2667–2676

38 Raghu G, Collard HR, Egan JJ, et al; ATS/ERS/JRS/ALAT Committee on Idiopathic Pulmonary Fibrosis. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. Am J Respir Crit Care Med 2011;183(6):788–824

39 Sverzellati N, Wells AU, Tomassetti S, et al. Biopsy-proved idiopathic pulmonary fibrosis: spectrum of nondiagnostic thin-section CT diagnoses. Radiology 2010;254(3):957–964

40 Flaherty KR, King TE Jr, Raghu G, et al. Idiopathic interstitial pneumonia: what is the effect of a multidisciplinary approach to diagnosis? Am J Respir Crit Care Med 2004;170(8):904–910
41 Tomassetti S, Piciucchi S, Tantalocco P, Dubini A, Poletti V. The multidisciplinary approach in the diagnosis of idiopathic pulmonary fibrosis: a patient case-based review. Eur Respir Rev 2015; 24(135):69–77
42 Tomassetti S, Wells AU, Costabel U, et al. The diagnostic role of cryobiopsy in the multidisciplinary diagnosis of idiopathic pulmonary fibrosis. Paper presented at: European Respiratory Society Annual Meeting; 2013; Barcelona, Spain
43 Tomassetti S, Albera C, Aronne D, et al. Documento AIPO-SIMeR sulla Fibrosi Polmonare Idiopatica. Rass Patol Appar Respir 2015; 30:29
44 Fischer A, du Bois R. Interstitial lung disease in connective tissue disorders. Lancet 2012;380(9842):689–698
45 Cottin V. Interstitial lung disease. Eur Respir Rev 2013;22(127): 26–32
46 Fischer A, Richeldi L. Cross-disciplinary collaboration in connective tissue disease-related lung disease. Semin Respir Crit Care Med 2014;35(2):159–165
47 Tomassetti S, Ryu JH, Poletti V. Staging systems and disease severity assessment in interstitial lung diseases. Curr Opin Pulm Med 2015;21(5):463–469
48 Ryerson CJ, Vittinghoff E, Ley B, et al. Predicting survival across chronic interstitial lung disease: the ILD-GAP model. Chest 2014; 145(4):723–728
49 de Lauretis A, Veeraraghavan S, Renzoni E. Review series: Aspects of interstitial lung disease: connective tissue disease-associated interstitial lung disease: how does it differ from IPF? How should the clinical approach differ? Chron Respir Dis 2011;8(1):53–82
50 Sato T, Fujita J, Yamadori I, et al. Non-specific interstitial pneumonia; as the first clinical presentation of various collagen vascular disorders. Rheumatol Int 2006;26(6):551–555
51 Kinder BW, Collard HR, Koth L, et al. Idiopathic nonspecific interstitial pneumonia: lung manifestation of undifferentiated connective tissue disease? Am J Respir Crit Care Med 2007; 176(7):691–697
52 Park IN, Jegal Y, Kim DS, et al. Clinical course and lung function change of idiopathic nonspecific interstitial pneumonia. Eur Respir J 2009;33(1):68–76
53 Corte TJ, Copley SJ, Desai SR, et al. Significance of connective tissue disease features in idiopathic interstitial pneumonia. Eur Respir J 2012;39(3):661–668
54 Mosca M, Neri R, Bombardieri S. Undifferentiated connective tissue diseases (UCTD): a review of the literature and a proposal for preliminary classification criteria. Clin Exp Rheumatol 1999; 17(5):615–620
55 Fischer A, West SG, Swigris JJ, Brown KK, du Bois RM. Connective tissue disease-associated interstitial lung disease: a call for clarification. Chest 2010;138(2):251–256
56 Omote N, Taniguchi H, Kondoh Y, et al. Lung-dominant connective tissue disease: clinical, radiologic, and histologic features. Chest 2015;148(6):1438–1446
57 Vij R, Noth I, Strek ME. Autoimmune-featured interstitial lung disease: a distinct entity. Chest 2011;140(5):1292–1299
58 Cottin V. Idiopathic interstitial pneumonias with connective tissue diseases features: a review. Respirology 2016;21(2): 245–258
59 Fischer A, Antoniou KM, Brown KK, et al; "ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD". An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J 2015;46(4):976–987
60 Cottin V, Nunes H, Brillet PY, et al; Groupe d'Etude et de Recherche sur les Maladies Orphelines Pulmonaires (GERM O P). Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J 2005;26(4):586–593
61 Chilosi M, Poletti V, Rossi A. The pathogenesis of COPD and IPF: distinct horns of the same devil? Respir Res 2012;13:3
62 Vancheri C, Failla M, Crimi N, Raghu G. Idiopathic pulmonary fibrosis: a disease with similarities and links to cancer biology. Eur Respir J 2010;35(3):496–504
63 Tomassetti S, Gurioli C, Ryu JH, et al. The impact of lung cancer on survival of idiopathic pulmonary fibrosis. Chest 2015;147(1): 157–164
64 Samara KD, Margaritopoulos G, Wells AU, Siafakas NM, Antoniou KM. Smoking and pulmonary fibrosis: novel insights. Pulm Med 2011;2011:461439
65 Marten K, Milne D, Antoniou KM, et al. Non-specific interstitial pneumonia in cigarette smokers: a CT study. Eur Radiol 2009; 19(7):1679–1685
66 Yoneshige A, Hagiyama M, Inoue T, et al. Increased ectodomain shedding of cell adhesion molecule 1 as a cause of type II alveolar epithelial cell apoptosis in patients with idiopathic interstitial pneumonia. Respir Res 2015;16:90
67 Shinohara T, Kadota N, Hino H, Naruse K, Ohtsuki Y, Ogushi F. Improvement in idiopathic nonspecific interstitial pneumonia after smoking cessation. Respir Med Case Rep 2015;14:7–9
68 Sugino K, Ota H, Fukasawa Y, Uekusa T, Homma S. Pathological characteristics in idiopathic nonspecific interstitial pneumonia with emphysema and pulmonary hypertension. Respirol Case Rep 2013;1(2):39–42
69 Hallowell RW, Reed RM, Fraig M, Horton MR, Girgis RE. Severe pulmonary hypertension in idiopathic nonspecific interstitial pneumonia. Pulm Circ 2012;2(1):101–106
70 Talbert JL, Schwartz DA, Steele MP. Familial interstitial pneumonia (FIP). Clin Pulm Med 2014;21(3):120–127
71 Armanios M. Telomeres and age-related disease: how telomere biology informs clinical paradigms. J Clin Invest 2013;123(3): 996–1002
72 Silhan LL, Shah PD, Chambers DC, et al. Lung transplantation in telomerase mutation carriers with pulmonary fibrosis. Eur Respir J 2014;44(1):178–187
73 Lee HY, Seo JB, Steele MP, et al. High-resolution CT scan findings in familial interstitial pneumonia do not conform to those of idiopathic interstitial pneumonia. Chest 2012;142(6):1577–1583
74 Furuhashi K, Enomoto N, Fujisawa T, et al. Hermansky-Pudlak syndrome with nonspecific interstitial pneumonia. Intern Med 2014;53(5):449–453
75 Meyer KC, Raghu G, Baughman RP, et al; American Thoracic Society Committee on BAL in Interstitial Lung Disease. An official American Thoracic Society clinical practice guideline: the clinical utility of bronchoalveolar lavage cellular analysis in interstitial lung disease. Am J Respir Crit Care Med 2012; 185(9):1004–1014
76 Huo Z, Li J, Li S, et al. Organizing pneumonia components in nonspecific interstitial pneumonia (NSIP): a clinicopathological study of 33 NSIP cases. Histopathology 2016;68(3):347–355
77 Ryu YJ, Chung MP, Han J, et al. Bronchoalveolar lavage in fibrotic idiopathic interstitial pneumonias. Respir Med 2007;101(3): 655–660
78 Ohshimo S, Bonella F, Cui A, et al. Significance of bronchoalveolar lavage for the diagnosis of idiopathic pulmonary fibrosis. Am J Respir Crit Care Med 2009;179(11):1043–1047
79 Veeraraghavan S, Latsi PI, Wells AU, et al. BAL findings in idiopathic nonspecific interstitial pneumonia and usual interstitial pneumonia. Eur Respir J 2003;22(2):239–244
80 Tomassetti S, Cavazza A, Colby TV, et al. Transbronchial biopsy is useful in predicting UIP pattern. Respir Res 2012;13:96
81 Casoni GL, Tomassetti S, Cavazza A, et al. Transbronchial lung cryobiopsy in the diagnosis of fibrotic interstitial lung diseases. PLoS ONE 2014;9(2):e86716

82 Akira M, Inoue G, Yamamoto S, Sakatani M. Non-specific interstitial pneumonia: findings on sequential CT scans of nine patients. Thorax 2000;55(10):854–859

83 MacDonald SL, Rubens MB, Hansell DM, et al. Nonspecific interstitial pneumonia and usual interstitial pneumonia: comparative appearances at and diagnostic accuracy of thin-section CT. Radiology 2001;221(3):600–605

84 Johkoh T, Müller NL, Colby TV, et al. Nonspecific interstitial pneumonia: correlation between thin-section CT findings and pathologic subgroups in 55 patients. Radiology 2002;225(1): 199–204

85 Jegal Y, Kim DS, Shim TS, et al. Physiology is a stronger predictor of survival than pathology in fibrotic interstitial pneumonia. Am J Respir Crit Care Med 2005;171(6):639–644

86 Silva CI, Müller NL, Hansell DM, Lee KS, Nicholson AG, Wells AU. Nonspecific interstitial pneumonia and idiopathic pulmonary fibrosis: changes in pattern and distribution of disease over time. Radiology 2008;247(1):251–259

87 Silva CI, Müller NL, Lynch DA, et al. Chronic hypersensitivity pneumonitis: differentiation from idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia by using thin-section CT. Radiology 2008;246(1):288–297

88 Sumikawa H, Johkoh T, Fujimoto K, et al. Usual interstitial pneumonia and nonspecific interstitial pneumonia: correlation between CT findings at the site of biopsy with pathological diagnoses. Eur J Radiol 2012;81(10):2919–2924

89 Sumikawa H, Johkoh T, Ichikado K, et al. Nonspecific interstitial pneumonia: histologic correlation with high-resolution CT in 29 patients. Eur J Radiol 2009;70(1):35–40

90 Sumikawa H, Johkoh T, Fujimoto K, et al. Pathologically proved nonspecific interstitial pneumonia: CT pattern analysis as compared with usual interstitial pneumonia CT pattern. Radiology 2014;272(2):549–556

91 Mink SN, Maycher B. Comparative manifestations and diagnostic accuracy of high-resolution computed tomography in usual interstitial pneumonia and nonspecific interstitial pneumonia. Curr Opin Pulm Med 2012;18(5):530–534

92 Akira M, Inoue Y, Kitaichi M, Yamamoto S, Arai T, Toyokawa K. Usual interstitial pneumonia and nonspecific interstitial pneumonia with and without concurrent emphysema: thin-section CT findings. Radiology 2009;251(1):271–279

93 Aziz ZA, Wells AU, Hansell DM, et al. HRCT diagnosis of diffuse parenchymal lung disease: inter-observer variation. Thorax 2004;59(6):506–511

94 Hozumi H, Nakamura Y, Johkoh T, et al. Nonspecific interstitial pneumonia: prognostic significance of high-resolution computed tomography in 59 patients. J Comput Assist Tomogr 2011;35(5): 583–589

95 Akira M, Inoue Y, Arai T, Okuma T, Kawata Y. Long-term follow-up high-resolution CT findings in non-specific interstitial pneumonia. Thorax 2011;66(1):61–65

96 Lee HY, Lee KS, Jeong YJ, et al. High-resolution CT findings in fibrotic idiopathic interstitial pneumonias with little honeycombing: serial changes and prognostic implications. AJR Am J Roentgenol 2012;199(5):982–989

97 Kim MY, Song JW, Do KH, Jang SJ, Colby TV, Kim DS. Idiopathic nonspecific interstitial pneumonia: changes in high-resolution computed tomography on long-term follow-up. J Comput Assist Tomogr 2012;36(2):170–174

98 Sakamoto K, Taniguchi H, Kondoh Y, et al. Serum KL-6 in fibrotic NSIP: correlations with physiologic and radiologic parameters. Respir Med 2010;104(1):127–133

99 Travis WD, Matsui K, Moss J, Ferrans VJ. Idiopathic nonspecific interstitial pneumonia: prognostic significance of cellular and fibrosing patterns: survival comparison with usual interstitial pneumonia and desquamative interstitial pneumonia. Am J Surg Pathol 2000;24(1):19–33

100 Reghellin D, Poletti V, Tomassett S, et al. Cathepsin-K is a sensitive immunohistochemical marker for detection of micro-granulomas in hypersensitivity pneumonitis. Sarcoidosis Vasc Diffuse Lung Dis 2010;27(1):57–63

101 Chilosi M, Zamò A, Doglioni C, et al. Migratory marker expression in fibroblast foci of idiopathic pulmonary fibrosis. Respir Res 2006;7:95

102 Shrestha B, Sekiguchi H, Colby TV, et al. Distinctive pulmonary histopathology with increased IgG4-positive plasma cells in patients with autoimmune pancreatitis: report of 6 and 12 cases with similar histopathology. Am J Surg Pathol 2009;33(10): 1450–1462

103 Colby TV, Carrington CB. Infiltrative lung diseases. In: Thrulbeck WM, ed. Pathology of the Lung. New York, NY: Thieme; 1988: 425–517

104 Tansey D, Wells AU, Colby TV, et al. Variations in histological patterns of interstitial pneumonia between connective tissue disorders and their relationship to prognosis. Histopathology 2004;44(6):585–596

105 Yousem SA. The histological spectrum of pulmonary graft-versus-host disease in bone marrow transplant recipients. Hum Pathol 1995;26(6):668–675

106 Monaghan H, Wells AU, Colby TV, du Bois RM, Hansell DM, Nicholson AG. Prognostic implications of histologic patterns in multiple surgical lung biopsies from patients with idiopathic interstitial pneumonias. Chest 2004;125(2):522–526

107 Takeuchi Y, Miyagawa-Hayashino A, Chen F, et al. Pleuroparenchymal fibroelastosis and non-specific interstitial pneumonia: frequent pulmonary sequelae of haematopoietic stem cell transplantation. Histopathology 2015;66(4): 536–544

108 Nicholson AG, Addis BJ, Bharucha H, et al. Inter-observer variation between pathologists in diffuse parenchymal lung disease. Thorax 2004;59(6):500–505

109 Nicholson AG, Colby TV, du Bois RM, Hansell DM, Wells AU. The prognostic significance of the histologic pattern of interstitial pneumonia in patients presenting with the clinical entity of cryptogenic fibrosing alveolitis. Am J Respir Crit Care Med 2000;162(6):2213–2217

110 Kambouchner M, Levy P, Nicholson AG, et al. Prognostic relevance of histological variants in nonspecific interstitial pneumonia. Histopathology 2014;65(4):549–560

111 Kim HC, Ji W, Kim MY, et al. Interstitial pneumonia related to undifferentiated connective tissue disease: pathologic pattern and prognosis. Chest 2015;147(1):165–172

112 Katzenstein AL, Zisman DA, Litzky LA, Nguyen BT, Kotloff RM. Usual interstitial pneumonia: histologic study of biopsy and explant specimens. Am J Surg Pathol 2002;26(12):1567–1577. Available at: Katzestein_AJSP2002_pathology explanted lung IPF.pdf

113 Suda T, Kono M, Nakamura Y, et al. Distinct prognosis of idiopathic nonspecific interstitial pneumonia (NSIP) fulfilling criteria for undifferentiated connective tissue disease (UCTD). Respir Med 2010;104(10):1527–1534

114 Nunes H, Schubel K, Piver D, et al. Nonspecific interstitial pneumonia: survival is influenced by the underlying cause. Eur Respir J 2015;45(3):746–755

115 Kondoh Y, Johkoh T, Fukuoka J, et al. Broader criteria of undifferentiated connective tissue disease in idiopathic interstitial pneumonias. Respir Med 2015;109(3):389–396

116 Latsi PI, du Bois RM, Nicholson AG, et al. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. Am J Respir Crit Care Med 2003;168(5):531–537

117 Flaherty KR, Martinez FJ. Nonspecific interstitial pneumonia. Semin Respir Crit Care Med 2006;27(6):652–658

118 Park IN, Kim DS, Shim TS, et al. Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. Chest 2007;132(1):214–220

119 Wells AU, Kokosi M, Karagiannis K. Treatment strategies for idiopathic interstitial pneumonias. Curr Opin Pulm Med 2014; 20(5):442–448
120 Flaherty KR, Toews GB, Lynch JP III, et al. Steroids in idiopathic pulmonary fibrosis: a prospective assessment of adverse reactions, response to therapy, and survival. Am J Med 2001;110(4):278–282
121 Nanki N, Fujita J, Yamaji Y, et al. Nonspecific interstitial pneumonia/fibrosis completely recovered by adding cyclophosphamide to corticosteroids. Intern Med 2002;41(10):867–870
122 Lee JH, Chie EK, Kim K, et al. The influence of the treatment response on the impact of resection margin status after preoperative chemoradiotherapy in locally advanced rectal cancer. BMC Cancer 2013;13:576
123 Kondoh Y, Taniguchi H, Yokoi T, et al. Cyclophosphamide and low-dose prednisolone in idiopathic pulmonary fibrosis and fibrosing nonspecific interstitial pneumonia. Eur Respir J 2005;25(3):528–533
124 Corte TJ, Ellis R, Renzoni EA, et al. Use of intravenous cyclophosphamide in known or suspected, advanced non-specific interstitial pneumonia. Sarcoidosis Vasc Diffuse Lung Dis 2009;26(2): 132–138
125 Keir GJ, Maher TM, Hansell DM, et al. Severe interstitial lung disease in connective tissue disease: rituximab as rescue therapy. Eur Respir J 2012;40(3):641–648
126 Lee JY, Jin SM, Lee BJ, et al. Treatment response and long term follow-up results of nonspecific interstitial pneumonia. J Korean Med Sci 2012;27(6):661–667
127 Wells AU, Denton CP. Interstitial lung disease in connective tissue disease—mechanisms and management. Nat Rev Rheumatol 2014;10(12):728–739
128 Keir GJ, Maher TM, Ming D, et al. Rituximab in severe, treatment-refractory interstitial lung disease. Respirology 2014;19(3): 353–359
129 Corte TJ, Keir GJ, Dimopoulos K, et al; BPHIT Study Group. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. Am J Respir Crit Care Med 2014;190(2):208–217