Kerpel-Fronius A.

National Korányi Institute for Pulmonology, Budapest, Hungary

Non-Specific interstitial pneumonia

Abstract
Non-specific interstitial pneumonia (NSIP) is a subtype of fibrosing interstitial lung disease.

In this article, we discuss clinical, histological and radiological /HRCT / presentation of the disease. NSIP is often associated with systemic disease, including collagen vascular diseases and proper diagnosis of both lung features, and the underlying cause must be identified for long-term patient care.
Keywords: NSIP, ILD, HRCT, CTD-ILD

Introduction

Interstitial lung diseases (ILD) is an umbrella term for over 200 hundred different pathologies. Classification of these diseases is a difficult task, and a continuous review of these classifications takes place in pathology, radiology and pulmonology. In 1994 Katzenstein et al. has devised a classification consisting of these groups: usual interstitial pneumonia (UIP), desquamative interstitial pneumonia (DIP), respiratory bronchiolitis - ILD (RB-ILD), acute interstitial pneumonia (AIP) – and a new category for the pathologies that did not fit into these patterns – non-specific interstitial pneumonia, (NSIP). (1) In 2002 the American Thoracic Society and the European Respiratory Society joined forces to put forward a classification combining pathology findings and clinical data. It was suggested that the histology findings of a given entity should incorporate the term "pattern" to distinguish disease and a histology finding better. (2)

Histopathology

Signs of chronic inflammation and fibrosis dominate the histopathological pattern of NSIP – depending on the extent of each two subtypes are known, the slightly rarer fibrosing and the cellular form. As the disease progresses, some cellular NSIPs transform into fibrosing NSIP, so the distinction might only be temporal. Fibrosing NSIP overtime can be indistinguishable histologically from other types of end-stage fibrosing ILDs. (3,4)

The disease usually can be seen in patches surrounded by healthy lungs, and these are generally temporally and spatially homogenous. The absence of several pathological features is also important, for example, acute lung injury including hyaline membranes, granulomas, dominant airways disease or organizing pneumonia, or coarse fibrosis. Following Katzenstein's definition of NSIP pathology, several teams have revisited their histopathological specimens previously classified as IPF/UIP (Idiopathic Pulmonary Fibrosis/ Usual Interstitial Pattern) and found that approximately 10% of these can be reclassified as NSIP. Furthermore, in 26% of cases, discordant UIP was found- NSIP on one side, UIP on the other. (5,6)

From the time NSIP was recognized as a pathological pattern, the question remained whether clinically it is a discreet entity or the lung manifestation of systemic disease. NSIP pattern can be found in a wide range of conditions, including collagen vascular diseases (CVD), drug toxicity, immunosuppression, HIV/AIDS, and bone marrow recipients. Many patients, however, do not have an underlying condition, despite showing radiological and clinical signs of the disease, and NSIP pattern is also present on biopsy. These are classified as idiopathic NSIP: in 2002 idiopathic NSIP was given a provisional status, and only in 2013 was it considered a definite diagnosis. (2,7,8)

However, idiopathic NSIP might be rarer then diagnosed - as Park et al. demonstrated – from 83 NSIPs considered idiopathic at the time of diagnosis eight was diagnosed with CVD within 21 months. (9)In 2015 the new term interstitial pneumonia with autoimmune features (IPAF) was coined by the European Respiratory Society/ American Thoracic Society Task Force on Undifferentiated Forms of Connective Tissue Disease-associated Interstitial Lung Disease to describe the fluidity between CVDs and ILDs, i.e. to identify individuals with IIP and features suggestive of, but not definitive for, a CTD. NSIP patterns are very typical in IPAF cases – maybe in the future, a new classification will again reconsider idiopathic NSIP as an entity.(10, 11,12)

Clinical features

Clinical presentation of NSIP is highly unspecific – dry cough and dyspnea are typical; these may be accompanied by fever. Due to a large number of CVD patients, the pattern is more often seen in females between 40-50yrs of age; however, idiopathic NSIP has a 1:1 male: female ratio, and a somewhat older population. Digital clubbing is observed rarer than in patients with IPF – and since the disease is often associated with a CVD, arthralgia, and oesophagal symptoms might be present. On physical examination, bilateral inspiratory crackles can be heard with a basal predominance, and on pulmonary function tests, restrictive ventilatory problems can be observed. If the patient presents with these symptoms at a pulmonology clinic, it is crucial to check for basic CVD signs, for example, arthritic joints, finger gangrene or dysphagia. (13,14)

Radiological features

As with most interstitial lung diseases, chest X-rays might be normal in initial stages, with ground glass opacities or ill-defined consolidations present with advanced disease. The key to definitive radiological diagnosis is a good-quality high-resolution CT examination allowing us to see lung parenchyma detail down to the level of the secondary pulmonary nodules. The CT is done in expiration and inspiration, with a usual slice thickness of 1-1,2mms, non-contrast enhanced, using specific high-resolution algorithms. The examination is usually performed in a supine position, but if discreet basal abnormalities are visible, additional scans in the prone position are useful. (Some institutions routinely add a prone position to all HRCT examinations).

HRCT criteria are well defined in UIP, NSIP criteria, on the other hand, are vaguer. This might be due to the fact that there is morphological overlap between NSIP and several other ILDs including UIP, COP or HP both radiologically and histologically.

In first HRCT descriptions of NSIP, the radiological features most commonly emphasized were basal dominant ground-glass opacities and consolidations, with honeycombing uncommon. Later the overlap between UIP and NSIP was recognized, so honeycombing is now not considered an exclusion criterion of NSIP diagnosis. (15,16,17,18)

Typical NSIP radiological pattern is basal dominant, bilateral diffuse or peripheral reticulation with traction bronchiectasis and volume loss. Ground glass opacities and so-called subpleural sparing are common features. GGOs can be seen in several ILDs, it can be argued that the presence of GGOs does not mean an NSIP diagnosis, however, if completely lacking, alternative diagnosis (i.e. UIP) should be considered. Foci of GGOs are thought to represent active inflammation, especially in cellular NSIP. Subpleural sparing, although only seen in approx. 40% of cases if present is highly suggestive of NSIP. (18)

Once again it must be emphasized that a radiological NSIP diagnosis does not correspond to the diagnosis of idiopathic NSIP – multidisciplinary teams consisting of clinicians (pulmonologist and/or rheumatologists), radiologists, pathologists should discuss the individual cases – underlying processes should be actively looked for. In our institution, 5% of all the cases presented to the ILD team were proven to be idiopathic NSIP, 11% had CVD associated ILD. In comparison, IPF was diagnosed in 25%. If the patient's general health allows for a lung biopsy, according to the latest guidelines, idiopathic NSIP should only be confirmed following the procedure. It is however imperative to give relevant information to the pathologists – in a recent study when ten pathologists had to diagnose specimens without clinical data interobserver concordance had a kappa value of 0.29 in NSIP, as opposed to 0.42 of UIP. The difficulty of correctly diagnosing NSIP can be seen in the study by Walsh, who observed that concordance within MDTs in 7 different countries was 0.42 for NSIP, compared to 0,71 in IPF or 0.73 for CTD-ILDs (19).

Prognosis and treatment

The overall prognosis of idiopathic NSIP is better than that of IPF. Systemic corticosteroids even as monotherapy can be useful – combination with cyclophosphamide or azathioprine can be considered. If non-idiopathic, treating the underlying disease can alleviate symptoms. More recently nintedanib was approved as a treatment for fibrosing, scleroderma associated ILDs, including NSIP. (20,21)

Abbreviations

ILD: interstitial lung disease,
HRCT: high-resolution computed tomography
UIP: usual interstitial pneumonia,
IPF: idiopathic pulmonary fibrosis,
NSIP: nonspecific interstitial pneumonia
OP: organizing pneumonia,
RB-ILD: respiratory bronchiolitis-associated interstitial lung disease,
DIP: desquamative interstitial pneumonia,
CTD-ILD: Interstitial Lung Disease Associated with Collagen-Vascular Disease,
CHP: chronic hypersensitivity pneumonitis
GGO: ground glass opacity,

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Obrazová príloha

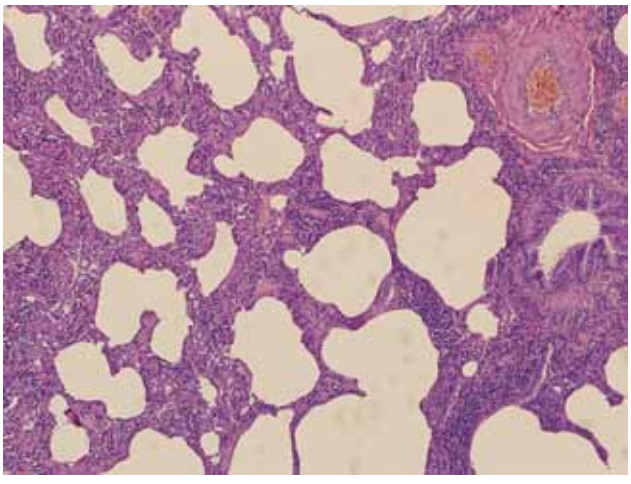

Fig. 1. NSIP hematoxylin-eosin, original magnification X100, chronic inflammation can be seen with widened intralobular septae, courtesy of Dr Tünde Harkó

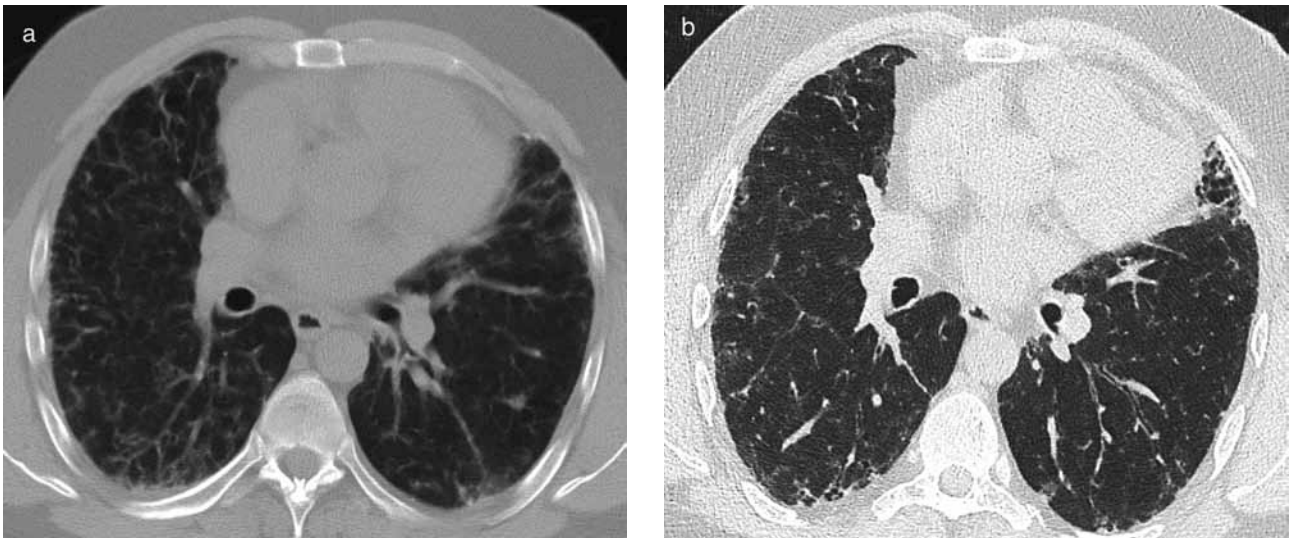

Fig. 2. Temporal changes in NSIP 45yrsold male with histologically proven NSIP. a. Transverse thin-section CT: 2012NSIP with ground glass opacities can be seen, with few signs of fibrosis. b2018 6 yrs later traction bronchiectasis and signs of fibrosis are more prominent, while GGOs diminished

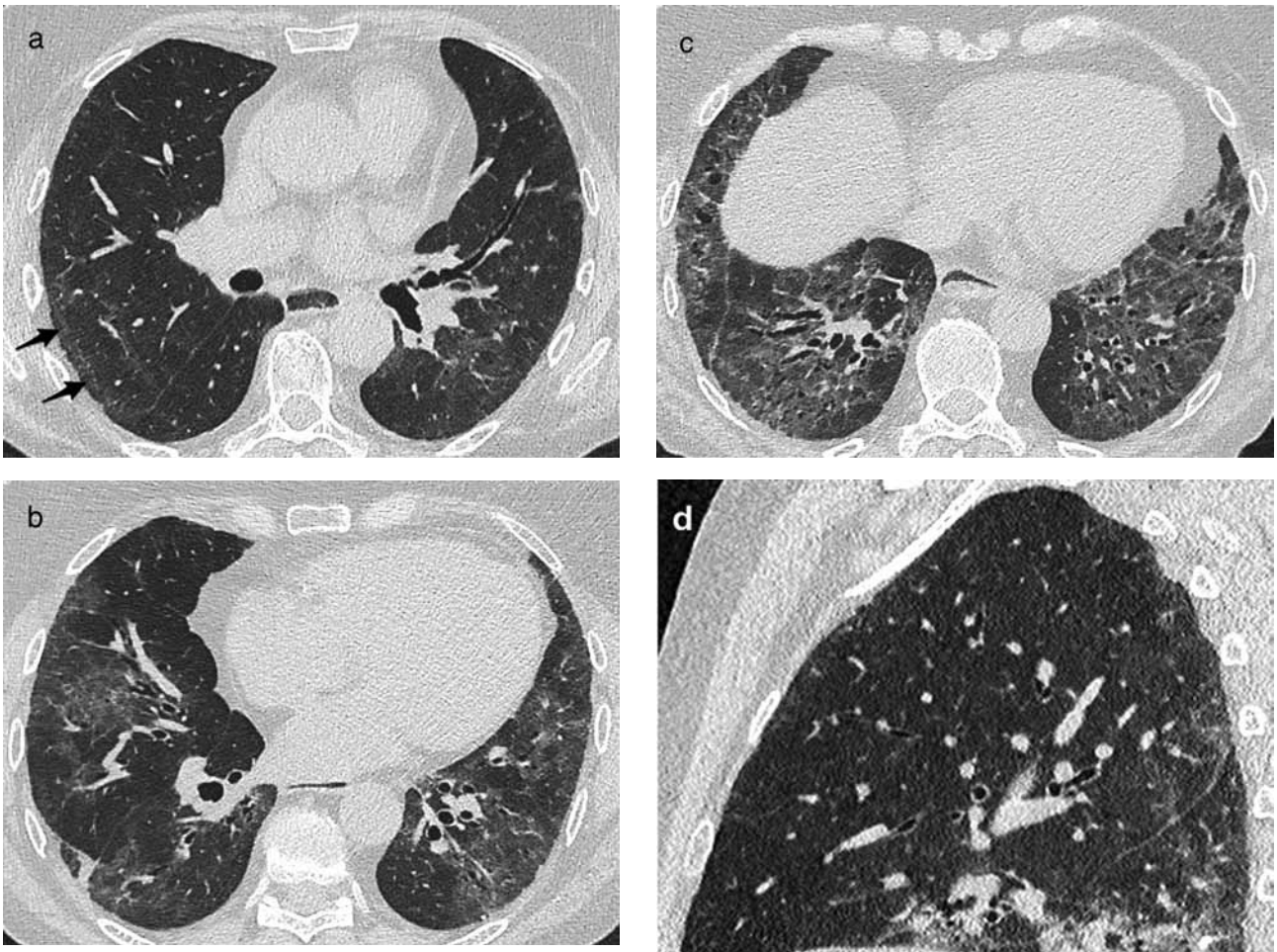

Fig. 3. Radiological signs of NSIP 71 yrs old female with a history of scleroderma. a.,b,c Transverse thin-section CT: Bilateral symmetrical GGOs can be seen with traction bronchiectasis, subpleural sparing (arrows) Note the dilated oesophagus, d. On the sagittal view apicobasal dominance can be better assessed