(RESEARCH ARTICLE)

Clinical, radiological and evolutionary aspects of non-specific interstitial Pneumonia

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Abstract

Introduction: Non-specific interstitial pneumonia (NSIP) is an interstitial lung disease that may be idiopathic or secondary to connective tissue disease, toxins or numerous other causes.

Materials and methods: This is a retrospective study of 30 cases of non-specific interstitial lung disease collected in the radiology and pneumology departments of the Hassan II University Hospital of Fez, spread over a period of 4 years.

Results: We collected 30 cases followed for NSIP. The mean age was 49.5 years, with extremes ranging from 26 to 70 years. A clear female predominance was noted (83%). Smoking intoxication was found in 13% of cases. Clinical symptoms were dominated by dyspnea in 26 cases, cough in 19 patients, chest pain in 4 cases and fever in only 1 patient. A restrictive ventilatory disorder was present in 87% of cases.

The radiological appearance was in favor of cellular NSIP in 10 patients and fibrosing NSIP in 20 cases. Elemental scanographic lesions were dominated by intralobular reticulations in 97% of cases, presence of ground glass in 83% of cases, bronchiectasis in 87% and septal lines in 80% of cases. Honeycomb and micronodules were present in 20%. Abnormalities were bilateral with basal topography predominant in 26 cases (87%). Lung biopsy was performed in 4 patients. NSIP was idiopathic in 11 cases and associated with a connective tissue disease in 19 cases. The etiologies were dominated by systemic scleroderma found in 11 cases, followed by anti-synthetase syndrome (4 cases), rheumatoid arthritis (3 cases), Gougerot Sjogren's syndrome (2 cases), systemic lupus erythematosus (1 case). Systemic corticosteroid therapy was prescribed in 26 patients and immunosuppressants in second intention in 21 cases, 4 patients were lost to follow-up and did not receive treatment. The evolution under treatment was marked by a clear clinical improvement in 14 patients, a stability in 8 patients and an aggravation in 4 patients.

Conclusion: The final diagnosis of NSIP relies on a multidisciplinary discussion between clinicians, radiologists and expert pathologists; it is essential to make the differential diagnosis with UIP as the majority of patients with NSIP have a better prognosis and respond well to corticosteroid treatment.

Keywords: Nonspecific Interstitial Pneumonia; Chest CT; Usual Interstitial Pneumonia; Connective Tissue Disease; Lung; Evolution.

1. Introduction

Nonspecific Interstitial Pneumonia (NSIP) has been individualized within the diffuse interstitial lung diseases (ILDs) on pathological criteria [1].

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It is manifested mainly by a dry cough and dyspnea. Bronchoalveolar lavage (BAL) and biology are aspecific. The chest CT scan allows the diagnosis to be suspected, but histological examination of a lung biopsy remains the gold standard and, according to the ATS/ERS criteria, allows a diagnosis with high probability [2].

Although most often idiopathic, NSIP can occur in various clinical situations: connective tissue disease, chronic hypersensitivity pneumonitis, drug-induced lung disease, HIV infection and chronic inflammatory bowel disease [3].

2. Materials and methods

2.1. Type of study

This is a retrospective study of 30 cases of NSIP collected in the radiology and pneumology departments of the Hassan II University Hospital of Fez, spread over a period of 4 years (between January 2017 and December 2020).

2.2. Inclusion Criteria

Are included in our study, all patients followed in the department of pneumology for NSIP, who have benefited from imaging examinations in the department of radiology of the HASSAN II University Hospital of Fez, and who have been discussed in multidisciplinary discussion between January 2017 and December 2020.

2.3. Exclusion Criteria

All patients who underwent an imaging examination outside the Hassan II University Hospital of Fez and patients for whom the diagnosis of NSIP was reviewed after confrontation with the clinico-biological data and the evolutionary profile on imaging.

2.4. Data collection

Data were collected from the HOSIX clinico-biological and radiological data archiving system. We created a database for each patient included in the study using an operating form including epidemiological, clinico-biological, imaging results, treatment and evolution of the patients. All patients underwent an exhaustive clinico-biological workup completed by a thoracic CT scan (64 Slice). The diagnosis was retained in multidisciplinary discussion based on these data and on the evolutionary profile of the patients.

2.5. Computed tomography protocol

CT scans were performed using a 64-slice GE scan. The acquisitions were performed in the supine position at the end of inspiration.

The CT parameters were as follows: slice thickness of 5 mm with a reconstruction of 1.25 mm.

2.6. Statistical analysis

The statistical analysis was performed using SPSS version 26 software.

3. Results

3.1. Epidemiological and clinico-biological characteristics

We collected 30 cases of NSIP. The mean age was 49.5 years, with extremes ranging from 26 to 70 years. A clear female predominance was noted (83% of cases). The majority of patients (87%) were nonsmokers. Exposure to moldy hay in 7 cases, oven smoke in 4 cases and avian exposure in 2 cases was observed.

Clinical symptoms were dominated by dyspnea, which was present in 26 cases (87%), cough in 19 patients (63%), chest pain in 4 cases (13%) and fever in only 1 patient (3%). A restrictive ventilatory disorder was present in 87% of cases.

Only 11 patients underwent bronchopulmonary lavage. Neutrophilic alveolitis was found in 4 cases, macrophagic in 2 cases, mixed in 2 cases and lymphocytic in 3 cases.

3.2. Radiological features

The radiological appearance was suggestive of cellular NSIP in 10 patients (Figure 1) and fibrosing NSIP in 20 cases (Figure 2). Elemental CT lesions were dominated by intra-lobular reticulations in 97% of cases, ground glass in 83% (figure 3), bronchiectasis and bronchiolectasis in 87% (figure 4), septal lines in 80% and peribronchovascular thickening in 27%. Honeycomb (figure 5) and micronodules were present in only 20% of cases.

The abnormalities were bilateral and diffuse in all patients. A basal predominance was found in 26 cases (87%) (Figure 3). Apical predominance was found in only 3 cases (10%) and the absence of an apico-basal gradient was noted in only one case. The abnormalities were peripheral in 24 patients (80%) and mixed with peripheral predominance in 6 cases. Subpleural sparing was present in 6 cases (20%) (Figure 6). Mediastinal adenopathy and pleural effusion were present in 3 patients (10%), esophageal dilatation in 3 patients followed for scleroderma.

3.3. Etiologies

NSIP was idiopathic in 11 cases and associated with a connective tissue disease in 19 cases. The causes were dominated by systemic scleroderma (11 cases), followed by anti-synthetase syndrome (4 cases), rheumatoid arthritis (3 cases), Gougerot Sjogren's syndrome (2 cases) and systemic lupus erythematosus (1 case).

The majority of these patients were already being followed for systemic disease before the development of pulmonary involvement, in only 3 patients (10%) ; the NSIP was secondary to scleroderma diagnosed later after immunological testing.

3.4. Histological features

Lung biopsy was indicated in all patients with idiopathic NSIP (11 cases). It was performed in only 4 patients whose results were suggestive of cellular NSIP in 2 patients and fibrosing NSIP in 2 cases. 7 patients did not benefit from a biopsy because of comorbidities or respiratory functional deterioration.

3.5. Treatment and evolution

Systemic corticosteroid therapy was prescribed in 26 patients and immunosuppressants as a second-line therapy in 21 cases, 4 patients were lost to follow-up and did not receive treatment.

The clinical evolution was marked by a clear improvement in 14 patients, stability in 8 patients and deterioration in 4 patients. This aggravation was secondary to: poor therapeutic compliance in one patient, toxicity related to the immunosuppressant treatment (Imurel) in 2 patients and associated comorbidities (hypertension, diabetes) in one patient.

These 4 patients with deterioration were followed for fibrosing NSIP, whereas almost all patients followed for cellular NSIP (9 patients) showed clinical improvement.

The radiological evolution after one year was marked by an improvement with regression of ground-glass areas in 6 patients (Figure 7), stability of imaging in 12 patients and aggravation of lesions in 2 patients (Figure 8), 10 patients did not benefit from CT scan control.

It was found that in the majority of our patients who had clinical improvement after one year had radiological stability (n=8), while the rest of the patients (n=6) had clinical and radiological improvement.

Among the 4 patients with clinical deterioration, 2 patients also had radiological deterioration, however the other 2 did not have CT monitoring.
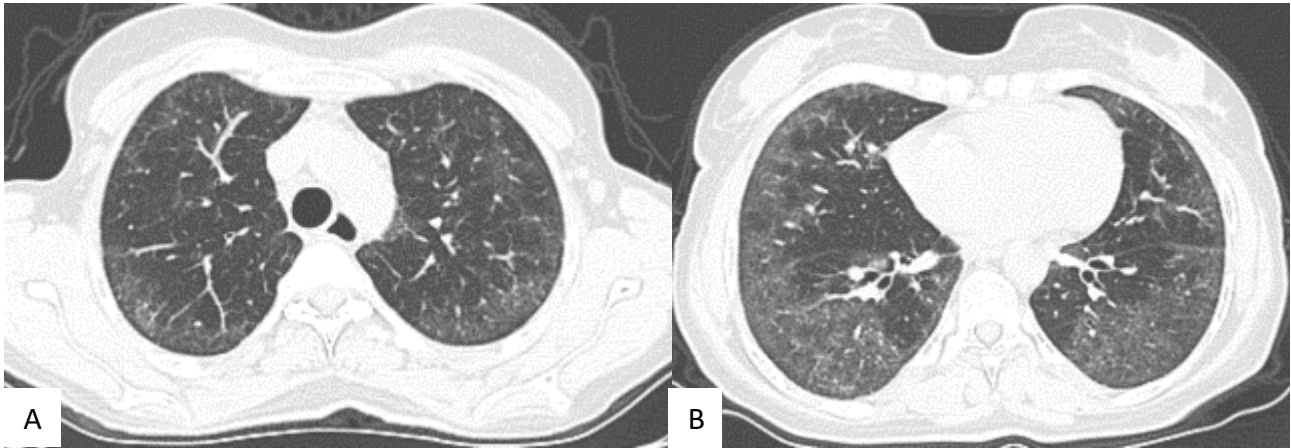
Figure 1 Parenchymal window chest CT in a patient followed for scleroderma in axial (A, B) sections: diffuse bilateral ground-glass areas more marked at the basal level, peripheral distribution associated with some intra-lobular reticulations with sub pleural sparing suggestive of cellular NSIP.
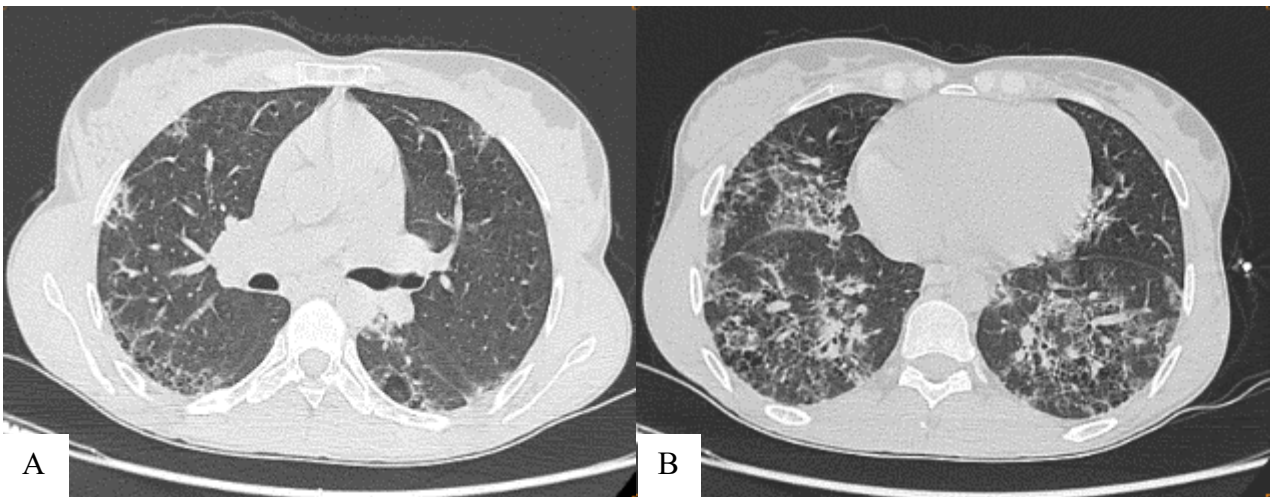

Figure 2 Parenchymal window chest CT in axial (A, B) sections in a patient followed for systemic lupus erythematosus: basal and subpleural interstitial syndrome made of intra-lobular reticulations, bronchiectasis and traction bronchiolectasis as well as cystic lesions joined at the basal level realizing a "honeycomb" aspect; related to fibrosing NSIP.
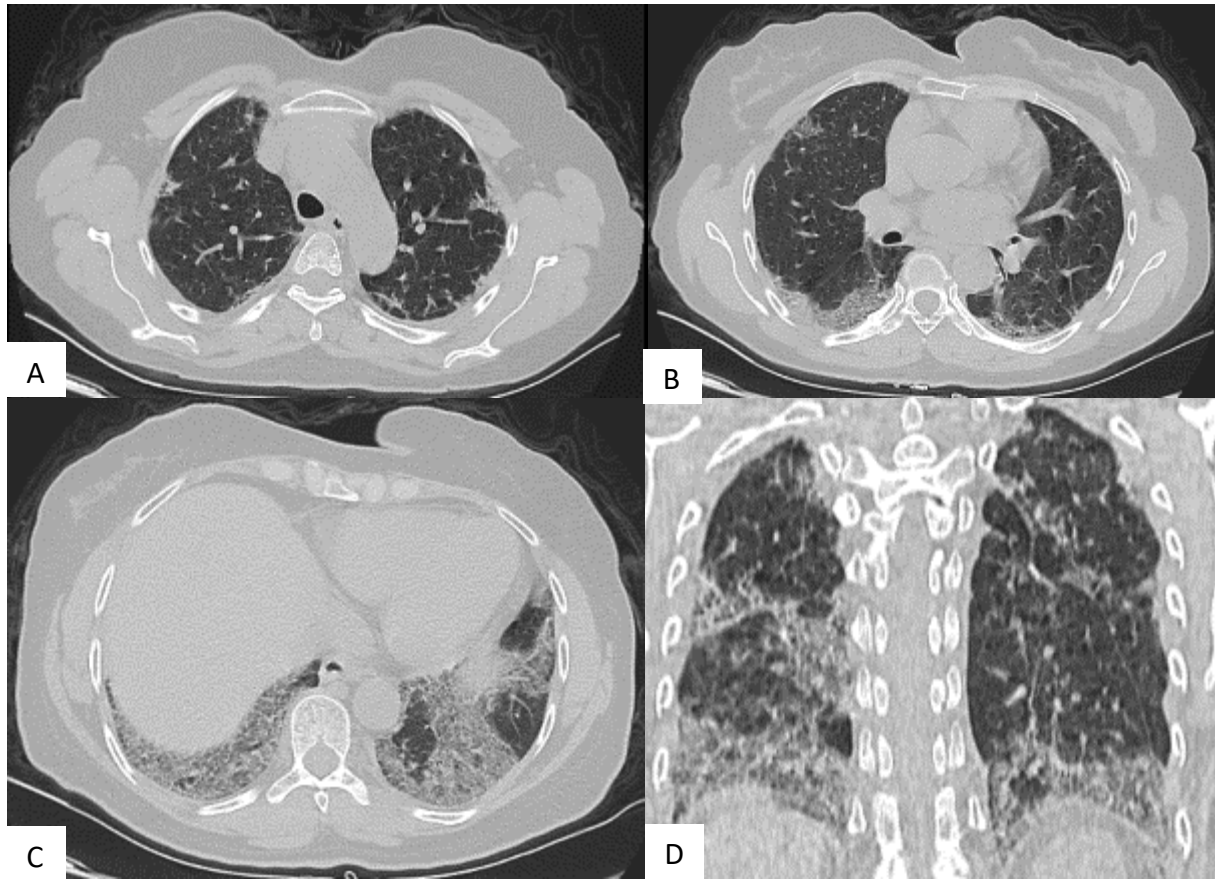
Figure 3 Chest CT in a patient followed for anti-synthetase syndrome in axial (A, B, C) and coronal (D) sections : bilateral diffuse ground glass areas associated with intra-lobular reticulations more marked at basal and peripheral level
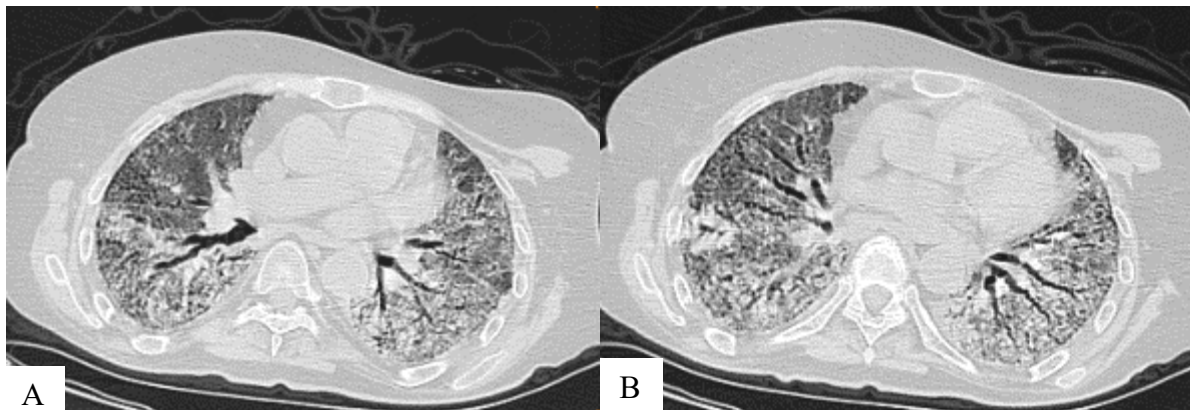

Figure 4 Parenchymal window chest CT in axial (A, B) sections: Multiple bronchiectasias associated with bilateral ground glass areas more marked at the posterobasal level, as well as intra-lobular reticulations and inter-lobular septal thickening.
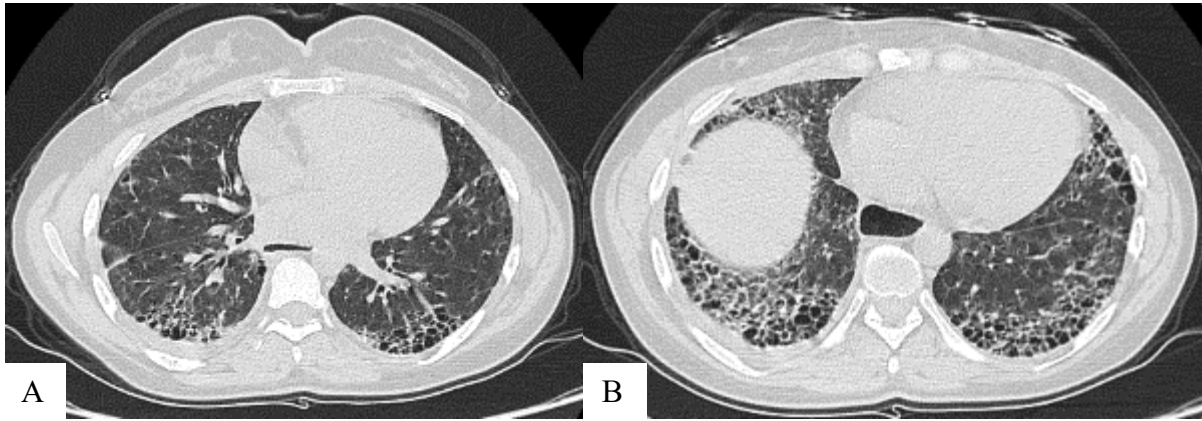
Figure 5 Parenchymal window chest CT in axial (A, B) sections : bilateral sub pleural honeycomb appearance predominantly in the posterior segments of the lower lobes, with some intra-lobular reticulations associated with fibrosing NSIP confirmed by biopsy.
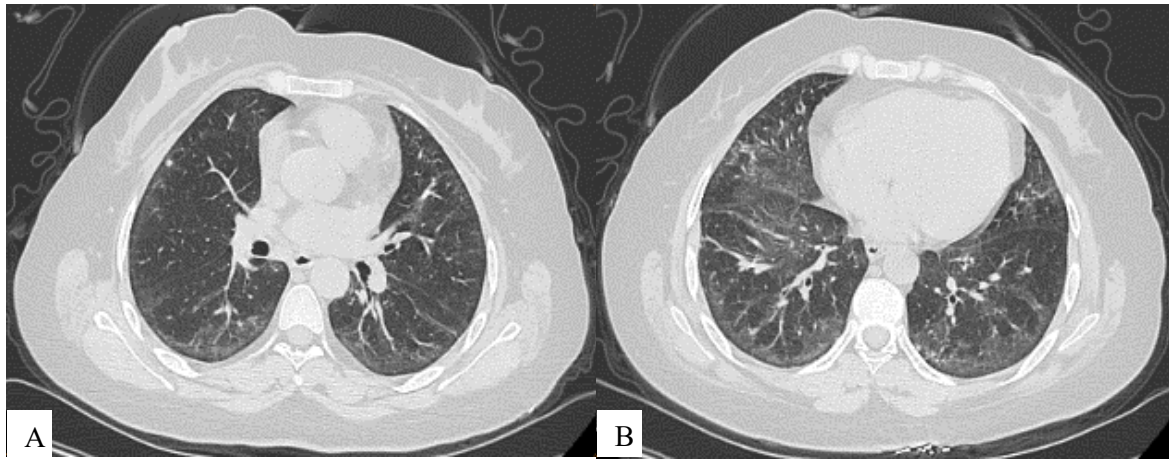

Figure 6 Parenchymal window chest CT in axial sections (A, B) : interstitial syndrome made of bilateral peripheral and basal ground glass areas associated with intra-lobular reticulations and some subpleural micronodules. Note the presence of a subpleural sparing band.

Figure 7 Chest CT in the parenchymal window on 12/2020 (A, B) and 09/2021 (C, D) and in the mediastinal window (E, F): regression of diffuse ground-glass patches associated with intra-lobular reticulations without apico-basal gradient with subpleural sparing band. Mediastinal ADPs and esophageal dilatation were associated.
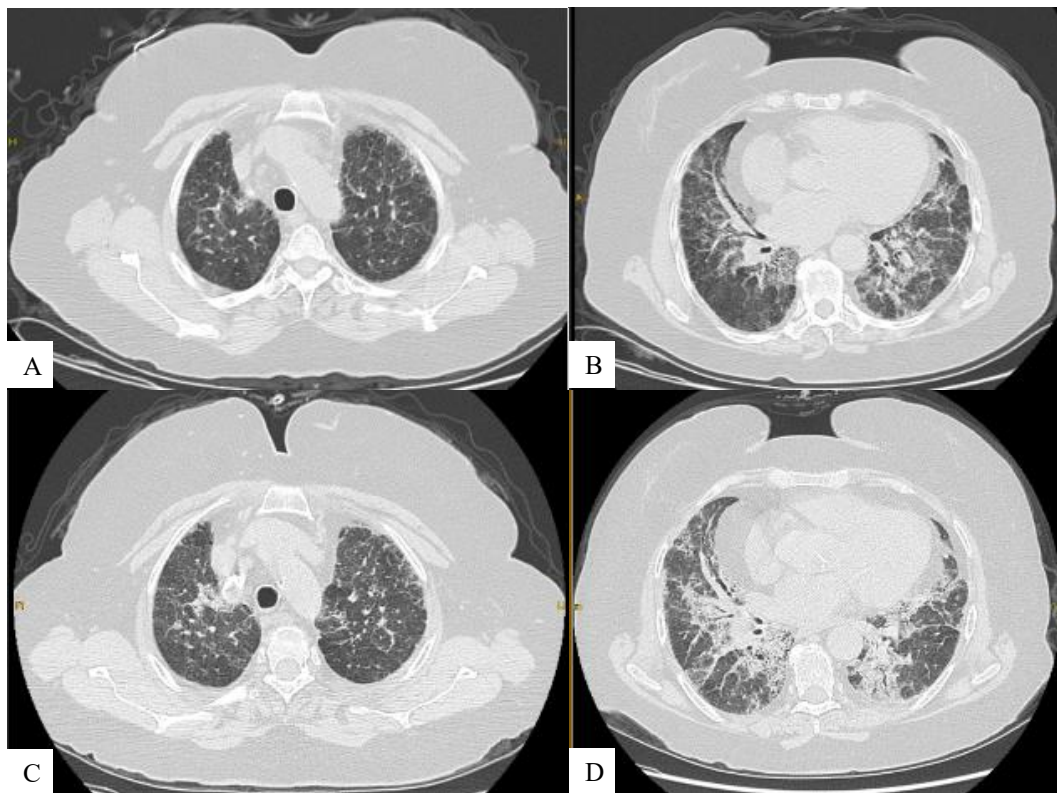

Figure 8 Parenchymal window chest CT : of 01/2018 (A, B) and 06/2019 (C, D) in a patient followed for fibrosing NSIP on biopsy : Majoration of ground-glass patches becoming diffuse, as well as intra-lobular reticulations and traction bronchiectasis more marked at the pulmonary bases.

4. Discussion

NSIP was first described as a histopathological pattern observed in HIV-infected patients. The initial description of histological features included mild to moderate lymphoid infiltration, predominantly distributed in a peribronchiolar and perivascular fashion [4].

In 1994, Katzenstein and Fiorelli described the histologic features of NSIP in their paper of 101 open lung biopsies. They reported 64 cases with varying degrees of inflammatory or fibrotic processes that did not meet the histological criteria of other specific interstitial pneumonia, namely, UIP, desquamative interstitial pneumonia, or lymphoid interstitial pneumonia. The key distinguishing histologic feature was temporal uniformity, in contrast to the temporal heterogeneity seen in UIP [5].

NSIP was considered a provisional clinical entity of its own in the 2002 ATS and ERS classification of idiopathic interstitial pneumonias (IIP) [6]. Although idiopathic NSIP was formally included as a separate IIP in 2013, PINS as a whole shares many common features with other ILDs and is known to be associated with a wide range of pathologies, especially in ILDs related to connective tissue disease [7].

In terms of frequency, NSIP is the second most common form of ILDs, accounting for 14% to 36% of all cases, compared with 47% to 64% for UIP. Some epidemiological characteristics distinguish NSIP from UIP : there is a female prevalence (51-67% women depending on the series), patients are younger (age at diagnosis: 43-58 years) (Table 1) and less often smoke cigarettes (up to 69% are non-smokers) [5, 8, 9].

These data from the literature are consistent with our results because the majority of our patients were in this age range (17 patients between 45 and 65 years) with a female predominance of 83% and almost the majority of patients (87%) were nonsmokers.

The clinical presentation of NSIP is similar to that of ILDs [10]. It is non-specific and often insidious. The two most frequent symptoms are subacute dyspnea and dry cough. In addition, fever and other signs such as anorexia, fatigue or weight loss may be present (Table 1). In our serie, dyspnea and cough dominated the clinical presentation with a percentage of 87% and 63% respectively. Only one patient presented with fever.

Table 1 Main clinical characteristics of patients with PINS according to different series

References	Number of patients	Age (average, extremes)	Gender (M/F)	Symptoms
Katzenstein et Fiorelli [5]	64	46 (9-78)	26/38	Dyspnea (80%), cough (33%), fever (22%)
Bjoraker et coll [11]	14	57 (40-73)	8/6	Dyspnea (100%), cough (85%)
Cottin et coll [12]	12	52 (31-68)	6/6	Dyspnea (100%), cough (67%), weight loss (42%)
Kim et coll [13]	23	55 (43-69)	1/22	Dyspnea (83%), cough (83%)
Nagai et coll [14]	31	58 (40-72)	15/16	Dyspnea (100%), cough (100%), fever (32%)

Pulmonary function testing classically show a restrictive ventilatory disorder with a decrease in Vital Capacity. Carbon monoxide diffusing capacity (DLCO) will be decreased. Mild resting hypoxemia may also be present [2,15]. In our series spirometry revealed a restrictive ventilatory disorder in 87% of cases.

The cellularity of the BAL is usually high, and may be predominantly lymphocytic, neutrophilic, or mixed. Although alveolar lymphocytosis is common in idiopathic NSIP, the lymphocyte count is highly variable, measured between 5 and 40% according to studies, and depends on the more or less cellular or fibrosing character of NSIP [16, 17]. Some authors

have suggested that a lymphocyte threshold of 30% would distinguish idiopathic NSIP from UIP [18]. However, this point is highly debated, and it is likely that BAL is not very discriminating. The results of this examination must therefore be interpreted in the clinico-radiological context to support the hypothesis of idiopathic NSIP, but not to confirm it or exclude UIP. In our serie, the BAL was performed in 11 cases: Neutrophilic alveolitis was found in 4 cases, macrophagic in 2 cases, mixed in 2 cases and lymphocytic in 3 cases.

NSIP can have heterogeneous appearances on CT, and unlike UIP, no specific appearance has been validated [18]. Typical forms are variably associated with: ground glass appearance (50-100% of cases) ; intra-lobular reticulations (87%) ; traction bronchiectasis and bronchiolectasis (82%) ; and lower lobe volume loss (77%) [3]. Alveolar condensations are sometimes observed (13%). Peribronchovascular thickening may also be present (7%). A honeycomb appearance is possible but rare (5%) [19]. These data from the literature are in line with our results because the elementary CT lesions found in our patients were dominated by intra-lobular reticulations in 97% of cases, a ground glass appearance in 83% of cases, bronchiectasis in 87% and peribronchovascular thickening in 27%.

CT abnormalities in NSIP are often diffuse, bilateral and symmetrical, but predominate in the lower lung territories (>90%). Although the distribution is frequently peripheral, it has been shown that in approximately 21% of patients with NSIP, the involvement respects the lung parenchyma immediately adjacent to the pleura. This respect for subpleural areas can be used to differentiate fibrosing NSIP from UIP [19,20]. In our serie, abnormalities were bilateral and diffuse in all patients with a predominant basal topography in 87% of patients. The abnormalities were peripheral in 80% of patients and mixed with peripheral predominance in 20%. Respect for subpleural areas was present in 20% of cases.

Although most often idiopathic, NSIP can be encountered in a variety of clinical situations: connective tissue disease, hypersensitivity pneumonitis, drug-induced pneumonitis, HIV infection, and chronic inflammatory bowel disease [5, 8]. Fujita et al. conducted a retrospective study of 46 patients in Japan who, based on clinical, radiographic, physiologic, and pathologic criteria, were diagnosed with NSIP. Of the 46 patients, 26 (62%) had underlying connectivitis, including polymyositis/ dermatomyositis (12), systemic scleroderma (5), rheumatoid arthritis (2), Sjögren's syndrome (2), ulcerative colitis (1), and primary biliary cirrhosis (1) [15]. Although most often prior to or concomitant with the diagnosis of respiratory disease, connectivitis appears during follow-up in 3-19% of NSIP cases initially labeled "idiopathic" [6].

In our serie, NSIP was associated with a connective tissue disease in 63% of the cases, the etiologies were predominantly systemic scleroderma found in 11 cases, anti-synthetase syndrome (4 cases), rheumatoid arthritis (3 cases), Gougerot Sjogren's syndrome (2 cases), systemic lupus erythematosus (1 case). The majority of these patients were already being followed for systemic diseases before the onset of pulmonary involvement, only 10% of cases were secondary to scleroderma diagnosed later after immunological testing.

Surgical lung biopsy (SLB) for diagnosis is not necessary when NSIP is of known cause, especially in Connective tissue disease. In the majority of cases of idiopathic NSIP, a SLB is necessary to confirm the diagnosis. Nevertheless, the risks of the surgical procedure (age, comorbidities and respiratory function deterioration) must be weighed against the therapeutic challenges [19].

Lung biopsy was indicated in all our patients with idiopathic NSIP (11 cases). It was performed in only 4 patients with 2 cases of cellular NSIP and 2 others of fibrosing NSIP, 7 patients did not benefit from a biopsy because of comorbidities or respiratory functional alteration.

The differential diagnosis should mainly rule out UIP. The existence of a basal and peripheral honeycomb appearance for UIP and extensive ground glass appearance for NSIP, especially if the subpleural area is spared, is the best discriminating CT sign [21].

Approximately 1/3 of patients with NSIP respond objectively to treatment; the majority remain stable. It is nevertheless difficult to give therapeutic recommendations in the absence of controlled trials. Treatment is based on systemic corticosteroid therapy combined with an immunosuppressive agent, which may be cyclophosphamide or azathioprine, either immediately or at a later stage, depending on the severity of the respiratory impact [3].

Systemic corticosteroid therapy was prescribed in 26 of our patients and immunosuppressants as a second-line treatment in 21 cases. The evolution under treatment was marked by a clear clinical improvement in 14 patients, stability in 8 patients and worsening in 4 patients. This worsening was secondary to: poor therapeutic compliance in

one patient, toxicity related to the immunosuppressive treatment (Imurel) in 2 patients and associated comorbidities (hypertension, diabetes) in one patient.

Travis et al. examined the histologic features of open lung biopsies from 101 patients with IIP. They compared survival rates and found that among patients identified as having NSIP (29/101), patients with cellular histology (7/29), compared with those with fibrosing disease (22/29), had better 5-year (100% versus 90%) and 10-year (100% versus 35%) survival, respectively. Although patients with fibrosing NSIP had worse outcomes than those with cellular NSIP, but they had better survival rates than a cohort of IPF at 5 (90% vs. 43%) and 10 years (35% vs. 15%) [22].

Follow-up of patients with PINS showed that those with predominant ground glass on initial CT tended to improve on treatment with a better long-term prognosis than patients with fibrotic CT signs. Progression to a typical IPF appearance is possible in 25% of patients. In a study by Screaton et al, all patients with predominantly inflammatory lesions on the initial CT scan showed signs of improvement after 1 year of evolution, whereas those with predominantly fibrotic initial involvement had a highly variable evolution: they either improved, deteriorated, or remained stable [20].

In our serie, the 4 patients with deterioration were followed for fibrosing NSIP, while almost all patients followed for cellular NSIP (9 patients) showed clinical improvement. This means that patients with cellular NSIP responded well to treatment compared to patients with fibrosing NSIP.

In our group, a CT scan was performed in 20 patients, the radiological evolution after one year was marked by an improvement with regression of the ground glass areas in 6 patients, a stability of the imaging in 12 patients and a worsening of the lesions in 2 patients.

It was found that in the majority of our patients who had clinical improvement after one year had radiological stability (n=8), while the rest of the patients (n=6) had clinico-radiological improvement. This means that the clinical response preceded the radiological response in the majority of cases.

List of Abbreviations

- NSIP: Non-specific interstitial pneumonia
- UIP: Usual interstitial pneumonia
- CT: Computed Tomography
- ILDs: interstitial lung diseases
- BAL: Bronchoalveolar lavage
- ATS: American Thoracic Society
- ERS: European Respiratory Society
- IIP: idiopathic interstitial pneumonias
- DLCO: Carbon monoxide diffusing capacity
- SLB: Surgical lung biopsy

5. Conclusion

In conclusion our study showed that the majority of patients followed for NSIP responded well to treatment and therefore had a better prognosis specifically for patients with cellular NSIP.

In addition, the follow-up of our patients has shown that the clinical response preceded the radiological response in the majority of cases.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that they have no competing interests

Statement of ethical approval

Ethics committee approval for this study, was approved by the Ethics Committee for Biomedical Research Casablanca, Morocco, in accordance with the Declaration of Helsinki, under reference 17/15.

Statement of informed consent

Written informed consent was obtained for all patients. Anonymity and confidentiality were respected for all participants

Availability of data and material:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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