Original Article

Clinical Profile of Idiopathic Non-specific Interstitial Pneumonia: A Retrospective Study from Western India

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Abstract

Background. Non-specific interstitial pneumonia (NSIP) has now been accepted to be a distinct clinical entity. However, very limited data is available in western Indian population regarding its clinical presentation, treatment options and survival of patients diagnosed with idiopathic NSIP.

Methods. A retrospective, observational analysis of clincial, radiological, treatment and survival of patients data collected from hospital records who were diagnosed with idiopathic NSIP over the six years was carried out.

Results. Out of a total of 146 patients of interstitial lung disease (ILD), 46 (31.5%) patients diagnosed with idiopathic non-specific interstitial pneumonia were included in the study. There were 12 male patients. Mean age of female was 60.6 years and 60.5 years for male patients. Clubbing was seen in 12 (26%) patients. Fifteen (32.6%) patients were on anti-tuberculosis medications prior to the diagnosis of idiopathic NSIP. The mean forced vital capacity (FVC) in the present study was 56%. High resolution computed tomography (HRCT) of the chest revealed reticulation with basal predominance in 35 (76%) patients and ground-glass opacities in 9 (19%). Median survival from initial visit was 29.6 months; while that from symptom onset was 46.2 months ($p=0.03$). Stabilisation of disease was seen in 26 (56.5%). Twenty patients died during the study period.

Conclusions. Idiopathic NSIP is a disease of the elderly with female predominance with a five-year mortality of 25%. Late presentation worsened the prognosis. **[Indian J Chest Dis Allied Sci 2018;60:141-145]**

Key words: Interstitial lung disease, Idiopathic interstitial pneumonia, Lung.

Introduction

Interstitial lung diseases (ILDs) are a group of disorders characterised by varying degrees of fibrosis and inflammation of the lung parenchyma or interstitium.[1] Combining clinical, radiological and pathological information is pivotal for accurate diagnosis of ILD.

Non-specific interstitial pneumonia (NSIP) has now been accepted to be a distinct clinical entity and has been recognised as a type of idiopathic interstitial pneumonia (IIP).[2,3] Many diseases are known to cause NSIP type of illness of the lungs, such as, collagen vascular disorders. There are very limited studies on idiopathic NSIP from our country. Katzenstein and Fiorelli defined NSIP as a distinct histological subtype of IIP characterised by varying degrees of alveolar wall inflammation and fibrosis in a pattern that suggests temporal homogeneity.[4] We present a retrospective analysis of our data including clinical presentation, treatment options and survival of patients diagnosed with idiopathic NSIP in western Indian population.

Material and Methods

Study Design

This was a retrospective observational study of patients at two centres, during the period January 2008 to March 2016. The evaluation and clinical follow-up of patients was done by the same physicians from the enrollment till the end of the study. The patients from 2008 to 2011 were included and subsequently studied on follow-up visits till 2016. On an average, about 50 patients were diagnosed with ILD per year as recorded in clinical record forms were included in the study and data were analysed.

The inclusion criteria were as follows: (1) patients diagnosed as having idiopathic NSIP on biopsy and (2) patients diagnosed to have idiopathic NSIP on clinico-radiological correlation. Informed consent was obtained from all the individual participants. Those patients who did not wish to participate in the study were excluded. The consent was also taken for the data to be used subsequently for retrospective studies. Separate consent was obtained for performing bronchoscopy. Patient confidentiality was

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maintained throughout the study. Ethics committee of the Hospital approved the study.

Data Collection

Case record forms (CRFs) were reviewed for the following details: age, gender, education, occupation, family income, addictions, duration of cough and breathlessness, delay (in months) in diagnosing ILD, and history of treatment with anti-tuberculosis drugs. A complete history regarding occupational, environmental and medication exposure was also reviewed. Detailed dermatological examinations were done in all these patients for any dermatological manifestations. The patients also underwent a detailed review of any rheumatological manifestations, especially presence of arthralgias, swallowing difficulties, myopathic symptoms, ocular and oral dryness and Raynaud's phenomenon.

All patients underwent a baseline spirometry-forced vital capacity (FVC), at the point of enrollment and subsequently every three months. However, diffusion capacity of carbon-monoxide (DLCO) could not be performed in all patients, and therefore, this data was not included in the study parameters. The reference range was based on the recommendations of the European Respiratory Society task force with correction factor applied for Indian population wherever possible.

Patients were subjected for high resolution computed tomography (HRCT) of the chest as 1 mm collimation at 10 mm intervals with prone and expiratory images. The protocols consisted of 1-1.5 mm collimation sections reconstructed with a high-spatial-frequency algorithm at 1.25-1.5 cm intervals. The images were photographed at window settings appropriate for viewing the lung parenchyma (window level from –600 to –700 Hounsfield units (HU); window width from 1200 to 1500 HU). HRCT findings were revealed by experienced radiologists as per the recommendations of the American Thoracic Society (ATS)/ European Respiratory Society (ERS) joint statement.[2,6-9]

Patients were classified under various subgroups of ILDs according to the latest guidelines.[9] However, patients with typical HRCT findings of NSIP were included in the study. In six minute walk distance (6MWD) test, the distance covered and the desaturation was noted; which was repeated every three months. Detailed serological testing was done in all patients suspected to have NSIP. Patients with negative anti-nuclear antibody (ANA), rheumatoid factor (RA), extractable nuclear antigens (Jo-1 and Scl-70) and anticyclic citrullinated peptide (anti-CCP) were included. Patients with findings suggestive of an alternative diagnosis to NSIP were excluded from the study.

Fiberoptic bronchoscopy and transbronchial lung biopsy (TBLB) was performed in all the patients. BAL was routinely collected from the right middle lobes for uniformity in samples as per guidelines; except in very selective cases where it was done from other lobes. The sample was refrigerated immediately and transported to a nearby centre experienced in processing BAL samples. The differential count was performed.

The TBLB samples were reported by an experienced histopathologist working in the field of lung histopathology for at least 10 years. NSIP was diagnosed on typical pathologic descriptions.[4,8,10] A BAL for acid-fast bacilli culture was performed in all the patients. 2D-echocardiography was performed to assess the resting pulmonary artery pressures. Open lung biopsy was not done.

Patients were started on steroids at 1 mg/Kg per day and tapered at the end of six weeks as per the ATS/ERS joint statement 2002.[1,2,11,12] Improvement in symptom complex with either improvement in FVC by 10% or decline in FVC value by less than 10% from the baseline was taken as stabilisation of the disease. Patients not responding to steroids at the end of six months on spirometry, 6MWD and symptom complex were treated with a combination of azathioprine (50 mg/Kg per day) and N-acetylcysteine.

Dose of azathioprine was increased by 0.25 mg/Kg per day every week to a maximum of 3 mg/Kg/day, *i.e.* 125 mg to 150 mg per day. Patients were monitored monthly for cytopaenias, hepatic enzyme derangements and number of infective and non-infective exacerbations and mortality.

There are definite guidelines for the management of idiopathic pulmonary fibrosis,[13] however, there is a lack of prospective, randomised, controlled trials for the treatment of idiopathic NSIP pointing towards a lack of concrete evidence in the use of immuno-suppressive agents.[12] Patients were followed-up for a period of at least five years or till death, whichever was later. Monthly follow-up visits were recorded and after three months, six weekly visits were recorded with a recording of three-monthly FVC and 6MWD values in the CRFs, which were subsequently retrieved from the CRFs.

Statistical Analysis

Statistical analysis was done with Windows Med calc Version 12. Descriptive statistics were completed using medians and means, as appropriate. P values (determined by X2 or Mid- P exact or Fisher's exact tests) were recorded; alpha was inferred at 0.05; 2-sided P values were recorded. Survival analysis was calculated using Kaplan-Meier survival estimates and plotted on separate graphs.[24]

Results

Out of a total 146 patients with a diagnosis of ILD, 46 (31.5%) patients fulfilled the clinico-radiologic and pathologic correlation of idiopathic NSIP and included in the study. There were 12 (30%) males within the age group of 35 to 40 years with a mean age of 60.5 years. Seventeen (11.6%) patients had secondary NSIP due to collagen vascular disorder.

The average duration of cough was 19.4 months and breathlessness was 19.8 months. Three patients had fever for more than one month and were diagnosed as pyrexia of unknown origin. Serial weight loss was seen in three patients. Clubbing was seen in 12 (26%) of patients. Comorbid conditions (diabetes mellitus in 8 patients, hypertension in 4 patients and hypothyroidism in 2) were observed in 14 (30.4%) patients. Prior to diagnosis of NSIP, 15 (32.6%) patients were on anti-tuberculosis medications.

Twenty-three (50%) of the patients had desaturation of more than 4% on 6MWD. The mean FVC in our study was 56% (range 32% – 90%), and 25 (54%) of the patients had FVC less than 60%.

High resolution computed tomography revealed intra- and inter-lobular septal thickening (reticulation) with basal predominance in 35 (76%) patients and ground-glass opacities in 9 (19%) patients. Two patients had minimal honey-combing in few areas; besides the septal thickening.

Bronchoalveolar lavage showed lymphocytic predominance in 24 (52%) patients, macrophage predominance in 8 (17.3%) and mixed pattern in 14 (30%) patients. Pathologic pattern on TBLB was seen in 44 (95.7%) patients. Of these, 30 (65%) patients could not be differentiated into cellular or fibrotic subtype on histopathology. Two patients were diagnosed pathologically as unclassifiable fibrosis. On the basis of a multi-disciplinary discussion (clinical-pathological-radiological correlation), cellular NSIP was diagnosed in 9 (19.5%) and fibrotic NSIP in 37 (80.5%) patients.

Median survival from initial visit was 29.7 months while that from symptom onset was 46.2 months (p=0.03) (Figure 1). Median survival in patients with FVC <40% was 41.5 months as compared to 47.9 months with FVC >60% (p=0.061) (Figure 2). Patients with ground-glass opacities on HRCT chest had a median survival of 54 months while the ones with reticulation (septal thickening) had a survival of 36 months (p=0.31). Cellular NSIP survival rate at the end of five years was 44.5%; while that of fibrotic NSIP was 29.7% (p=0.06). Mortality was observed in 43.5% of patients.

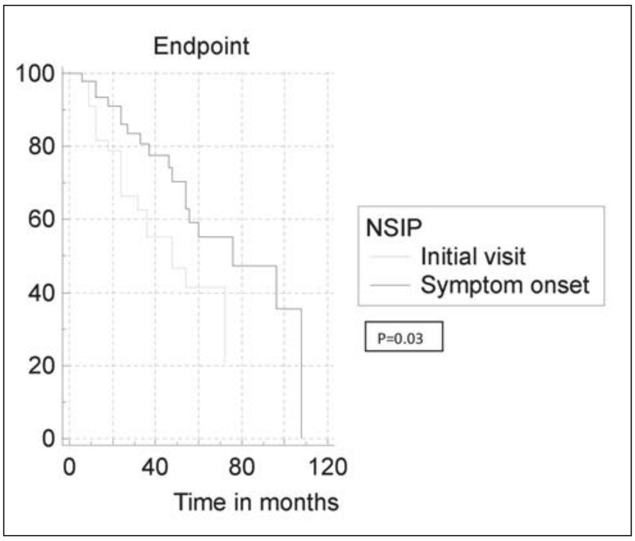

Figure 1. Kaplan-Meier Survival curves in non-specific interstitial pneumonia patients from symptom onset and initial visit.

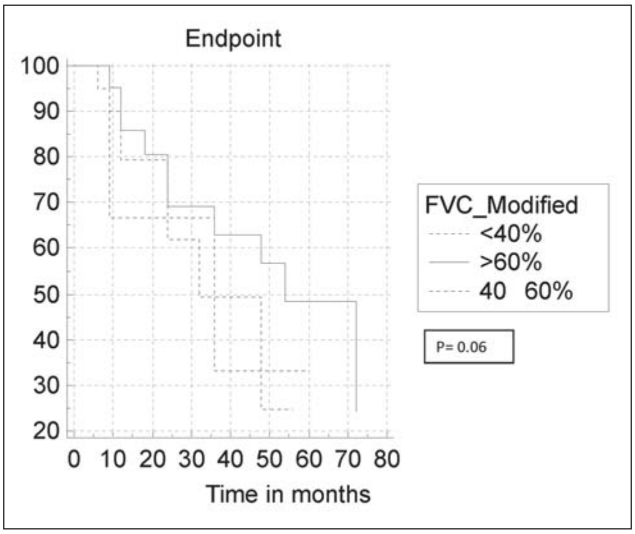

Figure 2. Kaplan-Meier survival curve in patients with non-specific interstitial pneumonia in correlation with functional residual capacity on presentation.

Non responders on steroid treatment were given azathioprine with N-acetylcysteine. Azathioprine was given to 33 (1.7%) of patients. Patients on azathioprine had a median survival of 46.7 months as compared to those who were not given azathioprine 44.8 months (p=0.6). Stabilisation of the disease was seen in 26 (56.5%) patients. Most of these patients required long term steroids or azathioprine as maintenance therapy; except two patients who had complete remission.

Discussion

Our study made some interesting observations regarding patients with NSIP. The mean duration before first consultation with a pulmonologist with experience in ILD was almost one-and-a-half years. One-fourth of the patients had clubbing. Comorbidities, like diabetes, hypertension, ischaemic heart disease and hypothyroidism were observed in one-third of the patients. One-third of the patients were empirically given anti-tuberculosis medications without any sputum examination, based on chest radiograph findings and symptom of cough.

This was before the presentation to our centre and subsequently being diagnosed as ILD. Therefore, it can be hypothesised that the patients receiving anti-tuberculosis medications were incorrectly diagnosed. In our study, it was observed that 75% patients had fibrotic NSIP variant.

Prognosis significantly varied when patients presented late for treatment. Patients with better lung function tests on presentation had better prognosis as compared with those having lower FVC; though not statistically significant. The patients with cellular NSIP had a better prognosis as compared to fibrotic NSIP variants. Most of our patients had stabilisation of the disease with the lung functions remained static with clinical remission. Appoximately less than half of our patients had died at the end of five years. In the present study we found that patients with NSIP had a better survival as compared to patients with IPF.[14]

Female predominance was seen in our study which is in contrast with earlier studies[4,8,9,11,15-17] almost all other studies on NSIP; except in the study by Travis *et al*[5] which showed a male predominance (15 out of 22). The recent systematic review of 12 studies by Travis *et al*[16] showed that the mean age at presentation was 52 years with age ranged from 26 to 73 years. Park *et al*[11] reported significant desaturation in two-third of patients on 6MWD with a statistical significance between the recurrence and non-recurrence groups in fibrotic NSIP.

Most of the patients in other studies presented with mild restriction, as compared to our study where patients presented with moderate restriction. Lee *et al*[9], observed a mean FVC of 63% in their study, while Park *et al*[11] observed it as 63.6%.

In the study by Lee *et al*[9], ground-glass opacities (GGO) was predominant finding in 89% of patients followed by consolidation, traction bronchiectasis, reticulation and honey-combing in very small numbers. In contrast, Travis *et al*[5] reported 87% of patients with reticulation, 82% with traction bronchiectasis, and GGO was seen in only 44% of patients. A mixed pattern was observed in more than 90% of patients of NSIP by Park *et al.*[11] Hartman *et al*[18] has outlined the varied appearances of NSIP on HRCT chest and the diagnostic accuracy of certain radiological features. They also mention that honey-combing may be found on HRCT in patients with NSIP but is never a dominant finding. Lynch, Sumikawa and Misumi have clearly defined the prognostic factors on HRCT chest in patients with usual interstitial pneumonitis (UIP).[19-21] However, in patient with NSIP, the HRCT findings may vary as per the patient cohort and there are no established prognostic factors as in patients of UIP subtype of ILD.

Various studies have shown lymphocytic bronchoalveolar lavage (BAL) in NSIP patients.[6] Fujita *et al*[22] in 1998 reported modest elevation in lymphocytes upto 28% in 24 patients of NSIP. The only study that showed neutrophilic predominance was by Veeraraghavan *et al*[7], where all the 19 patients were of fibrotic subtype.

There are no established prognostic treatment parameters in patients of idiopathic NSIP. In a recent Korean study by Lee *et al*[9], 25% of the patients relapsed and had to be treated with azathioprine. However, they could not establish any statistically significant parameters influencing the treatment or outcome, neither in patients who were steroid responders nor those who had relapsed and received azathioprine.

Travis *et al*[5], reported that survival in patients with fibrotic NSIP was worse than in patients with cellular NSIP. Park *et al*[11] reported that the survival in patients with cellular NSIP was 74% at the end of five years. In our study, we did not find any much statistically significant difference in survival rate in these subsets of NSIP patients.

Results of our study on stabilisation improvement after treatment are in contrast with Daniil *et al.*[8] Lee *et al*[9] in their study where 86% were responders, reported three deaths. They also observed that amongst these responders, 40% relapsed later on or steroid dependent. In another retrospective study by Park *et al*[11] of 83 patients, the 5-year survival rate was 74%; whereas Cottin *et al*[15] observed a survival rate of about 83%. In a recent study by Nunes *et al*[23], the authors have shown that the mortality was significantly affected by the type of NSIP with the idiopathic type having a significantly worse prognosis as compared to collagen vascular disorder associated NSIP. Large scale studies have to be undertaken to establish this finding.

Conclusions

Idiopathic non-specific interstitial pneumonia is a disease of the elderly with a female predominance and have 20% five-year mortality rate. Late presentation worsened the prognosis. Majority of the patients may be treated with immunomodulators, more than half of the patients stabilised on treatment and almost half of the patients died during the course of the study.

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