Case report

Cases non-specific interstitial pneumonia and hypersensitivity pneumonia: A new pathologic diagnosis or overlap syndrome

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ABSTRACT

ATS/ERS evaluation of ILD's has recently considered NSIP as a single entity and it has historically been considered a provisional diagnosis. As more cases are reviewed, pathologic characteristics may become more precise with less overlap and help in diagnosis of complex cases.

Here, we present a series of cases of HP and NSIP recently admitted to Masih Daneshvari Hospital with hope to characterize them better and eventually have less ambiguity about nature of NSIP.

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1. Introduction

Researchers have presented article on differences between NSIP and UIP (Unspecifc Interstitial Pneumonia) in this Journal's number 3 issue 4 of year 2008 that were contributed probably to more severe inflammatory condition in NSIP compared to UIP. In this article also, more significant difference in HRCT findings between NSIP and UIP were discussed which can differentiate these two cases from each other. Review by ATS/ERS on interstitial lung diseases, distinguishes NSIP and HP as separate entities. As more cases are reviewed, pathologic characteristics may become more precise with less overlap and help in diagnosis of complex cases.1-3

Case review of three new patients showed that there can be overlap between the two ILD’s, HP and NSIP such that pathologic differentiation between the cases despite new methods is difficult which can be due to overlap between the two or new terminology in the field of ILD studies.

2. Case 1

The first patient is a 32-year-old lady from out of Tehran who presents to this center with increasing dyspnea for 2 months and findings consistent with interstitial fibrosis in lung apices on CT scan. She has been diagnosed with possible sarcoidosis or chronic HP a year prior to admission based on lack of granuloma found in lung biopsy and was referred for diagnostic evaluation. Patient noted that in the last 10 days dyspnea has increased and she was now considered FC IV. She notes pulmonary symptoms began 3 years ago with dry coughs and increasing dyspnea such that she is currently oxygen dependent. Medications were fluoxetine, atrovent, salmeterol, Azaram 50 mg bid, ranitidine and prednisolone 25 mg qd. She denies any drug allergies. She has family history of asthma in uncle. On physical exam vital signs were BP = 100/60, HR = 98, RR = 30 and oral T = 36.7 °C. She was in no acute distress. She had no head and neck jugular venous distension or lymphadenopathy. Cardiac exam was normal with heart sounds S1, S2 heard and no murmurs, rubs or gallops present. Lung exam showed ronchi at both bases. Abdomen was soft, nontender with no organomegaly. No clubbing, cyanosis or edema was noted. Neurology exam was normal.

Spiral Aorta Thoracic CT showed bilateral symmetrical interstitial fibrosis more prominent in upper lobes with posterior retracted main stem bronchi in favor with sarcoidosis.

Pathology slides from a year ago from Mashad were reviewed which were compatible with NSIP and evidence of acute exacerbation (proliferative phase). Presence of individual interstitial giant cells and focal bronchiolization was noted with recommendation to consider HP. Review of microscopy included lung parenchyma with temporally uniform interstitial inflammation and mild scattered fibrosis. Predominant infiltrative cells were small lymphocytes and occasional plasma cells. Lymphocyte aggregations were noted with accentuation around respiratory bronchioles. There was marked alveolar pneumocyte hyperplasia, fibroblastic foci, and pleural infiltration with chronic inflammatory cells.

Spirometry showed FEV1 17%, FVC 15% and FEF 25 75 23% predicted.

Sputum smear for BK was negative times three.

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Laboratory tests showed normal liver and kidney function tests and CBC. ESR was 28 mm/h and RF was positive. Other rheumatology titers were ANA (IF) negative, anti-ds-DNA 0.1 mg/dl, anti-ccp Ab 1.4 IU/ml, Sco 37.7, anti-centromere Ab 1.4 IU/ml, Jo Ab 7.6 IU/L and within the normal range. Patient was anti-HIV (ELISA) negative. ACE level was normal.

Patient was admitted with continuation of current medications.

In this patient granulomas were not found on pathology and presence of individual interstitial giant cells and focal bronchiolization was noted with recommendation to consider HP. Diagnosis to be considered is HP maybe due to history of mycoplasma pneumonia or dry coughs.

3. Case 2

The second case is a 30-year-old male farmer with history of exposure to toxins and well drilling in the oil industry who presents with progressive dyspnea and right-sided pleuritic chest pain for the past year. Patient’s functional class has varied between I and IV. He notes worsening of symptoms in the sitting position. He has had weakness and fevers with chills in the afternoons with nightly sweats for the past year. He has been hospitalized with diagnosis of pneumonia, but never fully recovered after discharge and continued to have dry coughs which were worse on exertion. He has had decreased appetite with weight loss of 15 kg in the past 8 months. He denies cough or sputum and has been referred by specialist from the city of Ahvaz where he was worked up with chest X-ray showing interstitial infiltrate in base of two lungs, restrictive spirometry, normal bronchoscopy and smear for BK. He has continued to have exertional dyspnea and as a result was referred to this center. Medications on admission were prednisolone started at 60 mg/d and tapered over 6 months to the current dose of 5 mg/d, theophylline 200 mg qd and omeprazole. He is nonsmoker and does not drink alcohol or abuse substance. He has history of pancreatic cancer in his father. On physical exam vital signs are BP = 100/60, PR = 100, RR = 16 and oral T = 37.2 °C. The patient was a young man alert and oriented providing history. He had no jugular venous distension or head and neck lymphadenopathy. Cardiac exam was normal with heart sounds S1 and S2 present with no murmurs, rubs or gallops auscultated. Lung exam showed decreased breath sounds in the right lung base and hyperresonance on percussion. Abdominal exam showed epigastric tenderness with no organomegaly. There was no clubbing, cyanosis or edema noted. Neurology exam was normal.

HRCT of lung showed uniform ground glass opacities in dependent part of lower lung zone, mosaic pattern of attenuation in cyanosis or edema noted. Neurology exam was normal. Pulmonary exam showed crepitation in base of left lung. Abdominal exam was normal. There was no clubbing, cyanosis or edema noted. Pathology report noted lung tissue with mild alveolar architectural distortion due to diffuse interstitial edema, chronic inflammatory cell infiltration mostly small lymphocytes and some eosinophils and in some areas also interstitial fibrosis.

Although, in this case neutrophilia in PBC and Masson Bodies on pathology are consistent with HP.

Diagnosis to be considered is NSIP maybe due to paraneoplastic process.

4. Case 3

The third patient is a 15-year-old girl who presents with complaint of fever and decreased weight of 2–3 kg during the past month and arthralgia in the knees for the past 8 days. The patient was hospitalized one month prior to this admission with provisional diagnosis of chronic sarcoidosis with normal bronchoscopy and BAL negative for malignancy and TBLB not diagnostic. She denies any other past medical history, taking any medications or having any known drug allergies. She was up-to-date on her immunizations. She has family history of breast cancer in her mother. On physical exam, vital signs were BP = 100/70, PR = 85, RR = 20 and oral T = 36.9 °C. The patient was in no acute distress. Her skin was pale. No lymphadenopathy was palpated. Cardiac exam was normal. Pulmonary exam showed crepitation in base of left lung. Abdominal exam was normal. There was no clubbing, cyanosis or edema or joint tenderness palpated. Neurology exam was normal.

HRCT was consistent with cystic lesions accompanied by thickened intralobal septae.

Paranasal CT was consistent with uniform opacity in posterior ethmoidal cells. Echocardiography was normal.

The patient underwent open lung biopsy via anterior thoracotomy. Pathology report was emphysematous change with paraseptal bleb formation, unclassified interstitial lung disease consistent with NSIP due to HP or collagen vascular disease, or idiopathic NSIP. It was recommended that due to extensive emphysematous change superimposed pathology on a background childhood disease be investigated.

Biopsies from RML and RLL were taken. Microscopic examination form RML biopsy showed lung parenchyma with emphysematous change, patchy interstitial thickening due to inflammatory cell infiltration including lymphocytes, histiocytes and a few eosinophils and mild fibrosis. Also noted was paraseptal cyst without any lining (bleb) and intralobalveolar macrophages. Biopsy of RLL showed lung parenchyma with diffuse interstitial thickening due to inflammation and slight fibrosis, fresh hemorrhage in alveolar spaces, edema fluid and few cast like PAS positive material. No granuloma or malignancy was noted.

Laboratory tests showed normal renal functions with leukocytosis (12.7 cell/Microl.) and neutrophilia on CBC. ESR was 41 mm/h, CRP was positive and RF was negative. Other tests were CANCA (ELISA) 4.0 U/ml, PANCA (ELISA) 0.8 U/ml, C3 1.47 g/l (Nephelometric), C4 0.36 g/l, ANA (IF) negative, anti-ds-DNA 0.61 which were within normal limits. Anti-HIV (ELISA) was nonreactive. Sputum smear for BK and fungi was negative.

Patient was hospitalized with current medications and underwent bronchoscopy with TBLB after which he developed pneumothorax with need for chest tube insertion. Inadequate biopsy specimen led him to have open lung biopsy. Hospital course was complicated with wound infection and treated with course of antibiotics ceftazidime. Upon recovery, patient was discharged with medications Azathioprin 50 mg/d to be increased to bid and prednisolone 50 mg/d.

In this patient, results of open lung biopsy were reported as consistent with NSIP pattern either idiopathic or secondary to another process. Pathology report noted lung tissue with mild alveolar architectural distortion due to diffuse interstitial edema, chronic inflammatory cell infiltration mostly small lymphocytes and some eosinophils and in some areas also interstitial fibrosis.

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Immunohistochemistry for HMB45, SMA was negative and for CD1a and S100 revealed few scattered immunoreactive cells in interstitial space. IHC for PC was negative.

Sputum smear was negative for fungi. Laboratory tests showed normal renal function tests with leukocytosis (15.5 cells/Microl) and neutrophilia (Neut 80%) on CBC as well as anemia with Hgb 9.9 g/dl, MCV 76.3 fl and RDW of 17.5 and increased. ACE level was 63 IU/L. Other tests included SSA/ROIg 9.0 U/ml and SSB/LaIG 6.0 U/ml which were within normal limits. Tests from previous hospitalization were ESR 87 mm/h and RF negative. Also noted from previous admission were Parvovirus B19 negative, anti-ds DNA 0.83, CANCA 4.4 u/ml, PANCA 2.2 u/ml, ANA negative which were within normal limits. HIV (RTPCR) and HCV antibody titers were negative. Urinalysis was normal.

Pathology report was emphysematous change with paraseptal bleb formation, unclassified interstitial lung disease consistent with NSIP due to HP or collagen vascular disease, or idiopathic NSIP. It was recommended that due to extensive emphysematous change superimposed pathology on a background childhood disease be investigated. Diagnosis to be considered is NSIP due to collagen vascular disease and snifing glue.

5. NSIP and HP

The ability to diagnose NSIP (nonspecific interstitial pneumonia or a form of idiopathic interstitial lung disease) and other forms of chronic interstitial lung disease is considered significant as it not only agrees with different prognosis, but also may influence course of treatment. As a result, early diagnosis of interstitial lung disease and pulmonary referral is of significant prognostic value for the patient.2,4,5

Authors of this case series also recently performed a study on 61 cases, 11 NSIP and 50 UIP, where pathologic diagnosis was reviewed and searched for noninvasive comparative diagnostic features. Clinical symptomatology was not distinguishing. The study focuses particularly on thin section CT scan findings with 1-mm collimation. HRCT of 36 patients (60%) showed honeycombing and 24 patients (40%) bilateral ground-glass and irregular reticular pattern. Lack of sub-pleural honeycombing was seen in UIP. Predominant histologic features of NSIP were interstitial inflammation and fibrosis. Other characteristics found to be helpful diagnostically included time interval between symptom onset and diagnosis (based on HRCT finding, on average NSIP was diagnosed a few months earlier than UIP), mean age and gender.3

Pathologic characteristic of NSIP is uniform thickening of alveolar walls with a spectrum of cellular to fibrosing patterns. Recent ATS/ERS review of 305 cases of which 193 had sufficient data for diagnosis, has suggested NSIP as a separate entity rather than previously thought that it is more a temporary diagnosis. Exclusion of other interstitial lung diseases being of primary concern. NSIP is considered to have good prognosis. Additionally 66 patients were followed up from 0.6 to 19.44 years of which 8 patients passed away (7 from NSIP and 1 from nonrespiratory cause) and 1 patient underwent lung transplantation. Two patients subsequently showed Collagen Vascular Disease (scleroderma and polymyositis). Extensive pathology review of 67 probable cases is summarized as follows: varying amounts of interstitial inflammation and fibrosis uniformly appearing. Two varieties were distinguished: cellular (16% of cases) with mild to moderate chronic inflammatory interstitial infiltrate with little fibrosis and fibrosing (84% of cases) with interstitial thickening by uniform fibrosis of same age with preservation of alveolar architecture and various amounts of cellular inflammation. Clinical presentation was breathlessness and cough of 6–7 months, mostly women, never-smoker and in 6th decade of life. In cases of histological similarity between NSIP and HP, clinical history of antigen exposure guided diagnosis.6

Pulmonary drug toxicity another cause associated with NSIP is frequently caused by cytotoxic drugs such as cyclophosphamide, bleomycin, carbustine. NSIP has been reported with carbustine toxicity or noncytotoxic drugs such as amiodarone. Other noncytotoxic drugs associated with pulmonary toxicity include nitrofurantoin, sulfasalazine and gold salts.7

One study compared BAL findings in patients with sarcoidosis versus HP. They noted lymphocytosis consistent with sarcoidosis and Masson bodies have been observed in HP or extrinsic allergic alveolitis.8

Another form of interstitial lung disease that often presents with chronic respiratory symptoms and needs to be distinguished from NSIP is hypersensitivity pneumonitis for antigen avoidance and preventive measures.

Hypersensitivity pneumonitis or extrinsic allergic alveolitis is characterized by diffuse parenchymal and airways inflammation due to inhaled antigens previously sensitized to. Symptoms occur 4–8 h after exposure. Studies in England have shown that incidence is 0.9 per 100,000 person years, with mean age of diagnosis of 57, equal male to female ratio and patients less likely to be smokers. HP is classified into acute, sub-acute and chronic progressive. This disease has been associated with trades involving: farming, ventilation and water related contamination, birds/poultry, veterinary work and animal handling, grain and flour processing, milling and construction, plastics, painting, electronics, textile workers and others. Treatment is mainly through antigen avoidance and prevention with corticosteroids 0.5–1 mg/kg daily.9

A list of differential diagnoses for HP is provided below (Table 1). Clinical predictors of HP include exposure to known offending antigen, recurrent symptomatic episodes, presence of precipitating antibodies to offending agent, inspiratory crackles, and symptom onset 4–8 h after exposure and weight loss. Acute HP presents with flu like symptoms that resolve in 12–24 h. Sub-acute HP is more like chronic bronchitis and chronic disease presents as uncontrolled acute or sub-acute cases similar to end-stage pulmonary fibrosis. Patients are hypoxemic with exercise and even at rest. Recommended laboratory tests have shown leukocytosis, neutrophilia, elevated ESR, elevated quantitative immunoglobulins and CRP.

Chest X-ray in acute HP shows micro nodular or reticular opacities, mostly found in lower and middle lung. Sub-acute HP shows micronodular or reticular opacities in mid to upper lung and chronic HP shows progressive fibrotic changes with loss of volume, and significant upper lobe emphysema.

### Table 1

**Differential diagnosis for HP**

| Differential diagnoses                  | Pneumonia, viral    | Pneumonia, viral    |
|----------------------------------------|---------------------|---------------------|
| Asbestos                               | Polyposytis         | Polyposytis         |
| Chemical worker’s lung                 | Pulmonary eosinophilia | Pulmonary eosinophilia |
| Chlamydial pneumonias                  | Coal worker’s pneumoconiosis | Coal worker’s pneumoconiosis |
| Coal worker’s pneumoconiosis           | Farmer’s lung        | Farmer’s lung        |
| Farmer’s lung                          | Goodpasture syndrome | Goodpasture syndrome |
| Metastatic cancer, unknown primary site| Metastatic cancer, unknown primary site | Metastatic cancer, unknown primary site |
| Microscopic polyangitis                | Metastatic cancer, unknown primary site | Metastatic cancer, unknown primary site |
| Miliary tuberculosis                   | Metastatic cancer, unknown primary site | Metastatic cancer, unknown primary site |
| Mixed connective-tissue disease        | Metastatic cancer, unknown primary site | Metastatic cancer, unknown primary site |
| Mycoplasma infections                  | Metastatic cancer, unknown primary site | Metastatic cancer, unknown primary site |
| Pneumonia, bacterial                   | Metastatic cancer, unknown primary site | Metastatic cancer, unknown primary site |
| Pneumonia, community-acquired          | Metastatic cancer, unknown primary site | Metastatic cancer, unknown primary site |
| Sarcoidosis                            | Systemic lupus erythematosus | Systemic lupus erythematosus |
| Wegener granulomatosis                 |                     |                     |


Computed tomography further shows ground glass opacities. Pulmonary function test is restrictive with mixed obstruction in chronic disease and increased DLCO.

Diagnostic procedures include inhalation challenge, BAL findings of >20% lymphocytosis. Lung biopsy is consistent with small poorly formed non-caseating granulomas near respiratory or terminal bronchioles associated with multinucleated giant cells. Defining feature of chronic HP is bridging fibrosis between peri bronchiolar and peri lobular areas.10

Pathogens include microbes, animal and plant proteins and low molecular weight chemicals. The most common bacterial cause is thermophilic (heat-loving) actinomycetes (gram positive filamentous bacilli) that live in warm (50–60 °C) and moist environment such as in decaying vegetation. *Mycobacterium avium* has caused HP in hot tub users. Fungus etiology includes Aspergillus species observed to cause disease in corn and malt workers. Protein etiology has been associated with bird keeping and chemical agents include isocyanates found in foam, glue and spray paint. Exposure as short as 2 years and as long as 11 years to the agent has in some cases caused HP.

HRCT shows abnormality in 90% of patients. CT features of HP are lobular air trapping, centrilobular ground-glass opacities and absence of lower lobe predominance. In contrast, CT features of NSIP are relative sub-pleural sparing, absence of air trapping and absence of honeycombing.

Precipitating antibodies to offending antigen (usually IgG) is found in most cases of HP but are not specific. BAL CD4/CD8 ratio is <1 (normal being 1.8).11

In patients with ILD, connective tissue diseases (RA, Sjogren, MCTD, etc) and underlying medical condition such as cancer (in case of PM/DM) need to be investigated. Connective tissue disease may present with lung involvement. Some cases of limited scleroderma may not have positive routine antibodies and in suspicious cases (such as with Reynaud’s) non-commercially available tests such as anti body to Th/To ribonucleoprotein are recommended. Also to be considered are drug-induced and occupational diseases (asbestosis and silicosis).12

Isocyanates have been shown to cause chemical pneumonitis (HP). This toxicity has been reported in car company workers, foam production, injection molding, paint spraying and adhesive application. It has been associated with pulmonary disease anemia syndrome. Characteristic laboratory findings have been leukocytosis in PBC and increased neutrophils in BAL in acute stages.12

Further evidence supporting possible involvement of different pathology is gene expression signature variation between different forms of ILD, also HP and NSIP. In a study on this topic, it was found that HP signature included genes related to inflammation, T-cell activation and immune responses. IPF involved more remodeling, etc. Among the cases of NSIP, 2 showed IPF-like gene expression and one HP and the remaining resembled neither and may present idiopathic NSIP.13

As a result, when facing a pulmonary patient with chronic symptoms and findings suggestive of interstitial lung disease, exclusion of antigen exposure and its contribution to disease includes important part of history taking and also attention to underlying medical conditions particularly in cases suggestive of NSIP. ATS/ERS evaluation of ILDs has recently considered NSIP as a single entity and it has historically been considered a temporary diagnosis. As more cases are reviewed, pathologic characteristics may become more precise with less overlap and help in diagnosis of complex cases.

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