Case Report

A Rare Case of Interstitial Pneumonia with Autoimmune Features

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Abstract

A rare case of interstitial pneumonia with autoimmune features in a 53-year-old female is presented. She was treated successfully with immunosuppressive drug regimen. This case report underscores the importance of scrutinising patients with overlapping features of connective tissue disorders with interstitial lung disease and further outlines the strategy for the diagnostic and management issues of this condition. **[Indian J Chest Dis Allied Sci 2020;62:61-64]**

Key words: ILD, IPAF, SLE, Sjogren's syndrome, Systemic sclerosis

Introduction

Interstitial lung disease (ILD) accounts for significant morbidity and mortality in patients with connective tissue disease associated ILD (CTD-ILD). While some patients meet clear diagnostic criteria for a systemic rheumatological disease, there is a subset of patients not fulfilling all diagnostic criteria; but may still benefit from immunosuppressive therapy. In 2015, the American Thoracic Society (ATS) and European Respiratory Society (ERS) described a classification criteria for the recognition of patients with lung-predominant CTD lacking sufficient features of a defined CTD. This classification was called as interstitial pneumonia with autoimmune features (IPAF).[1]

The features from three domains are crucial for establishing diagnosis of IPAF: a clinical domain consisting of specific extra-thoracic features, a serologic domain including specific autoantibodies, and a morphologic domain comprising specific chest imaging, histopathologic or pulmonary physiologic features. Due to the rarity of the disease, data regarding treatment is largely derived from case series, and therefore, no treatment protocols have been established. We present a case of a 53-year-old female presented with ILD and features suggestive of CTD but did not fulfil the criteria for any defined CTD. She was diagnosed as IPAF and treated accordingly. The index of suspicion was based on clinical presentation, radiological findings and some laboratory abnormalities.

Case Report

A 53-year-old female presented with a three-week history of progressively increasing shortness of breath, now present even at rest [modified Medical Research Council (mMRC) grade 4]. This was associated with proximal weakness of upper and lower limbs in the form of difficulty in ascending stairs, rising up from squatting posture and lifting heavy objects. She also developed low-grade intermittent fever not associated with rigors. She denied wheezing, chest pain, palpitations, haemoptysis, joint pain, and difficulty in swallowing. There was no history of Raynaud's phenomenon.

Clinical examination revealed tachypnoea (respiratory rate 36/min) and fever (100.3 °F). There was no pallor, clubbing or cyanosis. The oxygen saturation at room air was 88%. She had bilateral ill-defined erythematous scaling rash on the extensor surface of the forearms (Figure 1).

Figure 1. III-defined erythematous plaques with mild loosely adherent scaling rash at the extensor surface of the forearm.

Neurological examination revealed bilaterally symmetric proximal muscle weakness in upper and lower limbs with power of 4/5. The strength of the neck muscles and at other joints was normal. The muscular tone was normal with no involuntary movements,

[Received: April 1, 2019; accepted after revision: December 3, 2019]

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normal deep tendon reflexes, no sensory loss and no muscular atrophy. On auscultation, vesicular breath sounds of equal intensity were audible bilaterally alongwith fine end-inspiratory 'velcro-like' crackles in bilateral infrascapular region.

Arterial blood gas analysis revealed pH–7.40, partial pressure of arterial carbon dioxide ($PaCO_2$)–29.4 mmHg, partial pressure of arterial oxygen (PaO_2)–55.7 mmHg, bicarbonate-–17.7 mmol/L, lactate–1.6 mmol/L. and serum K+–4.2 meq/L, suggestive of respiratory alkalosis with non-anion gap metabolic acidosis (NAGMA). The serum chloride and creatinine values were normal. There was no history of administration of intravenous fluids. The urinary pH was 5.6 and the urine anion gap was positive, suggesting type 1 renal tubular acidosis.

Laboratory parameters demonstrated a leucocyte count of 6000/mm^3, haemoglobin 11.9g/dL, platelet count 248000/mm^3, erythrocyte sedimentation rate 45mm/hour, and C-reactive protein 41.33mg/dL. Serum creatine phosphokinase (CPK) was 1,176 units/L (normal range 29–168 units/L) with a thyroid stimulating hormone (TSH)1.53μIU/mL (normal range 0.5–5.0 μIU/mL). Serum antinuclear antibody (ANA) was positive (3+; 1:1000, speckled-granular, enzyme immunoassay method); complement C3 level was low at 87mg/dL, (normal range 90-180) and C4 level was normal at 21mg/dL (normal range 15-57). Serum anti-dsDNA antibody was positive at 2.8 (positive>1.11). Anti-SS-A (3+), anti-Ro52 recombinant (3+), anti-SS-A antibody (2+) and U1-RNP/Sm (1+) antibodies were also positive. Anti-Jo-1 antibody, anti-La antibody, anti-cardiolipin antibody, rheumatoid factor and anti-cyclic citrullinated peptide antibody were negative. The level of 24-hour urinary protein was 338mg/24hours. Anti-phospholipid antibody and Coombs' tests were negative. Based on these findings, a diagnosis of connective disorder with overlap syndrome (Sjogren's syndrome [SS]) with systemic lupus erythematosus (SLE) was considered.

Chest radiograph revealed bilateral reticular opacities in the lower zones. The contrast-enhanced and high-resolution computed tomography (CT) of the thorax demonstrated discrete and coalescent fibro-atelectatic, fibro-nodular and ground-glass opacities with patchy consolidation in bilateral lung fields extending from upper to lower zone, with a predominance in the lower and sub-pleural locations (Figure 2 A,B). Pulmonary function testing could not be performed as patient was tachypnoeic.

Electromyography revealed myopathic changes in the deltoid, hip flexor, and extensor muscles. Muscle biopsy revealed non-specific inflammatory changes. Fibreoptic bronchoscopy with transbronchial lung biopsy showed features consistent with pneumonitis. Bronchial aspirates for acid-fast bacilli, fungus and pyogenic organisms were negative. Ophthalmological examination confirmed a positive Schirmer's test. The minor gland biopsy demonstrated inflammatory stromal infiltrate with loosely dispersed lympho-plasmacytes and absence of sialadenitis, granuloma or atypical cells. Skin biopsy showed mild epidermal papillomatosis and hyperkeratosis with mild dermal peri-capillary lymphohistiocytic infiltrate admixed with plasma cells.

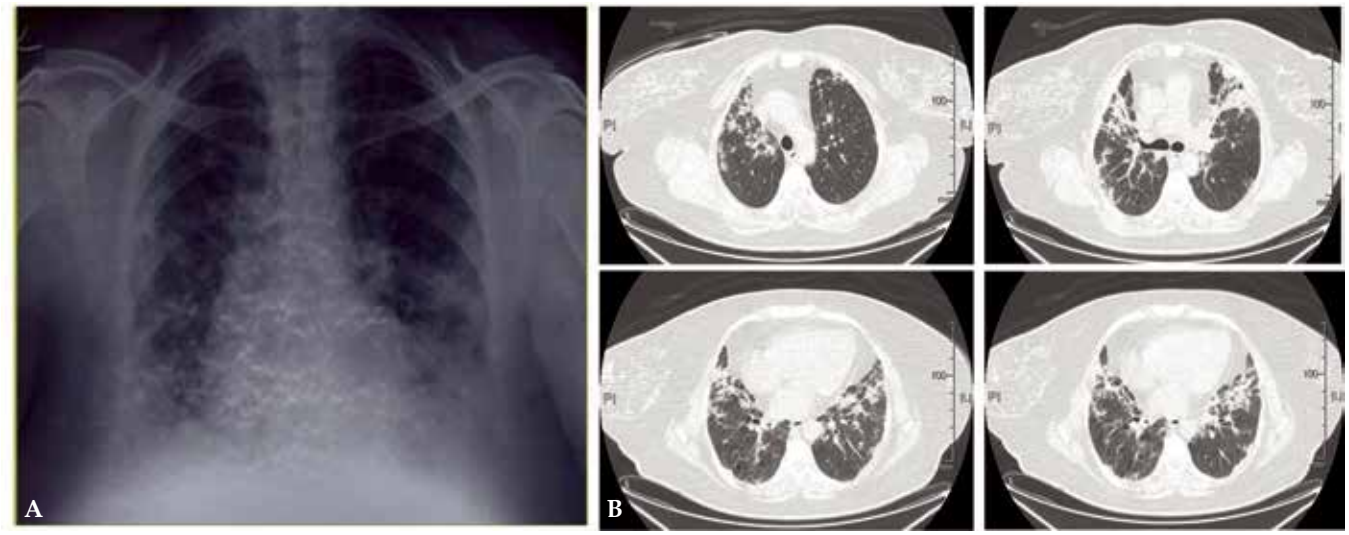
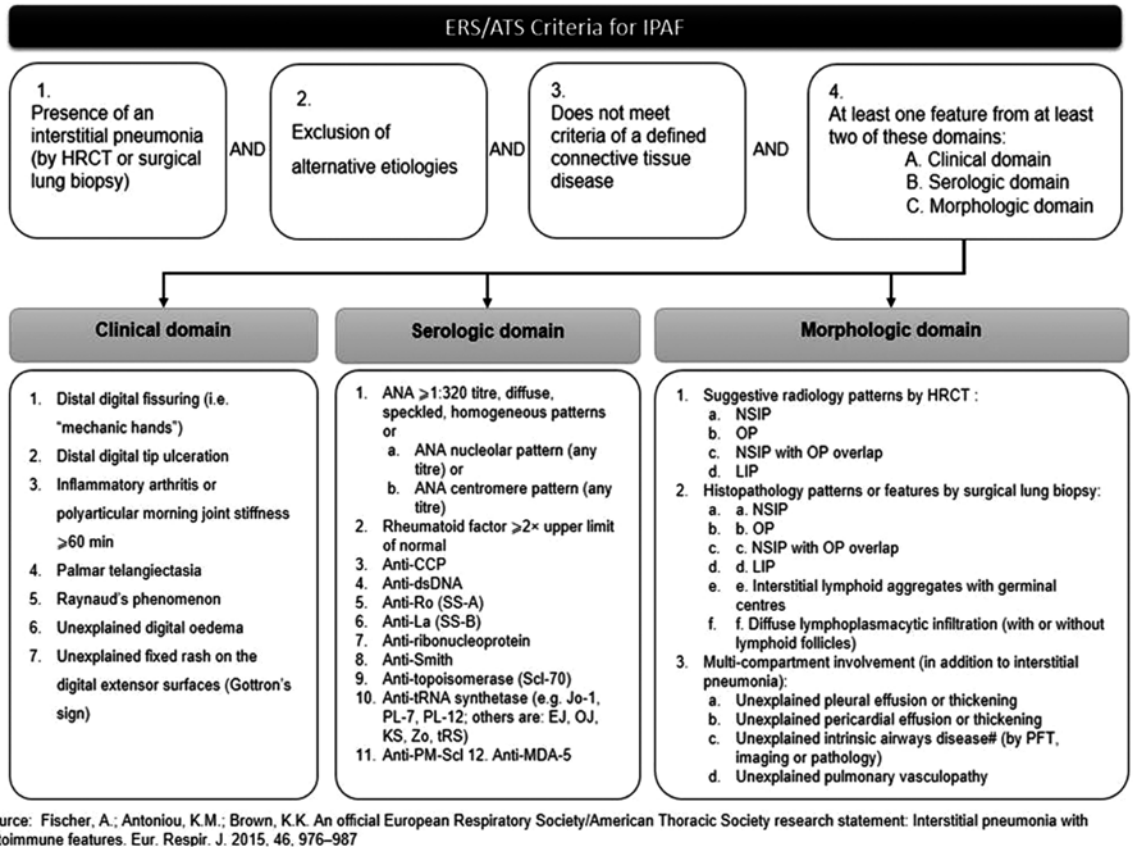


Figure 2. (A) Chest radiograph (postero-anterior view) showing reticular opacities in the lower zones bilaterally and (B) high resolution computed tomography of the thorax demonstrated discrete and coalescent fibro-atelectatic, fibro-nodular and ground-glass opacities with patchy consolidation in bilateral lung fields.



Source: Fischer, A.; Antoniou, K.M.; Brown, K.K. An official European Respiratory Society/American Thoracic Society research statement: Interstitial pneumonia with autoimmune features. Eur. Respir. J. 2015, 46, 976–987

Figure 3. ERS/ATS Criteria for interstitial pneumonia with autoimmune features.

Our patient failed to meet the American Cardiology of Rheumatology (ACR) criteria 2012[2] for diagnosing SS (any 2 of the serological parameters, ocular staining score ≥3 or lympfocytic sialadenitis). The patient also did not fulfil ACR 2016 for diagnosing SS as she did not have any symptoms of dry eyes, sensation of sand and/or gravel in eye, need of tear drops, dry mouth or frequent drinking of liquids to aid in swallowing.[3] Similarly, she did not fulfil ACR criteria for SLE.

Initially, we made a diagnosis of CTD-ILD (connective tissue disease-related interstitial lung disease) with clinical, serologic, pulmonary and morphological features stemming from a systemic autoimmune condition. However, the patient failed to fulfil the defined criteria of CTD-ILD. This group of patients are termed as interstitial pneumonia with autoimmune features (IPAF) in a recent official statement of the European Respiratory Society/American Thoracic Society in 2015 (Figure 3).[5] No specific treatment protocol for this condition has been described. Hence, it should be managed as per the established treatment regimen for the most closely resembling CTD.

We treated our patient with pulse doses of cyclophosphamide (1g every four weeks) and pulse methylprednisolone (1g/day) intravenously for three days, followed by prednisolone (1mg/kg) daily. Marked symptomatic relief and improvement in partial pressure of arterial oxygen from 55 to 64 mmHg was observed. The muscle power improved to 5/5 and serum CPK level reduced to 554U/L.

Discussion

Connective tissue disorders are systemic, autoimmune, multi-organ diseases with remarkably heterogeneous clinical features. These may involve the airway, parenchyma, pleura, pulmonary vasculature or the respiratory muscles. Interstitial lung disease is a commonly associated condition with CTDs that may lead to respiratory failure with higher morbidity and mortality. Of the ILD patterns, non-specific interstitial pneumonia (NSIP) is the commonest form; except in rheumatoid arthritis where usual interstitial pneumonia (UIP) is more commonly seen.[5]

Specific diagnostic criteria have been established for each CTD, based on clinical, serological and histopathological characteristics. However, there are many cases of ILD with subtle features of an autoimmune condition that are insufficient to meet

Table. A systematic review published in ERS in 2017 to identify specific characteristics of IPAF cases included four original studies[6]

Study	Number of Cases	Mean Age (in years)	Major Radiological/ Biopsy Finding	Outcome
Oldham *et al*[7]	144	63	UIP	Non UIP-IPAF better than UIP-IPAF
Chartrand *et al*[8]	56	54.6	NSIP	No mortality during follow-up (duration of 284.9±141.3 weeks)
Ahmad *et al*[9]	57	64.4	NSIP	No difference in mortality between NSIP or UIP patterns
Ito *et al*[10]	99	68	NSIP	NSIP and age were poor prognostic markers

Definition of abbreviations: ERS=European Respiratory Society; IPAF=Interstitial pneumonia with autoimmune features; UIP=Usual interstitial pneumonia; NSIP=Non-specific interstitial pneumonia.

the defined diagnostic criteria for any specific CTD. A similar diagnostic dilemma was encountered in this patient who had ILD and her clinical, serological and biopsy features were overlapping with SLE and SS; but did not fit in any one of the specific CTDs.

The terms like undifferentiated CTD associated ILD (UCTD-ILD), lung dominant CTD or autoimmune featured ILD were used in the past to describe such patients. In 2015, the European Respiratory Society (ERS) and American Thoracic Society (ATS) joint "Task Force on Undifferentiated Forms of CTD-ILD" proposed a consensus definition (Figure 3). However the task force had not given recommendations for clinical care, diagnostic testing or management of these patients.

Besides proposing the standard definition, systematic review (Table) also suggested that IPAF could be a primary autoimmune disease, which mainly focuses on the lung.[6] The hypothesis is based on the characteristic heterogeneity encountered in the clinical presentation and laboratory investigations of such patients. The standard treatment protocol of these patients has not been outlined yet. It is hoped that with more such cases being identified to fulfil the proposed clinical entity, there will be more understanding of this condition and the diagnostic criteria and management guidelines will become more robust.

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