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Case Report

Interstitial pneumonia with autoimmune features (IPAF): A distinct group of idiopathic interstitial pneumonia - A case report on organizing pneumonia with positive anti Scl-70

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Key words: idiopathic interstitial pneumonia, organizing pneumonia, interstitial pneumonia with autoimmune features, autoimmune diseases, extractable nuclear antigen antibodies, systemic sclerosis

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Introduction

The idiopathic interstitial pneumonias (IIPs) are a group of diffuse parenchymal lung diseases (DPLDs) commonly referred as interstitial lung diseases (ILD). They result from lung parenchymal injury due to inflammation and fibrosis and though they primarily affect the interstitium, the airspaces, peripheral airways and vessels also can get affected. [1] IIPs share similar clinical, radiologic and histopathologic features [2]. IIP consists of major IIPs, rare IIPs and unclassifiable IIPs. Idiopathic pulmonary fibrosis (IPF), non-specific interstitial pneumonia (NSIP), respiratory bronchiolitis-interstitial lung disease (RB-ILD), cryptogenic organizing pneumonia (COP), desquamative interstitial pneumonia (DIP) and acute interstitial pneumonia (AIP) are classified under major IIPs whereas idiopathic lymphoid interstitial pneumonia (ILIP) and idiopathic pleuroparenchymal fibroelastosis (IPPF) are grouped as rare IIPs (Figure 1) [3].

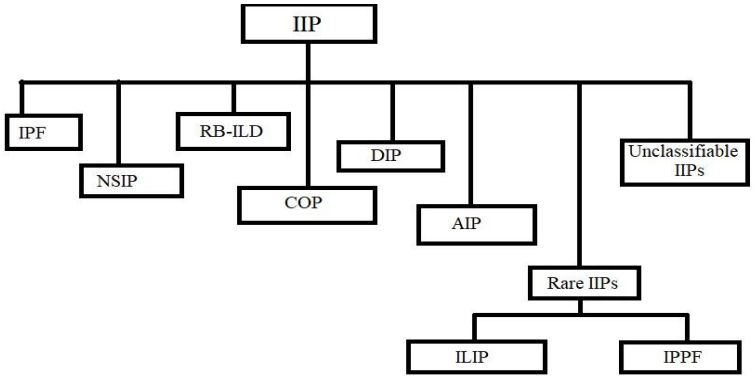

Figure 1: Classification of idiopathic interstitial pneumonia

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IIP is a diagnosis of exclusion. Known causes of interstitial pneumonia such as environmental exposures, medication toxicity or connective tissue disorders CTD should be excluded to arrive at the diagnosis of IIP [1].

The CTDs include a wide spectrum of heterogenous conditions such as systemic lupus erythematosus (SLE), scleroderma, myositis, antiphospholipid syndrome (APLS), and Sjögren syndrome. Presence of specific autoantibodies and immune-mediated chronic inflammation leading to tissue damage, collagen deposition and possible loss of function of the affected organ are the characteristic features [4,5] Lung involvement is a common complication of these CTDs and interstitial lung disease (ILD) accounts for significant morbidity and mortality. (5) But it should be noted that around 25% of patients with features of a systemic autoimmune CTD do not satisfy the recognized classification criteria for CTD [6].

A significant problem arose while attempting to categorize patients with interstitial pneumonia with features (clinical, serological or morphological) of a systemic autoimmune condition which was not sufficient for clinical diagnosis of such CTD. This group of patients who were earlier referred to using non-specific terms such as UCTD-ILD, lung-dominant CTD and autoimmune-featured ILD, have been assigned a new category namely interstitial pneumonia with autoimmune features (IPAF) as recommended by the Task Force on Undifferentiated Forms of CTD-ILD, a joint effort of the European Respiratory Society (ERS) and the American Thoracic Society (ATS) [2] (Figure 2). It is estimated that the prevalence of IPAF is around 7 to 34% of all ILDs [6].

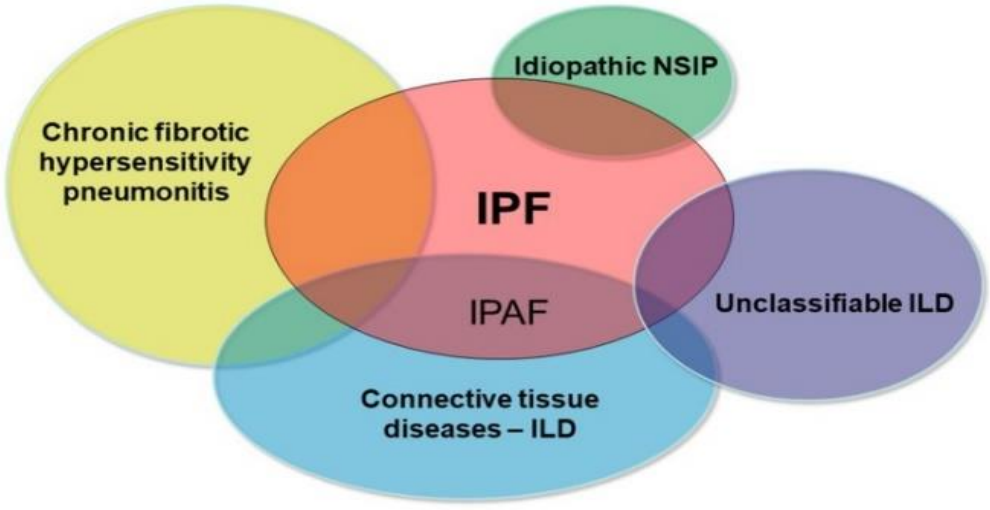

Figure 2: "Schematic representation of the main differential diagnoses of pulmonary fibrosis" by Fernandes, Nasser, Ahmad and Cottin (Own work) [CC-BY-SA-4.0 (https://creativecommons.org/licenses/by-sa/4.0)] via Front Med (Lausanne). 2019; 6: 209 Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6798044

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Case presentation

A 38-year-old woman, a known patient with hypothyroidism, was referred from District General Hospital (DGH) Kilinochchi to Teaching Hospital Jaffna (THJ) after she was found to have poorly resolving airspace and interstitial shadowing on her chest X-ray (CXR). She had a sub-acute onset of exertional breathlessness of mMRC Grade 111 and a dry cough for one month at presentation. She did not have fever or haemoptysis. She ~~also~~ complained of loss of appetite of recent onset. She denied any symptoms suggestive of autoimmune connective tissue disorder such as Raynaud phenomenon, arthritis, skin rashes or proximal myopathy. There was no history of exposure to any organic or inorganic antigens including avian antigens. She did not recall a past history, family history or contact of tuberculosis. She was tachypnoeic with an on-air oxygen saturation (SpO_2) of 91%. She was afebrile, not pale and haemodynamically stable. Auscultation demonstrated bilateral fine basal crepitations. All other systems examination were unremarkable. Arterial blood gas (ABG) analysis showed hypoxaemia without hypercapnia (type I respiratory failure). She was commenced on oxygen via nasal prongs. The basic blood investigations showed normal cell counts, unaltered liver function tests and renal functions. Erythrocyte sedimentation rate (ESR) was markedly elevated with a minimal rise in C-reactive protein (CRP). Sputum for acid fast bacilli (AFB) (3 samples) and Mantoux test were negative (Table 1) 12 lead electrocardiogram (ECG) was normal.

Table 1: Summary of investigations

Investigations	Days since admission					
	D_1	D_2	D_3	D_5	D_7	D_{41} (R/V)
WBC (× 10^3/μL)	9.10	7.67	15.99	-	11.49	8.09
N (%)	72.5	74.5	86.4	-	92.2	79.0
L (%)	21.3	18.9	9.0	-	5.5	19.0
E (%)	0.8	1.3	0	-	0.1	0.1
Hb (g/dL)	13.7	12.6	13.4	-	13.3	13.6
Plt (× 10^9/μL)	273	299	346	-	321	246
ALT (U/L)	13	-	11	-	23	37
AST (U/L)	37	-	15	-	13	-
ALP (U/L)	-	-	48	-	43	-
TP (g/L)	-	-	78	-	65	-
Alb (g/L)	-	-	33	-	28	-
SCr (μmol/L)	-	73	74	-	94	72
BU (mmol/L)	2.5	2.8	3.6		5.3	-
Na (mmol/L)	137	142	138	-	139	-
K (mmol/L)	4.9	4.3	4.1	-	3.8	-
CRP (mg/L)	18.6	16.9	17.2	6.4	1.5	1.0
ESR (mm/1st hour)	105	-	-	90	57	25
RT-PCR Covid-19	Negative					
ANA	Negative 1:80					
RF	Negative (<8 IU/ml)					
BAL						
Bacterial culture	*Pseudomonas* species isolated					
Fungal culture	No growth					
GeneXpert MTB/RIF	*Mycobacterium tuberculosis* not detected					

WBC, white blood cells; N, neutrophils; L, lymphocytes; E, eosinophils; Hb, haemoglobin; Plt, platelets; ALT, alanine transaminase; AST, aspartate transaminase; ALP, alkaline phosphatase; TP, total protein; Alb, albumin; S.cr, serum creatinine; BU, blood urea; Na, sodium; K, potassium; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factor; ANA, anti-neutrophil antibody; RT-PCR Covid-19, reverse transcriptase-polymerase chain reaction for novel corona virus disease 2019; BAL, bronchoalveolar lavage; (D_x), days since first admission; R/V, review

CXR showed bilateral lower zone airspace and interstitial shadowing (right > left) (Figure 3). High resolution computed tomography (HRCT) of the chest revealed bilateral basilar predominantly ground glass opacification and consolidation in the peripheral and peribronchovascular distribution with peri lobular arcades and parenchymal bands favouring organizing pneumonia. In addition, there were areas of overlying intralobular septal thickening in some areas suggesting a possibility of overlap with non-specific interstitial pneumonitis (Figure 4).

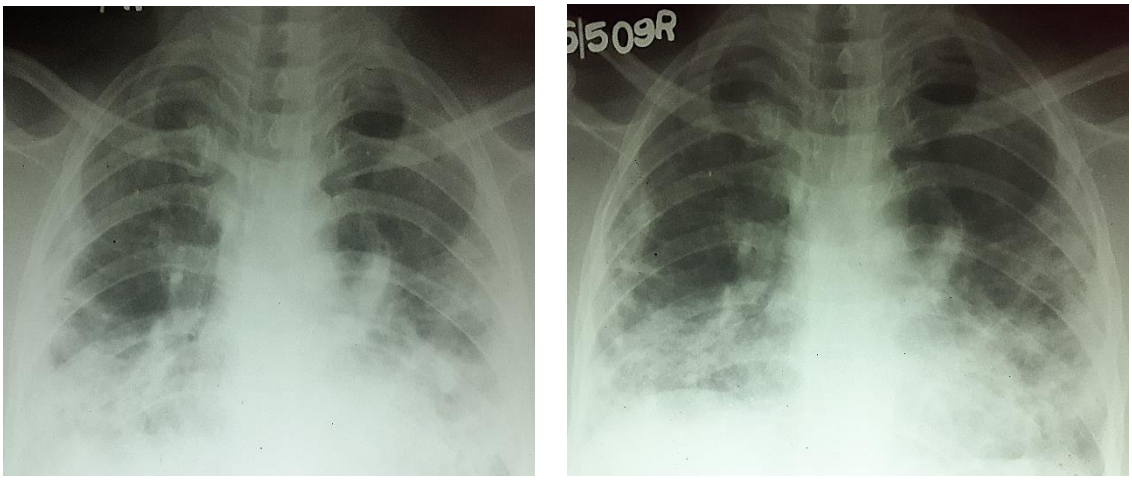

Figure 3: CXRs – Prior to treatment (left) and after treatment with steroids (right)

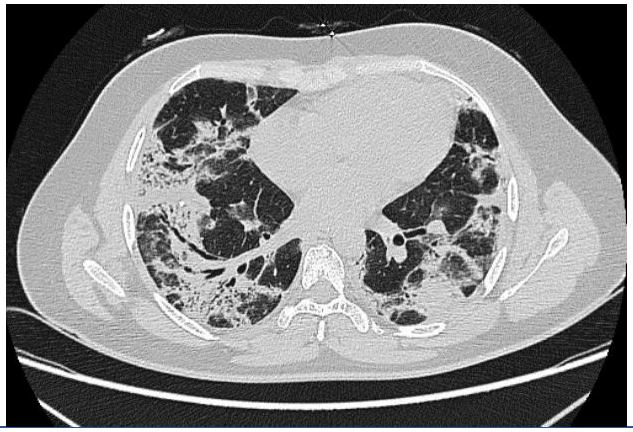

Figure 4: HRCT (lung window) revealed bilateral basilar predominant ground glass opacification and consolidation in the peripheral and peribronchovascular distribution with peri lobular arcades and parenchymal bands favouring organizing pneumonia

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However, there were no definite features of fibrosing interstitial lung disease, such as traction bronchiectasis or honeycombing in the HRCT. RT-PCR assay for Covid 19 was negative. Bronchoscopy was performed with the intent of getting BAL for microbiology and transbronchial lung biopsy. However, transbronchial lung biopsy was not performed because of profound desaturation during the procedure.

She was started on intravenous (IV) ceftazidime 1g 8 hourly and oral clarithromycin 500mg 12 hourly. She was initially started on IV methylprednisolone 125mg daily for 2 days. The dose of methylprednisolone was increased to 1000mg when she developed worsening respiratory failure with increase in the oxygen requirement to 60%. Steroid treatment was combined with oral alendronate 70mg weekly and oral calcium-vitamin D supplements as antiresorptive therapy. *Pseudomonas* was isolated on bacterial culture of BAL with sensitivity to all first line anti pseudomonas antibiotics. Rest of the BAL microbiology tests for TB and fungal studies were negative. After five doses of IV methylprednisolone, she was continued on oral prednisolone 40mg daily. She was also initiated on oral cotrimoxazole 480mg daily as *Pneumocystis carinii* prophylaxis. Clinical improvement was noticeable on day 5 after commencement of systemic steroids with reduction in the oxygen requirement and work of breathing. She was completely weaned from oxygen within one week of steroids. Follow up CXR showed improvement of airspace opacification. She was transferred back to DGH-Kilinochchi with a plan of continuation of oral prednisolone. Review was arranged at the respiratory clinic at THJ.

As anti-nuclear antibody (ANA) and rheumatoid factor (RF) turned out to be negative and the patient showed dramatic improvement with steroids, extractable nuclear antigen (ENA) panel was done and revealed positive anti scleroderma 70 (anti-Scl-70) antibodies (Table 2).

Table 2: Antibodies against extractable nuclear antigen (ENA)

Investigations	**Results**
Anti Jo-1 antibody	Negative
Anti RNP antibody	Negative
Anti Scl 70 antibody	**Positive**
Anti Sm antibody	Negative
Anti Ro (SSA) antibody	Negative
Anti La (SSB) antibody	Negative

Oral azathioprine 100 mg daily was added to her medications as a steroid sparing agent and she was referred to the rheumatology clinic, THJ for follow-up. On routine review, at 6th week after admission, ESR was noted to be normal (Table 1) and CXR showed significant improvement in the pulmonary infiltrates (Figure 5). Lung function tests showed a restrictive pattern of moderate severity. Further evaluation for underlying systemic sclerosis was arranged at the rheumatology clinic.

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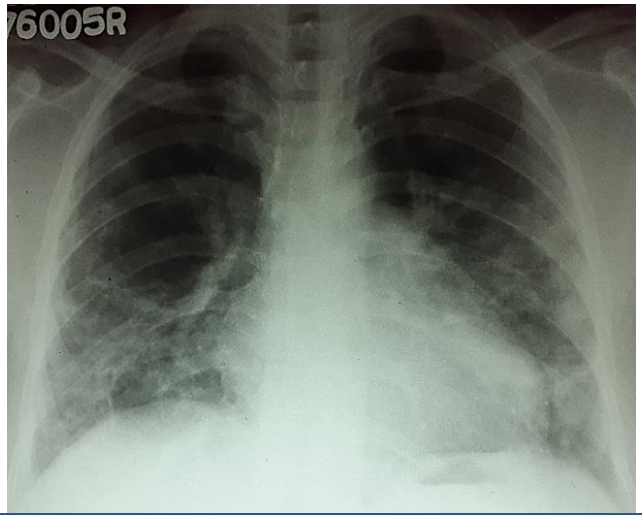

Figure 5: CXR on 6th week after treatment shows significant resolution of the pulmonary opacities

Discussion

According to the ERS/ATS Task Force on Undifferentiated Forms of CTD-ILD, classification criteria for IPAF consists of clinical, serological and morphological domains. (Table 3) The clinical domain comprises seven clinical features of autoimmune diseases and the serologic domain has 12 types of autoantibodies specific for various autoimmune connective tissue diseases while the morphological domain has HRCT and histopathologic findings of certain IIPs and evidence of multi-compartment involvement (in addition to interstitial pneumonia) [2].

Table 3: Classification criteria for interstitial pneumonia with autoimmune features (IPAF)

Presence of an interstitial pneumonia (by HRCT or surgical lung biopsy) *and*, Exclusion of alternative aetiologies *and*, Does not meet criteria of a defined connective tissue disease *and*, At least one feature from at least two of these domains: A. Clinical domain B. Serologic domain C. Morphologic domain	
A. Clinical domain • Distal digital fissuring (*i.e.,* "mechanic hands") • Distal digital tip ulceration • Inflammatory arthritis *or* polyarticular morning joint stiffness ≥60 min • Palmar telangiectasia • Raynaud's phenomenon • Unexplained digital oedema • Unexplained fixed rash on the digital extensor surfaces (Gottron's sign)	**C. Morphologic domain** • Suggestive radiology patterns by HRCT a. NSIP b. OP c. NSIP with OP overlap d. LIP • Histopathology patterns or features by surgical lung biopsy: a. NSIP b. OP c. NSIP with OP overlap

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B. Serologic domain • ANA ≥1:320 titre, diffuse, speckled, homogeneous patterns *or* a. ANA nucleolar pattern (any titre) *or* b. ANA centromere pattern (any titre) • Rheumatoid factor ≥2× upper limit of normal • Anti-CCP • Anti-dsDNA • Anti-Ro (SS-A) • Anti-La (SS-B) • Anti-ribonucleoprotein • Anti-Smith • Anti-topoisomerase (Scl-70) • Anti-tRNA synthetase (*e.g.* Jo-1, PL-7, PL-12; others are: EJ, OJ, KS, Zo, tRS) • Anti-PM-Scl • Anti-MDA-5	d. LIP e. Interstitial lymphoid aggregates with germinal centres f. Diffuse lymphoplasmacytic infiltration (with or without lymphoid follicles) • Multi-compartment involvement (in addition to interstitial pneumonia): a. Unexplained pleural effusion or thickening b. Unexplained pericardial effusion or thickening c. Unexplained intrinsic airways disease (by PFT, imaging or pathology) d. Unexplained pulmonary vasculopathy

HRCT: high-resolution computed tomography; ANA: antinuclear antibody; NSIP: non-specific interstitial pneumonia; OP: organising pneumonia; LIP: lymphoid interstitial pneumonia; PFT: pulmonary function testing.

A minimum of one feature each from at least two of the three domains is needed to satisfy these criteria. This patient satisfied the above criteria by having a positive Scl-70 and an OP pattern in the HRCT though none of the clinical features were present.

Bacterial pneumonia was considered less likely because of the normal FBC on admission with a relatively low CRP and characteristic HRCT findings suggestive of OP. The mild neutrophil leucocytosis witnessed on day 3 to day 5 could be due to treatment with steroids.

HRCT showed features of OP which is one of the suggestive radiology patterns. Despite the positive Scl-70, she had neither skin thickening of fingers (the diagnostic feature of systemic sclerosis) nor supportive features such as Raynaud phenomenon, ischaemic fingertip ulceration, calcinosis cutis, mucocutaneous telangiectasia, dysphagia or nailfold capillary changes. (10). HRCT did not reveal any ancillary finding such as a dilated oesophagus to suggest the possibility of scleroderma or scleroderma sine scleroderma. Anti-Scl-70 autoantibodies have almost never been seen in healthy persons [11]. However, they are also seen in patients with systemic lupus erythematosus and rheumatoid arthritis [11,12]. This patient did not have features suggestive of SLE or RA.

The mean age of patients with IPAF varies from 60 to 65 years with an equal sex ratio (6) although some studies show female predisposition [13,14,15]. Smoking appears to be associated with development of IPAF [15], although one single centre study concluded

that most patients with IPAF were non-smokers [14]. Over 90% of patients have at least one of the serological criteria [13] with ANA being the commonest followed by anti-Ro (SSA) and anti-tRNA-synthetase antibodies [14]. The most frequent HRCT and/or histological pattern was noted to be NSIP [13,14,15].

The underlying pathophysiology of IPAF is not clear and it is believed to be somewhat similar to that of IPF and CTD-ILD [6] (Figure 6). Nevertheless, IPAF patients were found to differ from IPF and CTD-ILD with regard to demographics, rate of progression, overall prognosis and genomic factors. Genotype analysis showed that patients with IPAF had short leukocyte telomere lengths (LTL) compared to IPF. Also, the MUC*5B* minor allele has been found to be overrepresented in them [16]. MUC*5B* codes for the protein called Mucin 5B, which is a major constituent of mucus in the respiratory tract [17].

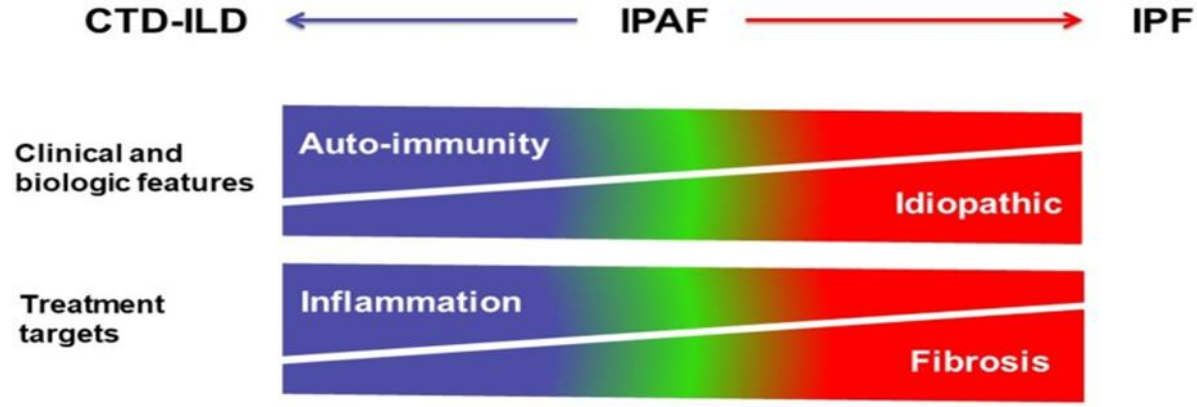

Figure 6: "Schematic representation of the spectrum of interstitial lung diseases with or without autoimmunity." By Fernandes, Nasser, Ahmad and Cottin (Own work) [CC-BY-SA-4.0 https://creativecommons.org/licenses/by-sa/4.0)] Front Med (Lausanne). 2019; 6: 209 Available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6798044

Management needs to be carefully tailored to the patient because of the wide heterogeneity of IPAF. (Figure 6) Further studies are needed to establish the optimal treatment strategy for IPAF as the available data is scarce. Pulmonary rehabilitation therapy, prevention of infection, long-term oxygen therapy and treatment of gastro-oesophageal reflux are some common management strategies that could be used, as in case of other ILDs. (6) As IPAF shows similarities to CTD-ILD, such as autoantibody positivity and HRCT features, and based on the observation that lung function improved after immunosuppressive therapy, it is advised to start early immunosuppressive treatment for patients with IPAF even though they do not have extrapulmonary features [18].

IPAF remains an orphan lung disease as there is no randomized controlled trial (RCT) evidence to support immunomodulation in IPAF. In the absence of a consensus regarding treatment, various therapeutic agents have been used to treat IPAF with mixed results. Mycophenolate and rituximab have shown some promising results [19,20]. Corticosteroids and immunosuppressants such as cyclophosphamide, azathioprine or

cyclosporine are thought to be effective in treating IPAF based on extrapolated evidence from CTD ILD [6,21,22] Antifibrotics such as ninetadanib and pirfenidone could be used in patients IPAF with evidence of the progressive fibrosing interstitial lung disease phenotype based on evidence from the INBUILD study [23,24]. The heterogenicity of IPAF needs to be kept in mind when making management decisions. Treatment response to the different immunomodulators or antifibrotics might vary between individuals depending on the HRCT or histopathological pattern and clinical and serological characteristics.

The organising pneumonia pattern seen in our patient is usually responsive to steroids. Most patients show an impressive clinical response within one week. However, radiological resolution might take several weeks. Macrolides and 2nd line immunosuppressive medications such as cyclophosphamide, mycophenolate mofetil, rituximab and cyclosporin can be used in steroid refractory or steroid dependant disease [25].

Prognosis in IPAF appears to be intermediate between that of IPF and CTD-ILD. Poor prognosis in IPAF is linked to higher age, smoking history and anti-RNP positivity (6). Prognosis also depends on the pathological or radiological pattern (UIP versus Non-UIP). UIP pattern is associated with worse prognosis than Non-UIP pattern [26].

Conclusion

Interstitial pneumonia with autoimmune features (IPAF) is a new categorization introduced to distinguish a subset of idiopathic interstitial pneumonia (IIPs) with features of autoimmunity that are not enough for the diagnosis of a specific autoimmune disease. Management for this relatively new group of IIPs is not established though various treatment options targeting inflammation and fibrosis are considered. Further research and clinical trials are warranted to address anomalies found in this classification system and to develop a commonly accepted treatment strategy.

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