International Journal of Advances in Medicine
Manchandani UK et al. Int J Adv Med. 2025 Jul;12(4):447-450
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20251944

Case Report

Interstitial lung disease as initial presentation of ANCA associated vasculitis

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Received: 16 May 2025
Accepted: 09 June 2025

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ABSTRACT

Interstitial lung disease (ILD) can occur in relation to many autoimmune processes. Occasionally, ILD may also occur in the presence of anti-neutrophil cytoplasmic antibodies (ANCA). In this paper, we report the case of a 60-year-old female with a long-standing history of ILD who later developed anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and glomerulonephritis. Her clinical progression, where ILD emerged prior to systemic manifestations of AAV, supports the hypothesis that rarely ILD may be an early manifestation of ANCA-associated vasculitis. Additionally, we reviewed existing literature examining the connection between ILD and AAV. The published data suggest that ILD may precede ANCA-associated vasculitis, reinforcing the importance of a multidisciplinary approach for optimal management. Further research is necessary to further understand the underlying mechanisms linking ILD and AAV and to develop evidence-based treatment guidelines.

Keywords: Acute kidney injury, Antineutrophil cytoplasmic antibody, Associated vasculitis, ANCA associated vasculitis, Interstitial lung disease, MPO-ANCA, Pulmonary fibrosis

INTRODUCTION

Interstitial lung disease (ILD) encompasses a broad spectrum of pulmonary conditions characterized by fibrosis and inflammation of the interstitial tissue. This includes idiopathic pulmonary fibrosis (IPF), connective tissue disease (CTD)-associated ILD, interstitial pneumonia with autoimmune features (IPAF) and hypersensitivity pneumonitis (HP). The European respiratory society and American thoracic society classify IPAF as idiopathic interstitial pneumonia with features suggestive, but not definitive, of CTD, as these patients do not meet the American college of rheumatology (ACR) criteria for a defined autoimmune disease.[1] Recent research has identified a relationship between ILD and anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV). Studies have indicated that ILD in ANCA-positive patients sometimes precede the onset of ANCA-associated vasculitis and glomerulonephritis.[2-5] However, further research is required to better understand ILD as an initial manifestation of ANCA-associated vasculitis.

Usual interstitial pneumonia (UIP) is the predominant morphological pattern of ILD associated with microscopic polyangiitis (MPA) and is frequently observed in patients with MPO-ANCA (prevalence ranging from 12.9% to 78%).[3,6,7] In this article we report the case of a patient with history of ILD and MPO-ANCA who subsequently developed ANCA-associated vasculitis and glomerulonephritis. Additionally, we review existing literature to enhance the understanding of ILD in ANCA-positive patients and its potential role as a precursor to glomerulonephritis.

CASE REPORT

A 60-year-old female with a medical history of gastroesophageal reflux disease, Raynaud's phenomenon and undifferentiated connective tissue disease (UCTD) presented for care at the office in 2011. She was initially diagnosed with UCTD in 1993 and treated with hydroxychloroquine. Interstitial lung disease (ILD) was diagnosed based on CT chest changes in 2003.

Laboratory investigations from 2006 were notable for a normal CBC and CMP, positive ANA at 1:2560, elevated SS-A antibodies at 42 units and low C3 complement at 13 mg/dl. Recent labs showed the presence of MPO-ANCA along with elevated ESR and C-reactive protein (CRP). ANCA serology prior to 2011 WAS not available. Baseline CBC and metabolic panel were within normal limits (Table 1).

Initial CT chest in 2003 was performed at an outside center (images not available) and reported as mediastinal and subcarinal lymphadenopathy, bibasilar reticular opacities and a mildly dilated esophagus. The patient was being treated at our clinic from 2011 onwards. She was managed with Mycophenolate and steroids. In 2023, the patient experienced an ILD flare-up with increasing shortness of breath and cough while on mycophenolate mofetil (MMF) 1500 mg per day and 10 mg prednisone daily.

This ILD flare was managed with increased doses of MMF (2000 mg daily) and prednisone taper. A month following the ILD flare, she was admitted to the hospital for anemia and hypokalemia. She had outpatient endoscopy and colonoscopy prior to hospitalization with some benign polyps but no site of bleeding. She received a blood transfusion and IV iron in the hospital. There was elevation of her serum creatinine from 0.59 mg/dl to 1.38 mg/dl. During post-hospitalization follow-up she complained of redness of eyes. She was diagnosed with episcleritis and also found to have active pauci-immune crescentic glomerulonephritis on renal biopsy for elevated creatinine.

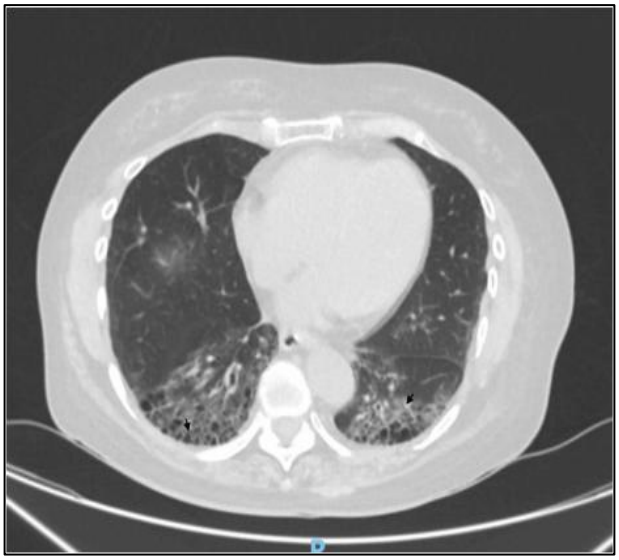

Figure 1: Computed tomography (CT) Chest showed peripheral reticulations, traction bronchiectasis and exuberant honeycombing within the lung bases (arrows).

Treatment included prednisone 50 mg daily and rituximab 1000 mg administered on days 1 and 14 for ANCA-associated vasculitis. On six-month follow-up, her renal function improved (serum creatinine 0.94 mg/dl). Most recent CT chest (Figure 1) is noted for peripheral reticulations, traction bronchiectasis and exuberant honeycombing within the lung bases and anterior margin of the upper lobes. Table 1 shows labs from 18 months prior (baseline), during glomerulonephritis and 6 months follow up.

Table 1: Labs from 18 months prior (baseline), during glomerulonephritis and 6 month follow up.

Labs	Units of measurement	Reference range	18 months prior	During glomerulonephritis*	6 months follow up
WBC count	K/ul	3.80-10.50	5.08	11.61	7.37
RBC count	M/ul	3.80-5.20	4.57	4.85	4.84
Haemoglobin	g/dl	11.5-15.5	12.3	13.5	13.5
Platelet count	K/ul	150-400	222	216	224
Sodium	mmol/l	135-145	140	140	137
Potassium	mmol/l	3.5-5.3	4.7	3.8	3.5
Chloride	mmol/l	96-108	104	101	93
Carbon dioxide	mmol/l	22-31	26	26	31
Blood urea nitrogen	mg/dl	7-23	15	26	26
Creatinine	mg/dl	050-1.30	0.59	1.31	0.94
eGFR	ML/min/1.73m^2	>=60	104	47	69
Erythrocyte sedimentation rate	mm/hour	0-2-	11	3	18
C-reactive protein	mg/l	<=4	4	3	5

*Patient was on prednisone 40 mg daily during these labs. K/uL=thousands per microliter; M/uL=millions per microliter; g/dl=grams per deciliter; mmol/L=millimoles per liter; mg/dl=milligrams per deciliter; mm/hr=millimeters per hour; mg/L=milligrams per liter.

DISCUSSION

Antineutrophil cytoplasmic antibodies (ANCA) encompass a group of autoantibodies targeting proteins within neutrophils and monocytes. The two primary types of ANCA are directed against proteinase 3 (PR3) and myeloperoxidase (MPO), corresponding to c-ANCA and p-ANCA patterns, respectively.[8] ANCA are closely linked to various autoimmune diseases collectively known as ANCA-associated vasculitides (AAV), including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA).[9]

The pattern of respiratory tract involvement is largely determined by the serotype specificity of ANCA. PR3-ANCA is typically associated with upper airway involvement, lung nodules and cavities, while MPO-ANCA is connected to lower respiratory tract diseases, including interstitial lung disease (ILD).[10] Studies have indicated an increased incidence of MPO-ANCA positivity and MPA development in patients with idiopathic pulmonary fibrosis (IPF), which is the most prevalent type of ILD.[4,11] Hervier et al studied 12 patients with PF and ANCA-positive vasculitis, all had positive MPO-ANCA. Three patients had PF diagnosed prior to the onset of ANCA vasculitis, one after ANCA-V and eight diagnosed PF simultaneously with vasculitis.[12]

Maillet et al studied patients across 21 centers in France and Belgium and reported that out of 112 patients screened, 62 had AAV, including 55 with MPO-ANCA. Of the patients with AAV, (32 patients) 52% were diagnosed with ILD before AAV development and (24 patients) 39% were diagnosed simultaneously.[5] Patients with ILD and MPO-ANCA often present with subacute onset of exertional dyspnea and may exhibit, posing a significant risk for disease progression. Although the pathogenesis of ILD in ANCA-associated vasculitis (AAV) remains incompletely understood, immune system activation plays a crucial role. MPO-ANCA has demonstrated pro-fibrotic activity in animal models, suggesting a direct contribution to progressive lung fibrosis.[13,14] Bronchoalveolar lavage (BAL) in patients with idiopathic pulmonary fibrosis (IPF) reveals neutrophilia.

Activated neutrophils express MPO on cell membranes, leading to MPO-ANCA production and release neutrophil extracellular traps (NETs), which are implicated in the pathogenesis of AAV and may induce lung fibrosis.[15-17] Additionally, MPO increases the production of toxic metabolites, including reactive oxidative species (ROS), resulting in endothelial damage and fibroblast proliferation.[18] Tugeon et al highlighted a genetic predisposition, with polymorphism in the promoter region of mucin 5B (MUC5B) identified as the most significant risk factor for IPF.[19] Advances in understanding the underlying pathogenesis of ILD and ANCA-associated vasculitis underscore the importance of immunosuppressive agents such as glucocorticoids, rituximab and cyclophosphamide in managing ANCA positive ILD. Although there are no randomized controlled trials for the treatment of AAV-ILD, anecdotal evidence suggests treating ILD associated with MPA according to the organ involved with vasculitis.[20]

CONCLUSION

Interstitial lung disease in patients with ANCA positivity presents a complex clinical scenario involving the lower respiratory system and systemic vasculitis. Evidence suggests that ILD may precede the development of ANCA-associated vasculitis (AAV) and glomerulonephritis, highlighting the need for a multidisciplinary approach involving pulmonologists, nephrologists and rheumatologists to provide optimal care. Further research is required to improve understanding of the underlying pathogenic mechanisms and develop new treatment approaches.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Manchandani UK, Khan S, Gupta D, Gupta V, Shah D, Talwar A. Interstitial lung disease as initial presentation of ANCA associated vasculitis. Int J Adv Med 2025;12:447-50.