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Short report Open Access

Idiopathic pulmonary fibrosis and p-ANCA positivity predating manifestations of systemic vasculitis

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Abstract

The occurrence of perinuclear anti-neutrophilic cytoplasmic antibodies (p-ANCA) in pulmonary fibrosis has been reported in a number of small studies, however, the appearance of p-ANCA in already established idiopathic pulmonary fibrosis (IPF), predating the manifestations of vasculitis has not been widely appreciated. We report 2 cases with radiographic evidence of established IPF where p-ANCA was negative at the time of diagnosis and became positive during the course of the disease, for a variable period of time, prior to the subsequent development of systemic vasculitis. Our cases suggest a possible rationale for serial p-ANCA measurements in patients with pulmonary fibrosis even in the absence of features suggestive of vasculitis. Furthermore, the required frequency of ANCA measurement in the absence of clinical features of vasculitis is unknown. Larger studies with repetitive p-ANCA measurement in tandem with ongoing clinical assessment for vasculitis are required to assess the prevalence of ANCA and to confirm our observation.

Keywords: Pulmonary fibrosis, vasculitis, ANCA, microscopic polyangiitis

Introduction

Anti neutrophilic cytoplasmic antibodies (ANCA) are directed against enzymes in the granules of polymorphonuclear leukocytes. ANCA positivity has been associated with vasculitides with the potential for pulmonary involvement. Cytoplasmic anti-neutrophilic cytoplasmic antibodies (c-ANCA) has high sensitivity and specificity for patients with granulomatosis with polyangiitis, whereas, perinuclear anti-neutrophilic cytoplasmic antibodies (p-ANCA) is characteristically associated with small vessel vasculitis (mainly-Churg-Strauss syndrome, pauci-immune glomerulonephritis and microscopic polyangiitis). ANCA is therefore an important serological biomarker for diagnosing and monitoring systemic vasculitis.

The occurrence of p-ANCA in pulmonary fibrosis has been reported in a number of small studies [1,2], however, the appearance of p-ANCA in already established idiopathic pulmonary fibrosis (IPF), predating the manifestations of vasculitis has not been widely appreciated [2]. We report 2 cases with radiographic evidence of established IPF where p-ANCA was negative at the time of diagnosis and became positive prior to the subsequent development of systemic vasculitis.

Short report

Case 1

A 70 year old non-smoking, female, presented with progressive breathlessness on exertion and bi-basal crackles on chest auscultation. A high resolution computed tomography of thorax (**Figure 1**) demonstrated the changes consistent with usual interstitial pneumonia (UIP). Pulmonary function testing demonstrated a pattern consistent with restrictive lung disease **Table 1**. Her p-ANCA was negative at the time of diagnosis (**Figure 2**). Her IPF remained stable radiologically; however there was a gradual decline in DLCO to 44% predicted at 3 years. At this time, p-ANCA was noted to be positive and remained positive until two years later when her MPO titres suddenly increased and were associated with the development of mononeuritis, manifesting as right foot drop and stage 3 renal diseases. These manifestations, together with p-ANCA positivity were consistent with systemic vasculitis. The clinical and laboratory findings are suggestive of microscopic polyangiitis. Her TLC at this time was 68% predicted with a DLCO of 38% predicted. She was commenced on immunosuppressive treatment (cyclophosphamide and steroids) which resulted in improvement in foot drop, stabilization

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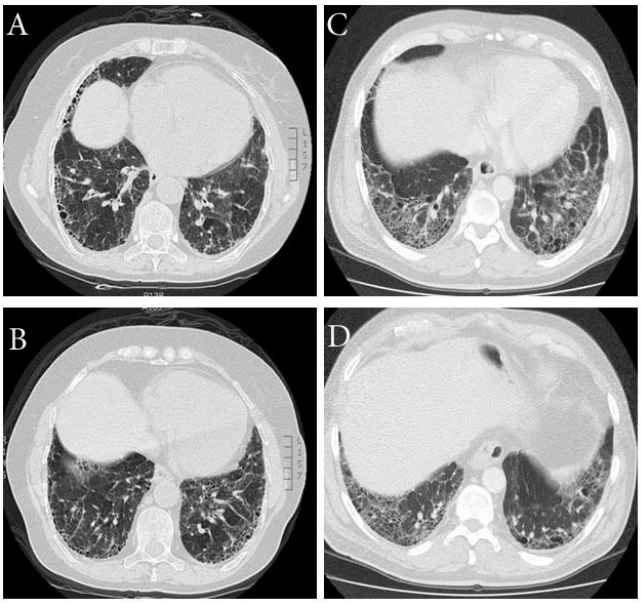


Figure 1. Axial high resolution computerized tomography of the case 1 (**A** and **B**) and case 2 (**C** and **D**) showing peripheral subpleural honeycomb cyst formation symmetrically at both lung bases. More centrally there is groundglass opacification suggesting fine fibrosis and some architectural distortion. Findings are consistent with usual interstitial pneumonia (UIP).

Table 1. Pulmonary function testing.

	2007	10/2011	07/2012	01/2013
FEV1	1.97 (95%)	1.39 (88%)	1.33 (80.5%)	1.07 (69%)
FVC	1.97 (81%)	1.77 (91%)	1.60 (82.7%)	1.30 (70%)
FEV1/FVC	82%	82.7%	78.8%	79%
TLC	73%	--	67.8%	63.6%
DLCO	94%	43.5%	37.5%	32.8%

FEV1: Forced expiratory volume in one second
%: Percentage predicted; FVC: Forced vital capacity
TLC: Total lung capacity
DLCO: Diffusion capacity for carbon monoxide

p-ANCA positive. He remained p-ANCA positive and twelve months later his MPO titres rose with subsequent development of haemoptysis and acute respiratory and renal failure (**Figure 3**).

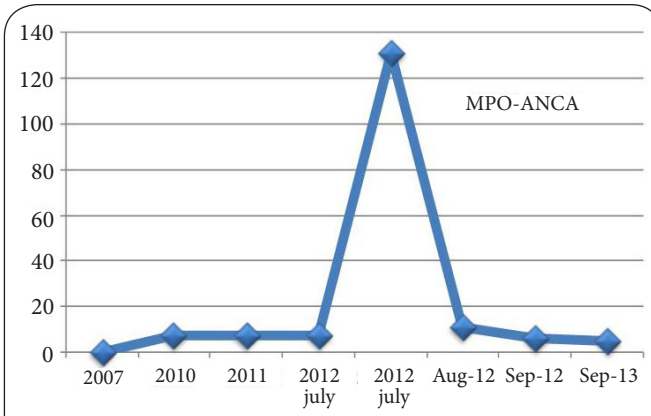


Figure 2. MPO-ANCA titres during the course of the disease. There was sudden rise with characteristic manifestations of systemic vasculitis and subsequent stabilization with immunosuppressant treatment.

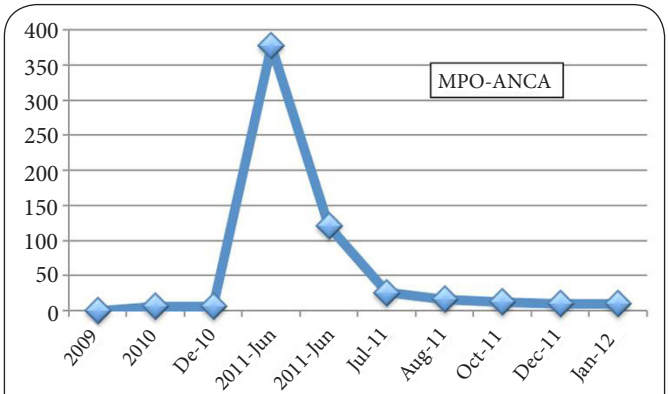


Figure 3. MPO-ANCA titres of the case 2 during the course of the disease. There was sudden rise with clinical manifestations of systemic vasculitis and subsequent stabilization with haemodialysis and immunosuppressant treatment.

of renal profile and a reduction in measured MPO titres. She remains clinically stable and subsequently maintained on azathioprine and low dose steroids.

Case 2

Our second case, a 64 year old, male, ex-smoker of 18 years (40 pack year history), initially presented to another institution with a two month history of breathlessness on exertion. Auscultation of his chest revealed bi-basal crackles. A diagnosis of IPF with UIP pattern was made based on radiology (**Figures 1C** and **1D**) and consistent lung function testing. His TLC at this time was 77% predicted with a DLCO of 53% predicted. His p-ANCA at the time of diagnosis was negative. Two years later, he was referred for lung transplant assessment and was noted to be

He was managed with plasma exchange, haemodialysis and immunosuppressant treatment. There was slow improvement in the patient's clinical status with co-existent radiological improvement observed on serial chest x-rays. His MPO titres also decreased in response to therapy. He remained on stable on immunosuppressant therapy (cyclophosphamide and steroids), and haemodialysis for one year but unfortunately suffered a fatal cardiac arrhythmia while an inpatient for the management of a fracture.

Discussion

The temporal relationship between p-ANCA positivity in already established pulmonary fibrosis and the development of vasculitis is poorly understood. Here, we report two cases

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in which p-ANCA was negative at the time of diagnosis of pulmonary fibrosis and became positive during follow-up, predating the onset of fulminant vasculitis. There are no reported differences in the clinical or radio graphical characteristics of p-ANCA positive as compared to p-ANCA negative pulmonary fibrosis at the time of initial diagnosis [3]. However, in the presence of p-ANCA positivity, the clinical course of the disease may be affected, with increased morbidity and mortality observed [3,4]. In our report there was lack of histological confirmation, however, diagnosis of microscopic polyangitis was made clinically in combination with positive MPO-ANCA testing [5].

The exact pathophysiological mechanism of the relationship between ANCA and pulmonary fibrosis remains undetermined. The predominant histological and radiological pattern for pulmonary fibrosis that has been reported in such cases is UIP [6]. Early histological studies did not detect marked differences in the degree of lung fibrosis among various types of vasculitis, suggesting that ANCA may cause a generalized type of tissue injury, possibly through the release of activated neutrophils. In one report, cumulative cigarette smoking tended to be higher in ANCA-positive patients with pulmonary fibrosis than in ANCA-negative cases [2]. Cigarette smoke has the potential to induce activated neutrophilic infiltration into the lung tissues [7]. Increased MPO on activated neutrophils promote degranulation and oxidative bursts that could lead to alveolar epithelial damage, fibroblastic proliferation and ultimately the development of fibrosis [8]. Another conceivable mechanism is that at early stages of the disease, ANCA levels remain below the threshold of conventional laboratory measurements and once the levels rise and become detectable by laboratory methods, the disease manifest itself clinically, with features of vasculitis [9]. However the reason for this remains beyond cogitation and may be related to unidentified infectious or noninfectious antigens, autoimmunity, impaired regenerative responses, and the antagonistically pleiotropic action of genes involved in wound healing or development [10,11].

Our cases suggest a possible rationale for serial p-ANCA measurements in patients with pulmonary fibrosis even in the absence of features suggestive of vasculitis. International IPF guidelines place high value on measuring autoimmune serology to distinguish IPF from pulmonary disease associated with connective tissue disease. However, the routine use of extended serological testing, in particular ANCA measurement has not been emphasized [12]. Furthermore, the required frequency of ANCA measurement in the absence of clinical features of vasculitis is unknown. Larger studies with repetitive p-ANCA measurement in tandem with ongoing clinical assessment for vasculitis are required to confirm or refute our observations.

Competing interests
The authors declare that they have no competing interests.

Authors' contributions

Authors' contributions	KK	DF	MH	MMM	MTH	MPK	BJP	DM
Research concept and design	✓	--	--	--	--	--	--	✓
Collection and/or assembly of data	✓	--	--	--	--	--	--	--
Data analysis and interpretation	✓	--	--	--	--	--	--	✓
Writing the article	✓	--	--	--	--	--	--	✓
Critical revision of the article	✓	--	--	✓	--	✓	--	✓
Final approval of article	✓	✓	✓	✓	✓	✓	✓	✓
Statistical analysis	✓	--	--	--	--	--	--	✓

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