Case Report:

p – ANCA positive systemic vasculitis in a known case of Idiopathic pulmonary fibrosis : case report

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Abstract:

When a patient presents with pulmonary fibrosis, we perform tests to rule out connective tissue diseases and vasculitis. We report a patient who was diagnosed as Idiopathic pulmonary fibrosis (IPF), p-ANCA negative status who after two years presented with renal disease. On repeating, the p-ANCA came positive. We present this rare case of Idiopathic pulmonary fibrosis on anti fibrotic treatment who later developed p-ANCA positive systemic vasculitis.

Key-words: Idiopathic pulmonary fibrosis, p-ANCA, systemic vasculitis

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 a case with radiographic evidence of established IPF where p-ANCA was negative at the time of diagnosis and became positive at presentation to us.

Case History:

A 69 year old Male presented with complains of abdominal pain since 3 days. Patient was a diagnosed case of Idiopathic pulmonary fibrosis since 2 years and was on perfinidone 1200mg/day. **Figure 1,2**

An ultrasound abdomen was performed which demonstrated grade II hyperechoic cortex in both kidneys but cortico medullary differentiation with smooth margins was maintained & the kidneys were normal in size shape and position. A simple cortical cyst of 2.5cm & 0.7 cm was seen in lower pole of left kidney. Spleen was mildly enlarged. Moderate prostatomegaly was seen. Rest of the organs visualised were normal in size and showed no obvious abnormailities. Serum creatinine was 3.0 mg/dl and BUN 37 mg/dl. Urine routine showed proteinuria of 5gm/day and microscopic hematuria. p-ANCA done was positive.

Kidney biopsy was done which showed fibrinoid change in few glomeruli on light microscopy & moderate degree of tubular atrophy & interstitial fibrosis. Patient received 6 cycles of endoxan infusion therapy and then continued with azathioprine.

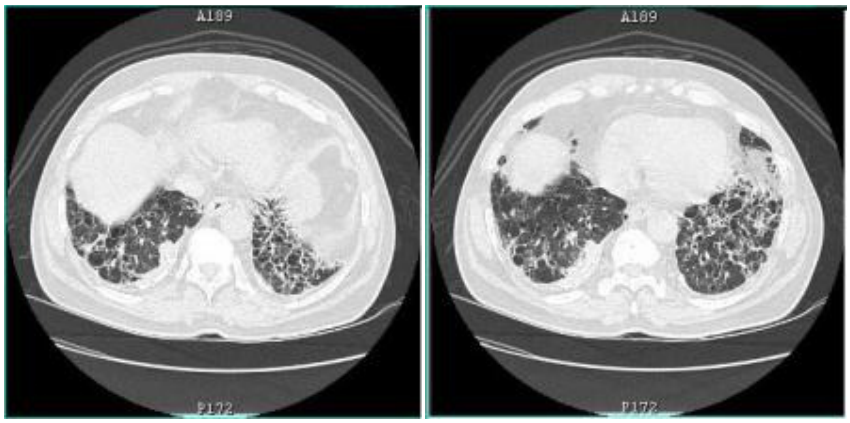

Figure 1 Figure 2

Figures 1 & 2 showing bilateral, peripheral extensive areas of honeycombing in lower lobes

Discussion:

The temporal relationship between p-ANCA positivity in already established pulmonary fibrosis and the development of vasculitis is poorly understood. Here, we report a case in which p-ANCA was negative at the time of diagnosis of pulmonary fibrosis and became positive during follow-up after 2 years thus 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].

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 [5]. 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. 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 [6].

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 [7]. However the reason for this remains beyond cogitation and may be related to unidentified infectious or non-infectious antigens, autoimmunity, impaired regenerative responses,and the antagonistically pleiotropic action of genes involved in wound healing or development [8]. Our case suggests 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 [9]. Furthermore, the required frequency of ANCA measurement in the absence of clinical features of vasculitis is unknown. Larger studies

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with repetitive p-ANCA measurement in tandem with ongoing clinical assessment for vasculitis are required to confirm or refute our observations.

Idiopathic pulmonary fibrosis (IPF), the most common form of idiopathic fibrotic lung diseases, has been associated with the production of circulating IgG autoantibodies to antigen(s) that are associated with alveolar lining cells,[10,11] and there is evidence for a local humoral immune response associated with B-lymphocyte aggregates in the IPF lungs.[12] However, there is a debate as to whether these antibodies are epiphenomenal and a secondary feature of tissue damage induced by some other mechanism, or a contributing factor to the ongoing fibrotic process.[13] Interestingly, autoimmunity was recently shown to be central in non-specific idiopathic pneumonia,[14] the second most frequent fibrotic lung disorder.

The prevalence of ANCA in patients with IPF has not been extensively studied. It was estimated to be 9% in a Japanese series of IPF patients published in an abstract form.[15] In Bichat hospital the percentage of ANCA positivity among patients with IPF was estimated to be 8% (4 among 46 patients seen within 4 years). ANCA could play a pathophysiological role in IPF as already shown in vasculitis by activating neutrophils, monocytes and endothelial cells which are known to express myeloperoxidase at their membrane. Interestingly, airway epithelial cells may also express myeloperoxidase[16] and may become a target for ANCA. One may speculate that ANCA may promote chronic lung injury and contribute to the vicious circle of lung fibrosis.

In conclusion, we suggest that a search for ANCA should be performed at diagnosis in every patient with pulmonary fibrosis as the presence of ANCA will increase the risk of development of a vasculitis and promote specific monitoring of the patients, especially if the specificity of ANCA is of anti-MPO specificity. Further studies with larger groups of patients are needed to prospectively determine whether ANCA play a pathophysiological role in fibrotic lung disorders.

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