Case Report

Microscopic Polyangiitis Associated with Primary Biliary Cirrhosis: a Causal or Casual Association?

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ABSTRACT. The association between microscopic polyangiitis (MPA) and primary biliary cirrhosis (PBC) has seldom been reported. We describe a patient with PBC and MPA who presented with polyarthritis and pulmonary nodules followed by pauci-immune crescentic glomerulonephritis and liver dysfunction. Detection of p-ANCA, antimyeloperoxidase, and antimitochondrial antibodies along with liver and renal histopathology allowed a diagnosis of MPA and PBC. We also discuss 2 other cases that could be unrecognized associations of both diseases. Further reports are necessary to clarify if the coexistence between PBC and MPA is causal or casual. (First Release Sept 15 2006; J Rheumatol 2006;33:2351–3)

Key Indexing Terms:
PRIMARY BILIARY CIRRHOSIS
VASCULITIS
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GLOMERULONEPHRITIS

Primary biliary cirrhosis (PBC) is an hepatic disease with an autoimmune pathogenesis. It is frequently associated with other rheumatic disorders such as Sjögren's syndrome, systemic sclerosis (Reynolds syndrome), or rheumatoid arthritis. However, the occurrence of primary vasculitis and PBC has seldom been reported[1]. Under the current nomenclature, only one case of microscopic polyangiitis (MPA) overlapping with PBC has been reported[2].

We describe a patient with MPA involving lung and kidney, with biopsy proven PBC. We discuss 2 additional cases that may represent additional examples of this coexistence reported under different names.

CASE REPORT

In 2000, a 59-year-old woman with chronic dry cough and dyspnea was admitted to our hospital. Eosinophil count of 1,100 cells/μl and microhematuria were found. Respiratory function (evaluated by spirometry) was unexpectedly normal, but a mild to moderate diffuse pulmonary fibrosis with several nodules was found by lung computed tomography. Cardiac function assessed by echocardiogram, immunoglobulin E, antinuclear antibodies (ANA), and rheumatoid factor (RF) were normal. An empirical therapeutic regimen including prednisone 5 mg/day and bronchodilators was started, with resolution of microhematuria and respiratory symptoms in the following 2 months.

Two years later, she developed symmetric polyarthritis involving wrists, elbows, shoulders, knees, and ankles, and systemic hypertension was detected. Laboratory screening showed C-reactive protein (CRP) of 11.3 mg/l, alkaline phosphatase (ALP) 966 U/l, aspartate aminotransferase (AST) 123 U/l, and alanine aminotransferase (ALT) 64 U/l. HIV and hepatitis B and C markers were absent, and microhematuria was again detected. She suddenly developed vertical binocular diplopia secondary to extraocular polyneuropathy. Perinuclear antineutrophil cytoplasm antibodies (p-ANCA; immunofluorescence 1:20), IgG antimitochondrial antibodies (AMA; immunofluorescence 1:5120) and IgG anticardiolipin antibodies were detected, whereas RF, ANA, anti-dsDNA, and antibodies to extractable nuclear antigen were all negative. Liver and kidney needle biopsies were performed. Liver histology showed a dense periductal inflammatory infiltration with active necrosis, periportal fibrosis, and biliary ductal neogenesis (Figure 1). Kidney histology provided evidence of patchy tubular atrophy, extracapillary hypercellularity (crescent formation) and segmental vascular fibrinoid necrosis with global sclerosis in 50% of glomeruli, while immunofluorescence staining for IgG, IgM, IgA, C3, and C4 were all negative (Figure 2). Diagnosis of MPA and PBC was made and therapy with ursodeoxycholic acid, azathioprine 50 mg/day, and prednisone 1 mg/kg/day was then started with a rapid response (resolution of diplopia and arthritis, and normalization of liver and kidney function tests), allowing its tapering to 5 mg/day over the following 3 months.

The patient remained stable until 2003 when she was admitted to our hospital due to sudden onset of malaise, fever, weight loss, and purpuric lesions in the lower limbs. On examination, hepatomegaly and pulmonary rales were present. CRP was 53 mg/l, ALP 644 U/l, AST 58 U/l, ALT 54 U/l. Microhematuria with > 250 cells/μl, creatinine clearance of 40 ml/min, and proteinuria of 812 mg/day were also detected. Raised antimyeloperoxidase antibodies (anti-MPO; 21.5 U, normal < 10) were found with normal antiproteinase-3 antibodies (anti-PR3; 0.5 U). Treatment with oral prednisone (1 mg/kg/day) progressively tapered and intravenous (IV) cyclophosphamide (500 mg in a monthly schedule) was started. Four months later, clinical and laboratory improvement was observed, while the creatinine clearance remained stable at approximately 40 ml/min.

Recently, she has developed oral and ocular dryness. Ophthalmologic evaluation detected keratoconjunctivitis sicca and ANA were positive (1:160) in a speckled pattern. Minor salivary gland biopsy was performed, showing grade II Sjögren's syndrome using Chisholm and Mason's classification.

DISCUSSION

Pulmonary involvement (mainly bronchial asthma, emphysema, and decreased diffusion capacity) is present in up to 56%

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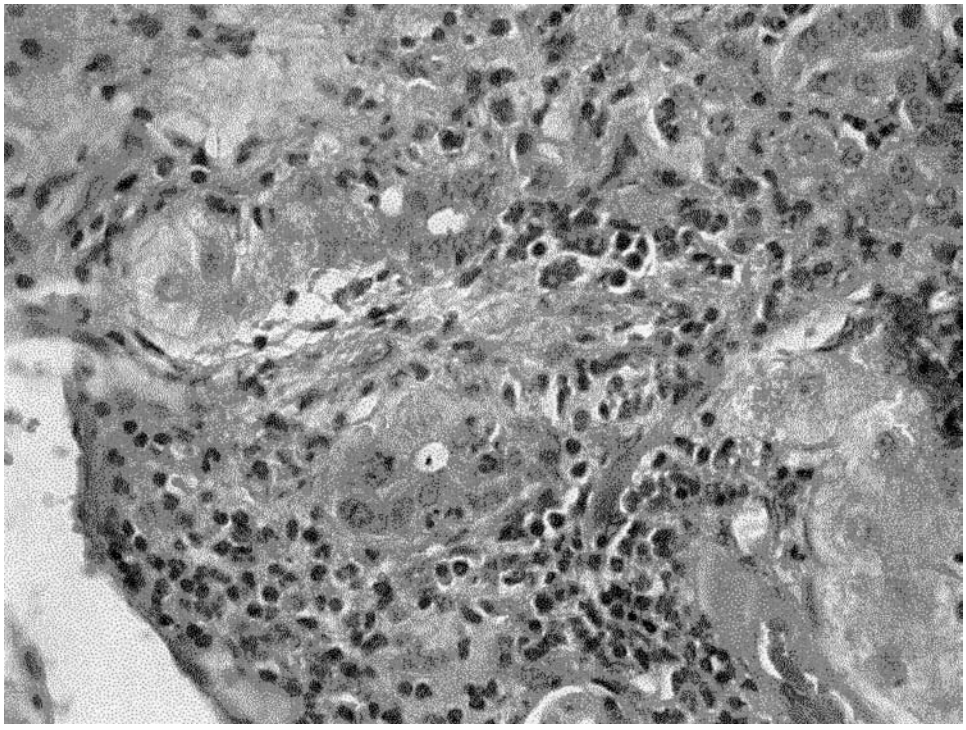

Figure 1. Liver biopsy showing a dense periductal inflammatory infiltration with active necrosis, periportal fibrosis, and biliary ductal neogenesis (hematoxylin and eosin, original magnification ×300).

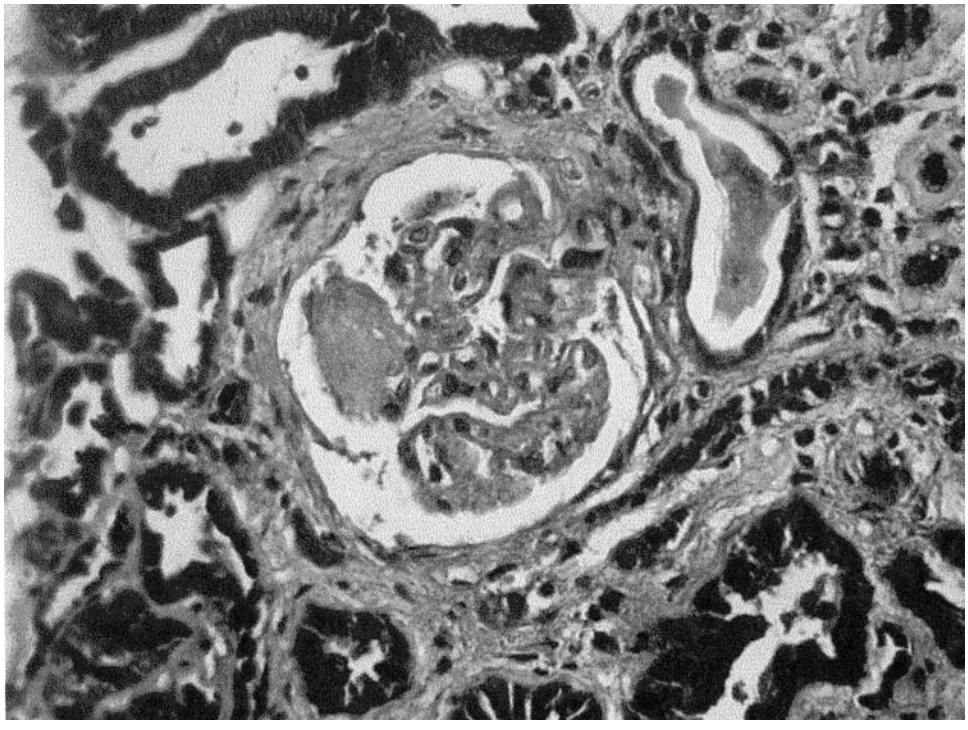

Figure 2. Kidney biopsy showing extracapillary hypercellularity (crescent formation) with early segmentary necrosis. (Masson's trichrome staining, original magnification ×300).

of patients with PBC[3], but glomerulonephritis has seldom been reported[4]. Interestingly, p-ANCA are present in 28% of patients with PBC and its presence correlates with disease severity[5]. Their pathogenetic role is a matter of debate[2].

Previously considered as an atypical presentation of polyarteritis nodosa (PAN) with glomerular involvement, MPA has been recognized as a distinct clinical entity since 1994[6]. Its clinical and serological features were described by

Guillevin, *et al*[7] in 1999 in a large study of 85 patients. MPA mainly affects small and medium-sized vessels with alveolar and glomerular predilection. p-ANCA with anti-MPO antibodies are frequently but not invariably positive[8].

An association between PBC and MPA was first reported by Iannone, *et al* in 2003[2]. They described a 54-year-old woman with chronic polyarthritis who evolved within a few years into MPA associated with PBC. However, in a systematic review of the literature, we found another 2 cases that could be unrecognized associations of both diseases. In 1992 (before the Chapel Hill consensus conference), Bissuel, *et al*[9] reported a 41-year-old woman with biopsy proven PBC who suddenly developed pulmonary hemorrhage and segmentary necrotizing glomerulonephritis associated with raised p-ANCA and anti-MPO antibodies. The authors documented this case as a pulmonary-renal syndrome in the course of PBC, rejecting the diagnosis of PAN based on the absence of vascular aneurysms, granulomas, and hepatitis B serology. In 2004[10], a 72-year-old woman with a 6-year history of PBC (positive AMA and biopsy proven) who suddenly developed rapidly progressive necrotizing glomerulonephritis with p-ANCA positivity was reported. This patient could be classified as an ANCA-associated idiopathic rapidly progressive glomerulonephritis, an entity closely related to MPA, except for the absence of pulmonary involvement.

An association between PBC and primary vasculitis has been rarely described, and there is currently no clear explanation for the simultaneous occurrence of both conditions[2,11]. Due to the scarcity of reports, it is not possible to establish either a true overlap syndrome or a casual association.

Using the current classification criteria for vasculitis[6], further reports are necessary to clarify if the coexistence between PBC and MPA is causal or casual. Pathogenetic studies to understand the mechanisms underlying the association of PBC with other autoimmune conditions are needed.

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