Cogan's syndrome and development of ANCA-associated renal vasculitis after lengthy disease remission

Sirs,

Cogan's syndrome (CS) is a chronic inflammatory disorder which most typically presents with a non-syphilitic interstitial keratitis and audiovestibular disturbance (1, 2). The incidence is rare with less than 250 cases described in the literature (1, 2, 5). As highlighted by Cody and Williams in 1960, the potential for systemic features including vasculitis have been clearly linked to this syndrome (1, 5, 10). When present, vasculitis typically develops within the first year of disease onset but has occasionally occurred several years later (6). Renal vasculitis in particular, has been rarely described in the literature (7). In addition, CS associated with an antineutrophil cytoplasmic antibody has been reported in only a small number of cases (8).

We report on a case of microscopic polyangiitis with necrotizing glomerulonephritis accompanied by a positive myeloperoxidase-specific antineutrophil cytoplasmic antibody (MPO-ANCA) in a patient with a longstanding history of Cogan's syndrome (CS).

In November 2006, a 63-year-old female with CS presented with generalized weakness, fatigue, new onset proteinuria, elevated creatinine and anti-myeloperoxidase (anti-MPO) >100 U/ml.

A diagnosis of CS was made during a rheumatologic evaluation in 1998. A moderately severe bilateral sensorineural hearing loss beginning in 1994, development of keratitis in 1995 and steroid responsiveness of ocular and auditory features supported the diagnosis. Laboratory studies in 1998, revealed a positive P-ANCA by indirect immunofluorescence, an anti-MPO by ELISA of 36, negative anti-PR3, C-ANCA, VDRL, as well as normal serum creatinine and urinalysis. Evidence for auditory, ocular or systemic involvement was lacking and therefore therapy unwarranted.

In early 2006, prednisone 10 mg once daily was administered when the anti-MPO elevated to greater than 100 U/ml with complaints of weakness and fatigue. These symptoms and the serology remitted, but in November of 2006 she was hospitalized after developing myalgia and arthralgia associated with an elevated creatinine and a positive anti-MPO.

On admission, she was hard of hearing with an otherwise normal exam. Laboratory studies revealed a serum creatinine 1.9mg/dl, white blood cell count 14,900 thous/mcl, hemoglobin 9.9 g/dl, platelets 460,000 thous/mcl, 24 hour urine 749mg protein and 1072mg creatinine, albumin 3.0 g/dl, 2+ P-ANCA, anti-MPO >100 U/ml, anti-Pr3 negative at 2, and CRP 10.6 (<10 mg/dl). Urinalysis; 3+ blood, 1+ protein, 1+ leukesterase, 6-10 squamous cells, WBC 20-40, bacteria 26-50, RBC 40-60, fine granular casts and without symptoms of dysuria.

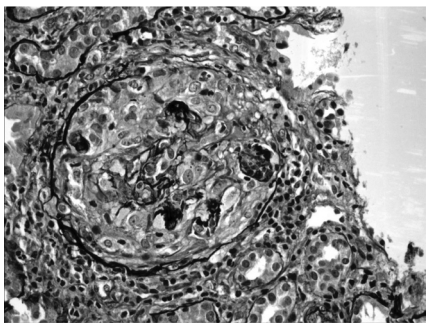

Fig. 1. Cellular crescent. Shown in this picture is a florid cellular crescent with ruptured Bowman's capsule (1-3 o'clock). The glomerular tuft is compressed by the extracapillary proliferation. (Silver, 40x).

Kidney biopsy revealed extracapillary crescentic and necrotizing glomerulonephritis (Fig. 1). Areas not involved by severe inflammation revealed acute tubular injury and numerous red blood cells in the tubular lumina. Four arteries were identified in the specimen and revealed severe transmural vasculitis with fibrinoid necrosis.

Treatment consisted of three days of intravenous methylprednisolone 1000mg and one cyclophosphamide pulse of 0.5gm/m^2 of body surface area (800mg). On discharge, the prednisone dose was 50mg daily, then two additional monthly cyclophosphamide infusions were given. Symptoms resolved, serum creatinine declined to 1.6 mg/dl, anti-MPO to 12 U/ml and the urinalysis was normal. Azathioprine 50mg three times daily was then initiated (8). In January 2009, the patient was clinically and serologically stable, with a creatinine of 1.2mg/dl and maintenance treatment of azathioprine 50mg daily without any steroids.

CS has been described in association with renal involvement and vasculitis (1). In a review of 78 cases of CS (18 originally from the Mayo Clinic and 60 from a review of the literature) for evidence of renal involvement, 14 had abnormal urinalysis and 3 had renal impairment. Histopathological findings at the renal biopsy were abnormal in 5/78 (3).

When present, systemic vasculitis associated with CS usually affects medium-sized vessels although any sized vessel may be affected (6, 9). In our case, the kidney biopsy findings, together with a positive P-ANCA (MPO) supports the diagnosis of small vessel vasculitis.

Positive ANCA in CS have uncommonly been reported. As reviewed by Ikeda and colleagues, only 5 cases of CS with positive serology for ANCA were reported in the literature up to 2002 (4). An additional case of CS, vasculitis and positive serology for ANCA was reported in 2007 (5).

The development of vasculitis generally occurs within a year from the diagnosis of CS (7). Interestingly, we observed a lengthy interval of remission of CS prior to the development of vasculitis.

The clinical course observed illustrates the potential for even late systemic involvement in CS, including renal vasculitis, and justifies the need to maintain vigilance in this condition. The early diagnosis and treatment of systemic vasculitis can significantly reduce its morbidity and mortality (3).

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