ANCA-Negative Pauci-Immune Crescentic Glomerulonephritis Linked with Non-Small Cell Carcinoma of the Lung

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Abstract

Introduction
Pauci-immune renal vasculitis with focal glomerular necrosis and crescent formation is usually associated with anti-neutrophil cytoplasmic antibodies (ANCAs). However, ANCAs are absent in up to 10% of cases, which constitutes a rarely studied variant of renal vasculitis [1]. Published data regarding kidney involvement and outcome in ANCA-negative pauci-immune vasculitis are scarce and often lack a clear-cut proof of ANCA negativity [1–3]. One of the reasons is the difficulty of establishing the absence of ANCAs.
Neutrophils are considered to play a major role in the pathogenesis of ANCA-negative pauci-immune crescentic glomerulonephritis (CrGN) [1, 4]. It is possible that neutrophils and their activation by interleukin-6 (IL-6) together with several cytokines play a crucial role in the pathogenesis of ANCA-negative as well as ANCA-positive CrGN [5].

IL-6 is a pleiotropic cytokine which regulates immune responses, hematopoiesis and acute phase reactions [4]. IL-6 production by cancer cells has been demonstrated to play an important role in tumor proliferation by autocrine stimulation in some cases of lung cancer [4, 6]. An elevated serum IL-6 level has often been found in large cell carcinoma frequently with leukocytosis and elevated levels of acute phase proteins [4]. Anti-IL-6 agents could provide a novel therapeutic strategy in patients with IL-6-producing lung cancer [5].

**Case Presentation**

A 69-year-old Caucasian female with a past medical history of hypertension, diabetes and atrial fibrillation was diagnosed with stage IV non-small cell lung cancer, after a lung nodule was incidentally discovered on a CT of the abdomen done for abdominal pain. She was also a chronic tobacco smoker with a 25-pack-year smoking history. Pathology from the biopsy of the right upper lobe nodule showed a moderately differentiated adenocarcinoma. A PET scan disclosed multiple, bilateral lung nodules with radiographic findings consistent with bronchoalveolar carcinoma.

She received 1 cycle of palliative chemotherapy (carboplatin/Alimta), but 2 days later, she was admitted to our institution because of severe left shoulder and chest wall pain. Serum creatinine (Scr) was normal on admission at Cr = 0.57 mg/dl. She had an extensive hospital stay and developed nonoliguric acute kidney injury (AKI) 1 day after a head CT with contrast was performed because she was experiencing headaches. Serum Cr levels elevated to 1.18 mg/dl. A urinalysis showed 300 protein and large blood with 481 red blood cells. A renal ultrasound showed evidence of medical renal disease, and the spot urine protein/creatinine ratio was 11. Serum Cr continued to rise with levels reaching values as high as 6.27 mg/dl with a glomerular filtration rate at 7 ml/min/1.73m², urine sodium fractional excretion was 1.1, BUN/Cr ratio <20 and urine sodium >40. She had no recent hypotension. Albumin was 1.6 g/dl, complement C3 and C4 were negative, but the antinuclear antibody was positive (speckled, 1:80), and the rheumatoid factor was negative. A skeletal survey was also negative. Acute hepatitis panel, HIV, cryoglobulin, serum protein electrophoresis, urine immunofixation, ANCA’s, double-stranded DNA, lupus anticoagulant, antihistone and antiglomerular basement membrane antibodies were all negative. A left renal biopsy showed CrGN (fig. 1) with a negative immunofluorescence and electron microscopy for immune deposits consistent with pauci-immune glomerulonephritis.

Steroids were started. Cyclophosphamide and azathioprine were also initiated with a prednisone taper. However, she developed severe neutropenia which responded to Neupogen, and therapy was switched to mycophenylate mofetil. While undergoing therapy, her urine protein/creatinine ratio improved to 0.5; a repeat urinalysis showed only small blood, and her serum creatinine improved to 1.9–2.8 mg/dl. Unfortunately, the patient passed away about 8 months after the diagnosis of pauci-immune glomerulonephritis from a septic shock.
Discussion

CrGN is classified into 3 main categories on the basis of direct immunofluorescence microscopic observations, i.e., an anti-glomerular basement membrane CrGN, an immune complex-mediated CrGN, and a pauci-immune CrGN that presents as focal necrotizing glomerulonephritis with little or no glomerular staining for immunoglobulin or complement [5, 7].

ANCA-negative pauci-immune CrGN has been demonstrated in only a limited number of case reports [5]. The prevalence is approximately 10–30% [1, 4]. ANCA-negative patients also have a higher prevalence of nephrotic syndrome and poorer renal survival than ANCA-positive patients [5]. However, the pathogenesis of ANCA-negative pauci-immune CrGN remains unclear [5].

Shimizu et al. [8] observed neutrophil infiltration in the glomerular lesion and elevated IL-6 and IL-8 levels in the acute phase of ANCA-negative CrGN. Morikawa et al. [5] reported a large amount of neutrophil infiltration in the glomerulus, with crescent formation, and significant elevated levels of IL-6, TGF-β, and IL-8 in the blood in their report of ANCA-negative pauci-immune CrGN patients associated with adenosquamous cell carcinoma of the lung. Ohlsson et al. [9] also found that plasma IL-6 levels were significantly elevated in patients with ANCA-associated vasculitis in the active phase, heralding a greater risk of relapse. In contrast to ANCA-associated vasculitis, IL-6 has rarely been reported in the pathogenesis of ANCA-negative CrGN.

Malignant tumor cells have also been reported to produce IL-6 [6]. IL-6-producing lung cancer has recently been described in several cases [5]. Yamaji et al. [6] showed that 53% of lung cancer cell lines produce IL-6 mRNA and protein with the expression level of mRNA being consistent with that of the protein.

IL-6 is a multifunctional cytokine which regulates immune responses, hematopoiesis and acute phase reactions [10]. It has been demonstrated that IL-6 plays an important role in the pathogenesis and progression of various malignancies [10]. In patients with lung cancer, IL-6 is associated with tumor proliferation and its prognosis [10]. To the best of our knowledge, only 1 previous case of ANCA-negative pauci-immune CrGN associated with lung malignancy has been reported in the literature [5].

IL-6 may play a pathogenic role with other cytokines, such as IL-8 and G-CSF, which activate neutrophils [5]. However, further clinical studies are needed to confirm the roles of IL-6 in the pathogenesis of ANCA-negative pauci-immune CrGN. And thus, therapy that blocks IL-6 might be effective for vasculitis [5]. A case of ANCA-positive pauci-immune CrGN associated with metastatic adenocarcinoma of the lung has been reported, and related cases have been reviewed and analyzed [11]. However, as the serum IL-6 level was not measured, there remains the possibility that the cancer cells did not secrete IL-6, and that other cytokines other than IL-6 were associated with this clinical presentation.

Disclosure Statement

The authors declare no conflicts of interest.
References

Fig. 1.  a Crescents in 3 glomeruli (black arrows) in background of tubular degenerative/regenerative changes and interstitial fibrosis. b, c High-power view of cellular crescents (black arrow) with mesangial and endocapillary hypercellularity (blue arrow), nuclear fragments ‘Karyorrhexis’ (red arrow) and fibrin. d Fibrocellular crescents (black arrows). e Altered blood in dilated collecting ducts (black arrows). f Electron microscopy showing mesangial hypercellularity (white arrows) and the focal disruption of glomerular capillary basement membranes (blue arrow) with no immune-type electron-dense deposits (HE staining, a ×10, b–e ×20; electron microscopy, ×3,910).