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Case Report

Paraneoplastic Seronegative Pauci-Immune Glomerulonephritis Associated with Lung Adenocarcinoma Responds to Rituximab: A Case Report

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Abstract
Anti-neutrophil cytoplasmic antibodies (ANCA) play an important role in the pathogenesis of pauci-immune renal vasculitis. However, in 10% of the cases, ANCA are absent. We present a case of a 64-year-old man with a chronic untreated hepatitis C virus infection and Middle Eastern thalassemia who was ANCA-negative when he was hospitalized due to acute kidney injury and accounts for an uncommon presentation of renal vasculitis. The patient had earlier reported to have undergone local lobectomy and adjuvant chemotherapy (carboplatin/pemetrexed) for lung adenocarcinoma a month prior. IL-6 has been reported to be involved in the pathophysiological cascade causing pauci-immune glomerulonephritis amongst non-small cell lung cancer patients. Previous studies with subgroup analysis have demonstrated that ANCA negativity has been associated with more chronic glomerular lesions and less crescent formation, which tends to have a critical outcome in the renal system. However, our patient underwent kidney biopsy exhibiting active crescentic glomerulonephritis, pauci-immune type with 5 cellular crescents amongst 15 glomeruli. To our knowledge, this is the third reported case of ANCA-negative vasculitis with typical presentation on biopsy in non-small cell lung cancer patients.

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Introduction

Rapidly progressive glomerulonephritis is a clinical syndrome presenting with rapid deterioration of the renal function with characteristic features of nephritic syndrome, such as proteinuria and hematuria. Crescent formation is the pathological finding in these cases and represents a nonspecific response to severe injury to the glomerular capillary wall as observed in kidney biopsy. Pauci-immune rapidly progressive glomerulonephritis, a type of rapidly progressive glomerulonephritis, is a necrotizing glomerulonephritis with few or no immune deposits by immunofluorescence and electron microscopy. Pauci-immune renal vasculitis with focal glomerular necrosis and crescent formation is usually associated with anti-neutrophil cytoplasmic antibodies (ANCA). However, it is noteworthy that in 10% of the cases, ANCA are absent, and this accounts for an uncommon presentation of renal vasculitis [1].

Case Report

A 64-year-old Caucasian man with a past medical history of chronic hepatitis C virus infection presented to the emergency room with acute kidney injury. He had recently been treated for localized non-small cell adenosquamous lung cancer and undergone lobectomy and adjuvant chemotherapy with carboplatin and pemetrexed, receiving his last dose 1 month prior to hospital presentation. On examination, the patient was afebrile with a blood pressure of 139/85, a heart rate of 82, a respiratory rate of 16, and a 98% saturation on room air. He was noted to be edematous with diffuse purpuric and petechial skin lesions. Initial laboratory findings were significant for normocytic anemia, with a hemoglobin level of 6.7 g/dL, WBC of 13.1 K/μL, serum creatinine of 11.60 mg/dL, BUN of 118, potassium of 4.7 and a proBNP of 90,193 pg/mL. Urinalysis showed slightly cloudy, red-colored urine with 100 mg/dL protein, 385 RBC/HPF, and 4 hyaline casts/LPF. Spot urine protein:creatinine ratio estimated 4.5 g of proteinuria per 24 h.

On admission, hemodialysis was initiated for volume overload and the patient received blood transfusion for his anemia. Serologies including ANA, anti-DNA, hepatitis B, cryoglobulin, HIV, anti-GBM antibody, anti-myeloperoxidase antibody, and anti-proteinase 3 antibody were negative and complement levels were normal. Renal ultrasound revealed no evidence of chronic renal disease, atrophy or hydronephrosis. Renal biopsy (Fig. 1–3) sent to the Weill Cornell Medical College revealed active crescentic glomerulonephritis (CrGN), of the pauci-immune type. CT scan-guided renal biopsy revealed very small metastatic bone lesions to the sacrum and T4 vertebrae, confirmed on repeat imaging 3 months later. The patient was treated with 1 g of SoluMedrol daily for 3 days, 2 cycles of plasmapheresis and induction therapy using rituximab 375 mg/m^2, and oral prednisone. His renal function subsequently improved and his purpuric rash resolved. He died 6 months later from progression of metastatic lung cancer.

Discussion

Pauci-immune glomerulonephritis is a devastating form of acute kidney injury. It is rare with an incidence of 3.1 cases per million per year in the United States. However, rates are significantly higher in Caucasian males and individuals older than 65 years [2, 3]. They usually present with clinical pictures varying from asymptomatic hematuria to more severe forms

that require rapid intervention. Laboratory testing usually reveals hematuria, proteinuria, and elevation in serum creatinine with active urinary sediment [4]. Clinically, patients complain of constitutional symptoms such as low-grade fever, fatigue, weight loss as well as other symptoms such as myalgia and arthralgia, which often precede the presentation of the disease [4, 5].

In a study of 85 patients with a diagnosis of pauci-immune CrGN reported by Chen et al. [6], it was noted that 28 patients (32.9%) were ANCA-negative (mean age 39.7 years) with a younger age of onset compared to ANCA-positive patients (mean age 57.6 years). The prevalence of fever, weight loss, muscle pain, and arthralgia was found to be lower in ANCA-negative patients compared to that in ANCA-positive pauci-immune CrGN patients. Furthermore, there was less prevalence of pulmonary involvement in ANCA-negative (10.7 vs. 36.8%; $\chi^2 = 6.33$, $p < 0.05$) compared to ANCA-positive patients and less ophthalmic, otic or nasal involvement (3.6 vs. 24.6%; $\chi^2 = 4.34$, $p < 0.05$) in the former. However, proteinuria and the prevalence of nephrotic syndrome are more common in patients that are ANCA-negative ($p < 0.01$ and $p < 0.001$, respectively). Renal survival was also worse in ANCA-negative patients compared to ANCA-positive patients ($p < 0.05$). Hung et al. [7] reported in their subgroup analysis of pauci-immune glomerulonephritis that ANCA-negative subjects had more chronic glomerular lesions compared to ANCA-positive patients who had more acute glomerular lesions. The chronicity of the renal disease in ANCA-negative patients is likely responsible for their poor treatment response and worse renal prognosis.

The pathogenesis of ANCA-negative pauci-immune CrGN still remains unclear. There are several theories that attempt to explain the phenomenon of ANCA-negative pauci-immune CrGN. Roth et al. [8] observed that purified immunoglobulins from ANCA-negative patients did not react with their sera but reacted with MPO antigens. It was reported that a ceruloplasmin fragment bound to the epitope of MPO reduced anti-MPO autoantibody detection by 30–50%. Hence, circulatory fragments of ceruloplasmin have been known to mask ANCA positivity, resulting in ANCA-negative vasculitis [9]. A second possibility is that in ANCA-negative pauci-immune CrGN, there are low levels of antibodies that are not detected by currently available assays. Finally, the third possibility is that a new undetected antigen, which is therefore testing negative in prevailing assays, drives the etiology of ANCA-negative pauci-immune CrGN.

In our case, the recent diagnosis of metastatic non-small cell lung adenocarcinoma suggests that our patient's ANCA-negative pauci-immune CrGN may be a paraneoplastic manifestation of his malignancy. A literature review from PubMed showed two additional cases of ANCA-negative pauci-immune CrGN associated with stage 4 non-small cell lung cancer. One of them was treated with steroids but died of renal failure and intestinal bleeding 2 weeks after the diagnosis and the other was treated with steroids, cyclophosphamide and azathioprine with death occurring 8 months after diagnosis [10, 11]. Morikawa et al. [10] reported a large amount of neutrophil infiltration in the glomerulus, with crescent formation, and significantly elevated serum levels of IL-6, TGF-β, and IL-8 with IL-6 producing adenosquamous lung cancer playing a key role in the pathogenesis of ANCA-negative pauci-immune glomerulonephritis.

Interestingly, in our case and the previous two reported cases of patients with non-small cell lung cancer who developed ANCA-negative pauci-immune CrGN, there was antecedent chemotherapy. Can the temporal relationship of carboplatin and pemetrexed infusion and the development of ANCA-negative pauci-immune CrGN suggest autoimmune syndrome induced by adjuvants (ASIA)? ASIA describes autoimmune syndromes that are triggered by a substance that modulates the immune system such as a vaccine [12]. Cytotoxic chemotherapy can

also be considered an adjuvant as it can modulate the immune system in the following ways: (1) it alters the normal balance of self-tolerance [13], (2) high cell turnover and cell destruction activates the immune system through increased synthesis of cytokines [14], and (3) chemotherapy itself generates autoantibodies [15].

Conclusion

We presented a case of ANCA-negative pauci-immune CrGN temporally related to non-small cell lung cancer. Our case highlights the importance of having a broad differential in renal failure patients post-chemotherapy. This rare manifestation prompts the following questions: (1) Are IL-6-producing adenocarcinomas capable of inducing ANCA-negative pauci-immune CrGN? (2) Is chemotherapy a potential trigger of ANCA-negative pauci-immune CrGN in non-small cell lung cancer? (3) How should ANCA-negative pauci-immune CrGN associated with non-small cell lung cancer be treated?

Statement of Ethics

The authors have no ethical conflicts to declare

Disclosure Statement

The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or nonfinancial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this case report. The authors do not have any conflicts of interest to disclose.

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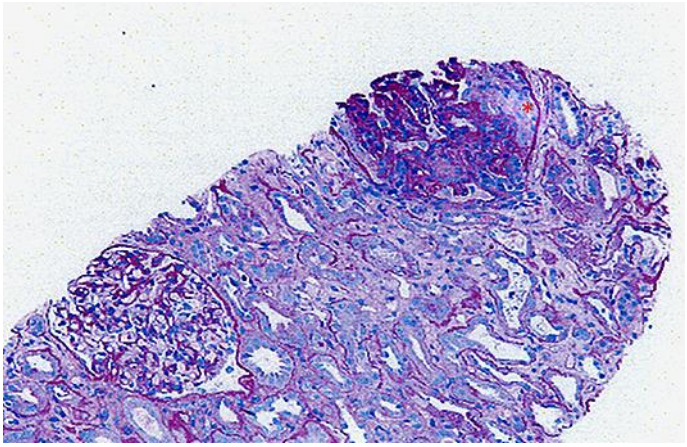

Fig. 1. PAS histochemistry (medium magnification) demonstrating an uninvolved glomerulus (left) and a glomerulus with segmental crescent formation (right). Asterisk marks the focus of crescent formation.

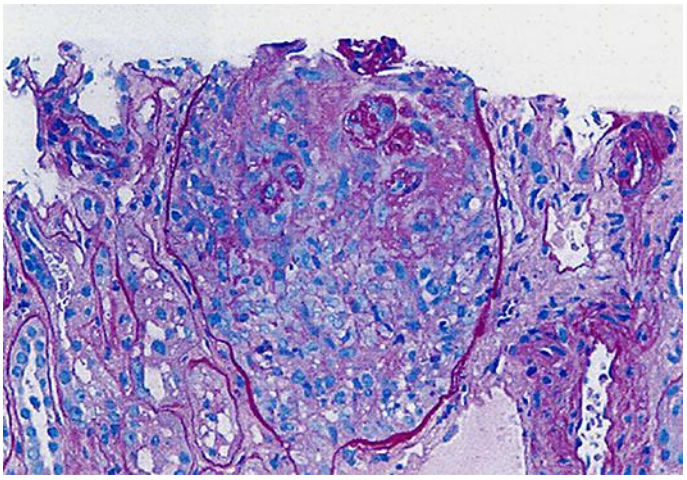

Fig. 2. PAS histochemistry (high magnification) demonstrating an involved glomerulus with segmental crescent formation (lower half of glomerulus).

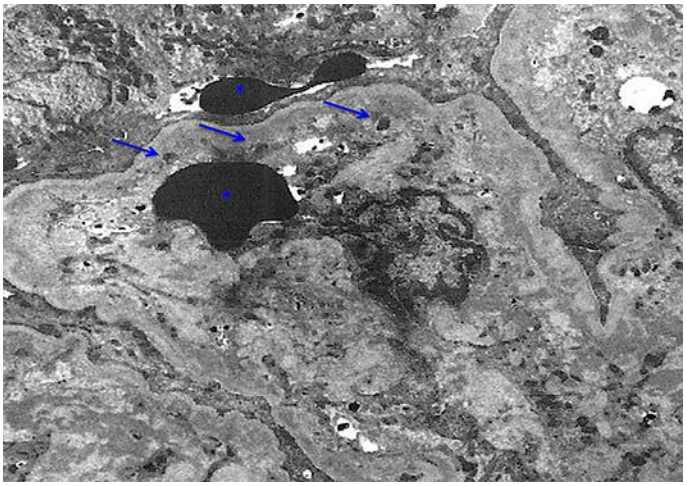

Fig. 3. EM demonstrating subendothelial electron-dense deposits. RBCs annotated with blue asterisks. Some dense deposits highlighted with blue arrows. No subepithelial electron-dense deposits are seen.