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CASE REPORT

Unique case of ANCA-negative pauci-immune necrotizing glomerulonephritis with diffuse alveolar hemorrhage, potentially associated with midostaurin

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Abstract
We present a 61-year-old male with *FLT3*-mutated acute myeloid leukemia treated with midostaurin who developed acute kidney injury requiring hemodialysis and pulmonary renal syndrome. Antibodies to proteinase-3, myeloperoxidase, and glomerular basement membrane were negative. Renal biopsy confirmed acute pauci-immune focal necrotizing glomerulonephritis (GN) with fibrin crescents indicating rapidly progressing glomerulonephritis. He improved with pulse methylprednisolone, intravenous cyclophosphamide, and plasma exchange with resolution of hemoptysis. This case highlights the importance of prompt renal biopsy to guide early initiation of life-saving therapies. To our knowledge, this is the first reported case of ANCA-negative pauci-immune necrotizing GN likely secondary to midostaurin.

Keywords Pauci-immune glomerulonephritis · ANCA negative · Midostaurin · Pulmonary renal syndrome

Introduction

Pauci-immune glomerulonephritis (GN) with diffuse alveolar hemorrhaging (DAH) and negative anti-neutrophil cytoplasmic antibody (ANCA) titers is not a common presentation of AKI. While most pauci-immune GN are associated with anti-proteinase-3 (anti-PR3) and anti-myeloperoxidase (anti-MPO) ANCA, a fraction of these patients may have undetectable antibodies, and thus pauci-immune GN cannot be excluded when faced with negative serologies. We present a unique case of rarely reported ANCA-negative necrotizing pauci-immune GN-associated pulmonary renal syndrome (PRS) and its first reported association with midostaurin.

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Case report

A 61-year-old male with relapsed *FLT3*-mutated acute myeloid leukemia (AML) presented to the emergency department (ED) with chest pain, cough, diarrhea, and occasional syncope. He was recently treated for relapsed AML with IV decitabine 20 mg/m^2 for 10 days, venetoclax 200 mg daily for 14 days and midostaurin 50 mg twice daily. Three days after discharge, he arrived to the ED with hypotension, which improved with IV fluids. He was pancytopenic on arrival with a platelet count of 36 K/μL, white blood cell count of 1.2 K/μL, and hemoglobin of 8.4 g/dL. He soon developed hemoptysis and microscopic hematuria. Chest X-ray and non-contrast computed tomography (CT) imaging of his chest, abdomen, and pelvis revealed extensive bilateral pulmonary infiltrates concerning for multifocal pneumonia versus DAH and was treated with empiric broad spectrum antibiotics. However, bronchoscopy performed showed the presence of blood in the BAL. No pulmonary biopsy was done. An esophagogastroduodenoscopy (EGD) revealed no active bleeding. He required many platelet transfusions throughout his hospitalization due to significant thrombocytopenia.

He had denied any prior history of hypertension or renal dysfunction. He had history of nephrolithiasis and prostate cancer, which never required treatment. His diagnosis of

AML was 10 years prior to presentation and was treated with intensive therapy and achieved remission which sustained until a year prior to current visit. His baseline creatinine was 0.76 mg/dL, measured a week prior to presentation. No urinary evaluation was required prior to the current presentation. Upon arrival to the ED, his creatinine was 1.90 mg/dL which improved to 1.06 mg/dL with IV fluids but increased to 2.55 mg/dL within a week of hospitalization, prompting Nephrology consultation. Urinalysis revealed more than 182 red blood cells (RBC)/high power field (HPF), 219 hyaline cast. Urinary protein-to-creatinine ratio was 1.53 g/g of creatinine. Renal ultrasound revealed a left kidney sized at 10.7 cm, right kidney sized at 15.3 cm, and diffusely echogenic renal cortices. Midostaurin and venetoclax were stopped within the first week of hospitalization. He was continued on IV fluids and started on Acyclovir, Posaconzole, Cefepime, Linezolid and Azithromycin. However, his renal function continued to decline and he had persistent hemoptysis. Immunologic workup was unrevealing: antinuclear antibody titer less than 1:40, undetectable levels of anti-double-stranded DNA antibody (dsDNA), anti-glomerular basement membrane (anti-GBM), anti-myeloperoxidase antibody (anti-MPO), anti-proteinase-3 antibody (anti-PR3), and normal C3 and C4 complement levels, negative hepatitis B and C serologies, and a negative HIV screen. Workup for IgA Nephropathy or thrombotic microangiopathy (TMA) was unrevealing with elevated haptoglobin, no schistocytes, and negative stool studies. Ischemic acute tubular necrosis (ATN) was suspected given his significant hypotension on arrival or drug-induced acute interstitial nephritis (AIN). The patient was started empirically on methylprednisolone 1 mg/kg every 12 h for his DAH, but his renal function continued to decline during this therapy. On the tenth hospital day, his creatinine increased to 7.11 mg/dL and hemodialysis was initiated for symptoms of uremia and volume overload.

Since the etiology of his renal dysfunction was not clear, a renal biopsy was sought. The renal biopsy showed acute pauci-immune focal necrotizing GN with fibrin crescents (seen in Fig. 1), ATN (seen in Fig. 1), 38% (14 out of 37 glomeruli) global glomerulosclerosis, and less than 5% interstitial fibrosis with tubular atrophy (IFTA). The crescents were composed primarily of fibrin with only early epithelial proliferation. Segmental necrosis with fibrin crescents was seen in 39% (9 out of the 23) of the glomeruli. Interestingly, the 38% globally sclerosed glomeruli were fully obsolescent and consistent with hypertensive nephrosclerosis not related to the acute GN.

He was already started on daily pulse dose methylprednisolone 500 mg for his DAH which we continued for a total of 3 days followed by daily prednisone 60 mg, IV cyclophosphamide every 2 weeks for three doses for induction, and daily plasma exchange until his hemoptysis resolved. He got four sessions of daily plasma exchange and then every 48 h for seven more sessions. Repeat bone marrow biopsy

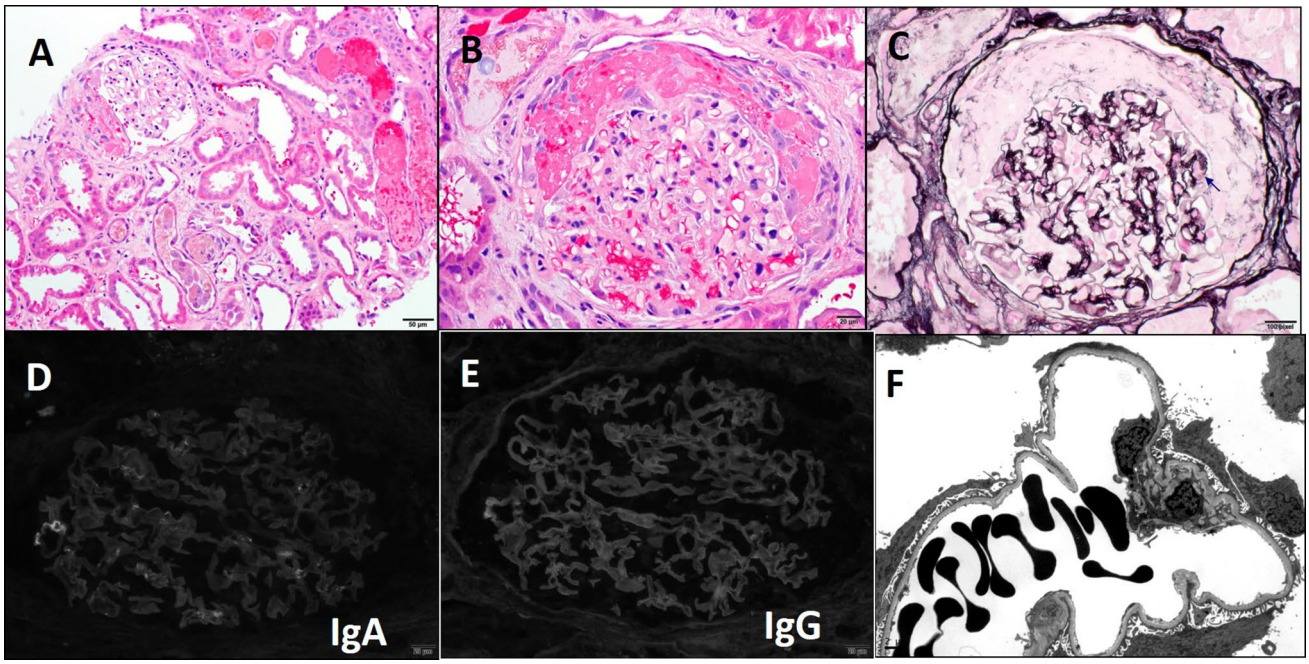
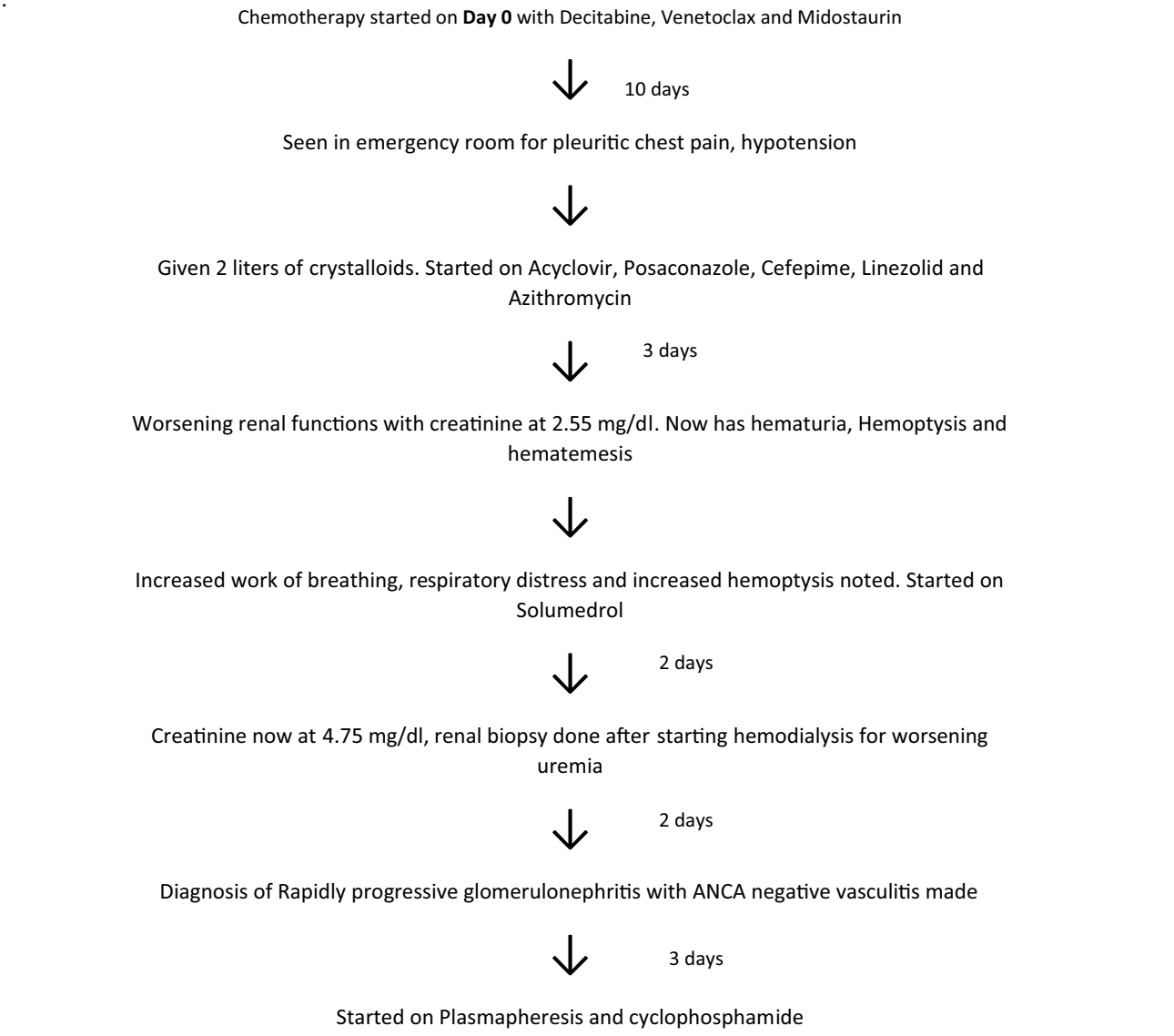


Fig. 1 **a** Acute tubular epithelial injury consistent with acute tubular necrosis (ATN) and mild arterial and arteriolar sclerosis. Red blood cell casts (right). Bar = 50 µm. **b** Crescent composed primarily of fibrin with early epithelial proliferation indicating very acute necrotizing glomerulonephritis. Bar = 20 µm. **c** Jones Silver stain: very segmentally interrupted Glomerular Basement Membrane (GBM arrow). **d** IgA trace mesangial deposits. **e** IgG negative glomerulus. **f** Electron microscopy with normal structure and no deposits

during this time showed no blasts, consistent with complete remission of AML with incomplete hematologic recovery. He was discharged with outpatient plasma exchange, maintenance IV cyclophosphamide, and prednisone taper over 5 months. This treatment reduced the need for hemodialysis to twice weekly for adequate clearance. His urine output had increased significantly within the first week of start of therapy. Details of events are highlighted below



Discussion

Pauci-immune GN is one of the most common types of crescentic glomerulonephritis (CrGN). Morphologically, the severe glomerular injury is characterized by focal necrotizing glomerulonephritis. Depending on direct immunofluorescence, CrGN is classified into anti-glomerular-basement membrane CrGN, immune complex-medicated GN and pauci-immune CrGN. Typically, pauci-immune GN are seropositive for ANCA and, therefore, called ANCA-associated CrGN. Interestingly, the prevalence of ANCA-negative pauci-immune GN is 10–30% [1, 2]. These patients are younger, have less frequent constitutional symptoms and have much less extra-renal manifestations. However, they have poorer renal outcomes with higher degree and prevalence of nephrotic syndrome [1, 3]. These findings suggest that ANCA may be a marker of generalized vasculitis in patients with pauci-immune CrGN. The pathogenesis of ANCA-negative disease is not very clear. Neutrophils are considered to play a major role in pathogenesis. Activated neutrophils generating reactive oxygen species have been found

in glomeruli of ANCA-positive CrGN patients. Immunohistochemical staining studies have shown that the degree of neutrophil infiltration was greater in ANCA-negative as compared to ANCA-positive CrGN [3]. Another possibility is that there are different circulating auto-antibodies (other than anti-PR3 and anti-MPO) present such as anti-moesin [4], anti-human lysosome-associated membrane protein-2 (hLAMP-2) [2, 5], and anti-endothelial cell membranes [6–8].

In our patient, AKI was initially suspected to be secondary to ischemic ATN or drug-related AIN. We attributed his hemoptysis to his thrombocytopenia and pneumonia. As his renal function worsened with persistent hemoptysis, PRS was suspected, with Goodpasture's or pauci-immune GN. Possibility of TMA or IgA nephropathy was also evaluated. Renal biopsy confirmation as shown in Fig. 1, quickly prompted treatment with pulse dose steroids, cyclophosphamide, and plasma exchange. After four daily cycles of plasma exchange, our patient's hemoptysis resolved. He remained non-oliguric, and we required only twice weekly hemodialysis for adequate clearance. Similar presentations described by Wang et al. [9] Saladi et al. [10], Munshi BD et al. [11] also demonstrate resolution in DAH and improvement in AKI with this treatment.

The underlying precipitant for our patient's pauci-immune GN is somewhat unclear, but the close timing between initiating his new chemotherapy regimen of midostaurin and venetoclax with subsequent development of acute kidney injury (AKI) increased suspicion for medication-related ANCA-negative pauci-immune GN. Midostaurin has been associated with AKI in about 11–12% of patients, and AKI was the most frequent adverse event leading to treatment discontinuation in the pivotal randomized phase 3 trial evaluating midostaurin in AML [12]. The causes of AKI are not specified in the reports or the FDA package insert [13]. One may speculate that the renal events included in this study were most likely related to volume depletion secondary to nausea, vomiting, or diarrhea which is the most common adverse events observed with midostaurin. However, it is difficult to predict in the absence of pathological evidence. This case is our attempt to expand the side effect profile of midostaurin. To the best of our knowledge, there are no reports published of glomerulonephritis associated with midostaurin use. Venetoclax and decitabine have not been reported to cause AKI. The possibility of an AML-related paraneoplastic process-induced GN was initially entertained as there have been case reports of a paraneoplastic ANCA-negative pauci-immune GN associated with lung adenocarcinoma, non-small cell lung carcinoma, and multiple myeloma, but there have been no case reports with association to AML itself. The patient's repeat bone marrow biopsy confirmed remission, making AML a very unlikely cause of the clinical presentation. Due to the temporal association between midostaurin intake and AKI, it was considered to be the most likely cause of pauci-immune GN in our patient.

Conclusion

Our case highlights that pauci-immune GN should not be completely excluded despite negative serologies for ANCA as a fraction of these pauci-immune GN will be ANCA negative. Of note, prompt treatment with pulse dose steroids, IV cyclophosphamide, and plasmapheresis hasten recovery of DAH and give the patient the highest chance of renal recovery. Moreover, this is the first reported case of midostaurin-associated glomerulonephritis. Thus, patients developing AKI on treatment with midostaurin should be monitored closely for any unexplained worsening of AKI. The medication should be stopped and renal biopsy performed to confirm the diagnosis and identify other potential cases of midostaurin-associated GN.

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Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent No identifiable information regarding the patient is being disclosed.

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