Approach to Acute Kidney Injury in a Patient with HIV

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CLINICAL PRESENTATION

We present a case of a 58-year-old White man with a medical history of hypertension controlled with olmesartan and hydrochlorothiazide, psoriasis, dyslipidemia, and human immunodeficiency virus type 1 infection (HIV-1). He was diagnosed with HIV-1 eight years ago and has been effectively treated with efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla®), maintaining good adherence and an undetectable viral load. Regarding kidney function, baseline serum creatinine (sCreat) was 1.3 mg/dL, and proteinuria between 30 and 50 mg/dL has been shown for the last seven years, and last evaluation with 50 mg/dL glucosuria.

He presented in a routine infectious disease consultation, where he reported a two-week history of heavy non-steroidal anti-inflammatory drugs (NSAID) consumption after a traumatic foot injury and a mild, self-limited cold. He had no other symptoms or remarkable signs on physical exam, besides his elevated blood pressure (160/80 mmHg). Laboratory work revealed new-onset macrocytic anemia (hemoglobin 6.6 g/dL, mean cell volume 108 fL), sCreat 7.5 mg/dL, urea 156 mg/dL, and non-anion gap metabolic acidosis (arterial pH 7.25, bicarbonate 13.9 mmol/L). He denied other symptoms during the past weeks, such as fever, skin rash, lumbar pain, decreased urine output, hematuria, or urinary foam.

The patient was admitted, and further studies were performed. A noteworthy finding was a folic acid deficiency (< 2 ng/mL), with normal B12 vitamin and iron stores. Haptoglobin was normal. He had elevated gamma-glutamyl transferase (GGT) (232 U/L) with normal alkaline phosphatase (ALP), transaminases, bilirubin, and lactate dehydrogenase (LDH). Parathyroid hormone was slightly elevated (194 pg/mL), with normal calcium-corrected albumin (8.7 mg/dL) and elevated phosphate (5.9 mg/dL). Complement levels, immunoglobulins, electrophoresis, and free light chains were normal. HIV viral load was undetectable. The hepatitis B core antibody and hepatitis B surface (HBs) antibody were positive, but the HBs antigen and hepatitis B viral load were negative. Hepatitis C serology was negative. Urinalysis results showed a density of 1.010, a pH of 6.5, a trace of protein, glucose at 500 mg/dL, and an unremarkable sediment. The protein-creatinine ratio (PCR) was 1.35 g/g, and the albumin-creatinine ratio (ACR) was 174 mg/g. Urinary eosinophils were negative. Renal ultrasound revealed slightly increased echogenicity.

The patient received a blood transfusion, folic acid supplementation was started, and intravenous fluids were instituted. Despite these measures, his kidney function continued to deteriorate, leading to a percutaneous kidney biopsy.

QUESTIONS

1. What is the most likely diagnosis, and do we need more information?
2. Considering the kidney biopsy results, what is the final diagnosis?
3. What are the recommended management strategies for this patient?

ANSWERS

1. What is the most likely diagnosis?

This case is about an acute kidney injury (AKI) in a 58-year-old man with a long history of well-controlled HIV-1 managed with antiretroviral therapy who had a recent history of NSAID abuse. The following approach structure was applied to simplify the diagnostic discussion:

Pre-renal AKI?

Pre-renal contribution was considered and corrected during the initial approach, given the initial severe anemia.

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The patient's alcohol consumption likely contributed to his anemia, as evidenced by severe folic acid deficiency and increased GGT with normal ALP and transaminases.[1] Also, the hemodynamic effects of NSAID were considered. However, other etiologies were explored, given the continued deterioration of kidney function despite optimized volume status and significant non-albumin proteinuria.

Post-renal AKI?

Post-renal AKI was excluded, since the patient had spontaneous diuresis and imaging excluded urinary tract dilations and evidence of obstruction.

Renal AKI?

Vascular, glomerular and tubulointerstitial pathologies were considered. Hypertensive emergency was excluded; although he had high blood pressure at admission and AKI, no other organ-target lesions were detected (his laboratory data did not support thrombotic microangiopathy, and no neurologic, ophthalmologic or cardiovascular involvement was apparent). Furthermore, there was no improvement after controlling blood pressure.

One of our main hypotheses was that AKI was related to NSAID, more specifically, acute interstitial nephritis (AIN). NSAID primarily cause AKI via hemodynamic alterations from prostaglandin production inhibition. However, they may also induce an allergic tubulointerstitial reaction. AKI associated with NSAID use is not frequent in healthy people, and the risk is increased in patients with concomitant use of renin-angiotensin-aldosterone system inhibitors and other drugs such as tenofovir and proton-pump inhibitors. Renal histology in AIN typically reveals tubular injury, including cellular vacuolation, brush border loss and inflammatory cell infiltration in the tubulointerstitial compartment.[2] Unlike classic drug-induced allergic nephritis, which typically features peripheral eosinophilia, eosinophiluria, fever, and rash, these symptoms are generally absent in NSAID-induced cases.[3]

The possibility of glomerulopathy was explored. The patient had recently experienced a self-limited upper respiratory tract infection, which can act as a trigger for nephritic or nephrotic syndromes. However, several clinical findings did not support these diagnoses: no evidence of hypervolemia (e.g., edema or hypertension), proteinuria was present but not of the albuminuric type, and urinalysis revealed no hematuria.

Infection-associated glomerulonephritis could also be considered since he had a recent respiratory infection. However, severe AKI is uncommon, and higher-grade proteinuria with albuminuric predominance would be expected, as well as complement consumption.[4,5] Other etiologies were considered but less probable, such as HIV-associated nephropathy (HIVAN) or other HIV-associated glomerulopathies. HIVAN usually presents as a rapidly progressive renal failure accompanied by moderate to nephrotic range proteinuria, and it is associated with enlarged, highly echogenic kidneys.[6] Nevertheless, our patient exhibited non-nephrotic non-albumin proteinuria and normal-sized kidneys.

Pure AKI or AKI on CKD?

The patient exhibited signs of chronic kidney dysfunction, such as mild hyperparathyroidism and slightly increased renal echogenicity. Given his history, it can be a consequence of long-term hypertension. Nevertheless, tenofovir disoproxil fumarate (TDF), commonly known as tenofovir, is the most frequently implicated antiretroviral in antiretroviral-induced nephrotoxicity. TDF toxicity can present either AKI or chronic kidney disease (CKD) and as full or partial Fanconi syndrome. The patient had normal anion gap metabolic acidosis and glycosuria despite normal glycemia, raising the suspicion of complete or partial Fanconi syndrome.

Biopsy or not biopsy?

Our central hypothesis was NSAID-induced AIN, yet the patient had persistent AKI at a risk of requiring dialysis despite discontinuation of NSAID. Due to ongoing diagnostic uncertainty and current and future risk of renal failure, a kidney biopsy was deemed necessary to obtain histological confirmation and guide definitive treatment.

2. Considering the kidney biopsy results, what is the final diagnosis?

Kidney biopsy revealed moderate multifocal mononuclear cell-dominant interstitial inflammation, few eosinophils and acute tubular necrosis (Figs. 1-3), without glomerular lesions (16 intact glomeruli). Few chronic lesions were identified, with interstitial fibrosis and tubular atrophy in 15% of the sample's cortical region and moderate arteriolar hyalinosis. Notably, rare endoluminal crystals, birefringent under polarized light, were found in the distal tubules. Immunofluorescence (8 glomeruli) was negative for immunoglobulin A, G, M, complement factors C1q and C3, Kappa and Lambda light chains, fibrin and albumin. Congo red was negative.

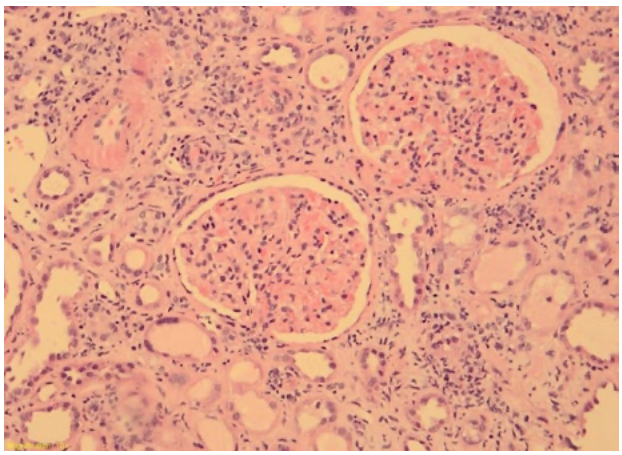

Figure 1. Hematoxylin and eosin stain – normal glomeruli; tubular necrosis (green arrow); interstitial inflammation (yellow arrow) (x20).

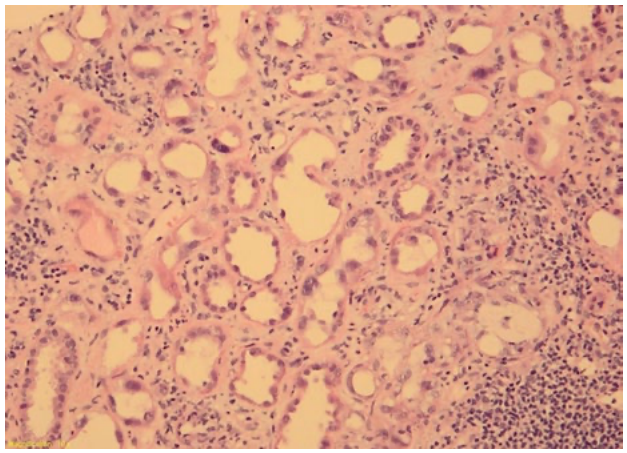

Figure 2. Hematoxylin and eosin stain- atypical nuclei (black arrow); interstitial inflammation (yellow arrow) (x20).

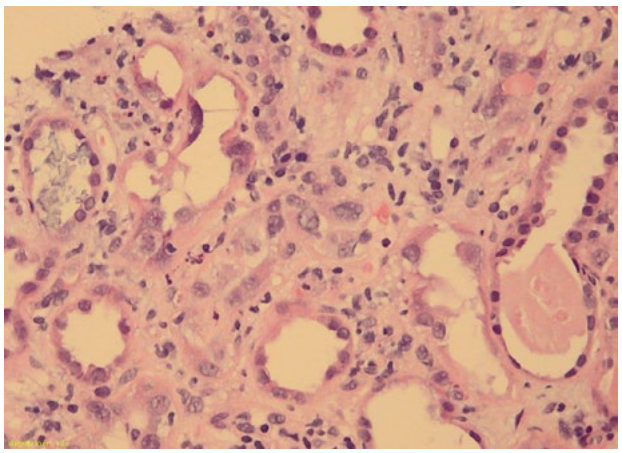

Figure 3. Hematoxylin and eosin stain- endoluminal crystals (black arrow); tubular nuclear atypia (yellow arrow) (x20).

These histopathological findings support the diagnosis of AIN with some degree of acute tubular necrosis (ATN) superimposed on chronic interstitial nephritis. NSAID are the most likely cause of AIN and ATN, with some contribution of anemia and hypovolemia to the latter.

The chronic component is more likely related to the prolonged use of TDF. TDF is particularly nephrotoxic to the proximal tubules. Its mechanism of intracellular toxicity is believed to involve mitochondrial depletion and structural alterations that may trigger tubular cell apoptosis. TDF is associated with a reduced glomerular filtration rate and histological findings of tubular interstitial fibrosis and tubular atrophy, which were observed in our patient.[6] Electron microscopy may show mitochondrial enlargement, depletion, and dysmorphic changes.[7]

The etiology of the crystals found within the tubules remains unclear. These may be considered in the context of TDF or NSAID use. Crystallopathy is associated with some antiviral drugs, such as protease inhibitors, which typically appear birefringent under polarized light. There are no clear reports linking TDF to crystal nephropathy[4,6,8]; however, an animal study regarding TDF renal toxicity reported ultrastructural changes in renal proximal tubules, including an increased number and irregular shape of mitochondria with sparse, fragmented cristae.[9]

3. What are the recommended management strategies for this patient?

The first step in AIN induced by NSAID is to suspend NSAID use entirely. Treatment of AIN with steroid therapy aims to improve kidney function by reversing acute renal inflammation, especially in cases of severe kidney failure.

Prendecki M *et al* presented a fourteen-year cohort study, with 48 patients with drug-induced AIN, including 12 patients with NSAID-related AIN, that suggested a benefit of steroid treatment of drug-induced AIN, relating to greater improvement in kidney function and less progression to end-stage renal disease.[10] Nevertheless, an eleven-year cohort study with 166 patients conducted at the Mayo Clinic, involving 111 patients with biopsy-confirmed drug-induced AIN, 15 with NSAID-related AIN, reported higher recovery rates—approximately 80%—compared to AIN caused by autoimmune diseases or infections; early diagnosis before biopsy was associated with better renal recovery, whereas moderate to severe interstitial fibrosis, tubular atrophy, and the need for dialysis were linked to non-recovery. In this cohort, corticosteroids were administered to 81% of patients, but their use did not significantly affect renal outcomes. Furthermore, among the NSAID-induced AIN group, a smaller proportion of patients received steroid therapy compared to those with other drug-induced AIN. In the group of patients with NSAID--induced AIN, 29% did not achieve renal recovery, and 40% progressed to end-stage renal disease.[11] Notably, neither cohort specifically compared steroid responsiveness

between NSAID-related AIN and other forms of drug-induced AIN due to the small sample size.

Therefore, despite some controversial data regarding its benefits, steroids may be considered in severe cases of drug-induced AIN, mainly when severe kidney injury persists despite discontinuation of the offending drug.[12,13]

Regarding HIV antiretroviral therapy, efavirenz/emtricitabine/tenofovir disoproxil fumarate (Atripla®) was widely used due to its convenient dosing schedule (one-pill-a-day), antiviral efficacy, and relatively favorable side-effect profile. However, given this emerging evidence, TDF should be avoided in patients with renal disease. Patients taking TDF should have careful kidney function monitoring along with protein-creatinine ratio and urinalysis to exclude tubular dysfunction.[14] Tenofovir alafenamide (TAF) is a prodrug of tenofovir that results in significantly higher intracellular concentrations and lower serum levels than TDF. It appears to be a good alternative as an equally effective treatment with fewer renal adverse effects and bone mineral density losses.[15,16] Nevertheless, there are currently other drugs with a more favorable kidney profile that should be preferred, particularly in cases of impaired kidney function, for whom, ideally, Tenofovir should be suspended.[12]

Treatment and case follow-up

Steroid therapy was initiated with prednisolone at a dose of 1 mg/kg/day for two weeks, followed by a gradual taper over eight weeks. Supportive treatment included oral sodium bicarbonate, folic acid, and erythropoiesis-stimulating agents to address metabolic acidosis and anemia. Renal function progressively improved, and dialysis was not required.

Shortly after hospital admission, the patient's antiretroviral regimen was switched to dolutegravir and lamivudine, with doses adjusted according to renal function. The patient maintained this regimen following discharge.

After 8 weeks, kidney function stabilized with a sCreat of 2.8 mg/dL, but he had ongoing proteinuria (RPC 1.03 g/g) and glycosuria, with no glycosuric medication prescribed. Two years later, an angiotensin-converting enzyme inhibitor was titrated to the maximum tolerated dose, and nephrotoxic agents were consistently avoided. Kidney function showed modest improvement (sCr 1.9 mg/dL), with a reduction in proteinuria (PCR 0.4 g/g) and no other urinary abnormalities observed.

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MDP: Material preparation, data collection and analysis, writing the original draft.

FP: Writing the original draft, conceptualization and supervision.

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CS: Conceptualization and supervision.

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