Clinical Images and Case Reports Journal

Case Report | Vol 3 Iss 9

Round up the Usual Suspects

Duncan B Johnstone[1*], Erum Malik[2] and Jared Hassler[3]

[1]University of Pittsburgh Medical Center, Renal-Electrolyte Section, Pittsburgh, USA

[2]Stanford University, Critical Care Medicine, Pittsburgh, USA

[3]Temple University Health System, Department of Pathology, Pittsburgh, USA

[*]**Corresponding author:** Duncan B Johnstone, University of Pittsburgh Medical Center, Renal-Electrolyte Section, Pittsburgh, USA. E-mail: Johnstonedb@upmc.edu

Received: October 28, 2021; **Accepted:** November 05, 2021; **Published:** November 14, 2021

Introduction

Human Immunodeficiency Virus (HIV) can cause kidney disease via diverse mechanisms including collapsing glomerulosclerosis, immune-complex glomerulonephritis, a microangiopathy, various medication toxicities, and more. We present a case report in which, like most detective stories, we considered all the usual suspects, but the final culprit causing kidney disease in this instance was both interesting and illustrative.

Case Presentation

A 20-year-old previously healthy Hispanic male patient was admitted to the hospital after presenting to the emergency department on a Sunday with fever, chills, and myalgias for two to three weeks, along with nausea, vomiting, diarrhea, and right sided abdominal/flank pain for almost one week. To treat his abdominal pain and myalgia, he had been taking both ibuprofen and acetaminophen a few times each day at doses that, respectively, did not exceed 600mg or 1000mg.

In the Emergency Room his temperature was 98.5, blood pressure 118/78, heart rate 95, respiratory rate 18, and pulse oximetry 99% on room air. For his abdominal pain and myalgias, ER physicians ordered an abdominal CT scan with contrast, and they administered intravenous ketorolac 30mg, two liters of lactated ringers, and 2mg of morphine. Upon review of his electronic medical record ER physicians found that, 2 weeks prior, he was seen at an affiliated ER across town for fever and malaise arising 3 weeks after having unprotected intercourse. The affiliated ER diagnosed him with new HIV infection based on negative HIV antibodies but positive HIV p24 antigen. That day his CD4 cell count was 166, CD8 cell count 205, and serum creatinine 0.98mg/dL.

While in the ER for his current presentation, the CT scan revealed left renal vein compression (Nutcracker syndrome) but no other abnormality that would explain abdominal pain. Laboratory tests showed positive HIV antibodies (new seroconversion since 2 weeks prior) along with acute renal failure, hyponatremia and a transaminitis as follows: sodium 123 mEq/L, potassium 3.5 mEq/L, total CO2 21 mEq/L, BUN 46 mg/dL, creatinine 5.24 mg/dL, AST 173 U/L, ALT 98 U/L, serum albumin 2.3 g/dL, white cell count 7.2 cells/mL, hemoglobin 14.5 g/dL, platelets 107 cells/mL. Urinalysis pH 5.0, SG 1.010, glucose negative, protein 300 mg/dL, blood large, leukocyte esterase positive, nitrite negative. He was admitted to the hospital for further management.

Overnight, a spot urine protein/creatinine ratio was 1.95 grams/gm, urine sodium 14, urine creatinine 165 with a FeNa of 0.4%, C3 and C4 complements were normal, creatinine kinase 641 U/L, chlamydia/gonococcal screen negative, treponemal EIA negative, and hepatitis panel was negative including hepatitis A Ab, hepatitis B sAg, hepatitis B sAb and core total Ab, and hepatitis C Ab. To the admitting Medicine team, the initial impression was acute renal failure with proteinuria due to a combination of HIVAN, along with acute tubular necrosis from a combination of NSAIDS, hypovolemia from his GI illness, and CT contrast dye.

We met the patient the following day. Urine output since admission (almost 24 hours) was 550 cc. Urine microscopy revealed many dark granular casts per low power field. Our impression was of a very scared young man. His abdominal pain lingered but had improved. Nausea and diarrhea had resolved. He denied dysgeusia and instead reported severe dry mouth, for which he was drinking water copiously. On exam his mouth had no thrush or ulcers. Lungs were without rales. Heart sounds were regular without murmur or rub. There was no asterixis or clonus with wrist or ankle dorsiflexion. Myalgias remained, particularly of the distal legs, with a hot and sharp quality, but without an overlying rash, without palpably tense muscles, and with warm feet that had 2+ dorsalis pedis and posterior tibialis pulses. His affect was terse and angry. He refused an abdominal exam and, after outlining our initial plans for him, he asked in no uncertain terms to be left alone.

We discussed our initial impressions with the primary team. Their first question was whether vascular surgery should be consulted about the Nutcracker Syndrome on CT? This was the only easy question: while there is an inconsistent association of hematuria, proteinuria and flank/pelvic pain with Nutcracker Syndrome his right sided abdominal/flank pain was contralateral to the left renal vein compression, and he had no testicular pain. The cause and clinical significance of his Nutcracker syndrome was not clear, but for now it was not germane to his acute presentation.

Their second question was how to approach his hyponatremia. Nausea is one of the strongest stimuli for ADH release, but to our surprise, his urine osmolality and urine specific gravity were not elevated. The cause of hyponatremia appeared to be his thirst, which was causing water intake greater than his ability to excrete water (reduced due to AKI). We recommended restriction of free water and, to slake his thirst, both artificial saliva spray and chewing gum. But why was he so thirsty? He did not have thrush, and the magnitude of thirst was much greater than is common with elevated BUN alone. We asked the patient (and tested) for MDMA, but both were negative.

The third question was whether he needed dialysis? On this day there was no immediate indication for dialysis and discussing that this was a possibility for future days with the patient went poorly due to his fear and trepidation. Most importantly (and leading to the fourth question), was the cause of renal failure really a combination of HIVAN and ATN? With respect to ATN as a possible cause, while dark granular casts were seen on urine microscopy overnight, the intravenous ketorolac and contrast dye administered in the ER were convenient but incorrect culprits because these were administered at the same time or slightly after (not before) the blood sample with a creatinine of 5.25mg/dL. The timing was wrong. We considered ATN from other causes, such as severe hypovolemia from his GI illness, rhabdomyolysis, or substance abuse with inadvertent nephrotoxicity, but the initial ER vital signs did not suggest severe volume depletion, his creatinine kinase was normal, his urine drug screen was negative including cocaine, and he was emphatic about taking no pills other than the analgesics at the doses described on admission. Granular casts are helpful for distinguishing ATN from pre-renal azotemia but are not specific for ATN and can be seen in a range of other intrinsic kidney diseases. We favored a cause other than ATN, supported by the low urine sodium and low FeNa.

With respect to HIVAN as a possible cause for his severe renal failure we felt it was both "too soon and too fast." As initially described by Winston, Klotman and Klotman [1], HIVAN requires many years of viremia to manifest and is usually diagnosed at the time the CD4 count begins to chronically decline. As such, HIVAN was accepted as an AIDS-defining illness. In both humans with HIV and animal models, viremia is necessary but not sufficient for HIVAN; chronic infection of podocytes with expression of both Nef and Vpr is required [2]. A renal ultrasound revealed kidneys of 12-12.2 cm with high echogenicity (Figure 1). HIV infection causes enlarged, highly echogenic kidneys, and while the kidneys in patients with ATN are usually not echogenic, there are exceptions in both animal models and humans [3]. In the end, while echogenic kidneys are classically associated with HIVAN, and can rarely be seen with ATN, our initial impression was that neither ATN nor HIVAN explained his acute renal failure 2 weeks after HIV seroconversion.

We asked our infectious disease colleagues if the assumption he was newly infected 5-6 weeks ago could be wrong. If he had false negative serologies 2 weeks prior, and instead was infected many years ago, then HIVAN might not be "too soon." However, current HIV testing has a near 100% sensitivity. Even with new seroconversion, 4th gen HIV testing has only a 1% false negative serology at 42 days. We asked the young man whether he had been tested for HIV in prior years and he reported several negative HIV tests at free clinics in past years, and he knew that his unprotected intercourse 5-6 weeks prior to this admission was with a person who subsequently revealed his HIV+ status, a tragic admission. HIVAN as a possible cause for his renal failure would also be "too fast." The median time from biopsy confirmed diagnosis of HIVAN to initiation of dialysis was roughly 300 days in the largest biopsy cohort study. Since HIVAN should not be this early, and should not be this rapid, we felt we were missing something.

The very echogenic appearance of the kidneys on sonogram could also be explained by infiltrative processes of the kidney, such as allergic interstitial nephritis. In subsequent discussions the young man confirmed taking no prescription medications, no herbal medications, no muscle enhancers or performance drugs, and no other-the-counter medications except the few doses of ibuprofen/acetaminophen as he reported on admission. We decided that he must be having an interstitial nephritis due to HIV itself, which is seen with diffuse infiltrative lymphocytosis syndrome (DILS).

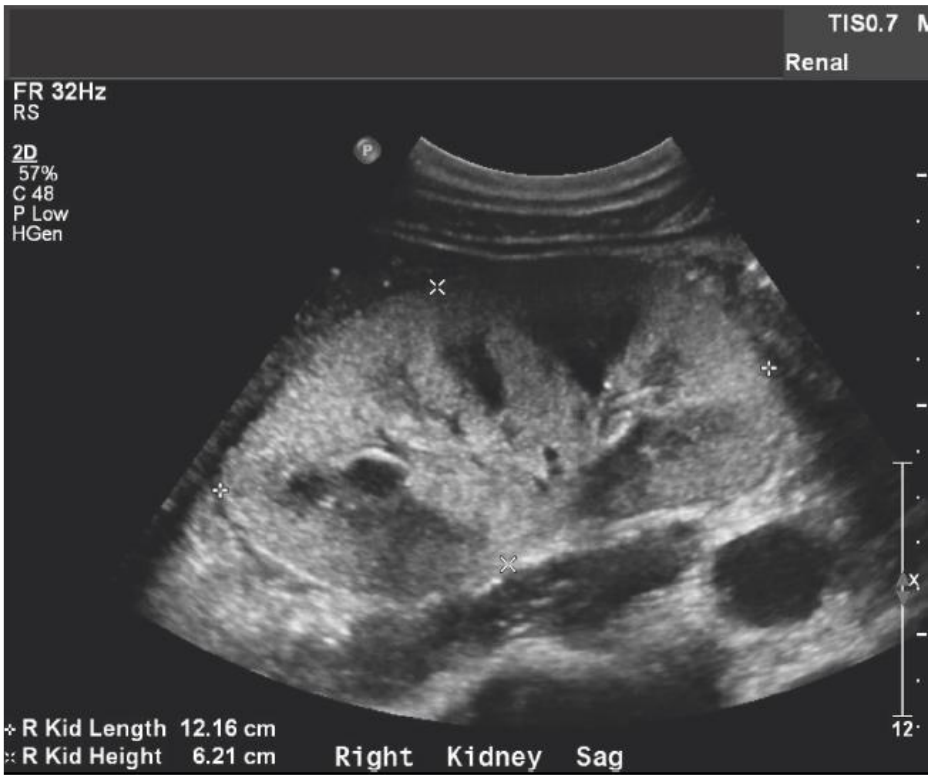

Figure 1: Retroperitoneal ultrasound. In this sagittal section, a rim of liver parenchyma is visible along the left hand side. By comparison the right kidney is significantly echogenic, but the length of 12.16cm is a bit larger than usual, not smaller.

DILS is an uncommon presentation in HIV patients in which CD4 dysregulation results in CD8-infiltration of various organs, most often the salivary glands causing Sicca syndrome, but other organs can be affected, including the lungs, liver, peripheral nerves, bowels, and kidneys. The time course of DILS after HIV infection is variable but has only been described in patients with established HIV (59.5 +/- 43.8 months after seroconversion) not in patients like ours during the acute seroconversion phase. DILS has never been reported as early as the time of seroconversion, but we reasoned that DILS could unite his acute renal failure with his unexplained Sicca syndrome, mild transaminitis, mild myositis, and his unexplained peripheral neuropathy.

At this point in his hospital stay, he was becoming oliguric with a creatinine of 9.74 and rising, and a sodium of 119 and falling. We recommended initiation of dialysis, hopefully on a temporary basis, followed by kidney biopsy. He initially refused both biopsy and dialysis. During this time, to support our suspicion that the renal failure was due to DILS, we rechecked his peripheral CD8 count, which can sometimes rise at the time that CD8 cells are also infiltrating visceral organs. His CD8 count of 205/mL 2-3 weeks ago was now elevated at 1975/mL and his HIV viral titre was above 3 million U/mL. Two days later, with a creatinine of 11.6, he awoke with spontaneous epistaxis and a small hematochezia, which led him to agree to hemodialysis for two consecutive days, followed by CT-guided kidney biopsy by the nephrology team, with DDAVP infused at 0.3 mcg/kg at the start of the procedure.

Kidney biopsy was remarkable for severe interstitial inflammation seen on both H&E and PAS stains (Figure 2A and 2B). In addition, the glomeruli showed marked podocyte hypertrophy and hyperplasia, with prominent protein droplets in the extra-capillary spaces and tubules, and collapse of several glomerular capillaries, seen on both PAS and Jones stains (Figure 2C and 2D). Immunohistochemical characterization of the infiltrating inflammatory cells revealed a predominance of CD3+, CD8+ lymphocytes. These biopsy findings confirmed our suspicion of interstitial nephritis due to DILS and also revealed that he did, surprisingly, have HIVAN.

He started prednisone 1mg/kg/day and anti-retroviral therapy while inpatient, and his symptoms of xerostomia and neuropathy improved daily, along with an increase in urine output. He was placed on low dose losartan. His hospital course continued to be complicated by marked anxiety regarding his diagnosis, and difficulty adjusting to hemodialysis, which we continued to explain we hoped would be temporary. He left the hospital against medical advice, but fortunately went across town, and discussions with those nephrologists permitted continuity of care.

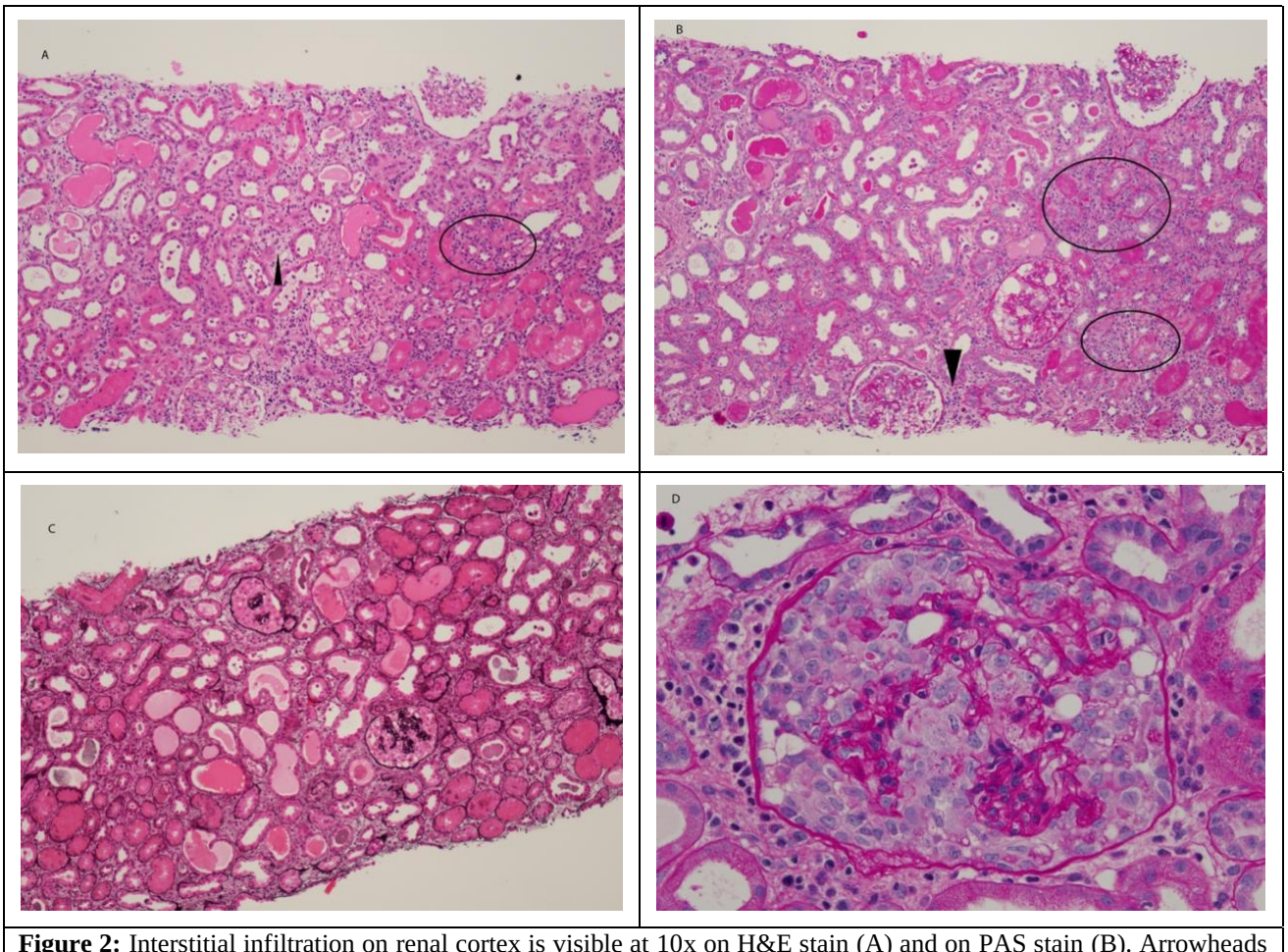

Figure 2: Interstitial infiltration on renal cortex is visible at 10x on H&E stain (A) and on PAS stain (B). Arrowheads point to interstitial edema, which is present between most tubules. Interstitial inflammation is present throughout, and the elipses encircle lymphocytic infiltrates with scattered eosinophils. Collapsing glomeruli are evident by Jones stain at 10x (C), and on PAS stain at 40x there is severe podocyte hypertrophy with hyperplasia and prominent protein droplets (D).

Discussion

We present the story of a young man with acute renal failure that occurred 5-6 weeks after infection with HIV, at the time of his seroconversion. The initial impression of his acute renal failure was ATN and HIVAN. After evaluating the likelihood of these diagnoses, we discuss why we suspected an HIV-mediated interstitial nephritis known as Diffuse Infiltrative Lymphocytosis Syndrome, or DILS, despite the fact that DILS has never been reported this early after HIV infection. To our surprise, his kidney biopsy revealed both DILS and HIVAN simultaneously. This is first report of both conditions occurring simultaneously, all the more remarkable because neither diagnosis "should" occur so soon after viral infection.

DILS was characterized in 1989 as a multi-organ disorder in HIV-1 positive patients with prominent Sicca symptoms accompanied by CD8 positive, non-granulomatous, lymphocytic infiltration of one or more organs [4]. The organ most commonly affected is the salivary gland, with lesser involvement of the lungs, liver, gastrointestinal tract, muscles, peripheral nervous system, and kidneys [5-7]. Because DILS resolves with the use of HAART therapy, this syndrome was more common during the era in which HAART therapy was delayed, often for several years, to offset the side effects and benefits of therapy. There are fewer reports of DILS in recent years due to the contemporary practice of starting HAART therapy much earlier, when outpatient care is established. The incidence of DILS in HIV-positive patients in the modern treatment era, based on Taiwan's comprehensive national database, is 0.1%-0.3%.

Among the rare patients who develop DILS, kidney involvement is uncommon, with an incidence of 6-8% from several studies. DILS nephropathy is characterized by enlarged kidneys, azotemia with tubular proteinuria, and tubulointerstitial nephritis on biopsy, predominantly of CD8+ lymphocytes, with some monocytes and plasma cells. Glomeruli are largely spared. In two cases of renal failure from DILS, steroids led to improvement in symptoms and renal failure, with a recurrence of renal failure when steroids were discontinued, then improvement again with re-initiation of steroid therapy [5].

HIV associated nephropathy, or HIVAN, is characterized by involvement of all renal compartments including glomeruli, tubules and interstitium [6]. Podocyte hypertrophy and hyperplasia are seen on renal biopsy, with a collapsing FSGS appearance without capillary involvement. Other features on biopsy include microcystic renal tubular dilatation, interstitial inflammation, fibrosis, and tubuloreticular inclusions due to interferon dysregulation. Clinically, HIVAN manifests with proteinuria, often the nephrotic syndrome, with rapidly declining eGFR over a period of months. HIVAN typically arises after years of viremia and is an AIDS-defining illness. The high rate of HIVAN among Black patients correlates with G1 and G2 risk alleles of APOL1, which are common among people of West African Descent. Our patient identified as Latino, for whom the risk of HIVAN is intermediate between patients who identify as White versus Black. Skorecki and colleagues found, at a time when MYH9 was felt to be the risk locus for FSGS, that the intermediate risk of HIVAN among Latino patients can be explained by two subpopulations in New York City: one with high % West-African ancestry, who likely carry the risk alleles and are prone to HIVAN, and those with low % West-African ancestry, who lack the risk alleles and have a HIVAN risk similar to White patients. Based on these data, we hypothesize (but after he left against advice cannot prove) that our patient carried 2 copies of G1/G2 risk alleles of APOL1.

Although HIVAN is a nephropathy of chronic viremia, it has been described twice before with acute HIV infection. The first report was by the same group in New York City that characterized much of what we know about HIVAN.8 Their patient was a 35-year-old male who was HIV negative 4 months before his admission to the hospital for acute renal failure. He started dialysis, underwent kidney biopsy that revealed HIVAN, and started HAART therapy. His response to HAART was excellent, allowing him to come off dialysis, and six weeks later his serum creatinine was 1.4 with proteinuria of 1.5 g/g by spot ratio. The second report of HIVAN in a patient with acute HIV was seen in Chicago [9]. A gentleman with acute renal failure and proteinuria had HIVAN on biopsy, with a positive viral load of 775,000 copies/mL, but he did not seroconvert until 4 months later.

In summary, this case report describes a young man with simultaneous DILS and HIVAN, which has never been described before in the literature, and which is all the more remarkable because both pathologies occurred at the time of acute seroconversion, just 6 weeks after viral transmission.

Teaching Points:

1. As a rule, HIVAN arises from toxicity to podocytes after years of viremia.	**1b.** For every "rule" there are rare exceptions, as in this clinical scenario.
2. Echogenicity by sonogram is traditionally associated with fibrosis from CKD or an infiltrative AKI, and is also severe with HIVAN.	**2b.** ATN is most often non-echogenic, but experts emphasize this is not reliable. The marked echogenicity here led us to suspect interstitial nephritis.
3. DILS is an auto-immunity from HIV in which dysregulated CD8+ cells attack multiple organs, sometimes including kidneys.	**3b.** Occam's razor versus Hiccum's dictum: in this case, DILS explained all of his symptoms and half of the biopsy findings.

REFERENCES

1. Winston JA, Klotman ME, Klotman PE. HIV-associated nephropathy is a late, not early, manifestation of HIV-1 infection. Kidney Int. 1999; 55: 1036-1040.
2. Rosenberg AZ, Naicker S, Winkler CA, et al. HIV-associated nephropathies: epidemiology, pathology, mechanisms and treatment. Nat Rev Nephrol. 2015; 11: 150-160.
3. O'Neill WC. Sonographic evaluation of renal failure. Am J Kidney Dis. 2000; 35: 1021-1038.
4. Itescu S, Brancato LJ, Winchester R. A sicca syndrome in HIV infection: association with HLA-DR5 and CD8 lymphocytosis. Lancet. 1989; 2: 466-468.
5. Izzedine H, Brocheriou I, Valantin MA, et al. A case of acute renal failure associated with diffuse infiltrative lymphocytosis syndrome. Nat Clin Pract Nephrol. 2008; 4: 110-114.
6. Cohen SD, Chawla LS, Kimmel PL. Acute kidney injury in patients with human immunodeficiency virus infection. Curr Opin Crit Care. 2008; 14: 647-653.
7. Yoo J, Baumstein D, Kuppachi S, et al. Diffuse infiltrative lymphocytosis syndrome presenting as reversible acute kidney injury associated with Gram-negative bacterial infection in patients with newly diagnosed HIV infection. Am J Kidney Dis. 2011; 57: 75.

8. Winston JA, Bruggeman LA, Ross MD, et al. Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. N Engl J Med. 2001; 344: 1979-1984.
9. Levin ML, Palella F, Shah S, et al. HIV-associated nephropathy occurring before HIV antibody seroconversion. Am J Kidney Dis. 2001; 37: 39.