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Ritonavir-induced acute kidney injury: kidney biopsy findings and review of literature

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Abstract

Ritonavir therapy is not generally considered nephrotoxic. We report a case of acute kidney injury secondary to ritonavir, with kidney biopsy demonstrating extensive acute tubular injury. This is the first report of a kidney biopsy and pathology in acute kidney injury associated with ritonavir. A review of published medical literature on the topic is also presented.

Keywords

ritonavir; acute renal failure; kidney biopsy; human immunodeficiency virus

Background

Most cases of acute kidney injury (AKI) due to highly active antiretroviral therapy (HAART) in patients with human immune deficiency virus (HIV) infection are generally attributed to therapy with indinavir or tenofovir. Ritonavir-boosted protease inhibitors are recommended as a preferred first-line treatment of HIV infected adults and adolescents. [1] Ritonavir is not typically considered nephrotoxic.

We report two episodes of AKI associated with ritonavir use in a patient with HIV and discuss kidney biopsy findings that demonstrated extensive acute tubular injury. We also describe characteristics of 9 previous cases of ritonavir-associated AKI reported in the medical literature.

Case report

A 45-year-old African-American man was admitted to Johns Hopkins Hospital with intermittent epistaxis for 1 month. He had a history of HIV (diagnosed 9 years ago), hepatitis C and hypertension. At the time of admission, his blood pressure (BP) was 142/94 mmHg, heart rate was 75 per minute and temperature was 36.6 °C. His examination did not

reveal any petechiae, ecchymoses or peripheral edema. On admission, his hemoglobin was 8.5 g/dl, platelet count was $20 \times 10^3/\mu\text{l}$ and creatinine was 1.4 mg/dl. He had mild elevation of aspartate aminotransferase (88 U/l) and a low albumin level (2.5 g/dl). Pro-thrombin time, total bilirubin, alanine amino-transferase and lactate dehydrogenase were normal. Five months prior to admission, his hemoglobin was 8.9 g/dl, platelet count was $67 \times 10^3/\mu\text{l}$ and creatinine was 0.6 mg/dl. His peripheral blood smear did not reveal schistocytes. A clinical diagnosis of immune-mediated thrombocytopenia (ITP) was made and was later confirmed by serological testing. Prednisone 60 mg daily was started and his platelet count gradually improved. His creatinine increased from 1.4 mg/dl to 2.1 mg/dl after admission but then declined to 1.5 mg/dl over the next 3 days (Figure 1). His admission urine protein to creatinine ratio was 0.6 g/g of creatinine. Urine microscopy was not performed on admission. On Day 6 of his hospitalization, HAART was initiated with ritonavir 100 mg po b.i.d., lamivudine 150 mg po b.i.d., abacavir 300 mg po b.i.d. and atazanavir 150 mg po b.i.d. His other medications at that time were prednisone, nifedipine, azithromycin and inhaled pentamidine. Over the next 48 h, during which he received two doses of HAART, his creatinine increased from 1.5 mg/dl to 3.9 mg/dl (Figure 1). On Day 8 of his hospitalization, HAART was discontinued and a nephrology consultation was requested.

At the time of our initial evaluation, his urinalysis revealed 100 red blood cells and 7 white blood cells per high power field and his urine sediment demonstrated red blood cell and granular casts. His cryoglobulin screen was weakly positive (0.6 volume percent); complement 3 and complement 4 levels were mildly decreased (complement 3, 74 mg/dl (reference 79 – 152); complement 4, 11 mg/dl (reference 12 – 42)) and perinuclear anti-neutrophil cytoplasmic antibodies (P-ANCA) (27.1 units (reference 0 – 20)) were weakly positive. Rest of the serologic workup was negative. A kidney biopsy was contemplated but deferred, as his platelet count remained less than $50 \times 10^3/\mu\text{l}$. His creatinine peaked at 4.4 mg/dl on Day 9 of hospitalization and then gradually decreased to 2.5 mg/dl by Day 13 of his hospitalization. At this point, he was discharged home on prednisone 50 mg/day. HAART therapy was not re-started.

Two weeks after discharge, he was re-admitted with recurrent epistaxis and per sis tent thrombocytopenia (platelet count $19 \times 10^3/\mu\text{l}$). His creatinine at the time of admission was 2 mg/dl. The dose of prednisone was increased to 60 mg/daily. On Day 3 of this second hospitalization, HAART was re-initiated with lopinavir/ritonavir 200 mg/50 mg, 2-tablets po b.i.d. and lamivudine/zidovudine 150 mg/300 mg po b.i.d. His other medications at the time were prednisone, nifedipine, valacyclovir, trimethoprim/sulfamethoxazole and azithromycin. On Day 4 of this second hospitalization, he was discharged home. His creatinine at the time of discharge was 1.9 mg/dl. He, however, returned to the emergency department within 12 h of discharge with weakness and oliguria. His initial BP in the emergency department was 118/63 mmHg and his creatinine on presentation had increased to 3.3 mg/dl. His platelet count and hemoglobin were unchanged. His HAART regimen was not re-started. His urinalysis and urine sediment were unchanged from his earlier hospitalization. He continued to be oliguric and, on Day 3 of this third hospitalization, his creatinine peaked at 5.2 mg/dl at which point he underwent a kidney biopsy.

Kidney biopsy findings

The kidney biopsy specimen contained 80% cortex with 18 glomeruli and 7 – 8 small arteries (up to inter lobular size). On light microscopy, the glomeruli showed segmental to global increase in mesangial matrix with 2 – 3 glomeruli demonstrating segmental increase in cellularity. Immunofluorescence showed granular mesangial staining for C3 (2+), IgG (1-2+ segmental), IgM (trace-1+ segmental), and kappa (1+ segmental) light chain, with rare granular lambda light chain. C1q staining was negative. Electron microscopy revealed numerous mildly degenerated, mesangial, intramembranous and subepithelial deposits,

including several large “hump-like” deposits; findings consistent with a resolving post-infectious glomerulonephritis. There was diffuse acute tubular injury with extensive isometric vacuolization, focal cell loss and simplification (Figure 2). This acute tubular injury was judged to underlie the AKI. There was no evidence of acute interstitial nephritis.

Clinical follow-up

Patient’s creatinine decreased and was 1.7 mg/dl 8 days after discontinuation of ritonavir-based HAART. At this time, HAART was restarted with efavirenz 600 mg daily, lamivudine 150 mg daily and zidovudine 300 mg po b.i.d. His creatinine remained stable on this regimen and he was discharged home. Two months after his discharge, his creatinine had decreased 0.7 mg/dl and continues to be at this level 2 years after the episodes of AKI. He was not re-challenged with ritonavir.

Discussion

This case report demonstrates two episodes of AKI precipitated with ritonavir use along with biopsy proven evidence of acute tubular injury. It extends the previous observations of AKI with ritonavir use reported in the medical literature [2, 3, 4, 5, 6, 7]. To our knowledge, this is the first reported case of a kidney biopsy performed in a patient with ritonavir induced AKI.

Our case is demonstrative of the highly complex clinical situations often encountered in HIV positive patients with underlying chronic kidney disease and/or AKI [8]. Many of these patients have several potential mechanisms of nephrotoxicity and kidney biopsy may be essential for proper diagnosis and treatment. We believe, that in our patient, the acute tubular injury with extensive vacuolization was the mechanism of AKI. Temporally, each episode of AKI was preceded by ritonavir use. Furthermore, recurrence of the AKI on re-challenge with ritonavir and complete resolution on discontinuation of therapy also supports the causative role of ritonavir. Our patient did not receive any other nephrotoxic agents or osmotic substances such as hetastarch or intravenous immunoglobulin prior to the kidney biopsy. Osmotic acute tubular injury is characterized by diffuse cell swelling and generalized cytoplasmic edema, often with tubular obstruction, in addition to the cytoplasmic vacuolization. This was not the pattern of injury seen in our patient [9]. The underlying resolving postinfectious glomerulonephritis may explain the elevated creatinine level, above his baseline, noted at the time of his first admission but does not explain the acute tubular injury and AKI.

Low levels of autoantibodies, as seen in our patient, are well described in patients with HIV. These autoantibodies are mostly non-pathogenic [10], but certainly contribute to the complexity of assessment when present. There was no evidence of a pauci-immune glomerulonephritis or vasculitis on kidney biopsy in our patient despite the elevated P-ANCA levels. He also had evidence of low-level Type III cryoglobulinemia but no related renal lesions were present. Despite the complex clinical situation and ambiguous laboratory results, kidney biopsy in conjunction with his clinical presentation, allowed us to make an accurate diagnosis of the cause of his AKI. He continues to have normal renal function more than 2 years after the episodes of AKI.

The mechanism of ritonavir induced acute tubular injury is unclear. After oral intake, only 3.5% of the unchanged drug is excreted in the urine and the remaining is excreted in feces [11]. There are five active metabolites of ritonavir but their effects have not been well defined. Ritonavir has been described as an inhibitor of proximal tubular cell transporters [12]. The role of this inhibition, if any, to acute tubular injury is not known.

The features of 9 prior cases of ritonavir-induced AKI [2, 3, 4, 5, 6, 7] are summarized in Table 1. Similar to our patient, some had rapid onset of AKI and in 4/9 patients re-challenge to ritonavir resulted in recurrent AKI. In 1 patient, ritonavir was re-introduced a third time with resulting AKI [7]. None of these patients underwent a kidney biopsy.

Antiretroviral drug induced AKI in patients undergoing treatment with HAART is usually related to tenofovir or indinavir. However, many of these patients are also receiving ritonavir. In a recent case series and review of literature summarizing tenofovir induced AKI [13], 21/27 patients were also on ritonavir. In 5/27, patients the kidney function did not return to normal despite discontinuing tenofovir and most of these patients (4/5) continued on ritonavir. Kidney biopsy was not performed in these 5 patients.

Conclusion

AKI can complicate ritonavir therapy in HIV infected individuals. Our case suggests that this AKI is due to acute tubular injury and that kidney biopsy is essential in making a proper diagnosis. We suggest monitoring creatinine with the initiation of HAART and consideration of ritonavir as a possible culprit in patients that develop AKI.

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Figure 1.
Acute kidney injury from ritonavir.

Figure 2. Kidney biopsy image under light microscopy. Tubular cells demonstrate extensive vacuolization (arrows) consistent with acute tubular injury.

Ritonavir-induced acute kidney injury: summary of reported cases.

Table 1

References	Cases	Age (y)	Sex	Prior history	Presentation	Ritonavir duration (days)	Other anti-retrovirals	Other medications		Creatinine (mg/dl)		
										Baseline	Peak	Follow-up
Duong et al. [5]	Case 1	54	M	CMV colitis Oropharyngeal candidiasis	AKI	10	Didanosine	Ganciclovir Pyrimethamine	Folinic acid Inhaled pentamidine	1.8	7.2	1.5
	Case 2	37	M	Cerebral toxo-plasmosis Cryptococcal meningitis CMV retinitis	AKI	10	Lamivudine Stavudine	Foscarnet Pyrimethamine	Clindamycin Fluconazole	1.5	2.1	1.7
	Case 3	54	M	Cerebral toxoplasmosis Cryptococcal meningitis	AKI	12	Lamivudine	Pyrimethamine Folinic acid Fluconazole	Acyclovir Minocycline Inhaled pentamidine	1.3	2.1	1.3
Chugh et al. [4]		40	M	Chronic kidney disease Proteinuria 1 – 2 g/day Horseshoe kidney	AKI Fluid overload	2	Lamivudine Zidovudine	Nifedipine		2.2	6.1	Baseline
Stricker et al. [6]		47	M		Fever AKI Pancreatitis	21	Lamivudine Stavudine	Azithromycin Ethambutol Dapsone Fluconazole	Acyclovir Mexiletene Erythropoietin Testosterone	“Normal”	12.4	“Normal”
Witzke et al. [7]	Case 1	54	M	CD4 = 31 per µl	Not described	7	Saquinavir	Acyclovir Pyrimethamine	Salicylic acid Ranitidine	1.2	2	Baseline
	Case 2	38	M	CMV retinitis	Watery diarrhea	immediate	Saquinavir Lamivudine	Foscarnet	Ganciclovir	0.8	4.8	2.7
	Case 3	35	U	CMV retinitis	Not described	4	Saquinavir Stavudine	Foscarnet Co-trimoxazole	Fluconazole	1.3	1.6	1.3
Benveniste et al. [2]		34	M	Schizophrenia Alcoholism Chronic hepatitis C	Fever Hepatitis Rhabdomyolysis	6	Stavudine Lamivudine	Isoniazid Rifampin Haloperidol	Levonepromazine Co-trimoxazole	0.8	4.7	1.9 1.5

AKI = acute kidney injury, M = male, U = unknown.