

A Case of aHUS-Associated Renal Failure Mistakenly Attributed to HIV Nephropathy

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Abstract

Human immunodeficiency virus infection has been implicated in multiple viral-based processes adversely affecting the renal system, including HIV-associated nephropathy (HIVAN), HIV-related immune complex disease, and the less well-described HIV-related thrombotic microangiopathy (TMA). While HIV nephropathy has an overall poor renal prognosis and is treated primarily with anti-viral therapy, the etiology of HIV-related (non-thrombotic thrombocytopenic purpura-associated) renal TMA may be causally linked to viral amplification of a dysregulated alternate complement cascade. Thus, if detected in its incipient stages, the associated renal injury may respond similarly to complement-inhibitory modalities as has been observed in cases of non-virally-linked TMA (aHUS), thus yielding significant recovery of kidney function. We report a case of a 43-year-old male patient with a history of advanced HIV disease and chronic renal insufficiency, previously attributed to HIVAN, who presented with acute renal decline, microangiopathic hemolytic anemia and thrombocytopenia, and biopsy-proven renal TMA, whose acute renal decompensation responded favorably to terminal complement blockade (eculizumab).

Keywords: aHUS; HIV; Eculizumab

Introduction

The tropism of the human immunodeficiency virus for a variety of immune-effector cells (T-lymphocytes/macrophages) and its ability to cause severe impairment of host-immune functions has been well described. This is in sharp contrast to

our limited understanding of the pathogenesis by which the virus brings about vasculopathy, including that within the renal compartment. In the last two decades, advanced HIV disease has been inculcated in the pathophysiology of multiple cases of thrombotic thrombocytopenic purpura (TTP), while its relationship with the systemic complement-mediated diathesis, atypical hemolytic-uremic syndrome (aHUS), remains largely under-appreciated. Although it has been known for some time that the virus can infect endothelial cells, there is a paucity of published experience elucidating the precise interaction of the virus with the endothelium and the complement cascade in causing non-TTP-related TMA; consequently, the therapeutic landscape remains largely undefined. Given the impressive clinical responses obtained in the clinical trials which enrolled aHUS patients who likely had a diverse spectrum of disease triggers, it would seem reasonable to surmise that similar core pathogenetic mechanisms may be in play in HIV-related aHUS and that therapeutic trials with complement-inhibitory agents would be warranted. We describe, herein, a case of a 43-year-old male with advanced HIV disease and a 3-year history of chronic renal insufficiency which, without the benefit of renal biopsy, had been initially ascribed to HIVAN. The patient presented to our institution in acute renal decline in the setting of an ADAMTS-13 replete, biopsy-proven thrombotic microangiopathy. Treatment with the monoclonal anti-C5 antibody, eculizumab, resulted in rapid resolution of the hemolytic anemia and thrombocytopenia, as well as a gradual, albeit clinically significant improvement in renal function.

Case Report

The patient is a 43-year-old Caucasian male with a history of HIV infection diagnosed in 2006, chronic renal failure attributed presumptively to HIV nephropathy, and intermittent non-compliance with medical therapy, who was brought to the ED by paramedics after being found down for an unspecified period of time. His latest CD4 count and viral load were 190 and 38,000 copies/mL, respectively. On arrival, the patient was confused and agitated. He was afebrile with a tachycardia in the 160 range and hypertensive with a blood pressure of 243/146. Laboratory evaluation revealed an anion gap metabolic acidosis with a serum bicarbonate of 15, acute renal failure with a BUN of 34 and a creatinine of 3.81 (baseline 2.0),

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a CPK level peaking at 522 U/L, a normocytic anemia with a hemoglobin of 12.0, and moderate thrombocytopenia with a platelet count of 75,000. Given the concern for trauma, he underwent CT scanning of the head, chest and pelvis and was found to have a subarachnoid hemorrhage and patchy infiltrates in the right middle and lower pulmonary lobes. He was admitted to the intensive care unit after being intubated for airway protection and placed on a labetalol drip for hypertensive crisis. On the evening of admission, he experienced a tonic-clonic seizure which responded to intravenous lorazepam and diphenylhydantoin. A repeat CT of the head revealed findings consistent with posterior reversible encephalopathy syndrome (PRES). Over the next 24 h, the patient's mental status steadily improved, allowing for extubation on day 2. To assess the patient's HIV status, an infectious disease consult was requested and given his CD4 count of less than 200, a three-drug HAART regimen (entravirine, ritonavir and darunavir) was initiated.

The patient's renal function eventually further declined, with his serum creatinine ultimately peaking at 6.16. A nephrology consultation suggested the acute renal dysfunction might have been related to hypovolemia and/or rhabdomyolysis, with acute worsening of HIV nephropathy felt to be less likely. Urinalysis showed proteinuria on dipstick with a quantitation of 500 mg/dL. A serological profile revealed unremarkable anti-nuclear antibody and anti-rheumatoid factor titers. Despite aggressive fluid resuscitation, the patient's renal function further deteriorated.

Throughout the patient's stay, his hemoglobin ranged between 7.0 and 9.2 g/dL. He remained thrombocytopenic with an initial platelet count of 75,000, which reached a nadir of 50,000 on hospital day 2. The hematology service was consulted on the third hospital day and a laboratory investigation for TMA was initiated. A serum LDH returned at 304 and subsequently peaked at 707, concomitant with a haptoglobin of < 10 g/L. A review of peripheral blood smears detected minimal to no schistocytosis and the ADAMS-TS 13 activity was found to be within normal range (> 66%). Serum C3 was found to be decreased at 60.3, while C4 and CH50 were within normal limits. An antiphospholipid antibody panel, a direct anti-globulin titer, and a DIC battery were all found to be unremarkable. With a high index of suspicion for an ADAMTS-13 replete TMA, a renal biopsy was requested by the hematology service but was initially declined by the nephrology service due to the perceived lack of utility.

With the lack of tissue confirmation acting as an impediment to our diagnostic efforts, it was recalled that in the pre-ADAMTS-13 era, skin biopsies were occasionally employed to detect platelet-fibrin aggregates in dermal vessels in patients with suspected TTP. Even more relevant is the published case in which punch skin biopsy proved helpful in a diagnostically challenging TMA case [1]. It was therefore decided to obtain a skin biopsy of non-lesional skin to assess for endothelial deposition of C5b-9 (membrane attack complex) within the cutaneous vasculature. Direct immunofluorescence (DIF) analysis identified prominent endothelial deposits of C5b-9 in the cutaneous microvessels of clinically unperturbed skin. This was felt to increase the likelihood that a systemic TMA was, indeed, responsible for the patient's acute renal deterioration (and likely his chronic renal insufficiency as well). Thus,

a renal biopsy was obtained, with light microscopy revealing intraluminal thrombi within glomeruli, segmental splitting of glomerular capillary walls, and hypertrophied endothelial cells. Electron microscopy detected focal subendothelial lucencies in the glomerular basement membrane (GBM) as well as focal splitting of the GBMs. These findings were felt to be typical of acute TMA. After receiving an anti-meningococcal vaccine and being placed on appropriate antibiotic prophylaxis, the patient was promptly initiated on the recommended eculizumab induction regimen 2 days after hospital discharge. Within 2 weeks of beginning induction therapy, there was complete resolution of the patient's microangiopathic hemolytic anemia/thrombocytopenia, and after 20 weeks of treatment, an improvement in his eGFR from 15 to 19 mL/min/1.73 m² consistent with a response of the acute component of his renal dysfunction.

Discussion

It has been approximately two decades since the HIV-related p24 antigen was first detected in the endothelial cells of an HIV-positive patient with TTP [2], thereby establishing a basis for its linkage with systemic thrombotic endotheliopathies. There have been numerous publications dating back to 1984 [3-7] describing the association of HIV disease with TTP and the putative mechanisms by which the virus may cause endothelial injury. Curiously, despite the major advances recently made in our understanding of the pathogenesis of aHUS, there remains a relative paucity of knowledge regarding the relationship of the HIV virus with this unique form of TMA.

Atypical hemolytic uremic syndrome is considered an ultra-orphan disease, with its prevalence estimated to be two cases in one million people worldwide [8]. Due to its ultra-orphan disease status, its global incidence is not precisely known. Approximately 90% of cases are believed to be related to hereditary mutations in complement-regulatory proteins [9-11], with the remainder being attributed to antibody-mediated destruction of a select group of these proteins. Involvement of the renal system is not an infrequent occurrence in the clinical spectrum of HIV disease, with the prevalence of HIV-related renal disease approximating 30%. HIV-associated nephropathy is the term used to describe HIV-related renal failure which is hypothesized to be the result of direct infection of renal epithelial cells by the virus in genetically susceptible hosts. The common clinical manifestations observed in HIVAN are African-American race, advanced HIV disease, severe proteinuria, and a rapid decline in renal function. The typical histopathology is a collapsing form of focal segmental glomerulosclerosis in a background of dilated renal tubules and significant interstitial inflammation. The core of therapy remains systemic treatment of the infection with highly active anti-retroviral therapy (HAART). Despite this intervention, the overall prognosis remains poor, with the majority of patients ultimately developing end-stage renal disease. It has been recommended that in patients suspected to have HIVAN based solely on clinical criteria, the true cause of renal failure should be established by tissue examination since nearly 40% of such patients will have an alternate histopathological diagnosis on

renal biopsy. A retrospective single-institution analysis [12] of 92 HIV patients with acute renal failure of whom 60 had undergone renal biopsy revealed that the most frequently observed histopathology (53%, 32 of 60) was TMA in group 1, while only 23% (14 of 60) showed a pattern consistent with HIVAN (group 2) [12]. Although no effort was made to define the form of TMA with measurement of ADAMTS-13 activities, it is likely that a significant percentage of patients in group 1 had an ADAMTS-13 replete TMA given the greater propensity for advanced renal injury associated with aHUS. The clinical profile associated with the patients with TMA was young Caucasian males with advanced HIV disease, low CD4 counts, and poor prognostic features; this essentially mirrored our patient's clinical features.

In summary, the limited awareness of this particular disorder occurring in the HIV-positive population coupled with the tendency to forego renal biopsy in such cases would appear to put HIV-positive patients with aHUS-related nephropathy at risk of having potentially reversible renal dysfunction erroneously attributed to HIVAN, thus depriving them of a reasonable chance for renal recovery. The availability of an effective complement-inhibitory therapy proven to improve or reverse TMA-related renal failure in a time-dependent fashion should compel physicians to diligently exclude this disorder in HIV-positive patients with this clinical presentation.

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