than usual treatment times may be needed in order to achieve adequate dialysis dose in this unusual access.

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References


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Mycobacterial-immune reconstitution inflammatory syndrome: a cause of acute interstitial nephritis during HIV infection

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Abstract

Kidney injury during HIV infection encompasses a wide variety of disorders, including acute interstitial nephritis. We report a case of acute granulomatous interstitial nephritis related to a mycobacterial-triggered immune reconstitution inflammatory syndrome (IRIS) in an HIV-infected patient. IRIS is an emerging health concern during HIV infection and should be considered in the diagnostic frame of acute renal failure during immune restoration.

Keywords: acute interstitial nephritis; HIV; immune reconstitution inflammatory syndrome; Mycobacterium

Background

Combined antiretroviral therapy (cART)-induced immune recovery greatly improves the prognosis of HIV infection. However, up to 25% of patients starting cART experience a clinical deterioration referred to as immune reconstitution inflammatory syndrome (IRIS) [1]. Kidney injury has been exceptionally reported as a consequence of IRIS. We report such a case triggered by a non-tuberculous mycobacterial infection.

Case report

An asymptomatic 37-year-old naive HIV-1-infected white male was started in September 2009 on cART based on
efavirenz, tenofovir and emtricitabine, together with cotrimoxazole chemoprophylaxis (Figure 1). His CD4+ T-cell count was 25/mm³ (4%) and plasma HIV-1 viral load (VL) 6.5 log_{10} copies/mL. His estimated glomerular filtration rate (eGFR) was 106 mL/min/1.73m² (serum creatinine level 76 μmol/L). At Day 34 after starting cART, he was diagnosed with a Mycobacterium avium infection. An anti-mycobacterial regimen based on clarithromycin, rifabutin, moxifloxacin and amikacin was started. Clinical condition gradually improved.

He was readmitted on Day 103 after starting cART for fever, cognitive impairment and acute renal failure. Serum creatinine level reached 560 μmol/L. Urinary abnormalities consisted of mild proteinuria (1.2 g/day) with tubular profile, without evidence for proximal defects. There was neither haematuria nor eosinophilia. CD4+ T-cell count was 88/mm³ (29%) while plasma VL had dropped to 2.4 log_{10} copies/mL. Brain magnetic resonance imaging and cerebrospinal fluid analysis were normal. As compared to initial assessment, computed tomography (CT) scan revealed kidney enlargement (Figure 2A and B), progression of retroperitoneal lymphadenitis and appearance of lung interstitial infiltrate. Analysis of urine, blood, bronchoalveolar fluid and bone marrow showed no evidence of M. avium or other pathogens. Kidney biopsy (Figure 2C–H) demonstrated severe acute interstitial nephritis (AIN) with non-caseating granulomatous infiltrates. Ziehl staining was negative. No glomerular lesion was found. Cellular infiltrates consisted of macrophages (60%) and T cells (40%), without B cells. T cells were mainly composed of CD8+ T cells (80%). A diagnosis of non-tuberculous mycobacterial IRIS with prominent kidney involvement was made. Prednisone was started at a dose of 1 mg/kg/day for 4 weeks and then gradually tapered during the next month. Four sessions of haemodialysis were performed. Cotrimoxazole and anti-mycobacterial therapy were continued while cART was adjusted (abacavir, lamivudine, raltegravir and enfuvirtide). Fever abated and neurological manifestations improved promptly. Renal function improved over the next month. At 10 months follow-up, serum creatinine level is 90 μmol/L (eGFR 73 mL/min/1.73m²) while CD4+ T-cell count is 124/mm³ (17%) and plasma VL < 1.3 log_{10} copies/mL.

Discussion

Acute kidney injury (AKI) during HIV infection encompasses a wide variety of diseases [2]. In this case, kidney biopsy pointed to granulomatous AIN and ruled out glomerular injury, lymphoma infiltration or isolated amikacin- and tenofovir-induced tubular necrosis. Drug-induced AIN was first considered since the patient was treated by cotrimoxazole and moxifloxacin. However, both treatments were pursued while kidney function improved. Massive kidney enlargement on CT scan, concomitant

worsening of lymphadenitis, appearance of lung infiltrates and cognitive impairment were suggestive of a systemic inflammatory response and argued for considering another diagnosis. Interestingly, sarcoidosis may occur during immune restoration in HIV-infected patients [3]. However, the mean delay between starting cART and sarcoidosis is 29 ± 16 months, as compared to 3 months in our patient. We therefore considered that this patient developed a non-tuberculous mycobacterial IRIS that culminated in a granulomatous AIN with renal failure.

IRIS is characterized by the paradoxical worsening during immune recovery of manifestations of opportunistic infections [1]. Mycobacterial infections are the main pathogens associated with IRIS. Mycobacterial IRIS is thought to be the consequence of a recovered Th1 immune response against mycobacterial antigens that overshoots its goal.

Fig. 2. A–H: CT scan and kidney pathology: kidney enlargement and acute granulomatous interstitial nephritis. (A, B) Sagittal CT scan showing bilateral kidney enlargement at diagnosis of M. avium complex infection (A, with iodine contrast) and at recognition of acute kidney failure (B, without iodine contrast). (C) Low power view showing diffuse inflammatory granulomas in kidney interstitial tissue (Masson’s trichrom, original magnification ×20). (D–H) Kidney interstitial tissue infiltrates are composed of T cells (CD3+, Panel D) and macrophages (CD68+, Panel E), without B cells (CD20−, Panel F) (immunohistochemistry, brown nuclei, original magnification ×20). T cells are mainly composed of CD8+ T cells (CD4−, Panel G and CD8+, Panel H) (immunohistochemistry, brown nuclei, original magnification ×400).
and causes inflammatory tissue damage. Manifestations of mycobacterial IRIS are protean, including fever, lymphadenopathy and pulmonary, intra-abdominal or neurological manifestations [4].

The diagnosis of mycobacterial-related IRIS in the face of an inflammatory process occurring after cART initiation relies on a multiparametric assessment [1]. First, HIV-infected patients must respond positively to cART, with evidence of controlled HIV replication (decrease in plasma VL > 2 log10 copies/mL). Second, a negative in-depth evidence of controlled HIV replication (decrease in plasma infected patients must respond positively to cART, with relies on a multiparametric assessment [1]. First, HIV-infected patients treated for a Mycobacterium tuberculosis co-infection. Particular to our case is that IRIS-related kidney injury was triggered by M. avium. In all cases, renal pathology demonstrated acute tubulointerstitial nephritis with mononuclear cell infiltrates mainly composed of macrophages and lymphocytes. Non-caseating granulomas were demonstrated in three patients not receiving corticosteroids prior to renal biopsy [7–9]. Immunophenotyping of infiltrates is available in one case and demonstrated prominent CD4+ T cells with few CD8+ T cells and very few B cells [5]. However, in our case, immunohistochemistry staining by demonstrating the dominance of macrophages supports the role of the innate immune system in the pathogenesis of mycobacterial IRIS.

In all cases of IRIS-related kidney injury reported so far, management was based on a short course of prednisone (1 mg/kg/day), with prompt renal response. This approach was proved efficient in a controlled clinical trial in patients with paradoxical tuberculosis IRIS [10]. Simultaneously, optimizing the anti-mycobacterial therapy is pivotal to suppressing replication of the triggering pathogen and to reduce mycobacterial antigen load. Lastly, cART interruption is not recommended, as IRIS must be balanced against the risks of AIDS progression.

IRIS should therefore be considered as a diagnosis when facing AIN following efficient cART initiation. This is mandatory in countries with high endemicity for mycobacterial infections, where increasing access to cART might enhance the prevalence of this condition, which is reversible by a short course of corticosteroids.

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