CASE REPORT

First case of acute granulomatous interstitial nephritis with immune reconstitution inflammatory syndrome in a patient with HIV coinfecting with disseminated *Mycobacterium kansasii*

Vikas Kapoor,¹ Azka Latif,¹ Faiza Hassan Warraich,¹ Aneela Majeed²

¹Department of Hematology and Oncology, University of Arizona Arizona Health Sciences Center, Tucson, Arizona, USA

²Department of Infectious Diseases, University of Arizona Arizona Health Sciences Center, Tucson, Arizona, USA

Correspondence to

Dr Aneela Majeed,
amajeed@deptofmed.arizona.edu

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SUMMARY

Restoration of immune response by highly active antiretroviral therapy (HAART) effectively improved the overall prognosis of HIV infection. However, 25%–31.7% of patients experience paradoxical worsening of pre-existing infections or unmasking of subclinical infections after starting HAART therapy, which is termed as immune reconstitution inflammatory syndrome (IRIS). Acute granulomatous interstitial nephritis as a consequence of IRIS has never been reported with *Mycobacterium kansasii* coinfection. Here, we describe an HIV/AIDS patient coinfecting with disseminated *M. kansasii* infection, who presented with acute kidney injury 4.5 months after initiation of HAART. The diagnostic workup revealed IRIS was the cause of acute kidney injury. Short-term course of prednisone (1 mg/kg/day) along with antimycobacterial and HAART regimen achieved significant improvement.

BACKGROUND

Restoration of immune response by highly active antiretroviral therapy (HAART) effectively improved the overall prognosis of HIV infection. However, 25%–31.7% of patients experience paradoxical worsening of pre-existing infections or unmasking of subclinical infections after starting HAART, which is termed as immune reconstitution inflammatory syndrome (IRIS).¹ There are no specific laboratory tests for this syndrome but diagnostic criteria includes high HIV viral load (VL) and low CD4 T cells counts at initiation of HAART, reduced HIV VL and rapid rise in CD4 T cells following HAART initiation, temporal association between commencement of HAART and onset of clinical features which cannot be explained by recently acquired infection or drug toxicity (4–8 weeks).² Acute granulomatous interstitial nephritis (AGIN) as manifestation of IRIS in patients with HIV/AIDS has rarely been published. To the best of our knowledge, AGIN as a consequence of IRIS has not yet been reported with *M. kansasii*.

CASE PRESENTATION

A 55-year-old male with a 5-year history of HIV/AIDS, presented to the outpatient clinic with complaints of painful, itchy skin lesions on bilateral lower extremities and abdomen for 4 weeks.

Lesions initially appeared on right ankle and then spread in an ascending fashion to abdomen. He also complained of cough for few days, haematuria for 10 days and unintentional weight loss of 70 pounds over the last 3 months. Patient had no significant comorbidities and family history was also unremarkable. On physical examination, multiple tender erythematous papules and nodules were visualised on bilateral lower extremities and lower abdomen. Some lesions were purulent, while others were scabbed. Abdominal examination revealed non-tender hepatosplenomegaly. He was on tenofovir, emtricitabine and efavirenz-based therapy since 2015 but was non-adherent and was not taking medication willingly for last 1 year. Laboratory findings included pancytopenia with white cell count $0.9 \times 10^9/L$, haemoglobin 8.2 mg/dL, platelet count $77 \times 10^9/L$, CD4 count 18 cells/ μL and HIV VL of 89 copies/mL. Liver function tests were elevated with alkaline phosphatase 968 U/L, alanine aminotransferase 67 U/L and aspartate aminotransferase 68 U/L. Renal function tests were within normal limits. Urinalysis revealed positive leucocytes esterase along with trace red blood cells (RBC). Extensive workup including chest X-ray, abdominal ultrasound, CT scan of chest, abdomen and pelvis was performed. CT scan chest revealed 2 cm cavitary nodule within right middle lobe and mass-like infiltrates in right lower lobe. CT scan abdomen and pelvis showed mesenteric lymphadenopathy, hepatosplenomegaly and ill-defined left renal mass along with perinephric fluid collection. Histological examination of cutaneous lesions showed acute inflammation with granulation tissue and foamy histiocytes. Numerous acid fast bacilli (AFB) were seen on Ziehl-Neelsen stain (figure 1). Subsequently, cutaneous, sputum and bronchoalveolar lavage fluid cultures were positive for *M. kansasii*. Acute and chronic inflammation was seen on renal mass biopsy, while no organism was seen on microscopy. A diagnosis of disseminated *M. kansasii* was made, and rifampin, ethambutol and isoniazid were initiated. Improvement in cutaneous lesions was observed within 2 weeks; therefore, HAART consisting of tenofovir, emtricitabine and dolutegravir was initiated. Follow-up laboratory testing after 6 weeks revealed creatinine of 150 $\mu mol/L$. Due to concern of tenofovir toxicity,

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Figure 1 Biopsy of cutaneous lesions showing inflammatory infiltrate with granulation tissue on (A) H&E stain and (B) acid fast bacilli on Ziehl-Neelson stain.

HAART regimen was modified to abacavir, dolutegravir and lamivudine. Four months after this, the patient was presented with the complaint of fatigue and increased urinary frequency for 1 week. Physical examination was unremarkable.

INVESTIGATIONS

Laboratory testing at this encounter showed renal function deterioration with raised serum creatinine of 415 $\mu\text{mol/L}$. Overall, his virological status had improved with reduced HIV VL (<20 copies/mL) and raised CD4 cells (101 cells/ μL). Other laboratory findings included serum phosphate 2.0 mmol/L, parathyroid hormone 0.85 pmol/L and serum vitamin D 20 nmol/L. Urine analysis showed 2+protein, trace RBC and urinary protein/creatinine ratio of 110 mg/mmol. Abdomen and pelvis CT scan revealed progression of abdominal and pelvic lymphadenopathy, hepatomegaly and complete resolution of previous renal findings (figure 2). Renal biopsy showed AGIN with few scattered AFB (figure 3).

DIFFERENTIAL DIAGNOSIS

Potential nephrotoxicity secondary from tenofovir was initially thought to be the cause of deranged renal function. However, it was ruled out when renal function failed to improve after discontinuation of the drug along with the absence of other indicative features such as Fanconi syndrome. Acute interstitial nephritis due to ethambutol was another plausible diagnosis but suspicion was low due to the absence of neural toxicity or optic neuritis. One possibility included HIV nephropathy from the advanced HIV/AIDS, which was ruled out after lack of characteristic renal biopsy findings. Lastly, disseminated *M. kansasii* infection was considered, but in-depth microbiological analysis testified that previously recognised disseminated *M. kansasii* infection was under control by antimycobacterial therapy.

Figure 2 CT scan showing (A) left renal mass and hepatomegaly and (B) resolution of earlier findings on follow-up CT scan 4.5 months later.

Figure 3 Renal biopsy showing (A) acute granulomatous interstitial nephritis on H&E stain and (B) acid fast bacillus on Ziehl-Neelson stain.

TREATMENT

Based on the clinical features and laboratory findings, a diagnosis of *M. kansasii*-induced IRIS with renal involvement was made. HAART and antimycobacterium therapy were continued and prednisone at a dose of 1 mg/kg was administered for 4 weeks with subsequent tapering of dose.

OUTCOME AND FOLLOW-UP

After 4 weeks of steroid therapy, his renal function improved with creatinine of 106 $\mu\text{mol/L}$ from 415 $\mu\text{mol/L}$.

DISCUSSION

HAART suppresses HIV replication via restoration of immune response. During first 3–6 months after HAART initiation, increase in CD4 lymphocytes occurs initially due to increased memory T cells which is presumably secondary from decreased apoptosis of T lymphocytes and redistribution of lymphocytes from peripheral lymphoid tissues into blood circulation. This is followed by thymopoiesis leading to slow increase in naive CD4 and CD8 T lymphocytes.^{3 4} During this restoration phase, following the commencement of HAART, rapid rise in CD4 T cells is associated with systemic or local inflammatory response against foreign antigens, including both subclinical or residual pathogens and non-infectious antigens.²

This inflammatory response secondary to HAART initiation may resolve with supportive therapy without any specific intervention. However, it was observed in a randomised placebo-controlled trial that patients receiving 4 weeks of prednisone therapy experienced earlier resolution of symptoms, decreased hospital stay and improvement in quality of life without excess adverse effects, when compared with patients receiving placebo.⁵

According to a meta-analysis, reported incidence of IRIS is 37.7% in patients with HIV/AIDS co-infected with cytomegalovirus, 19.5% in patients with *cryptococcus*, 15.7% in patients with *Mycobacterium tuberculosis*, 16.7% in patients with multifocal leukoencephalopathy and 6.4% in patients with Kaposi sarcoma.⁶ Clinical manifestation of IRIS is strongly related to the site of pre-existing opportunistic infection. AGIN secondary to IRIS is an unusual occurrence and so far only a few cases have been reported in patients co-infected with *M. tuberculosis* or *Mycobacterium avium* complex. We report first such case triggered by *M. kansasii*. Diagnostic features in favour of IRIS in this patient include low HIV VL (<20 copies/mL), high CD4 counts (101 cells/ μL) and manifestation of AGIN shortly after initiation of HAART and renal biopsy results consistent with IRIS. Other suggestive features included worsening hypercalcaemia and hyperphosphataemia with decreased parathyroid hormone indicating an underlying granulomatous pathology. Further,

significantly improved renal function following steroid therapy supports the diagnosis of AGIN secondary to IRIS.

A preventive strategy for IRIS includes treatment of pre-existing infections prior to the commencement of HAART. However, delay in HAART can significantly increase mortality and risk of other opportunistic infections, predominantly in patients with CD4 count less than 100 cells/ μ L.⁷ Therefore, HAART initiation should not be delayed more than 2 weeks in patients with low CD4 counts (<50 cells/ μ L),⁸ while at the same time careful monitoring of patients for development of IRIS is required, because better clinical outcomes significantly rely on early diagnosis followed by timely intervention.

Learning points

- ▶ Acute granulomatous interstitial nephritis in a patient with HIV/AIDS shortly after highly active antiretroviral therapy (HAART) initiation can be a manifestation of immune reconstitution inflammatory syndrome (IRIS) and should be sought after differential diagnosis.
- ▶ *Mycobacterium kansasii* can lead to acute granulomatous interstitial nephritis as a consequence of IRIS following HAART.
- ▶ Treatment of opportunistic infections in a patient with HIV/AIDS prior to HAART initiation can reduce the chances of IRIS, but initiation of HAART should not be significantly delayed due to increased mortality in patients with CD4 counts <50 cells/mL.
- ▶ After commencement of HAART, renal function should be regularly monitored in severely immunocompromised patient with HIV/AIDS coinfecting with any opportunistic infection.

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