

## CASE REPORT

# ACUTE GOUTY ARTHRITIS AS A MANIFESTATION OF IMMUNE RECONSTITUTION INFLAMMATORY SYNDROME AFTER INITIATION OF ANTIRETROVIRAL THERAPY

Walter de Araujo EYER-SILVA(1), Maria Cecília da Fonseca SALGADO(1), Jorge Francisco da Cunha PINTO(1), Fernando Raphael de Almeida FERRY(1), Rogério NEVES-MOTTA(1), Marcelo Costa Velho Mendes de AZEVEDO(1) & Carlos Alberto MORAIS-DE-SÁ(1)

### SUMMARY

Immune reconstitution inflammatory syndrome (IRIS) in HIV-infected subjects initiating antiretroviral therapy most commonly involves new or worsening manifestations of previously subclinical or overt infectious diseases. Reports of non-infectious IRIS are much less common but represent important diagnostic and treatment challenges. We report on a 34-year-old HIV-infected male patient with no history of gout who developed acute gouty arthritis in a single joint one month after initiating highly active antiretroviral therapy.

**KEYWORDS:** Antiretroviral therapy; Gout; HIV infection; IRIS.

### INTRODUCTION

Reports of unusual symptoms and signs appearing in HIV-infected patients soon after initiation of antiretroviral therapy and associated with increasing CD4 cell counts have been reported since the advent of highly active antiretroviral therapy (HAART). This paradoxical clinical worsening, which has been termed immune reconstitution inflammatory syndrome (IRIS), most commonly involves new or worsening manifestations of previously subclinical or overt infectious diseases such as tuberculosis, *Mycobacterium avium* infections, cryptococcal meningitis, herpes zoster and cytomegalovirus disease<sup>5</sup>. Reports of non-infectious IRIS are much less common but represent important diagnostic and treatment challenges. We report on a patient who had no history of articular disease who developed gouty arthritis in a single joint after initiating HAART.

### CASE REPORT

A previously asymptomatic, mildly overweight 34-year-old HIV infected male was started on a highly active antiretroviral regimen (lamivudine, tenofovir, atazanavir and ritonavir) due to a progressive decline of CD4 cell counts. At the time of HAART initiation his CD4 cell count was 166 cells/mm<sup>3</sup> (a drop from 680 cells/mm<sup>3</sup> to 166 cells/mm<sup>3</sup> had been recorded in an 18-month period). Three weeks after initiation of HAART he presented with an abrupt onset of severe pain, redness and swelling in the area of the first right metatarsophalangeal joint. He complained of exquisite soft tissue tenderness to the point that he could

not put on his right shoe. Laboratory evaluation was remarkable for mild hyperuricemia (7.7mg/dL; normal range 3.5-7.2mg/dL; uric acid urinary excretion was not measured). Serum uric acid had not been measured before the acute gout presentation. No abnormalities were found on plain radiology. The patient had no past history of gout or other rheumatological disorders, but informed that his father was a long-term gout sufferer. He also had no history of urolithiasis and was not under any other medication besides HAART and sulphametoxazole/trimethoprim thrice weekly. General measures of rest, a low-purine diet, and avoidance of alcohol intake were instituted. Colchicine and a nonsteroidal anti-inflammatory drug were started with slow resolution over the ensuing three months. During this period the patient experienced disabling, ongoing symptoms with intense inflammation, desquamation and a toothpaste-like, chalky discharge (Fig. 1). Despite the severity of the presentation and its temporal association with the initiation of the antiviral regimen, a decision was made not to interrupt HAART. Allopurinol was initiated one month after the acute presentation and a better clinical control was achieved. A progressive recovery of the CD4 cell count was recorded: 306 cells/mm<sup>3</sup> and 459 cells/mm<sup>3</sup> two and five months after initiation of HAART, respectively. The plasma HIV viral load dropped from 817.111 copies/mL to 57 copies/mL before and five months after HAART initiation, respectively. Six months after the acute presentation the patient still experienced gout flares associated with binge alcohol consumption (mainly beer) and non compliance with the prescribed diet. One year after presentation the patient was asymptomatic. No other joint has ever been affected. The serum uric acid returned to normal levels (7.2 mg/dL and 4.0 mg/dL, one and five months after acute gout presentation, respectively).

(1) Clínica Médica B, 10ª Enfermaria, Hospital Universitário Gaffrée e Guinle, Departamento de Medicina Geral, Universidade Federal do Estado do Rio de Janeiro (UNI-RIO), Rio de Janeiro, Brazil.

**Correspondence to:** Prof. Walter A. Eyer-Silva, 10ª Enfermaria, Hospital Universitário Gaffrée e Guinle, Rua Mariz e Barros 775, 20270-004 Rio de Janeiro, RJ, Brasil. E-mail: walter-eyer@unirio.br



**Fig. 1** - Severe acute gouty arthritis of the first right metatarsophalangeal joint in a 34-year-old HIV-infected male patient. This image was taken one month after acute gout presentation. Intense redness and shiny swelling with skin desquamation can be seen. The lesion was warm, exquisitely tender and an eventual chalky discharge erupted.



**Fig. 2** - Marked resolution three months after acute presentation.

## DISCUSSION

Non-infectious IRIS cases are being reported much less frequently than the clinical worsening or the unmasking of infectious disorders. One of the first such cases was reported in 1998<sup>1</sup> from a 36 year-old woman who developed systemic lupus erythematosus associated with rising antinuclear antibody titers after initiation of HAART. Since then, a variety of non-infectious IRIS cases have been reported, including sarcoidosis<sup>7</sup>, lymphoid pneumonitis<sup>7</sup>, cutaneous reaction to tattoo pigment<sup>11</sup>, alopecia universalis and Graves disease<sup>10</sup>, rheumatoid arthritis<sup>2</sup>, and Guillain-Barré syndrome<sup>8</sup>. SEBENY *et al.*<sup>9</sup> have previously reported on a 53-year-old HIV-infected male patient with a history of intermittent attacks of gout who developed severe polyarticular gouty arthritis one week after initiation of a HAART regimen consisting of tenofovir, emtricitabine and efavirenz.

Gout has rarely been reported in association with HIV infection<sup>4</sup>. The present case shares resemblance to the previously reported patient who presented with polyarticular gouty arthritis as a manifestation of IRIS<sup>9</sup>. In contrast to the case reported by SEBENY *et al.*<sup>9</sup>, our patient had no prior history of gout and presented with monoarticular disease. Interestingly, he presented a relentless acute gout syndrome associated with exquisite pain that lasted three months and went on to develop signs of a draining tophus, which is uncommon in patients without prior signs and symptoms of gout. It has been suggested that improvements in neutrophil function and decreasing levels of the anti-inflammatory IL-10 cytokine after initiation of HAART may result in a restored ability to react against monosodium urate crystals<sup>9</sup>. The effect of individual antiretroviral agents on uric acid metabolism should also be considered. It is known that the nucleoside analogs stavudine and didanosine are associated with hyperuricemia, whereas the nucleotide analog tenofovir seems to lower serum uric acid<sup>12</sup>. It has also been suggested that ritonavir-including regimens may be associated with an increased risk of hyperuricemia and gout<sup>3,6</sup>.

Physicians caring for HIV-infected patients should be aware that severe acute gouty arthritis may emerge as a non-infectious manifestation of IRIS in HIV-infected patients initiating HAART.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## FINANCIAL SUPPORT

There was no financial support.

## RESUMO

### **Gota aguda como manifestação da síndrome inflamatória de reconstituição imune após início de terapia antirretroviral**

A síndrome inflamatória da reconstituição imune (IRIS) observada quando do início da terapia antirretroviral em indivíduos com infecção pelo HIV envolve mais comumente manifestações novas ou piora clínica de desordens infecciosas, previamente subclínicas ou não. Muito mais raras são as descrições de casos de IRIS de natureza não-infecciosa, embora representem importantes desafios ao diagnóstico e tratamento. Neste relato descrevemos um paciente HIV-positivo do sexo masculino, de 34 anos, sem antecedentes de gota e que desenvolveu monoartrite de gota um mês após início de terapia antirretroviral de alta atividade.

## REFERENCES

1. Behrens G, Knuth C, Schedel I, Mendila M, Schmidt RE. Highly active antiretroviral therapy. *Lancet*. 1998;351:1057-8; author reply 1058-9.
2. Bell C, Nelson M, Kaye S. A case of immune reconstitution rheumatoid arthritis. *Int J STD AIDS*. 2002;13:580-1.
3. Creighton S, Miller R, Edwards S, Copas A, French P. Is ritonavir boosting associated with gout? *Int J STD AIDS*. 2005;16:362-4.
4. Disla E, Stein S, Acevedo M, Cuppari G. Gouty arthritis in the acquired immunodeficiency syndrome. An unusual but aggressive case. *Arthritis Rheum*. 1995;38:570-2.

5. Ledergerber B, Egger M, Erard V, Weber R, Hirschel B, Furrer H, *et al.* AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. *JAMA*. 1999;282:2220-6.
6. Mehlhaff DL, Stein DS. Gout secondary to ritonavir and didanosine. *AIDS*. 1996;10:1744.
7. Mirmirani P, Maurer TA, Herndier B, McGrath M, Weinstein MD, Berger TG. Sarcoidosis in a patient with AIDS: a manifestation of immune restoration syndrome. *J Am Acad Dermatol*. 1999;41:285-6.
8. Piliero PJ, Fish DG, Preston S, Cunningham D, Kinchelov T, Salgo M, *et al.* Guillain-Barré syndrome associated with immune reconstitution. *Clin Infect Dis*. 2003;36:e111-4.
9. Sebeny PJ, Keith MP, Love KM, Dwyer TX, Ganesan A. Refractory polyarticular gouty arthritis as a manifestation of immune reconstitution inflammatory syndrome. *J Clin Rheumatol*. 2010;16:40-2.
10. Sereti I, Sarlis NJ, Arioglu E, Turner ML, Mican JM. Alopecia universalis and Graves' disease in the setting of immune restoration after highly active antiretroviral therapy. *AIDS*. 2001;15:138-40.
11. Silvestre JF, Albares MP, Ramon R, Botella R. Cutaneous intolerance to tattoos in a patient with human immunodeficiency virus: a manifestation of the immune restoration syndrome. *Arch Dermatol*. 2001;137:669-70.
12. Walker UA, Hoffmann C, Enters M, Thoden J, Behrens G, Mitzel SL. High serum urate in HIV-infected persons: the choice of the antiretroviral drug matters. *AIDS*. 2006;20:1556-8.

Received: 8 February 2012

Accepted: 2 May 2012