CASE REPORT

Rhinology, 46, 243-245, 2008

A frontal mucocele caused by an immune reconstitution inflammatory syndrome in a patient with HIV infection*

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SUMMARY

We describe a 55-year-old bisexual Belgian man with a multi-drug resistant HIV infection who developed an Immune Reconstitution Inflammatory Syndrome (IRIS) presenting as a mucocele of the frontal sinus, one year after starting a new effective darunavir containing antiretroviral treatment regimen. His CD4$^+$ lymphocyte count had increased from 3 cells/mm^3 prior to the start of the latter treatment to 196 cells/mm^3 just before he developed the IRIS phenomenon. IRIS is a paradoxical clinical deterioration during highly active antiretroviral treatment (HAART), due to an exaggerated immune-inflammatory reaction. With the increasing numbers of persons living with HIV infection and the increased use of HAART it is expected that in the future more otolaryngological manifestations of IRIS will be detected.

Key words: HIV infection, sinusitis, mucocele, Immune Reconstitution Inflammatory Syndrome

INTRODUCTION

Since the availability of Highly Active Antiretroviral Therapy (HAART), HIV infection is now a chronic controllable infection. The goal of HAART is immune restoration, resulting in a decrease of opportunistic infections. However, this immune restoration can be associated with a paradoxical clinical deterioration, due to an exaggerated immune-inflammatory reaction against live or dead pathogens [1-3]. Such a paradoxal reaction is called Immune Reconstitution Inflammatory Syndrome (IRIS). The occurrence of IRIS has been reported with a multitude of organisms such as *Mycobacterium tuberculosis* (TB), *Mycobacterium Avium Complex* (MAC), herpes viruses, cytomegalovirus, *Cryptococcus neoformans* and many others [1-3]. Other IRIS manifestations not clearly related to infectious agents have also been described, such as Graves disease, sarcoidosis, other auto-immune disorders [4-6] and malignancies like Kaposi's sarcoma and lymphoma [3].

We describe a patient with a multi-drug resistant HIV infection who developed IRIS presenting as a mucocele of the frontal sinus, one year after starting a new effective antiretroviral treatment regimen.

CASE REPORT

December 2006, a 55-year-old, bisexual Belgian man, HIV-seropositive since 1981, presented at the Antwerp University hospital with progressive worsening of a left-sided frontal sinus pain since 5 days and a painful swelling of his left eye since 2 days.

His medical history revealed several opportunistic infections: episodes of oral candidiasis, hairy leukoplakia and recurrent herpes simplex since 1993, penile condylomata, molluscum contagiosum and Kaposi's sarcoma skin lesions of his left leg in 1995. He had a history of chronic sinusitis, which was treated with an anterior ethmoïdectomy in 2005.

He was treated with antiretroviral treatment since March 1993, initially with zidovudine monotherapy, later with bi-therapy and finally with several HAART regimens. In July 2005 his failing antiretroviral therapy was stopped because it was causing too many side effects (mainly gastro-intestinal intolerance). Genotypic and phenotypic resistance testing revealed that his virus was resistant to all antiretrovirals commercially available in Belgium at that time. In November 2005 he complained of weakness, diarrhea and weight loss. His CD4$^+$ lymphocyte count was 3 cells/mm^3 and his viral load 391.000 copies/ml. He was enrolled in an open darunavir trial for patients with multi-drug resistant HIV infection. His antiretroviral treatment regimen included darunavir 600 mg bid, ritonavir 100 mg bid, tenofovir 245 mg qd and zidovudine 300mg bid. Since this new antiretroviral treatment was started his symptoms disappeared and his CD4$^+$ lymphocyte count increased rapidly. February 2006 his CD4$^+$ lymphocyte count was 93 cells/mm^3 and his viral load 321 copies/ml. November 2006 his CD4$^+$ lymphocyte

*Received for publication: July 25, 2007; accepted: October 22, 2007

count was 196 cells/mm^3 and his viral load, for the first time since his HIV infection was diagnosed, undetectable (<50 copies/ml).

On admission in December 2006, he was unable to open his left eye. Clinical examination revealed conjunctivitis of the left eye with severe swelling of the periorbital tissue. Exopthalmos and diplopia were present and movements of his left eye were impossible. His body temperature was 37,3°. The vision of his left eye was impaired 0.4-0.5.

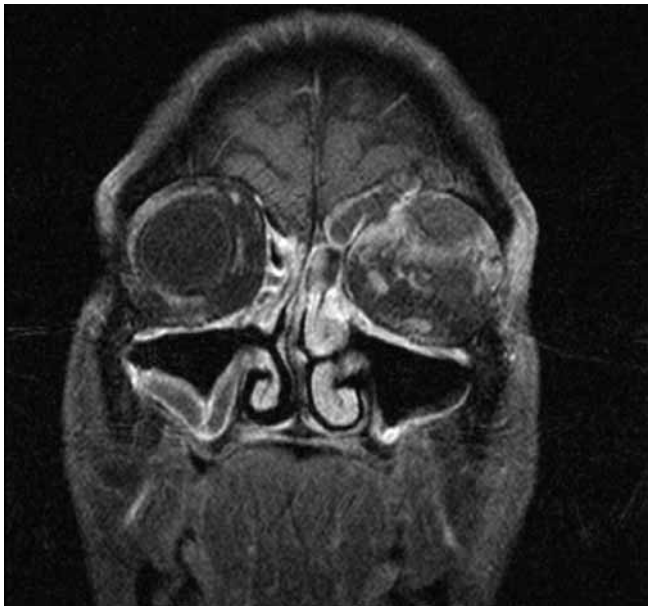

Figure 1. T1 Magnetic Resonnance Image: coronal section through the anterior ethmoid and maxillary sinuses, showing a frontal mucocele with orbital invasion. Orbital asymmetry as a consequence of left proptosis.

Laboratory tests revealed the following results: C-reactive protein 2,3 mg/dl (normal < 0.5 mg/dl), haemoglobin 13,3g/dl (normal 13,5 – 17,3 g/dl), platelets 163.000/μl (normal 140.000 – 440.000/∝l), leukocytes 9.200/∝l (normal 4300 – 10.000/∝l), lymphocytes 35% (normal 20-45%), LDH 708 UL (normal 105-333 IU/L), glucose 98 mg/dl (normal 75 – 110 mg/dl), BUN19 mg/dl (normal 19 – 45 mg/dl), creatinine 1,2 mg/dl (normal 0,70 – 1,40 mg/dl).

Multi-slice spiral computed tomography of the orbit with contrast (Figures 1 and 2) showed a homogeneous opacification with an intermediate density of the frontal sinus. The frontal sinus floor was eroded. The soft tissues of the frontal sinus extended into the left orbit. The image was described as a mucocele originating from the left frontal sinus and herniating into the orbit. As a result of this, the left superior rectus muscle was displaced downwards and the left optic nerve was slightly elongated. There was no evidence of an intracranial extension of the mucocele. Pansinusitis was present with bilateral opacification of the ethmoïdal cells, the maxillary sinuses, the left sphenoid sinus and the right ostio-meatal complex. Magnetic Resonance imaging (MRI) of the brain showed a soft tissue mass with intermediate signal intensity (T1-weighted image) and very high signal intensity (T2-weighted image) in the roof of the left orbit with proptosis of the left eyeball. After contrast administration a thick irregular wall surrounding the collection was seen.

On December 4th 2006, an endonasal fronto-ethmoidectomy was performed, with only minor improvement. On December 12th a surgical drainage of the abscess was followed by a complete restoration of the vision.

Direct microscopic investigation of material aspirated from the frontal mucocele did not reveal any pathogens. On culture, there was poor growth of a *Staphylococcus* species (non-aureus) and *Aspergillus fumigatus*. A biopsy of the mucocele tissue of the frontal sinus revealed granulomatous inflammatory tissue, but no etiological agent was found.

The patient was also treated with metronidazole, ceftriaxone, vancomycine and caspofungin.
On January 11th 2007, a third operation was necessary because of a recurrent mucocele. An obliteration of the left frontal sinus with abdominal fat tissue was performed (this intervention was already proposed after the first episode of mucocele, but was initially not accepted by the patient). After this third surgical intervention the patient improved again very quickly without any complication. His antiretroviral treatment was never interrupted. February 2007 his CD4$^+$ lymphocyte count was 294 cells/ mm^3 and his viral load remained undetectable.

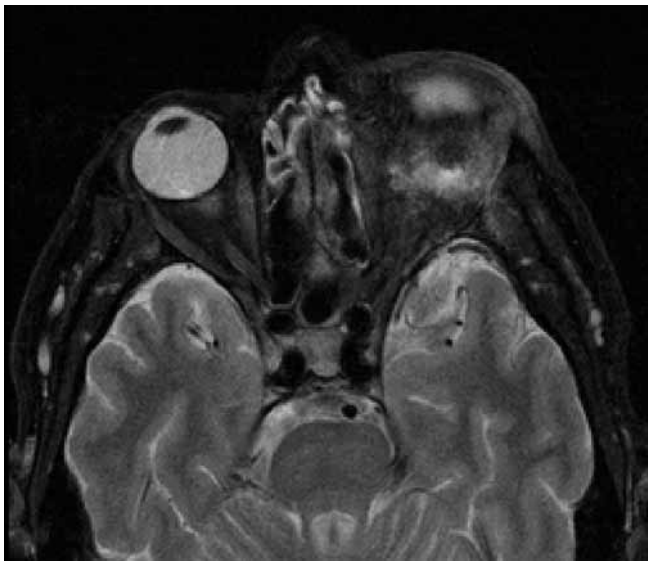

Figure 2. T2 Magnetic Resonnance Image, axial section through both orbits displaying ehtmoid inflammation, and left proptosis through inflammatory changes of the orbital content.

DISCUSSION

Sinusitis, both acute and chronic, is prevalent in patients with HIV. Patients with HIV infection have decreased mucociliary clearance of their sinuses, with predisposition to obstruction of the sinus ostia and microbial overgrowth [5-7]. Our patient before starting the very efficient darunavir treatment regimen was known to suffer since many years from chronic sinusitis but this never lead to the development of any important mucocele. We hypothesize that during the darunavir treatment regimen his immune system improved considerably causing an inflammatory reaction with the development of a mucocele. The fact that on biopsy granuloma tissue was found is characteristic of an IRIS phenomenon [1]. Whether the IRIS was triggered by an *Aspergillus* infection or any other pathogen is unclear.

This case is the second patient described in the literature with an IRIS presenting as sinusitis with an inflammatory pseudotumor. The only patient described so far was a 26-year-old, Puerto Rican HIV seropositive man who developed a similar manifestation of IRIS 20 weeks after the initiation of HAART [4]. The latter patient presented with a pseudotumor with on microscopic examination abundant mast cells but also without evidence of any pathogen.

As the number of HIV-infected individuals treated with HAART continues to increase, so too does the number of reports of novel manifestations of IRIS. Because the manifestations of IRIS vary widely, depending on the target to which the restored inflammatory response is directed, it is difficult to describe IRIS as a single clinical entity. The incidence of this disorder has been estimated to be 10% among persons starting antiretroviral therapy and as high as 25% among patients starting therapy who have a $CD4^+$ cell count of < 50 cells/mm^3 [3]. IRIS may develop within a week but in most cases within the first 3 months of starting an effective antiretroviral therapy. Late onset IRIS however also has been described [8]. The pathogenesis of this phenomenon remains poorly understood but is probably related to the quantitative and qualitative restoration of the cellular immune response and host genetic susceptibility [1,9]. In many cases, IRIS may be mild and resolve without treatment. In most patients IRIS develops when a patient is started for the first time on HAART. Our patient is rather exceptional because he developed IRIS 13 years after his first antiretroviral treatment regimen and one year after starting a new regimen containing the new protease inhibitor darunavir [10] because of a multi-resistant HIV infection.

With the increasing number of patients with HIV infection worldwide, the otolaryngologist will increasingly be confronted with persons with HIV infection. It can be expected that in the future other otolaryngological manifestations of IRIS will be detected. It is therefore important that otolaryngologists become aware of this new phenomenon.

ACKNOWLEDGEMENTS

J. Claes for reviewing the paper

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