Molluscum contagiosum-associated immune reconstitution inflammatory syndrome in human immunodeficiency virus infection

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A B S T R A C T

Immune reconstitution inflammatory syndrome (IRIS) is an excessive immune reaction to a pre-existing infection following the initiation of highly active antiretroviral therapy (HAART) in human immunodeficiency virus (HIV)-infected patients. IRIS is characterized by systemic symptoms, including fever, malaise, and weight loss, or local inflammatory responses. IRIS is most commonly associated with mycobacterial infection, and other pathogens include Cryptococcus species, Pneumocystis species, cytomegalovirus, herpes simplex virus, hepatitis B virus, human herpes virus 8, and molluscum contagiosum virus. Molluscum contagiosum usually manifests as asymptomatic, discrete, flesh-colored, and centrally umbilicated papules. It occurs in 5–18% of HIV-infected patients, and tends to be more extensive and persistent in these immunocompromised hosts. However, molluscum contagiosum-associated IRIS (MC-IRIS) was rarely reported. Two studies revealed that 2.0% (4/199) and 3.4% (2/59) of HIV-infected patients developed molluscum contagiosum within 12 weeks and 6 months of HAART treatment, respectively. Here, we report an HIV-infected patient manifesting prominent inflammatory response to newly diagnosed molluscum contagiosum after starting HAART, and summarize the other five reported MC-IRIS cases with clinical details available in the English literature.

A C K N O W L E D G M E N T S

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Introduction

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Molluscum contagiosum usually manifests as asymptomatic, discrete, flesh-colored, and centrally umbilicated papules. It occurs in 5–18% of HIV-infected patients, and tends to be more extensive and persistent in these immunocompromised hosts. However, molluscum contagiosum-associated IRIS (MC-IRIS) was rarely reported. Two studies revealed that 2.0% (4/199) and 3.4% (2/59) of HIV-infected patients developed molluscum contagiosum within 12 weeks and 6 months of HAART treatment, respectively. Here, we report an HIV-infected patient manifesting prominent inflammatory response to newly diagnosed molluscum contagiosum after starting HAART, and summarize the other five reported MC-IRIS cases with clinical details available in the English literature.

Case Report

A 40-year-old Taiwanese male presented to our dermatologic clinic with multiple itchy erythematous papules and pustules over the neck and arms for 2 months. Four months before his presentation to our dermatologic clinic, he was diagnosed to have HIV infection with acquired immunodeficiency syndrome, and HAART consisting of efavirenz, abacavir, and lamivudine was initiated 3 months before his presentation to our clinic (Figure 1A). The duration from the diagnosis of HIV infection to the onset of MC-IRIS was 2 months, and the duration from the initiation of HAART to the onset of MC-IRIS was 1 month (Figure 1A). He was afebrile at our clinic. On examination, there were multiple 3–5-mm crusted papules and pustules on an erythematous and edematous base over the neck and antecubital fossa (Figure 1B). At
the periphery of the inflamed lesions, some smaller flesh-colored and dome-shaped papules were present. A skin biopsy was performed on one pustule on the left arm (Figure 1C), which revealed molluscum contagiosum with intense inflammation, characterized by endophytic epidermal hyperplasia with molluscum bodies, surrounded by a dense infiltrate in the dermis (H&E, 20×). (F) Disrupted epithelium with molluscum bodies surrounded by a dense inflammatory infiltrate in the upper dermis (H&E, 20×). HAART = highly active antiretroviral therapy; H&E = haematoxylin and eosin; HIV = human immunodeficiency virus; MC-IRIS = molluscum contagiosum-associated immune reconstitution inflammatory syndrome.

Discussion

The incidence of IRIS is 10—25% in HAART-treated HIV patients. To establish the diagnosis of IRIS, first, the individual must be HIV positive and have received antiretroviral therapy, with a decreased HIV RNA level and an increased CD4+ T-lymphocyte count from baseline. Second, the clinical deterioration is related to HAART initiation, and cannot be explained by the side effects or toxicity of medication, treatment failure, or nonadherence to antiretroviral therapy. The patient had been taking efavirenz, abacavir, and lamivudine for 35 days when MC-IRIS occurred. None of these
medications were known to cause skin eruptions similar to the presentation in our patient, and the patient showed good compliance with the medications, leading to laboratory improvement in CD4 counts and viral loads. Therefore, the possibility of medication-related eruptions was excluded in this patient.

There are two distinct patterns of IRIS, namely, paradoxical and unmasking IRIS. Paradoxical IRIS is caused by a recognized infection that had an earlier favorable response to therapy before HAART, but symptoms and signs recurred or worsened acutely after the initiation of HAART. Unmasking IRIS, as in our patient, is caused by an infection that is newly recognized after the initiation of HAART and presented with an evident inflammatory response. In a retrospective cohort study, the median time to IRIS diagnosis was 8 weeks (range, 3–24 weeks), with at least a 25% increase in CD4 cell count from the baseline (<200 cells/μL) in most patients (75.6%), after the initiation of HAART. Although molluscum contagiosum affects 13.2% of HIV-infected patients, only six cases of MC-IRIS, including our case, have been reported with details to date (Table 1). Five other cases of MC-IRIS were reported in two case series without the details of their clinical presentation and therefore they were not included in Table 1. In some reports, molluscum contagiosum that occurred after the initiation of HAART was described without an evident inflammatory response, which is essential for IRIS, and therefore these cases were also excluded from analysis. 3

In the six cases of MC-IRIS for whom the clinical details were available (Table 1), the male-to-female ratio was 5:1, with their age ranging from 11 years to 65 years. There were three cases of paradoxical MC-IRIS and three of unmasking MC-IRIS. The lesion of MC-IRIS usually occurs within 90 days after HAART, with the exception of a 25-year-old male who had MC-IRIS after nearly 300 days of HAART. In our case, the duration from the initiation of HAART to the development of MC-IRIS is about 35 days. Skin lesions mostly occurred on the face (3/6, 50%), extremities (3/6, 50%), and trunk (3/6, 50%), but were uncommonly noted on genital areas (1/6, 17%). All reported cases of MC-IRIS manifested only severe inflammation in the skin without systemic symptoms. The skin lesions showed a tendency to resolve spontaneously.

The typical clinical manifestation of MC-IRIS is coalescent erythematous papules or dome-shaped nodules with crust or pus formation and some with central umbilication. The typical pathological findings are lobulated epidermal growth consisting of keratinocytes with large intracytoplasmic eosinophilic inclusion bodies and an inflammatory response characterized by a monocellular lymphocyte infiltration of the papillary dermis surrounding the viral lesions without epidermotropism. Dense eosinophilic and neutrophilic infiltration in the upper dermis, similar to the findings in our patients, had not been reported in other cases.

All patients had increased blood CD4 count when MC-IRIS occurred, although the CD4 level varied between 20 cells/μL and 790 cells/μL. In our case, the CD4 cell count increased to 170 cells/μL from the baseline value of 5 cells/μL. Three of the six patients did not receive any treatment directed to molluscum contagiosum, and the lesions resolved spontaneously under continuous HAART. Based on these observations, treatment targeting molluscum contagiosum seemed not necessary in MC-IRIS.

The mechanism of IRIS is still unclear. The serum level of proinflammatory mediators, including C-reactive protein and cytokines [e.g., interleukin (IL)-6, IL-12, and tumor necrosis factor-α], were elevated in patients with IRIS. IL-10 was reduced, suggesting that the regulatory function may be impaired. However, proinflammatory cytokines could activate matrix metalloproteinase, which might contribute to tissue damage in IRIS. Barber et al proposed that uncoupling of innate and adaptive immunity was responsible for IRIS. They hypothesized that activation of macrophage, whose functions were inhibited in advanced HIV infection, accumulation of antigen, and excessive priming of innate immune cells might lead to an excessive inflammatory response.

In conclusion, molluscum contagiosum is not rare in HIV-infected patients, but MC-IRIS is rare. We present a new case of MC-IRIS in an HIV-infected man following the initiation of HAART. The inflammation has been limited to the skin in all reported cases of MC-IRIS, and the lesions showed a tendency toward spontaneous resolution under continuous HAART. By reporting this case, we hope to increase the awareness of physicians regarding the characteristic clinical and pathologic features of MC-IRIS.

References


