

# HIV 감염인에서 면역재구성증후군의 형태로 발현한 대상포진

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## Herpes Zoster Immune Reconstitution Inflammatory Syndrome in a HIV-infected Patient: Case Report and Literature Review

According to current evidence, human immunodeficiency virus (HIV)-infected patients who have undergone treatment with antiretroviral therapy are at greater risk of developing herpes zoster, not when they are severely immunocompromised, but, paradoxically, when their immune system is recovering. This is a manifestation of the immune reconstitution inflammatory syndrome (IRIS). Here we report on a case of IRIS, presented as herpes zoster in a HIV-infected patient after undergoing highly active antiretroviral therapy (HAART).

**Key Words:** Human immunodeficiency virus, Immune reconstitution inflammatory syndrome, Herpes zoster

### Introduction

Immune reconstitution inflammatory syndrome (IRIS) is an inflammatory reaction to microbial and autoimmune antigens that occurs as a result of immune recovery after highly active antiretroviral therapy (HAART) in human immunodeficiency virus (HIV)-positive patients [1]. The most frequent IRIS manifestation was herpes zoster (40%), followed by tuberculosis (16%), *Mycobacterium avium* complex (MAC; 12%), Kaposi's sarcoma (10%), other nontuberculous mycobacteria (6%), and molluscum contagiosum (4%)[2]. Compared with HIV-negative adults, the risk of developing herpes zoster among HIV-positive adults is 12-17 times greater. There is also a greater risk of recurrence and death [3].

Here we report on a case of an HIV-positive male patient with immune system recovery after treatment with HAART, who presented with a herpes zoster infection. This is the first case report in Korea.

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## Case Report

A 38-year old Korean male, was diagnosed with AIDS, and subsequently underwent HAART, consisting of lamivudine, zidovudine, and ritonavir-boosted lopinavir for a period of one month. The patient presented to the hospital with a three-day history of fever and multiple vesicles on his right anterior chest and back and complained of severe pain.

Except for HIV infection, the patient did not have any particular medical history, including admission and operation history. He was an ex-smoker who had a smoking history of 18 pack years and no alcohol history. At the time of admission, blood pressure was 130/80 mmHg, pulse rate was 98/min, respiratory rate was 18/min, and body temperature was 37.8°C. Grouped vesicular lesions were observed on the right trunk at the level of the T5-T6 dermatomes, which were assumed to be the result of herpes zoster, a manifestation of IRIS (Fig. 1). Physical examination showed no other remarkable findings.

Prior to treatment with HAART, the patient's initial CD4+ count was 88 cells/mm<sup>3</sup> (normal range, 400 cells/mm<sup>3</sup> to 1,000 cells/mm<sup>3</sup>), with a CD4+ cell percentage of 9.7 (normal range, 28.4% to 56.4%), and an HIV-1 viral load of 10,600 copies/mL.

HAART was initiated on September 24, and vesicular lesions were observed on October 26.

One month after initiation of HAART, the patient's CD4+ count had increased to 162 cells/mm<sup>3</sup> and the CD4+ cell percentage

had increased to 18.6%, and HIV-1 viral load had decreased to 332 copies/mL. The hemoglobin level was 11.2 g/dL, C-reactive protein (CRP) was 0.42, and other laboratory findings were within normal limits.

While maintaining HAART, the patient was treated with Acyclovir (10 mg/kg IV q8h for seven days) and vesicle needle-puncture followed by application of a cold pack of Alum solution 0.3% for 30 minutes three times per day. After therapy, the number of vesicles showed a decrease and gradually became crusts. The patient was discharged with a prescription for Famciclovir (250 mg PO tid) for seven days. He is currently undergoing follow up at the outpatient clinic and has not reported any additional complications so far.

## Discussion

IRIS may be defined as a progressive deterioration in clinical status directly resulting from enhancement of the immune response, leading to worsening opportunistic infection despite improvements in surrogate markers of HIV viral load [4, 5]. Some studies have presented case definitions of IRIS. These case definitions include five fundamental criteria [6]: (1) it must be a confirmed case of HIV, (2) there must be a temporal association between development of IRIS and initiation of HAART, (3) there must be specific host responses to HAART, such as an increase in CD4+ cell count and a decrease in HIV viral load, (4) clinical deterioration must be characterized by an inflammatory process, and (5) other causes that may lead to a similar clinical presentation must be excluded.

The proportion of patients who developed IRIS was highest in those with cytomegalovirus retinitis, high in those with cryptococcal meningitis, progressive multifocal leukoencephalopathy, or tuberculosis, and least common in those with Kaposi's sarcoma or herpes zoster [7]. According to results of one multivariate regression study, patients on HAART and those with CD4+ counts between 50 and 200 cells/mm<sup>3</sup> appeared to be at the highest risk for a herpes zoster event [8].

In our case, the patient presented with herpes zoster as a manifestation of IRIS after one month of HAART. The CD4+ count increased from 88 cells/mm<sup>3</sup> to 162 cells/mm<sup>3</sup>, and the HIV viral load decreased from 106,000 copies/mL to 332 copies/mL.

This can be classified as unmasking IRIS not paradoxical IRIS. Because unmasking IRIS is defined as a clinical event in which opportunistic disease, which was not present at the time of initiation of ART, becomes clinically manifest as a result of



Figure 1. Herpes zoster during HAART. On anterior chest at the level of T5-T6.

ART-induced immune recovery. Whereas, paradoxical IRIS is used to denote IRIS among patients who are already receiving medication for an opportunistic disease, and in whom immune recovery after initiation of ART provokes the clinical deterioration of that disease during the initial treatment [9]. Other causes, including drug resistance or toxicity, drug malabsorption, non-adherence to regimen, delayed recovery of immune function after initiation of HAART, and superinfection by other pathogens were excluded [10]. Therefore, the diagnosis of IRIS is appropriate.

Introduction of HAART in management of HIV has resulted in a decreased rate of mortality. However, it has caused IRIS in 25% to 35% of patients undergoing HAART [6]; many studies have suggested that HAART may play a role in increasing the risk of zoster, which is reflected in large observational IRIS cohorts, where dermatomal varicella zoster has been reported to comprise 9–40% of cases of IRIS [1, 11].

The term between the onset of disease and initiation of HAART is so various that controversy remains with regard to defining a time limit over which the disease must manifest in order to be regarded as IRIS. The term has been reported to span from four weeks to 15 months [2, 12, 13]. Espinosa E and colleagues reported that herpes-zoster-associated IRIS may characteristically occur greater than 90 days out from initiation of HAART [2]. Sarah Rodgers and colleagues reported that the risk of developing herpes zoster within the time frames of 90 days before and 90 days after beginning HAART did not differ statistically, which suggests against IRIS as the cause of herpes zoster following initiation of HAART [14]. Many studies have agreed that onset of herpes zoster due to IRIS tended to increase after approximately four weeks. Our findings were also in agreement with the results of those studies in which the occurrence of herpes zoster as IRIS was demonstrated within approximately four weeks after starting HAART.

In patients who presented with IRIS while undergoing HAART, change of CD4 cell count, percentage, and HIV viral load were significant risk factors for development of this syndrome. Although herpes zoster can occur at any CD4+ count in HIV-infected adults, the frequency of disease is highest with CD4+ counts of  $<200$  cell/mm<sup>3</sup>. Development of IRIS after starting HAART is a rare occurrence in patients with relatively high CD4+ cell counts of  $>350$  cell/mm<sup>3</sup> [15]. Conversely, patients with a baseline CD4+ cell percentage of  $<10\%$  were reported as having a three-fold increased risk of developing IRIS [1, 16]. Our patient's baseline CD4+ cell count was 88 cell/mm<sup>3</sup>, which is 9.7% in CD4+ cell percentage, and, at the time he was diagnosed with herpes

zoster, the count was 162 cell/mm<sup>3</sup>. A rapid initial decrease in HIV-1 RNA level within 90 days of starting HAART has been proposed as a risk factor for IRIS [16]. Our patient's HIV viral load showed a decrease from 106,000 copies/mL to 332 copies/mL. The increased risk may be related to redistribution of memory CD4+ lymphocytes in response to HAART-induced reduction in HIV-1 RNA levels [17].

The diagnostic value of these CD8+ cells is still debatable. The number of circulating CD8+ cells does not necessarily reflect either their numbers in infected, inflamed tissues, or their functional competence [18]. Thus, CD8+ cells cannot be used as a laboratory marker for differentiation of HIV-IRIS from an opportunistic infection in immunosuppressed patients. In spite of these reports, findings of some studies have demonstrated the importance of CD8+ cells in the pathogenesis of IRIS, but not its significance as a diagnostic tool. The percentage of CD8+ cells at baseline and the magnitude of their increase one month after initiation of antiretroviral therapy have shown a strong association with an increased risk for herpes zoster [13].

Due to atypical or more complicated manifestations, varicella-zoster as IRIS can cause significant morbidity in HIV-infected individuals [8]. Complications observed in the setting of high CD4+ counts, such as with development of disseminated zoster and Ramsay Hunt syndrome, are suggestive of T-cell dysfunction despite good virologic control [19]. However, in general, atypical or complicated cases of herpes zoster are less common in the era of HAART [14]. The complication rate among patients, particularly of postherpetic neuralgia (PHN), was markedly higher than would be expected in an HIV-negative population of patients who are similar in age [8]. In our patient, no complications occurred during the follow up period.

HAART has become an important therapy in treatment of HIV patients. Many cases of IRIS have been reported annually throughout the world. However, a number of unanswered questions remain. Although some studies have presented case definitions of IRIS [6], the lack of consensus with regard to the definition of IRIS makes differentiation of IRIS from recurrence or relapse of an infection a challenge. In addition, a few risk factors, including CD4+ T-cell count, HIV-1 RNA level, and HAART regimen, have been reported, however, these are too complex to generalize as definite risk factors [6]. For these reasons, definition of IRIS is dependent on an exclusive diagnosis and on case presentations that show correlation with clinical and laboratory data.

Finally, in our patient, considering that the concentration of HIV RNA was reduced from 106,000 copies/mL to 332 copies/mL,

while the CD4<sup>+</sup> cell count rose from 88 cells/mm<sup>3</sup> to 162 cells/mm<sup>3</sup> after ART, and that there were clinical symptoms associated with an atypical inflammatory reaction to an opportunistic infection, this case satisfied all criteria suggested by French et al (2004) and Shelburne et al (2002) [1, 20].

We hope that the definition of IRIS will be clarified in the future through conduct of large prospective clinical trials and case series.

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