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Lung cancer as an immune reconstitution disease in an HIV-1 positive man receiving HAART

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Summary

A case of small-cell lung cancer with prompt worsening of the clinical course was observed in a patient with significant immune restoration after receiving effective highly active antiretroviral therapy (HAART) for seven months. Rapid and enormous enlargement of metastatic liver was the main symptom. Chest x-ray showed an enlargement of the left hilus. The patient died 22 days after the onset of the fulminant disease. We suggest that the occurrence and aggressive course of the lung cancer resulted from the development of immune reconstitution syndrome.

Key words: **Lung cancer • HIV-1 infection • immune reconstitution disease • IRD**

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Introduction

The introduction of highly active antiretroviral therapy (HAART) resulted in changes in the natural history of HIV infection. AIDS morbidity and mortality have declined significantly [9]. Despite this there is increasing incidence of non-AIDS defining neoplasmas in HIV-1 positive individuals in the post HAART-era [3,4,15]. Lung cancer is recognized in this group of patients with increased frequency and its prognosis has not improved [1,10,11,13,15]. Moreover, in many patients the advanced stage of the disease is observed at the time of diagnosis [1,12,15]. HIV-1 positive individuals develop lung cancer at a younger age than HIV-1 negative individuals, they often undergo a rapid course, and the survival time is very short (even four weeks) [1,3,4,10,11,13]. The impact of HAART on the occurrence of lung cancer has been observed, but its pathogenicity has not yet been determined [2,7,16]. The combination antiretroviral treatment can effectively suppress viral replication with subsequent immune restoration [14]. However, the immune deficiency remains. The function of the immune system is deteriorated by aberrant cytokine production. Sometimes, immune reconstitution syndrome may occur and a paradoxical, atypical inflammatory response is observed [14]. This altered immune response can be one of the predisposing factors for the development of malignancies, among which are lung cancers [2,6,10,11,15].

Case Report

We report a case of small-cell cancer which developed seven months after initiating HAART in an HIV-1 positive man. The 34-year-old man, IDU, HIV-1 positive for 10 years, had smoked 20 cigarettes/day for 20 years. In February 2003 he was referred to the outpatient department. Profound immune deficiency was observed. His CD4+ T cell count was 74 cells/μL and plasma HIV RNA level 275,000 copies/ml (by PCR ultrasensitive). Physical examination revealed oral thrush. No more abnormalities, including on chest x-ray, were seen.

The patient felt well and HAART with zydovudine, lamivudine, saquinavir, and ritonavir was initiated. He was in good condition during the next 6 months of observation. His CD4+ T lymphocyte count increased significantly and reached 355 cells/μL and plasma HIV RNA was less than the level of assay quantification by PCR ultrasensitive (50 copies/ml). There were no signs or symptoms of any disease and the antiretroviral therapy was continued. Two months later the patient was admitted, severely ill, to the department of infectious diseases. He suffered from fatigue, malaise, abdominal pain, and had lost 10 kg of weight during the previous month. Asthenia, wasting, extreme hepatomegaly, and ascites were noted. Computed tomography (CT) and ultrasonography (USG) of the abdomen revealed the abdominal cavity filled by a huge liver. There were several hypodense lesions up to 6 cm in diameter in it. Chest x-ray showed a left hilar enlargement. A biopsy of the liver sample disclosed undifferentiated neoplasmatic cells of unknown origin. Bone marrow examination suggested acute leukemia. The patient's condition deteriorated rapidly in the course of three weeks. Further diagnostics was possible. He died 22 days after admission to the department. A diagnosis of small-cell lung cancer with metastases to the lymph nodes and the liver was finally established at autopsy (Figures 1, 2).

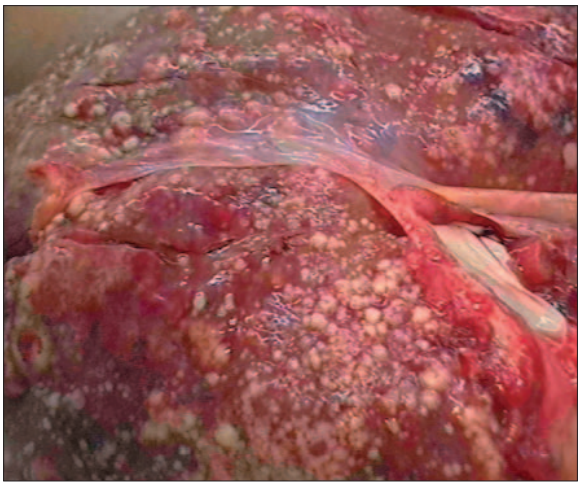

Figure 1. Small-cell lung cancer metastases to the liver (at autopsy)

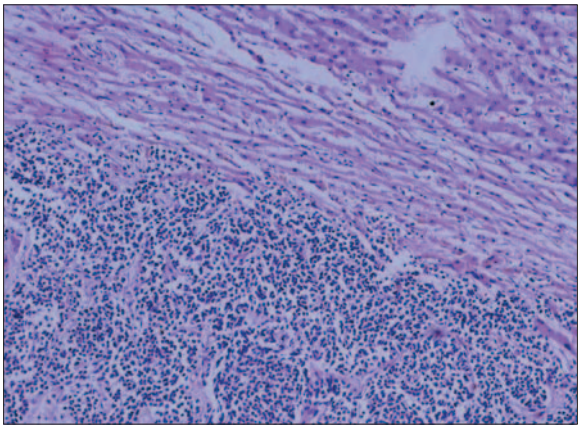

Figure 2. Metastatic liver. Sharply defined area of small-cell carcinoma is present in the bottom part of the specimen. The malignant cells are highly atypical and closely resemble cells of lung cancer, with dark clumped chromatin and little recognizable cytoplasm

Discussion

We have described a case of small-cell lung cancer that occurred in a man with excellent immune restoration after receiving potent HAART. The course of the malignancy was fulminant. It was impossible to start any chemotherapy due to the advanced stage of disease at admission and the rapid worsening of his clinical state. A proper diagnosis could be finally established at autopsy. Lung cancer in a patient with a good immune response was not expected. It developed eight months after the commencement of effective HAART, with a rapid rise in the CD4+ T cell count (+ 281 cells) and decline in plasma HIV RNA. The enormous enlargement of the liver and only small changes in the left lung hilus were the main symptoms.

The immune reconstitution may account for the unusual course of the lung cancer [2]. Prolonged immune activation is a characteristic feature of HIV-1 infection. It results in the deterioration of the immune mechanisms involving inflam-

matory cytokine production [14]. Moreover, immune reconstitution syndrome can occur due to dysregulated, uncontrolled response during HAART [14]. These mechanisms were probably responsible for the development of the small-cell lung cancer, the abrupt onset, and the fulminant course of the disease in our patient [2]. The patient had been a tobacco user for many years, which can also be a predisposing factor [3]. Wistuba et al. [16] observed an increased frequency of microsatellite alterations which could reflect a widespread genomic instability in HIV-associated lung carcinomas and may play a role in the development of HIV-associated tumors. We did not perform any genetic examinations in the patient, but we cannot exclude this as a predictive factor.

Conclusion

Several facts suggest a relationship between the development of lung cancer and the initiation of HAART. These are: the strict temporal relationship between the disease and HAART, inhibition of viral replication and immune recovery as a result of HAART, and the abrupt clinical presentation with the occurrence of a large, rapidly growing metastatic liver despite the fact that no clinical or radiological abnormalities were seen during the previous several months. Other malignancies have also been reported as immune reconstitution diseases which developed within a few months [5,8]. Thus we conclude that lung cancer may be another clinical entity in the increasing number of diseases referred to as immune restoration diseases. This rare case is evidence that in the era of HAART, very aggressive, non-AIDS defining malignancies can occur even in patients with good response to the antiretroviral therapy. Clinicians should be aware of malignancies especially in patients with advanced immune deficiency and immune reconstitution as a result of potent HAART.

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