

Case Reports

A Long-term Survival Case of Small Cell Lung Cancer in an HIV-infected Patient

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We report a case of small cell lung cancer in a patient with human immunodeficiency virus (HIV) infection. The patient was a 51-year-old man diagnosed 8 years previously as seropositive for HIV, who was admitted to our hospital for re-evaluation of antiretroviral medications due to multidrug resistance. Chest radiograph revealed an abnormal hilar shadow subsequently confirmed to be small cell lung cancer. He received chemotherapy concurrently with highly active antiretroviral therapy (HAART), and lived for 14 months after the diagnosis. The prognosis of lung cancer in HIV-seropositive patients is very poor, and adverse effects of chemotherapy occur more frequently than in other patients. However, the simultaneous antiretroviral agents and combination chemotherapy was successful. Such treatment may be effective despite an otherwise poor prognosis, including HIV infection.

Key words: small cell lung cancer – human immunodeficiency virus (HIV) – highly active antiretroviral therapy (HAART)

INTRODUCTION

Besides some opportunistic infections, malignant disorders occur in human immunodeficiency virus (HIV)-infected patients, including acquired immunodeficiency syndrome (AIDS)-related malignancies and non-AIDS-defining malignancies. Since HIV infection can now be well controlled by highly active antiretroviral therapy (HAART), the incidence and mortality of malignant disorders have increased in HIV-infected patients (1–3). The prognosis of such diseases is very poor in general, and chemotherapy is very difficult because adverse effects occur more frequently. In this report, we present a case of small cell lung cancer in an HIV-infected patient who received systemic chemotherapy concurrently with HAART, and survived for 14 months after the diagnosis. This relatively long-term survival may be attributed to three factors: HIV infection was well controlled, there were no opportunistic infections and adverse effects did not occur during chemotherapy. HAART increases the feasibility of effective treatment without serious adverse effects, thus it provides strong support

for the management of small cell lung cancer in HIV-infected patients.

CASE REPORT

A 51-year-old man seropositive for HIV since 8 years previously was admitted to our hospital in August 2002 to receive a modified antiretroviral drug treatment because of multidrug resistance. The patient had started to receive antiretroviral treatment in 1994 with three subsequent changes in the drug regimen. An abnormal shadow was found in a chest radiograph obtained on admission. No respiratory symptoms were observed and his performance status was zero at presentation. Fine crepitation was apparent by auscultation at the bases of both lungs on examination.

Laboratory findings on admission (Table 1) included increased neuron-specific enolase (NSE) and pro-gastrin-releasing peptide (ProGRP). The CD4(+) lymphocyte count was 324/ μ l, and HIV-RNA PCR was 4.1×10^4 copies/ml.

Chest radiograph (Fig. 1) and computed tomography of the chest (Fig. 2) and abdomen revealed a left hilar mass and enlargement of the left adrenal gland, respectively. Fiberoptic bronchoscopy showed a whitish left hilar tumor, and examination of a biopsy specimen revealed small cell carcinoma.

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Table 1. Laboratory data on admission

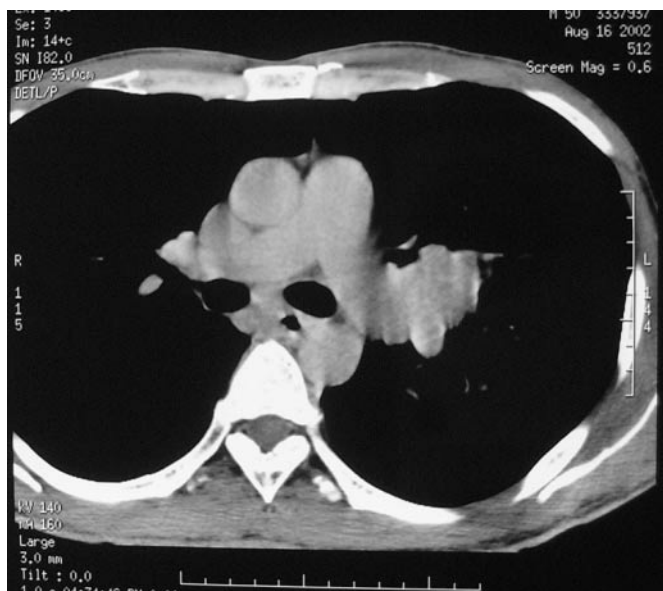
Peripheral blood	
White blood cells (neutrophils 43.8, lymphocytes 46.6, monocytes 8.0, eosinophils 0.6, basophils 1.0%)	7100/ μ l
Red blood cells	387×10^4 / μ l
Hemoglobin	147 g/dl
Hematocrit	42.7%
Platelets	17.3×10^4 / μ l
Biochemistry	
TP	7.1 g/dl
Albumin	4.4 g/dl
Na	144 mEq/l
K	4.0 mEq/l
Cl	105 mEq/l
Ca	9.7 mg/dl
Cr	0.6 mg/dl
BUN	
Aspartate aminotransferase	18 IU/l
Alanine aminotransferase	12 IU/l
Lactate dehydrogenase	227 IU/l
Al-P	374 IU/l
γ -GTP	43 U/l
T.bil	0.3 mg/dl
Glc	109 mg/dl
C-reactive protein	0.8 mg/dl
Tumor markers	
Carcinoembryonic antigen	4.6 ng/ml
Non-specific enolase	14.9 ng/ml
Pro-gastrin-releasing peptide	1951 pg/ml
HIV-related markers	
CD4 cell count	324/ μ l
HIV-RNA PCR	4.1×10^4 copies/ml

TP, total protein; Al-P, alkaline phosphatase; γ -GTP, γ -glutamyl transpeptidase; T.bil, total bilirubin; GLC, glucose.

No evidence of brain or bone metastasis was detected by systemic survey. The diagnosis of extensive stage disease of small cell lung cancer was confirmed.

The patient began a new HAART regimen, consisting of 250 mg of didanosine, 600 mg of abacavir sulfate, 600 mg of efavirenz, 2400 mg of amprenavir and 200 mg of ritonavir in September 2002. Systemic chemotherapy included 30 mg/m² of cisplatin and 60 mg/m² of irinotecan hydrochloride weekly for 3 weeks of a 4 week cycle administered 2 weeks later. Although the lesion was reduced by three courses of this treatment [partial response (PR), in accordance with Response Evaluation Criteria in Solid Tumors (RECIST)] (Fig. 3), the cancer relapsed with multiple brain, skin, liver and bone lesions 2 months after the completion of chemotherapy (Figs 4 and 5). Whole brain irradiation (40 Gy), and four courses of amrubicin hydrochloride (35 mg/m²) for three consecutive days of a 3 week cycle decreased the lesions (PR by RECIST), but the cancer relapsed again in brain, bone, liver, adrenal gland and skin.

Although two courses of carboplatin (area under the concentration–time curve of 5 mg/min/ml) on day 1 and etoposide (100 mg/m²) on days 1, 2 and 3 were administered

**Figure 1.** Chest radiograph shows a left hilar mass (August 2002).**Figure 2.** A left hilar mass is demonstrated by computed tomography of the chest (August 2002).

as third-line treatment, lesions were refractory [progressive disease (PD) by RECIST].

Before the fourth-line treatment was planned, the patient's level of consciousness had deteriorated because of the re-growth of the brain metastasis. We changed the level of therapy to best supportive care. The patient died in October 2003 due to cancer progression. Post-mortem examination revealed multiple metastatic small cell cancer lesions, but no opportunistic infections.

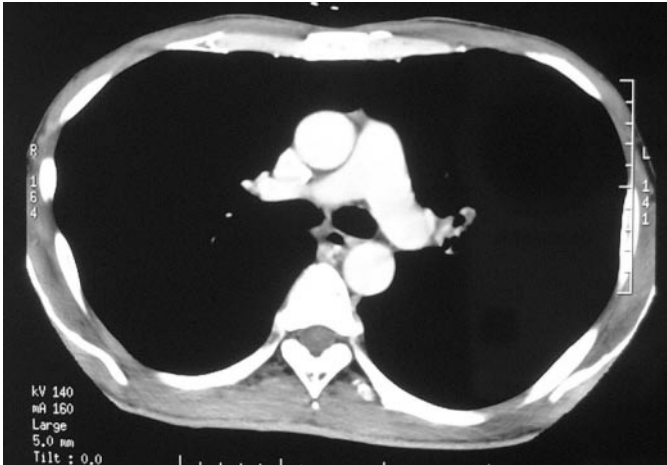


Figure 3. Computed tomography after the first treatment showing decreased size of the left hilar mass (December 2002).

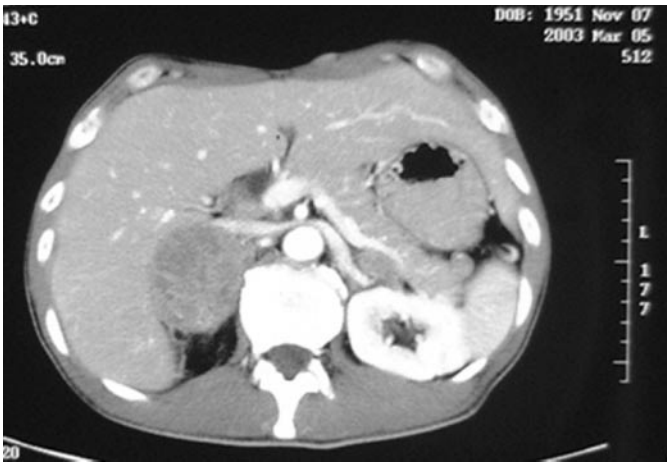


Figure 4. Abdominal computed tomography disclosed adrenal metastasis 2 months after completing initial treatment (February 2003).

We monitored NSE and ProGRP as tumor markers as well as HIV load and CD4(+) lymphocyte count during chemotherapy (Fig. 6). Tumor markers decreased in parallel with the degree of the response to chemotherapy. No severe CD4(+) lymphocytopenia was seen and the HIV load could be kept under 50 copies/ml by administration of HAART throughout the course.

DISCUSSION

Non-Hodgkin's lymphoma, Kaposi's sarcoma and invasive cervical cancer are common HIV-related malignancies, but non-HIV-defining malignancies, including colon, stomach and lung cancers, have increased in the HAART era (2,3). Lung cancer is the most common solid cancer, because HIV patients are more often smokers, which is the strongest risk factor for lung cancer (3). Parker *et al.* reported that the incidence of primary lung cancer is increased by 6.5-fold in HIV-infected

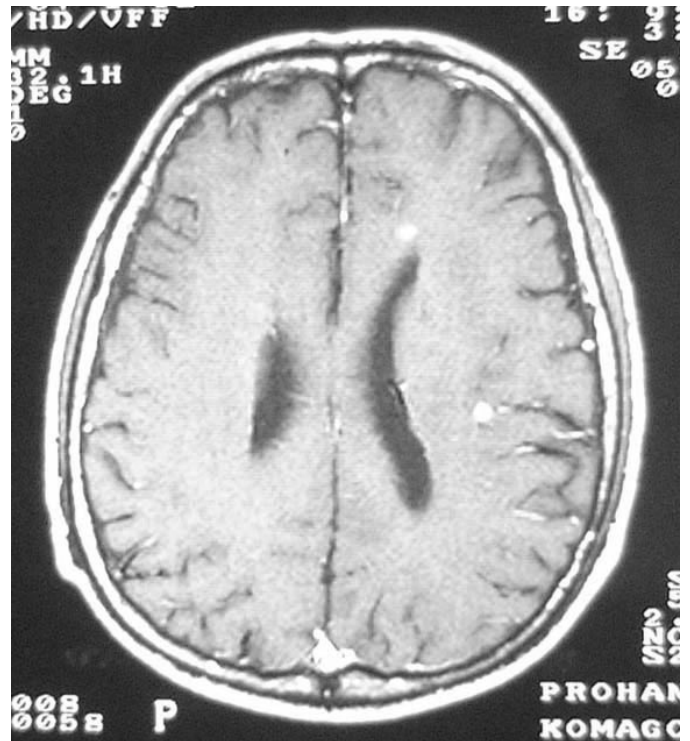


Figure 5. Magnetic resonance imaging of the brain detected multiple brain metastases (February 2003).

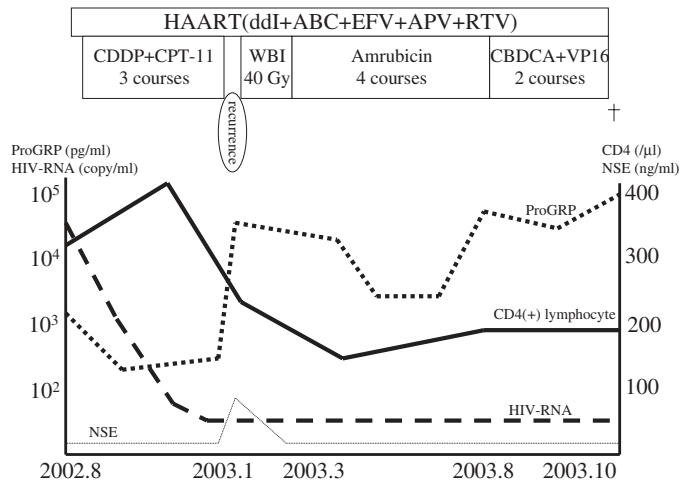


Figure 6. Patient's clinical course, treatment, tumor markers and HIV-related markers.

patients (4). It is because immune surveillance is impaired in their lungs(5).

The clinical courses of lung cancer in HIV-infected patients are generally more aggressive than in non-HIV patients. Tirelli *et al.* reported that the median overall survival in patients with HIV was significantly shorter than in those without (6). Tammemagi *et al.* indicated that the co-morbidity of HIV infections reduced lung cancer survival (7). A few cases of small cell lung cancer in HIV-infected patients have been

reported so far, and the prognosis of all cases was extremely poor (8).

In our case, we administered systemic chemotherapy concurrently with HAART. It is well known that hematopoiesis is compromised in HIV infection (9). Therefore, myelosuppression due to chemotherapy may be excessive, but there are reports of successful chemotherapy with concurrent antiretroviral therapy for HIV-related lymphoma (10). We used a similar method and could continue nine courses of chemotherapy without excessive adverse effects or opportunistic infections. CD4(+) lymphocyte count and HIV load were well controlled throughout the course.

However, one needs to consider the interaction between anticancer and antiretroviral drugs. Protease inhibitors, such as ritonavir or lopinavir/ritonavir, strongly inhibit the drug-metabolizing enzyme cytochrome P450 3A4 and thus increase the serum concentration of anticancer drugs in concurrent use (11). Specifically, toxicity of vincristine and paclitaxel, that are metabolized by cytochrome P450, have a risk of increase due to higher serum concentration. The combination of anticancer drugs and HAART requires such careful considerations of drug properties.

Our patient's long-term survival was based on good performance status, controlled HIV load, absence of opportunistic infections and the effectiveness of amrubicin hydrochloride, a new drug for small cell lung cancer. Amrubicin hydrochloride is a completely synthetic anthracycline derivative. For previously untreated small cell lung cancer, the response rate with amrubicin was 78.8%, and the median survival time was 11.7 months (12). This agent is also effective for relapsed small cell lung cancer.

In the era of HAART, the incidence and mortality of malignant disorders in HIV-infected patients is increasing. The management of such cases is complicated and difficult. Therefore, the relatively long survival of our patient is instructive. By controlling HIV infection with HAART,

chemotherapy could be optimized without excessive adverse effects; this approach can prolong survival in small cell lung cancer occurring in HIV-infected patients.

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