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CASE REPORT

Chemotherapy for thymic carcinoma in an adult patient with HIV infection

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Abstract A 69-year-old man was referred to our hospital in June 2010 after the diagnosis of an anterior mediastinal tumor and HIV infection. Histopathological examination of a CT-guided needle biopsy specimen showed undifferentiated thymic carcinoma. Chest CT revealed pleural dissemination, bone invasion, and left lung metastases. The final diagnosis was Masaoka stage IVb. Surgery was considered inappropriate. Instead, the patient first underwent highly active antiretroviral therapy for HIV infection, followed by four courses of cisplatin, doxorubicin, vincristine, and cyclophosphamide chemotherapy for thymic carcinoma. A partial response was achieved. To our knowledge, this is the first report of thymic carcinoma in an adult patient with HIV infection.

Keywords Thymic carcinoma · ADOC chemotherapy · HIV infection · HAART · Cytochrome

Introduction

Although the number of HIV-infected patients is increasing, the development of highly active antiretroviral therapy (HAART) has made it possible to control the disease. HIV infection has thus become a chronic disease, and the incidence of malignant tumors other than AIDS-defining malignancies has been increasing [1, 2].

Thymic epithelial tumors are reported to comprise approximately 25–46.1 % of all mediastinal tumors in adults and are classified as thymomas or thymic carcinomas [3, 4]. The incidence of thymic carcinoma is low, but this malignancy is associated with poor prognosis, with a 5-year survival rate of 35–50.5 % [3–5].

We report here a case of HIV infection complicated with thymic carcinoma. The patient was successfully treated with raltegravir (RAL)-containing HAART and cisplatin, doxorubicin, vincristine, and cyclophosphamide (ADOC) chemotherapy.

Case report

A 69-year-old man visited his local physician for cough and exertional dyspnea since April 2010, and was found to have an anterior mediastinal tumor on a chest radiograph. Subsequent follow-up and laboratory tests identified HIV infection in June 2010, and he was referred to our hospital for further management. In mid-July 2010, a CT-guided needle biopsy of the mediastinal tumor was performed due to pleural dissemination and infiltration of the left seventh rib. Histopathological examination of the biopsy material showed undifferentiated carcinoma of the thymus. In addition, diagnostic imaging showed pleural dissemination, bone invasion, and metastases in the left lung. The final

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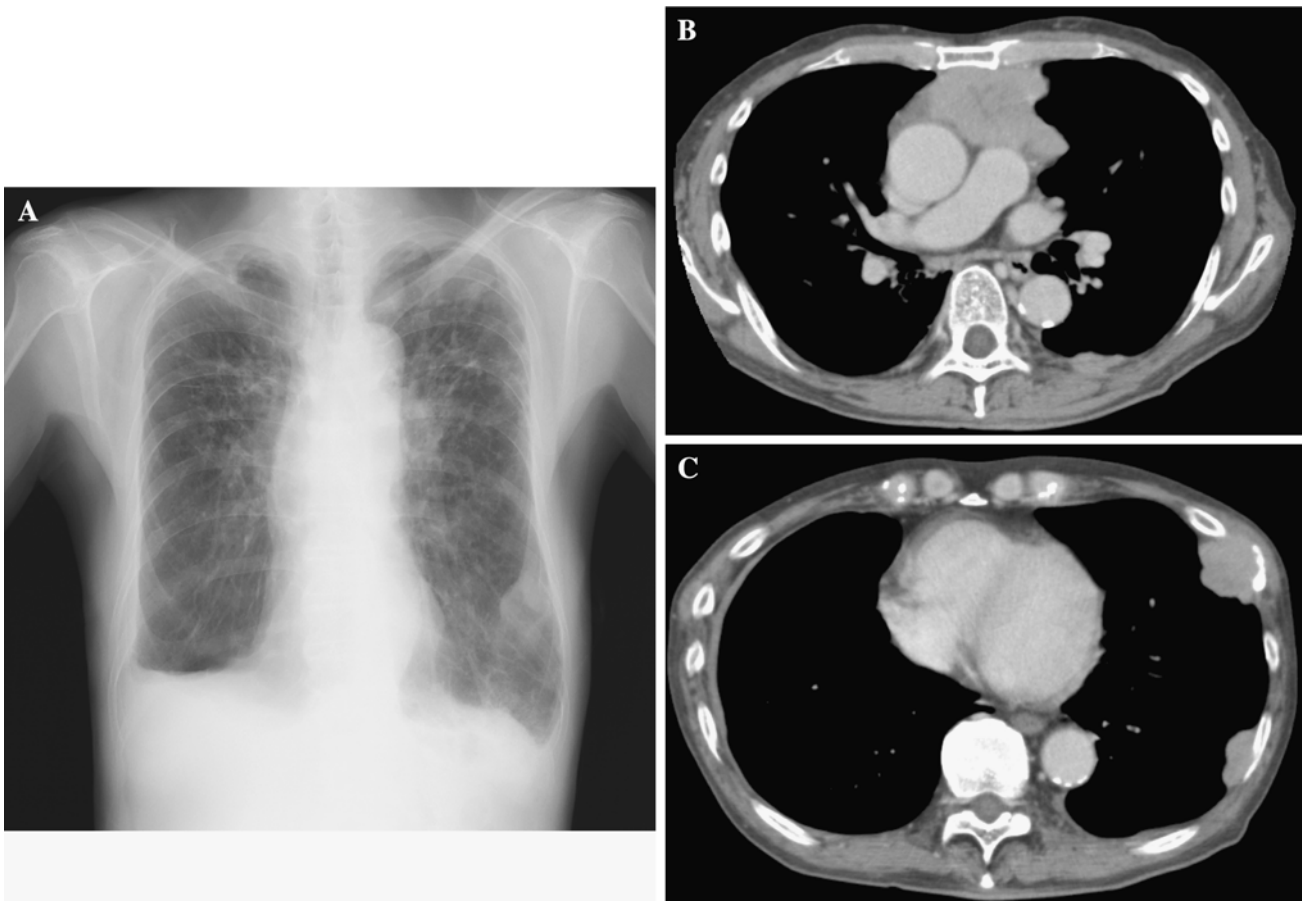

Fig. 1 **a** Chest radiograph on admission shows a mass protruding from the mediastinum into the left hilar region. **b**, **c** Enhanced chest CT scans on admission show the mediastinal mass and pleural dissemination

diagnosis was Masaoka stage IVb. The case was considered unsuitable for surgery. In late July 2010, the CD4 count was 379 cells/μL and viral load (VL) was 6.0×10^5 copies/mL. He received HAART, consisting of the combination of abacavir and lamivudine (ABC/3TC) and RAL for treatment of HIV infection. The patient was hospitalized for chemotherapy in late-August 2010. The medical history included hypertension, diabetes mellitus, and pulmonary tuberculosis (in 2006). He was a smoker of three packs of cigarettes per day for the preceding 45 years. On admission, physical examination showed no abnormal respiratory sounds and laboratory tests showed slightly reduced hemoglobin (11.7 g/dL), C-reactive protein 3.50 mg/dL, and elevated hemoglobin A1c (6.7 %). Analysis of various tumor markers showed high levels of CYFRA 21-1 (15.3 ng/mL) and 1-CTP (5.5 ng/mL). The CD4 count was 419 cells/μL and VL was 54 copies/mL. Chest radiography (Fig. 1a) showed a mass protruding from the mediastinum into the left hilar region, a nodular shadow and a granular shadow in the left upper and middle lung fields, respectively, and a nodular shadow in the lower left lung field. Enhanced chest CT scan (Fig. 1b, c) revealed a $7.3 \times 5.2 \times 8.5$ cm tumor with an irregular border and heterogeneous internal contrast that was slightly to the left and superior to the anterior mediastinum. The mass had extensive contact with the aorta, pulmonary artery, epicardium, and left lung. Pleural dissemination and bone invasion of the left seventh rib were noted. Multiple shadows of small nodules were seen in the left lung field, and metastases in the left lung were suspected. A pathologic specimen revealed medullary proliferation of large atypical cells with fibrous stroma. Hassall corpuscle-like structure was observed, but no apparent keratinization was identified. Mucin production was not evident. Immunohistochemically, CD5 and c-kit were positive for tumor cells, and the MIB-1 index of tumor cells was 10–20 %. No TdT-positive T lymphocytes were observed. The lesion was diagnosed as thymic carcinoma (undifferentiated carcinoma) (Fig. 2).

The patient was started on ADOC chemotherapy consisting of drip infusion of doxorubicin 40 mg/m^2 and cisplatin 50 mg/m^2 on day 1, vincristine 0.6 mg/m^2 on day 3, and cyclophosphamide 700 mg/m^2 on day 4. Four courses of this ADOC chemotherapy were administered, at roughly

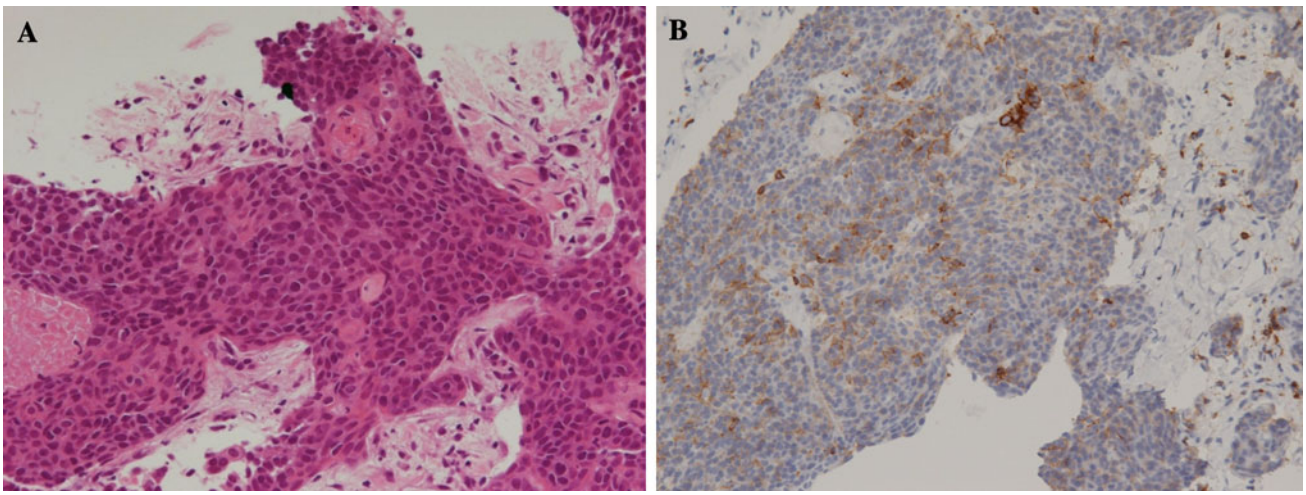

Fig. 2 **a** Microscopic findings of the CT-guided needle biopsy specimen diagnosed as undifferentiated thymic carcinoma (H&E stain). **b** Positive immunohistochemical staining for CD5 is seen in the cell membrane of tumor cells

4-week intervals, to allow for recovery of myelosuppression. Chest CT scan after chemotherapy showed a 5.1 × 3.7 × 6.0 cm tumor. The therapeutic efficacy was evaluated using Response Evaluation Criteria in Solid Tumors, and the evaluation was a partial response (Fig. 3). Hematological toxicity included grade 4 neutropenia and febrile neutropenia, while non-hematological toxicity included grade 1 anorexia, hiccups, and alopecia, but no hepatic or renal toxicity. The CD4 count was maintained at more than 300 cells/μL, and VL was suppressed to undetectable levels. Thus, disease control was achieved for both the thymic carcinoma and HIV infection. On the basis of the patient's history of pulmonary tuberculosis, acid-fast staining and sputum cultures were performed repeatedly, but results were negative. In the last outpatient visit, 9 months after diagnosis, the patient was in good general condition and no signs of recurrence or metastasis were noted.

Discussion

Thymic carcinomas, together with thymomas, are thymic epithelial tumors, and comprise approximately 14.1 % of thymic epithelial tumors [5]. Thymic carcinomas display clear cytological atypia and histological features and have the capacity to invade and metastasize both locally and to distant organs. At diagnosis, the thymic carcinoma is at an advanced stage in approximately 90 % of patients (at least Masaoka stage III, with invasion of surrounding organs) [5]. The indications for surgical treatment are limited compared with thymomas [3–5]. Our patient was diagnosed as Masaoka stage IVb [6] and was not considered a suitable candidate for surgery.

Thymic carcinomas do not show the high degree of sensitivity seen with thymomas, but some patients respond well to chemotherapeutic regimens that include cisplatin or carboplatin and anthracycline [7–12]. Koizumi et al. [9] described 8 patients with advanced thymic carcinoma who received ADOC chemotherapy, and reported a response rate of 75 % with a median survival time of 19 months. Yoh et al. [10] treated 12 patients with unresectable advanced thymic carcinoma by the cisplatin, vincristine, doxorubicin, and etoposide (CODE) regimen and reported a response rate of 41.7 % and median survival time of 46 months. Igawa et al. [11] administered carboplatin and paclitaxel to 11 treatment-naïve patients with unresectable thymic carcinoma, and reported a response rate of 36 % with a median survival time of 22.7 months. Lemma et al. [12] used the same combination of carboplatin plus paclitaxel for 23 treatment-naïve patients with advanced thymic carcinoma in a prospective phase II study, and reported a response rate of 21.7 % and median survival time of 20.0 months. On the other hand, a large percentage of thymic tumors are reported to express c-kit protein [13–15]. Strobel et al. [16] reported an objective response to imatinib, an inhibitor of c-kit protein, in a patient with thymic carcinoma, but results were negative in a later phase II study [17]. Thus, there are several reports on thymic tumors but the number of treated cases has always been small, and there is still no standard chemotherapy regimen for thymic carcinoma.

Following the development of HAART, which improved disease control, HIV infection began to be considered a chronic disease. Furthermore, an increased incidence of malignant tumors other than the AIDS-defining malignancies in HIV-infected individuals has been reported [1, 2]. However, although one case of both HIV

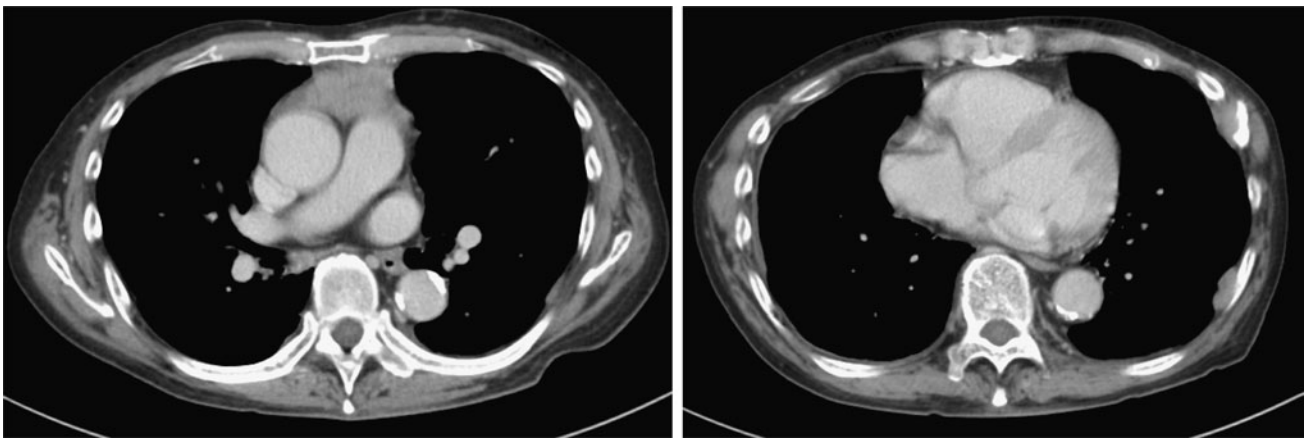

Fig. 3 **a**, **b** Chest CT scans after four cycles of ADOC chemotherapy show a decrease in both the mediastinal mass and pleural dissemination

infection and thymic carcinoma has been reported in a child [18], to our knowledge, there have been no such reports in adults, and the present case appears to be the first in the literature.

Decreased hemopoietic function in HIV patients [19] results in susceptibility to chemotherapy-induced myelosuppression, and therapy often cannot be completed due to treatment-related toxicities [20]. In addition, exacerbation of HIV and opportunistic infections associated with such myelosuppression is a concern. The present case is significant because a treatment regimen comprising the coadministration of HAART and antineoplastic drugs was used. Although there are no previous studies regarding coadministration of HAART and antineoplastic drugs for cases of HIV complicated by thymic carcinoma, the utility of this treatment regimen has been reported for HIV patients with lung cancer, Kaposi's sarcoma, and malignant lymphoma [20–23]. HAART offers the following advantages during anticancer treatment: (1) improved immune function by decreasing CD4-positive lymphocyte counts; (2) reduced myelosuppression by inhibition of HIV; and (3) reduced incidence of HIV infection-related conditions (chronic inflammation, tumorigenicity, renal impairment, arteriosclerosis, etc.) [24].

Some anti-HIV drugs either interact with antineoplastic drugs or cause similar toxicities, making it necessary to exercise caution when these drugs are administered at the same time. In particular, ritonavir (RTV), a protease inhibitor, is a very potent inhibitor of the cytochrome P (CYP) 450 3A4 drug-metabolizing enzyme in the liver. RTV can cause the blood concentrations of coadministered antineoplastic drugs to increase and may cause serious toxicities [25]. Potential cumulative toxicities between HAART and antineoplastic drugs are primarily related to nucleoside reverse transcriptase inhibitors (NRTIs) [26, 27]. Zidovudine causes myelosuppression (especially anemia and neutropenia), tenofovir is nephrotoxic, and stavudine and didanosine cause peripheral neuropathy. If these anti-HIV drugs are coadministered with antineoplastic drugs that can cause the same types of toxicities, there is a strong possibility that the toxicities will become even more severe [26, 27]. Thus, such coadministration should be avoided whenever possible. In the patient reported here, ABC/3TC, a combination of abacavir and lamivudine, which are NRTIs, and RAL, which is an integrase strand transfer inhibitor, was used, and these drugs did not alter the blood concentrations of antineoplastic drugs because they are not metabolized by CYP [27].

Coadministration of platinum-containing and anthracycline antineoplastic drugs, which constitute key agents in systemic chemotherapy for thymic carcinoma, can be expected to deliver a marked antineoplastic effect, despite the risk of myelosuppression [7–12]. In the present case, we selected ADOC chemotherapy on the basis of treatment outcome in the previous study [9] and the low incidence of drug interactions with ABC/3TC and RAL [27]. During chemotherapy, white blood cells, neutrophils, CD4 counts, and HIV viral load were monitored as closely as possible, and neutropenia and febrile neutropenia were rapidly treated, enabling completion of four courses of ADOC therapy.

In conclusion, we reported an HIV-infected patient with thymic carcinoma, who responded well to ADOC chemotherapy and HAART. For HIV-positive patients with malignant tumors, care should be exercised in selecting anti-HIV drugs to optimize therapeutic efficacy and reduce potential antineoplastic drug toxicities.

Conflict of interest No author has any conflict of interest.

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