Advanced Testicular Germ Cell Tumor in a Hemophilic Patient with Human Immunodeficiency Virus Infection

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A stage IIIIB anaplastic seminoma which occurred in an HIV-infected hemophilia is reported. The patient with hemophilia A was 36 years old and had been seropositive for HIV antibody for 3 years. Inguinal orchiectomy and subsequent chemoradiotherapy for retroperitoneal lymphadenopathy were performed and a marker negative partial response was obtained. In spite of a low initial CD4+ lymphocyte count (90/μl), the patient tolerated the treatment well without life-threatening opportunistic infection. Although factor VIII supplement was performed, continuous bleeding from the operative wound made postoperative care difficult.

Key words: hemophilia – AIDS – germ cell tumor

INTRODUCTION

Other than AIDS-defining malignancies such as non-Hodgkin's lymphoma, Kaposi's sarcoma and invasive cervical cancer, various malignant tumors have been described in patients with human immunodeficiency virus (HIV) infection (1). There is evidence of a higher incidence of testicular germ cell tumor in HIV-infected men than in those without HIV infection (2,3). Since the first description of testicular cancers in two homosexual men with AIDS (4), more than 80 cases have been reported (1). Histologically, a higher proportion of seminoma has been demonstrated (5) but not yet determined. Standard therapy including orchiectomy, retroperitoneal lymph node dissection, radiotherapy and systemic chemotherapy (PVB, PEB, etc.) has been employed in most cases with a favorable outcome (3). Some cases of advanced HIV infection, however, show deterioration of immune status and progression of AIDS. Survival of the patients has been demonstrated to be related to advanced HIV disease, but not to advanced tumor stage. The median survival times for patients without AIDS and CD4+ lymphocyte counts >200/μl versus those with AIDS or CD4+ lymphocyte counts <200/μl have been reported to be 40 and 26 months, respectively (5). We report here the treatment outcome of an HIV-infected hemophiliac with advanced testicular seminoma, which may be the first case in Japan. In spite of a low CD4+ lymphocyte count, standard therapy was well tolerated without severe side effects.

CASE REPORT

A 36-year-old Japanese male with hemophilia A was referred to our hospital on May 29, 1997 because of swelling of the right testis and a large mass occupying the right upper abdomen which had been noticed by the patient himself. In 1994 he had been diagnosed to be HIV antibody positive and was receiving the anti-retroviral agents AZT (zidovudine), ddI (didanosine) and saquinavir (Ro31-8958) in daily doses of 400, 334 and 1800 mg, respectively. The period of seroconversion, however, must have been much earlier because non-heated factor VIII concentrates have not been used for Japanese hemophiliacs since 1985. He had no palpable peripheral lymphadenopathy.

Computer tomographic (CT) scans and magnetic resonance image (MRI) revealed a bulky abdominal mass and a large mass in the right testis (Figs 1 and 2). Chest radiography including plain films and CT scans revealed no space-occupying lesions. Lactate dehydrogenase (LDH) was elevated to 2560 UI (normal range 269-467 UI). α-Fetoprotein and β-human chorionic gonadotropin remained within the normal range (stage IIIB) (6). The CD4+/CD8+ lymphocyte ratio was low at 0.3 and the CD4+ lymphocyte count was 90/μl without evidence of symptomatic HIV disease [A3 according to the Center for Disease Control (CDC) category (7)]. The plasma concentration of HIV-RNA was 10^2-10^3/ml. His factor VIII activity was <1%. He had been receiving heated factor VIII concentrates (made from donated blood) using his joint pain due to intraarticular hemorrhage as a marker for the treatment but its plasma levels were not measured. He was negative for factor VIII inhibitor by the Bethesda method and activated partial thromboplastin time (APTT) correction test.
Seminoma in a HIV-infected hemophiliac

Figure 1. Magnetic resonance image (T2 weighted image). A large mass occupies the patient’s testicle.

Figure 2. Abdominal computed tomography on admission (top) and after the last chemoradiotherapy (bottom). A bulky retroperitoneal mass, displacing the right kidney and producing right hydronephrosis, was markedly reduced in size after therapy. The hydronephrosis was also improved.

Table 1. Supplement of factor VIII concentrate

<table>
<thead>
<tr>
<th>Time</th>
<th>Dose (U/kg body weight)</th>
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<tr>
<td>30 min before operation</td>
<td>40</td>
</tr>
<tr>
<td>12 h after operation</td>
<td>30</td>
</tr>
<tr>
<td>Days 2–3</td>
<td>20</td>
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<td>Days 4–7</td>
<td>15</td>
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Right inguinal orchiectomy was performed under general anesthesia on June 2, 1997. Initially, a supplement of factor VIII concentrate was given according to the protocol described in Table 1, which maintained APTT at ~80% of control. Oozing of blood from the drainage tubes, however, continued and formed intrascrotal hematoma, which made a blood transfusion (1000 ml) necessary and prolonged the administration of factor VIII concentrates required to improve the condition.

The cut surface of the resected specimen was gray–white with scattered focal hemorrhages. Histologically, homogeneous neoplastic cells had clear cytoplasm and large nuclei with mild lymphocytic infiltration with increased mitotic activity (three to five mitotic figures per high power field) and were diagnosed as anaplastic seminoma (Fig. 3).

Irradiation with a total dose of 36 Gy was performed for the retroperitoneal metastatic lesion in combination with intravenous administration of cisplatin at a dose of 10 mg/body for an initial 4 days; sulfamethoxazole and trimethoprim at daily doses of 800 and 160 mg, respectively, were administered *per os* along with the chemoradiotherapy as a prophylactic treatment of *Pneumocystis carinii* pneumonia. Except for moderate neutropenia (612/μl), which was treated by granulocyte colony-stimulating factor (G-CSF; 75 μg/day for 7 days), therapy was well tolerated. Decline of his CD4+ lymphocytes was generally transient and mild except for the period when anti-retroviral agents were withdrawn because of possibly drug-induced general skin eruption (Fig. 4). Two of the anti-retroviral agents, however, were replaced by 3TC and nelfinavir (AG1343) to improve prolonged depression of CD4+ lymphocytes by chemoradiotherapy.

Although serum LDH returned to normal after the therapy, the retroperitoneal mass persisted and began to enlarge. To suppress tumor progression, three courses of systemic chemotherapy with cisplatin (30 mg/day for 4 days) and etoposide (VP-16; 150 mg/
day for 4 days) were performed. AZT was replaced with d4T before the therapy. Because of severe myelosuppression (WBC 700/μl) and subsequent sepsis, which was treated by systemic administration of antibiotics, the doses of the agents were changed (25 mg/day for 5 days and 120 mg/day for 5 days, respectively) in the second and third courses. Additional local radiotherapy (20 Gy) was applied along with the third course to augment therapeutic efficacy. A marker negative partial response was obtained (Figs 2 and 4) 10 days after the last irradiation. Since then the patient has been alive without enlargement of the metastatic tumor or elevation of serum LDH levels (1 year after the first visit). There has been no deterioration of the HIV infection (recent data are CD4+ lymphocyte counts 182/ml and plasma levels of HIV-RNA <400 copies/ml).

**DISCUSSION**

Treatment of testicular tumors in HIV-positive individuals is challenging. These patients are always at risk of progression to AIDS-related complex or flank AIDS. Although many authors recommend standard therapy for germ cell tumor in HIV-positive patients (5,8,9), rapid progression of HIV infection or fatal side effects have been reported in some cases with advanced HIV infection (1,2). Since radiotherapy and/or chemotherapy have suppressive effects on CD4+ lymphocytes, the condition of the individual including CDC category should be taken into account (1). We initially employed local radiotherapy for a massive retroperitoneal metastatic lesion. The dose of irradiation was set at 36 Gy considering pathological features of the tumor (anaplastic seminoma). Since synergistic cytotoxicity of cisplatin and radiotherapy has been demonstrated in experiments with animal models and cell lines (10), cisplatin was delivered along with the local radiotherapy. Although the initial CD4+ lymphocyte count was <200/μl, the patient tolerated the treatment well. The response of the tumor to the above treatment, however, was insufficient. Additional systemic chemotherapy at escalated doses and local radiotherapy were required to suppress tumor.

Figure 3. Top: hemisected tumor of the right testis. The gray–white, fleshy mass totally replaces the testis. Its size is approximately 15 x 10 cm. Bottom: a high-power detail of the tumor, showing sheets of neoplastic cells with clear cytoplasm and large nuclei with mild lymphocytic infiltration. Increased mitotic activity (three to five mitotic figures per high power field) indicates feature of anaplastic seminoma (H&E; original magnification, x200).

![Figure 3](https://academic.oup.com/jjco/article-abstract/28/9/567/851978)

Figure 4. Lactate dehydrogenase (LDH) and number of CD4+ lymphocytes before, during and after therapy. CDDP, cisplatin; G-CSF, granulocyte colony-stimulating factor.

![Figure 4](https://academic.oup.com/jjco/article-abstract/28/9/567/851978)
progression. Severe side effects were avoidable by G-CSF support and systemic administration of antibiotics. Our current experience suggests that asymptomatic patients who are HIV seropositive tolerate standard therapy for malignancies even if the CD4+ cell number is markedly depressed.

We continued administration of azidothymidine (AZT) even during the period of radiochemotherapy to prevent a further decline of the CD4+ lymphocyte count. Myelosuppression was mild and recovered well by support with G-CSF. Since bone marrow suppression has been reported to be the most significant toxicity of AZT (11), some authors state that AZT should not be viewed as necessary during chemotherapy (2,5). The present experience, however, suggests that AZT may be applicable under radiotherapy with chemotherapy.

Retroperitonel lymphadenectomy has been performed in HIV-positive patients with germ cell tumors when necessary. It may be the treatment of choice also in the present case because of insufficient tumor suppression by chemoradiotherapy. In the present case, oozing of blood from the operative wound continued in spite of factor VIII supplement. Blood transfusion and prolonged administration of factor VIII concentrate were required. Considering these aspects, major surgery such as retroperitoneal lymphadenectomy might be critical to the patient. How to manage postoperative bleeding may be the problem to be solved in order to apply the ideal therapy for hemophilic patients with germ cell tumors.

References