REVIEWS IN UROLOGY

Case of the Quarter: Kaposi Sarcoma in a Patient With Testicular Germ Cell Tumor and HIV: A Case Report and Literature Review

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KEYWORDS:
Testicular neoplasms; HIV; sarcoma; germ cells

Abstract

Testicular germ cell tumors are the leading cause of cancer in male patients 15 to 39 years old. Extensive treatments are available, and the regimen of choice depends on clinical, laboratory, and histopathologic characteristics. Patients with HIV are at increased risk of developing solid malignancies, including testicular germ cell tumors. All patients with HIV should start on highly active antiretroviral therapy, but the drug interactions between chemotherapy for testicular germ cell tumor and highly active antiretroviral therapy have not been extensively evaluated. This case review highlights the importance of optimal therapeutic agent selection in patients with HIV and solid malignancies.

Background

Testicular cancer is the leading cancer diagnosis among male patients 15 to 39 years of age, with 72 301 new patients diagnosed worldwide in 2022.[1,2] Testicular germ cell tumors (TGCTs) are classified according to histologic subtype into seminoma (60%) and nonseminoma (40%). Nonseminoma tumors include embryonal carcinomas, yolk sac tumors, teratomas, and choriocarcinomas.[3] Treatment recommendations vary by clinical stage and histologic subtype.[4] Patients with stage II or III disease as well as some patients with stage I disease and high-risk features will typically receive chemotherapy.[5] Bleomycin, etoposide, and cisplatin (BEP) is the most common chemotherapy regimen, but etoposide, ifosfamide, and cisplatin as well as paclitaxel, ifosfamide, and cisplatin are used to treat select patients.[5] Hematologic adverse events of grade 3 or greater severity that are associated with BEP are reported in approximately 3% of patients.[6] Adapting clinical score predictors to chemotherapy in this patient population is challenging because these patients are underrepresented in clinical trials. Prechemotherapy cytopenia, poor functional status, and a history of chemotherapy-associated toxicities, however, should be considered potential predictors for severe adverse events.

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Patients with HIV infection have an increased risk of developing malignancies.[7] Although TGCTs are not an AIDS-defining illness, the incidence ratio is increased in patients with HIV, ranging from 0.7 to 3.1 compared with the general population.[7,8] Clinical guidelines for TGCTs do not cite tailored treatment recommendations for patients with HIV.[9] Kaposi sarcoma (KS) is the most common AIDS-defining illness in the United States.[10] The current report presents the case of a patient with TGCT and concomitant KS who was treated with left radical orchiectomy followed by postoperative BEP for TGCT and with liposomal doxorubicin for KS in an effort to highlight the importance of optimal treatment selection in this patient population. The case report addresses potential drug interactions between chemotherapy for TGCT and highly active antiretroviral therapy (HAART). In this era of precision medicine, patient-tailored approaches that optimize treatment and consider drug interactions are of paramount importance. Written informed consent was obtained from the patient and their primary oncologist for the publication of this case report.

KEY POINTS

- We reviewed a case of a male patient with TGCT and an incidental finding of HIV and KS.
- Patients with HIV have an increased risk of developing multiple solid malignancies. Special consideration is required when encountering patients at risk of solid malignancies.
- Kaposi sarcoma, a disorder of the vascular endothelium, can have cutaneous, mucosal, and visceral manifestations. Lesions are classically characterized as purplish or dark brown nodules.

ABBREVIATIONS

BEP	bleomycin, etoposide, and cisplatin
HAART	highly active antiretroviral therapy
KS	Kaposi sarcoma
PET/CT	positron emission tomography/computed tomography
TGCT	testicular germ cell tumor

Case Report

The patient is a 45-year-old man who presented with a left testicular mass and pain in late 2022. Ultrasonography and magnetic resonance imaging showed evidence suggestive of TGCT, with a mass measuring 5.4 cm (Figure 1 and Figure 2). One month later, the patient underwent left radical orchiectomy, with final pathology showing a mixed TGCT comprising 60% embryonal carcinoma and 40% seminoma. Rete testis invasion and focal lymphovascular invasion were identified. Based on the eighth edition of the AJCC Cancer Staging Manual, the disease was stage IIA (pT1b, pN1, cM0, S1). Two months after orchiectomy, the patient's α_1-feto protein level was 172 µg/L (172 ng/mL), his human chorionic gonadotropin level was less than 3.0 IU/L (3.0 mIU/mL), his lactate dehydrogenase level was 2.7 µkat/L (162 U/L), his hemoglobin level was 129 g/L (12.9 g/dL), his white blood cell count was 4.8 $\times 10^9$/L (48 000/µL), his absolute lymphocyte count was 1.7 $\times 10^9$/L (1700/µL), and his platelet count was 252 $\times 10^9$/L (252 $\times 10^3$/µL) (Table 1). Positron emission tomography/computed tomography (PET/CT) showed interval development of retrocrural, retroperitoneal, and pelvic

Table 1. Tumor Marker Kinetics Over Time

	Postsurgical value	Values after 3 rounds of BEP	Follow-up values (late 2023)
α_1-feto protein, ng/mL	172	7.0	4.1
Human chorionic gonadotropin, mIU/mL	<3.0	<5.0	<5.0
Lactate dehydrogenase, U/L	162	133	104

Abbreviation: BEP, bleomycin, etoposide, and cisplatin.

SI conversion factor: To convert ng/mL to µg/L, multiply by 1. To convert mIU/mL to IU/L, multiply by 1. To convert U/L to µkat/L, multiply by 0.0167.

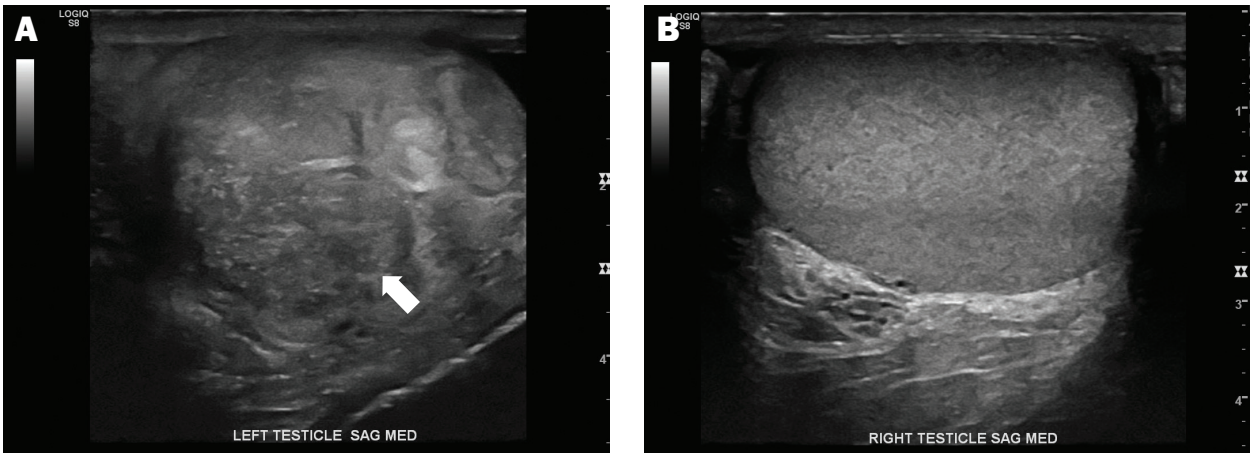

Figure 1. In an ultrasonogram, (**A**) the left testicle measures 4.8 × 3.7 × 3.3 cm, with left testicular heterogeneity (yellow arrow); (**B**) the right testicle measures 4.3 × 2.9 × 3.5 cm.
Abbreviations: MED, medial; SAG, sagittal.

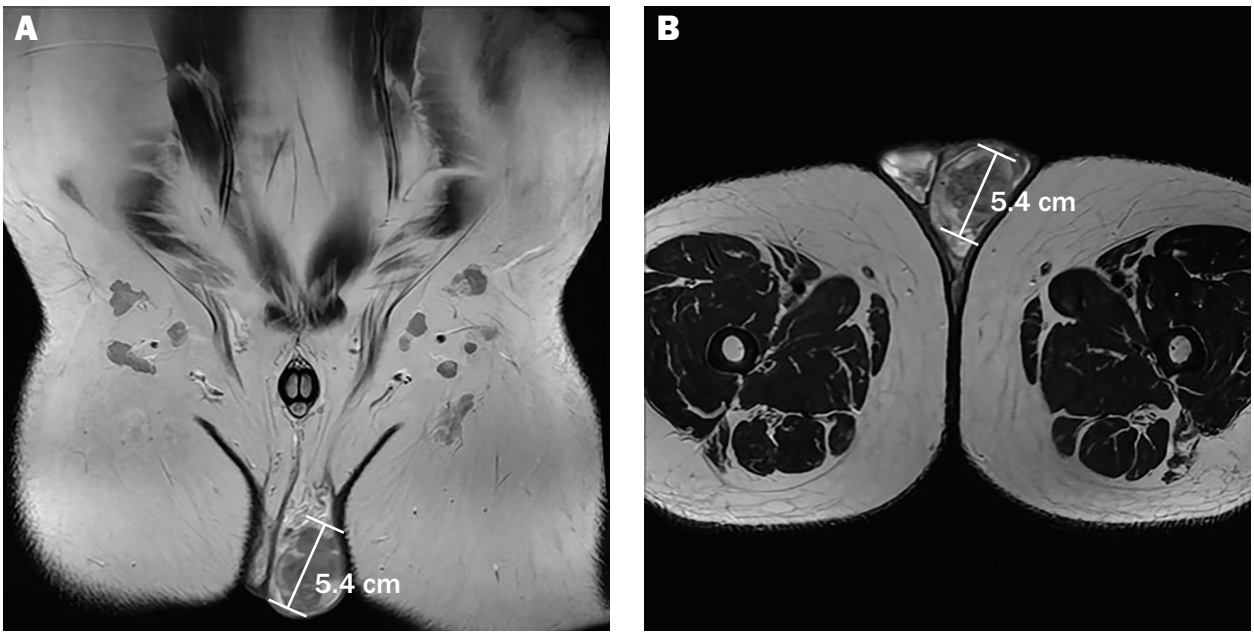

Figure 2. Magnetic resonance image shows (**A**) coronal and (**B**) axial windows of a diffuse heterogeneous mass within the left testicle (5.4 × 3.8 cm).

lymphadenopathy as well as cervical lymphadenopathy and multiple bilateral pulmonary nodules consistent with metastatic disease. Retroperitoneal adenopathy measured 5.1 cm, with a standardized uptake value maximum of 35.6. The patient initiated BEP in early 2023 and completed 3 cycles. Chemotherapy was subsequently discontinued because of substantial bone marrow suppression that required multiple blood transfusions. A restaging PET/CT scan showed resolved lung metastases as well as substantially improved metastatic lymphadenopathy in the neck, chest, abdomen, and pelvis, with only a few

moderately metabolic lymph nodes remaining in the retroperitoneum. At this time, the patient's tumor markers were as follows: human chorionic gonadotropin level, less than 5.0 IU/L (5.0 mIU/mL); α_1-feto protein, 7.0 µg/L (7.0 ng/mL); lactate dehydrogenase, 2.2 µkat/L (133 U/L); hemoglobin, 92 g/L (9.2 g/dL); white blood cell count, 2.1 $\times 10^9$/L (2100/µL); absolute lymphocyte count, 0.5 $\times 10^9$/L (500/µL); and platelet count, 38 $\times 10^9$/L (38 $\times 10^3$/µL) (Table 1).

In late 2023, the patient continued to show signs of systemic illness for which he underwent extensive laboratory evaluation and tested positive for HIV. His physical evaluation was positive for generalized dermatosis, with erythematous papules on the tongue, fingers, and nose. Biopsy of right inner thigh and left abdominal lesions were consistent with KS. A diagnosis of AIDS was made, and the patient initiated HAART. The patient was started on liposomal doxorubicin for KS. At that time, his viral load was less than 1000 copies/mL, and his CD4 count was 70 $\times 10^6$/L (70/mm^3). During follow-up in early 2024, the patient's α_1-feto protein level was 4.1 µg/L (4.1 ng/mL), and his carcinoembryonic antigen was less than 2.0 µg/L (2.0 ng/mL). He had a human chorionic gonadotropin level less than 5.0 IU/L (5.0 mIU/mL), a lactate dehydrogenase level of 1.7 µkat/L (104 U/L), a hemoglobin level of 87 g/L (8.7 g/dL), a white blood cell count of 1.9 $\times 10^9$/L (1900/µL), an absolute lymphocyte count of 0.9 $\times 10^9$/L (900/µL), and a platelet count of 88 $\times 10^9$/L (88 $\times 10^3$/µL) (Table 1). Following the first cycle of liposomal doxorubicin, PET/CT imaging showed new lymphadenopathy comprising a 1.4-cm right inguinal lymph node, a 1.5-cm left inguinal lymph node, a 2-cm left para-aortic node, a 1.7-cm left external iliac node, and scattered retroperitoneal nodes. The patient's current viral load is undetectable, with a recent CD4 count of 88/mm^3. The patient has completed 2 cycles of liposomal doxorubicin.

Discussion

This report describes the case of an adult male patient with a mixed TGCT treated with orchiectomy who underwent postoperative chemotherapy because his tumor markers were persistently elevated. The patient presented with bone marrow suppression while undergoing chemotherapy, as evidenced by pancytopenia in his laboratory reports. The patient's history was notably negative for any risk factors predictive of this response. He consequently required multiple blood transfusions, and chemotherapy was discontinued. During follow-up, the patient continued to show signs of systemic illness, and after evaluation, a diagnosis of HIV was made. It is noteworthy that the patient did not have a history of HIV, high-risk sexual practices, or sexually transmitted infections. For this reason, inoculation was presumed to have occurred during blood transfusions.

Scrotal ultrasonography is the preferred initial diagnostic modality for evaluating TGCT. Clinical staging is performed by assessing tumor marker levels, chemistry panels, liver function tests, and chest and abdominal imaging. Radical inguinal orchiectomy is both diagnostic and therapeutic. Special consideration for items such as sperm banking needs to be made by all patients who desire future fertility.[9,11] Final histopathologic findings, risk stratification, and clinical staging are followed by an individualized discussion to determine the need for additional treatment. Treatment guidelines for TGCTs do not make a distinction between patients living with HIV and patients living without HIV.[9]

For patients with HIV, the standard of care includes treatment with HAART, especially for patients with CD4 counts below 500 $\times 10^6$/L (500/mm^3), regardless of concomitant disease.[12] Highly active antiretroviral therapy involves a combination of different drug classes, but it generally includes 2 nucleoside reverse transcriptase inhibitors plus 1 non-nucleoside reverse transcriptase inhibitor or an integrase inhibitor.[13] Consideration of potential drug interactions between HAART and chemotherapy ought to be made in the disease management of this subset of patients.

The incidence rate of TGCT in patients living with HIV ranges from 0.7 to 3.1 compared with the general population, but most studies evaluating concomitant use of chemotherapy and HAART focus on AIDS-defining malignancies. Simonelli et al[14] evaluated virus resistance patterns and chemotherapy response in 2 sets of patients living with HIV and receiving treatment for non-Hodgkin lymphoma. The first group was

treated with cyclophosphamide, doxorubicin, vincristine, and prednisone, and the second group was treated with rituximab, cyclophosphamide, doxorubicin, and etoposide. Their results showed that simultaneous administration of HAART and chemotherapy is feasible and can achieve good virologic and oncologic response. The authors reported a response rate to chemotherapy of 84.4% in the cyclophosphamide, doxorubicin, vincristine, and prednisone group and 68.4% in the rituximab, cyclophosphamide, doxorubicin, and etoposide group. There was no difference in the rate of chemotherapy-related adverse events between the groups, suggesting that these drugs can be safely co-administered. A total of 9 nonresponders were encountered across both groups. After obtaining the HIV genotypes of the nonresponders, analysis demonstrated that between baseline and the time of virologic failure, variations occur in the *RT* and *P* genes and that resistance patterns are carried before and during chemotherapy. This analysis suggests that although HAART and chemotherapy are safe to co-administer, new viral variations could arise throughout chemotherapy, leading to potentially resistant strains.[14] Though Simonelli et al did not evaluate patients with TGCT, the chemotherapy regimens their study used contain individual drugs, such as etoposide, that are also part of the standard of care for TGCTs. Prospective clinical trials evaluating HAART and chemotherapy interactions in patients with HIV are necessary. Because the patient in the current case report is believed to have acquired HIV infection during blood transfusions after chemotherapy-induced bone marrow suppression, no interaction between HAART and chemotherapy was documented. Considering his immunocompromised status, however, recurrent lymphadenopathy could be suspected as part of the disease activity. The main differential is between recurrent TGCT and KS. Should this disease prove to be related to TGCT, the safety of administering chemotherapy concomitantly with HAART will need to be examined.

Kaposi sarcoma primarily affects the vascular endothelium and manifests in mucocutaneous tissues, with viscera less frequently involved.[10] Four clinical variants exist: classic, endemic, iatrogenic, and epidemic. Epidemic KS, or AIDS-KS, is the most common form in the United States.[10] In patients with AIDS-KS, CD4 count is a determinant associated with the development of KS. Lower CD4 counts, such as those less than 200 $\times 10^6$/L (200/mm^3), are associated with increased incidence rates of KS.[15] Cutaneous lesions are classically described as purplish or dark brown nodules that range in size from small and millimetric lesions to lesions of several centimeters. Systemic involvement can occur anywhere but is more commonly described in the oral cavity, gastrointestinal tract, and respiratory system. Treatment consists of HAART for local manifestations of KS, with directed modalities aimed at alleviating cosmetic symptoms.[16] Systemic chemotherapy, however, is warranted for advanced disease. Liposomal doxorubicin and daunorubicin are considered first-line therapy. The combination of liposomal doxorubicin and HAART was evaluated in a study by Martín-Carbonero et al,[17] in which 28 patients with HIV with moderately advanced KS (ie, at least 10 cutaneous lesions or mucosal or visceral involvement) were randomly assigned to initiate HAART with liposomal doxorubicin or HAART alone. After 48 weeks, a response rate of 76% was seen in the combination arm as opposed to the 20% response rate in the arm that received HAART alone. This study demonstrated the efficacy and feasibility of both regimens in the treatment of patients with HIV who have moderate to severe KS.[17] The patient in this case report had manifestations of KS on the skin and oral mucosa, classifying his disease as moderate to severe. He was started on liposomal doxorubicin and awaits inguinal node biopsy.

Conclusions

In recent years, there has been extensive progress in treatment for patients with HIV. As patients with HIV live longer, there is an increased risk of solid malignancies as a result of their decreased effector immunity capacity, and TGCTs have an increased incidence rate within this population. Although TGCTs are highly curable, special consideration needs to be given to potential interactions between HAART and

chemotherapy regimens. This case report of a patient with TGCT and AIDS-KS highlights the need for the inclusion of patients living with HIV in trials evaluating chemotherapy efficacy, particularly for solid neoplasms for which this population is at increased risk.

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