Case Report

Malignant transformation of testicular teratoma to primitive neuroectodermal tumor

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Abstract

Teratoma is a common germ cell tumor that affects young adult males. A small number of testicular teratomas have the potential for malignant transformation along endodermal, ectodermal, or mesodermal lines. The metastatic mixed germ cell tumor we reported consists of the primitive neuroectodermal tumor (PNET) with mature teratoma. PNET is a highly aggressive tumor with a poor prognosis given its poor response to standard platinum-based chemotherapy. The primary treatment for PNET is surgical resection. Malignant transformation of teratoma to PNET is a rare phenomenon. Only a few cases of malignant transformation of teratomas to PNET are reported in the literature. Here, we present a rare case of PNET arising in a malignant mixed germ cell tumor in a 23-year-old male who underwent adjuvant adriamycin, cyclophosphamide (VAC) alternating with ifosfamide and etoposide (IE) chemotherapy and retroperitoneal lymph node dissection.

Keywords: Malignant transformation of teratoma, mixed germ cell tumor, primitive neuroectodermal tumor, retroperitoneal lymph node dissection

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INTRODUCTION

Teratoma is a nonseminomatous tumor derived from germ cells. Teratoma is a pluripotent tissue that has the potential to transform into PNET in a small number of cases.[1-4] PNET originates from primitive neuroepithelial cells and occurs in the central nervous system and the surrounding connective tissues. It is a primitive, undifferentiated small round cell malignant tumor divided into central and peripheral types based on tumor site.[5] About 3%–8% of the testicular teratomas have the potential for malignant transformation along endodermal, ectodermal, or mesodermal lines.[6] A few cases of teratoma undergo malignant transformation along the ectodermal line resulting in primitive neuroectodermal tumor (PNET).[7] The primary treatment for PNET is surgical resection due to high resistance to radiation and chemotherapy compared to germ cell tumors. Surgical resection may stop tumor expansion.[8,9] Malignant transformation of teratoma to PNET is a rare phenomenon. Only a few cases of malignant transformation of teratomas to PNET are reported in the literature. Here, we present a rare case of malignant transformation of testicular teratoma to PNET in a young adult male.

CASE REPORT

A 23-year-old man underwent right radical orchiectomy after presenting with right testicular swelling. A preoperative

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computed tomography (CT) of the chest, abdomen, and pelvis revealed enlargement of five retroperitoneal lymph nodes, largest measuring 2.1 cm, aortocaval 1.3 cm, preaortic 2.1 cm, aortocaval 1.6 cm, preaortic 1.3 cm, and aortocaval 1.2 cm. Initially, he was being worked up for possible lymphoma. Lactate dehydrogenase (LDH) = 609 U/L, (normal 140–271 U/L) and normal alpha-fetoprotein (AFP) = 32.7 ng/ml (<9.0). Testicular ultrasound confirmed the right testicular mass measuring 8.9 cm × 6.5 cm × 6.9 cm, which looked circumscribed, heterogeneous with some vascularity, and predominantly solid with small cystic areas. The patient underwent the right radical orchiectomy and was followed by oncology and urology. He was referred to a specialized cancer center for a second opinion regarding treatment. However, he has not been contacted about the appointment.

Three weeks after orchiectomy, the patient presented with lower quadrant pain radiating to the back. Patient also endorses appetite change, weight loss, fatigue, abdominal pain, nausea, vomiting, and adenopathy. Vitals are within the normal limits. Physical examination revealed a small right scrotal mass. Laboratory findings revealed increased LDH = 1897 U/L, normal 140–271 U/L), and normal AFP = 4.5 ng/ml (<9.0), beta-human chorionic gonadotropin (HCG) ≤0.5 (0–2 mIU/ml), and carcinoembryonic antigen = 0.5 ng/ml [<5.0]). CRP = 26.77 (<1.0 mg/dl). Hemoglobin level was 11 (12–16 mg/dl), as well as low iron, iron saturation, and total iron-binding capacity, consistent with anemia of chronic disease. Urinalysis was unremarkable. X-ray of the abdomen was unremarkable. Duplex ultrasound of the scrotum and testicles revealed right scrotal hematoma with no clinical findings to suggest abscess. A CT of the abdomen and pelvis revealed soft-tissue mass inferior to the right renal pole and extensive retroperitoneal lymphadenopathy, worsening compared to his prior examination concerning metastasis. No metastatic disease was detected outside the retroperitoneal lymph nodes. Small pulmonary nodules were too small to characterize. He was admitted for initiation of chemotherapy.

Pathology demonstrated a high-grade malignant blue cell tumor (80%) with mature teratoma (20%). Blue cell tumor invades hilar soft tissue, with tumor focally present in the mid spermatic cord. The patient was diagnosed with a nonseminomatous germ cell tumor. Tumor, node, metastasis staging was PT3N2M0S3 (Stage IIIC). Genetic analysis confirmed PNET with somatic malignant transformation. Outside consultation from NeoGenomics reported PNET component >80% arising in germ cell tumor consisting of teratoma and focal yolk sac tumor.

The patient underwent orchiectomy and had one cycle of bleomycin, etoposide, and cisplatin. However, the disease has rapidly progressed within 2 months. A specialized cancer center was consulted, and VAC/IE chemotherapy regimen was recommended. The VAC/IE regimen consists of vincristine sulfate, doxorubicin hydrochloride (Adriamycin), and cyclophosphamide, followed by ifosfamide and etoposide phosphate. We used the same therapeutic regimen used for Ewing's sarcoma. After 11 cycles of VAC/IE chemotherapy, he reported subjective improvement of lower back pain. LDH reduced to 484 U/L (140–271 U/L), with normal beta-HCG and alpha-fetoprotein. Restaging CT scan of the chest, abdomen, and pelvis revealed excellent partial response in the bulky retroperitoneal and right renal disease. PET CT scan 6 months later showed radiotracer uptake of multiple residual retroperitoneal lymph nodes as well as within the known right kidney lesion. No radiotracer uptake of the lungs, chest wall, or new lymph nodes. The radiographic studies and tumor markers remain stable for 3 months after completion of intensive chemotherapy to control the PNET component.

Retroperitoneal lymph node dissection (RPLND) is recommended if markers within the acceptable range and residual tumor in the retroperitoneum postchemotherapy measure >1 cm per the European Association of Urology Guidelines for management of testicular cancer after chemotherapy. The patient will proceed with RPLND to remove all the residual tumors for diagnostic and therapeutic purposes with curative intent. The RPLND is scheduled for 3 weeks.

DISCUSSION

Germ cell tumors are more prevalent in the Caucasian population. Predisposing factors include prior personal or family history of germ cell tumor, testicular dysgenesis, and cryptorchidism. Seminoma affects the male population at 35–45 years of life. It remains localized for a long time before it metastasizes to lymph nodes.

Unlike seminoma, nonseminomatous germ cell tumors affect male individuals at the age of 20–30 years. They usually present with a unilateral painless scrotal mass. Hematogenous metastasis occurs early in the disease course. They were noted to be resistant to radiotherapy.

Teratomas may undergo malignant transformation through which somatic teratomatous elements of a germ cell tumor transform to malignant nongerm cell tumors. It represents a rare phenomenon (3%–6% of metastatic testicular

GCTs). The most frequent malignant components include PNET, sarcomas, carcinoid, and osteosarcoma.[8]

About 30% of testicular germ cell tumors are mixed germ cell tumors. Tumors consist of different combinations of histology such as seminoma and teratoma, embryonal carcinoma and teratoma, seminoma and embryonal carcinoma, and choriocarcinoma and teratoma.[6] The metastatic mixed germ cell tumor we reported consists of the PNET with mature teratoma.

PNET is derived from GCT components which makes PNET definitive diagnosis and treatment challenges due to its nonspecific histology and poor response to standard chemotherapy. Malignant transformation of teratoma is a highly aggressive tumor. Surgical resection and chemotherapy are the main treatment.[3,4,10] PNET tumors have been described as chemoresistant tumors.[3] Several studies have demonstrated resistance to cisplatin-based chemotherapy.[11,12] Unresectable malignant transformation of teratoma to PNET has a poor prognosis.[2-4]

RPLND is the main therapeutic strategy for PNET. However, PNET is associated with high rates of relapse after RPLND. Majority of patients treated with surgery alone for metastatic PNET have relapsed and subsequently died. PNET is highly sensitive to VAC/IE, which is noted to be PNET-specific chemotherapy.[13] This PNET-based chemotherapy has been effective even in metastatic PNET that is surgically unresectable. It is thought to reduce tumor burden, which makes RPLND feasible. Al-Hader *et al*. described a case series of 12 patients with unresectable metastatic disease. Nine of those with metastatic disease who received adjuvant therapy have achieved objective response by RECIST criteria. Those who received adjuvant treatment are alive with no evidence of disease at 9–90 months, with a median duration of 32.7 months. This study showed that surgical resection combined with PNET-targeted chemotherapy occasionally improves long-term survival. Some patients in this study had no evidence of disease after resection.[13] Adjuvant VAC/IE is considered PNET-based chemotherapy and has been used and recommended before undergoing curative resection.[13-15] Considering 4 cycles of adjuvant VAC/IE after surgical resection is recommended.[14]

It is imperative to develop chemotherapy regimens targeting the most aggressive component of mixed cell tumor histology for a better outcome and disease control.[11,16] To date, no current guidelines regarding the optimal treatment of malignant transformation of testicular teratoma to PNET.[17] A few studies have shown promising results when RPLND is combined with adjuvant VAC/IE chemotherapy. Further research is needed to address more PNET-specific treatment strategies.

Treatment should be tailored and mired to the 2 different and concomitant tumors. PNET primary therapy is surgery. It is debatable therefore to start VAC after PEB. Probably, the patient would have benefitted from immediate surgical resection of the retroperitoneal disease or even after the first PEB cycle. Authors should discuss this issue.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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