Primitive neuroectodermal tumor arising from an untreated congenital undescended testicle

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A 26-year-old male with a personal history of schizophrenia initially presented with a 13 cm pelvic mass corresponding to a cryptorchidic testis. The patient was treated with primary and second-line chemotherapy for metastatic germ-cell tumor followed by surgical consolidation. Final pathology revealed a primitive neuroectodermal tumor (PNET) mixed with mature teratoma. Despite multidisciplinary management, significant patient non-compliance led to inadequate follow up and treatment delays ultimately resulting in death. To our knowledge, this is the only reported case of teratoma with malignant transformation arising from an untreated congenital undescended testicle.

Key Words: cryptorchidism, testicular neoplasms, teratoma, immature

Introduction

Teratomas are germ-cell tumors (GCT) that contain elements of two or more germ-cell layers: endoderm, mesoderm, and ectoderm. Seldom, teratomas may transform into somatic malignancies, such as sarcomas and carcinomas. This is called teratoma with malignant transformation (TMT). TMT represents a chemo-resistant phenotype of testicular cancer associated with dismal prognosis in stage II-III patients. Due to its rarity, teratoma with somatic-type malignancy (TSTM) remains a challenging entity in testicular cancer. Here, we report a case of TMT arising from an untreated congenital undescended testicle in a 26-year-old male with schizophrenia.

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Case report

A 26-year-old African-American male with a personal history of schizophrenia presented to the emergency department in August 2005 with a broken jaw after an altercation. During physical examination, he was found to have a bulky intraabdominal mass and a non-palpable left testicle. Imaging revealed a 13 cm heterogeneous enhancing pelvic mass corresponding to the untreated cryptorchidic left testicle without evidence of regional or distant disease. Unfortunately the patient refused further evaluation and was lost to follow up until September 2006 when he re-presented with an enlarging 17 cm lesion associated with new left para-aortic retroperitoneal lymphadenopathy, Figure 1.

After two cycles of bleomycin, etoposide, and cisplatin (BEP) for a presumed stage IIIB (pTXN2M0S2) mixed non-seminoma germ cell tumor (NSGCT), the serum tumor markers (STM) decreased (AFP: 159 to 11 ng/mL) and the mass diminished in size (17 cm to 13 cm). Unfortunately, the patient was lost to follow up thereafter and returned to the genitourinary

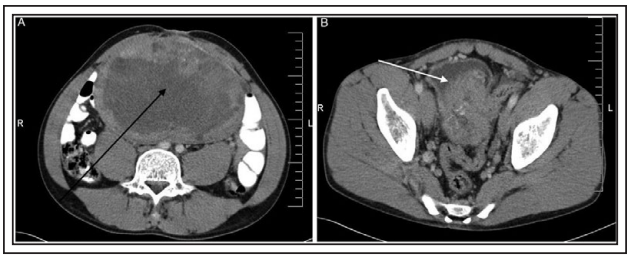

Figure 1. Abdominal-pelvic axial contrast-enhanced CT images. Heterogeneous enhancing 17 cm pelvic/retroperitoneal mass corresponding to the cryptorchidic left testicle (black arrow) with possible involvement of the left posterolateral aspect of the bladder (white arrow).

oncology clinic in September 2007 with a growing 19 cm mass and markedly elevated STM (AFP: 5310 ng/mL, LDH: 1069 U/L). After completing four cycles of second-line paclitaxel, ifosfamide, and cisplatin (TIP), STM remained mildly elevated with yet stable radiographic disease. The case was discussed at the multidisciplinary clinic and it was decided to pursue surgical consolidation. In June 2008, the patient underwent a left radial orchiectomy with partial cystectomy and full-bilateral template post-chemotherapy retroperitoneal lymph node dissection (RPLND), Figure 2. Although complex, the intervention was uneventful.

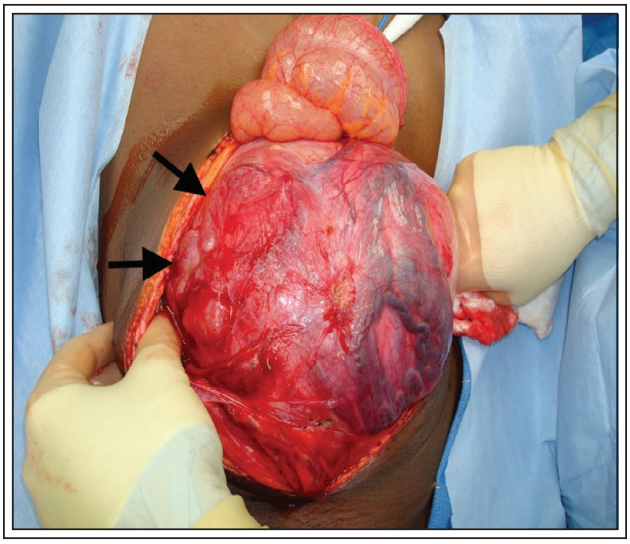

Figure 2. Intraoperative image of the left undescended intraabdominal testicular mass. 22 cm mass seen through a midline xyphopubic incision prior to resection (black arrows).

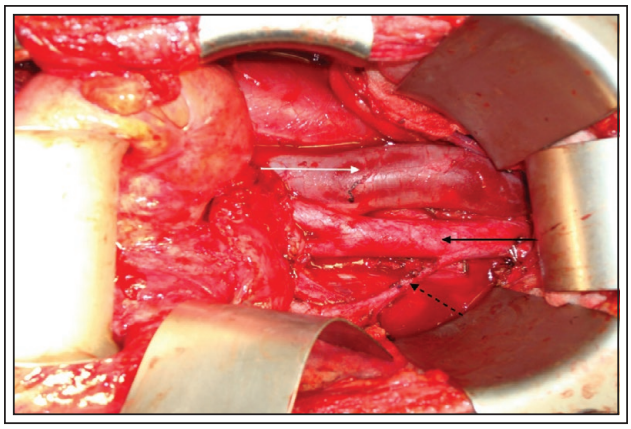

Figure 3. Intraoperative image of the retroperitoneal space after left orchiectomy and full-bilateral template retroperitoneal lymphadenectomy. Inferior vena cava (white arrow), abdominal aorta (black arrow), inferior mesenteric artery (dashed black arrow) post lymph node dissection using the split and roll technique.

Final pathology of the primary tumor revealed a predominant primitive neuroectodermal tumor (PNET) component mixed with mature teratoma. Tumor size was 22.0 cm. No lymphovascular invasion was identified and surgical margins were negative. A total of 23 retroperitoneal lymph nodes were free of malignancy. Immunoperoxidase staining was positive for AE1/AE3 and S-100 but negative for chromogranin, synaptophysin and CD56.

Unfortunately the patient failed to follow up after surgery and presented to the emergency department almost 1 year later in March 2009 with gastrointestinal symptoms. STM were elevated (AFP: 114 ng/mL) and imaging studies showed evidence of loco-regional recurrence with multiple lesions in the lower abdomen and upper pelvis with apparent bulky retroperitoneal lymphadenopathy. After two cycles of palliative gemcitabine and oxaliplatin, the patient was yet again lost to follow up and returned to the emergency department in December 2009 with peritonitis secondary to progressive disease eroding into the bowel. He underwent emergent laparotomy with bowel resection and needed a protracted convalescence, Figure 3. The patient refused further systemic treatments and ultimately expired in July 2010 from metastatic disease.

Discussion

TMT is relatively uncommon and is defined as a teratoma containing a malignant component of a type typically

encountered in other organs and tissues, e.g. sarcomas and carcinomas.[1] It may arise from primary, metastatic or extra-gonadal (mediastinum, retroperitoneum) germ cell tumors (GCT).[2,3] TMT typically affects younger men, although pediatric cases have been reported.[4] How malignant transformation occurs within a GCT is still a matter of debate with several theories postulated over the years. Ulbright at al suggested that malignant transformation arises either from differentiation of totipotent germ-cells to somatic tissues with concomitant malignant transformation, or from malignant transformation of pre-existing teratomatous elements.[3]

The current body of literature on this entity remains sparse with only few reports from high-volume institutions.[5-9] The presence of TMT significantly affects prognosis and management strategies need to be adjusted accordingly. When limited to the testis, the prognosis is not affected. In metastatic sites, TMT have a dismal prognosis as these tumors do not respond to conventional GCT chemotherapy.[5,6] Rice et al recently reported the largest series to date of non-PNET, non-mediastinal primary GCT with TMT.[7] In their experience, predictors of poor cancer specific survival were high grade sarcoma, high grade sarcomatoid yolk sac tumors, repeat RPLND and diagnosis of TMT at late relapse. Established GCT prognosticators such as stage and IGCCCG risk category did not perform well in the setting of TMT.

Clinicians may suspect malignant transformation in patients with systemic progression during treatment with conventional cisplatin-based chemotherapy despite normalizing STM. Furthermore, pathologists with expertise in genitourinary oncology are essential in establishing appropriate diagnosis to guide treatment decisions. The use of chemotherapeutic regimens tailored to the histology of the somatic-type malignancy has been suggested for these rare cases.[8,9] In one report of 10 patients treated accordingly, seven achieved a partial response with three patients achieving long term survival.[9] Therefore, the treatment of choice of TMT ought to consist in complete disease resection in combination with histology-specific chemotherapy.

PNET may be incorrectly reported as immature teratoma and are subdivided into peripheral and central.[10] Peripheral PNET is part of the Ewing sarcoma (EWS) family of tumors. These tumors carry EWS translocations clustered within a single gene locus on chromosome 22. Central PNET typically occurs in the central nervous system of children and does not express the EWS translocations. Characteristically PNETs arising from GCT exhibit features of central PNET.[11] Patients with PNET of GCT origin may benefit from a PNET-specific chemotherapy regimen consisting of cyclophosphamide, doxorubicin, and vincristine alternating with ifosfamide plus etoposide (CAV/IE) in the post-RPLND setting as well as in cases with inoperable disease.[12]

To the best of our knowledge, our case is the only report of TMT arising from an untreated congenital cryptorchidic testicle. Undescended testis or cryptorchidism occurs in 1% to 4% of full-term and 1% to 45% of preterm newborn boys.[13] A history of cryptorchidism is associated with a twofold to fivefold increased risk of testicular cancer.[14] Orchidopexy before puberty was found to decrease the likelihood of GCT development in boys with undescended testis. In a population-based study in Sweden, the risk among those treated at 13 years of age or older was twice the risk among those treated at younger ages.[15] Review of pathology in treated versus untreated cryptorchidism shows that seminoma is associated with persistently cryptorchidic (inguinal and abdominal) testes (74%) and non-seminoma is present in the majority of corrected or scrotal testes (63%).[14]

Conclusion

TMT remains a challenging entity in testicular cancer. Further studies are needed to better understand its carcinogenesis in order to identify actionable targets and optimize systemic therapy. A multidisciplinary approach is essential in the management of TMT. Aggressive and often serial resections at high-volume centers in combination with histologically adapted chemotherapy are critical in the successful management of these cases. □

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