Case Report

Lost in descent: Complications of cryptorchidism

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Abstract

Cryptorchidism is a relatively common and important clinical entity and can lead to an array of downstream complications if it is not corrected in a timely manner. Most notably with the development of testicular germ cell tumors. However, beyond the development of malignancy, there are other rare complications associated with cryptorchid testicular germ cell tumors which are more commonly seen in females with ovarian germ cell tumors, including torsion, rupture, and paraneoplastic syndromes. Presented is an instructive case (with literature review) of a patient who presented with NMDA encephalitis due to a torsed mixed germ cell tumor of an undescended testis, which subsequently ruptured leading to growing teratoma syndrome.

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Introduction

Cryptorchidism is a common congenital disorder in newborn males affecting approximately 2-4% of all male infants [1]. The cryptorchid testis can be located anywhere along the normal path of descent, including in the abdominal cavity, inguinal canal, or high scrotum [2], and often spontaneously resolves during the first year of life. Cryptorchidism has been established as a risk factor for the development of testicular germ cell tumors (GCTs); about 10% of testicular GCTs occur in males with a history of cryptorchidism [3]. Based on well-established data, surgical correction of cryptorchidism is typically performed before the age of 18 months, as this reduces the risk of malignancy.

Beyond development of malignancy, there are other rare complications associated with cryptorchid testicular GCTs which are more commonly seen in females with ovarian GCTs, including torsion, rupture, and paraneoplastic syndromes (such as NMDA receptor encephalitis). We present a case of a 25-year-old male who presented with recurrent seizures due to NMDA encephalitis, subsequently found to have a torsed mixed GCT of an undescended testis which subsequently ruptured. This article includes a literature review and discusses the possible complications of untreated cryptorchidism and NMDA receptor encephalitis.

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Case report

A 25-year-old male with a past medical history of obsessive compulsive disorder and intellectual disability presented with recurrent episodes of seizures. The patient was admitted to the neurocritical care unit and was intubated for airway protection due to repeated convulsive episodes and a worsening Glasgow Coma Score (GCS). Initial nonenhanced head CT and brain MRI were normal.

The patient continued to decline over the next few days, developing fevers, tachypnea, and tachycardia. A contrast-enhanced CT of the chest, abdomen, and pelvis was obtained to evaluate for potential sources of infection. The abdominal CT revealed a 10 cm pelvic mass that was contiguous with tissue extending into the left inguinal canal, and predominantly composed of soft tissue with small foci of macroscopic fat and calcification (Fig. 1A). Pelvic ultrasound showed a heterogeneous mass without significant blood flow (Fig. 1B). Subsequent scrotal ultrasound demonstrated a single right-sided testis and an absent left spermatic cord and testis. Lab work demonstrated an elevated alpha-fetoprotein at 39 and an elevated lactate dehydrogenase at 554, supporting the diagnosis of left-sided cryptorchidism with a testicular GCT.

Given the patient's young age and the presence of a pelvic tumor, a paraneoplastic etiology for the seizures was considered most likely. The diagnosis of NMDA receptor encephalitis was clinched due to the presence of serum NMDA receptor antibodies. The patient underwent further imaging with PET/CT and repeat brain MRI. PET/CT demonstrated increased radiotracer uptake in the pericallosal region of the brain, corresponding to findings of cingulate gyrus swelling with increased T2 signal and diffusion restriction on MRI, compatible with inflammation (Fig. 2). PET also demonstrated decreased uptake within bilateral occipital lobes, a classic finding in NMDA receptor encephalitis (Fig. 3).

A biopsy of the mass was planned; however, the patient had an acute drop in hemoglobin from 11.9 to 7.9 g/dL. Repeat CT of the abdomen and pelvis revealed new enlargement and heterogeneity of the pelvic mass with associated hemoperitoneum, indicative of rupture. Further scrutiny of the initial CT images in 3-D processing software demonstrated a twisted vascular pedicle, compatible with torsion as the cause of tumor rupture (Fig. 4). The mass was surgically resected later that day, with final pathology demonstrating a mixed GCT with adjacent testicular tissue (70% mature teratoma, 30% seminoma) (Fig. 5).

In addition to removal of his abdominal tumor, the patient received high dose steroids, rituximab, and plasmapheresis as treatment for NMDA receptor encephalitis. At the time of discharge, the patient demonstrated significant neurological improvement. He continues to follow with neurology with family reporting a return to baseline mental status within a couple months. Repeat brain MRI one month following discharge showed resolution of previously demonstrated FLAIR and diffusion signal abnormalities.

The patient started VIP (cisplatin, etoposide and ifosfamide) for treatment of the mixed GCT. A CT abdomen/pelvis approximately 1 month following discharge demonstrated new circumscribed peritoneal masses. Follow-up CT abdomen/pelvis 5 months later revealed increased size of these lesions despite normalization of tumor markers after chemotherapy (Fig. 6). Exploratory laparotomy with omentectomy and resection of numerous peritoneal masses was performed, with pathology demonstrating metastatic mature teratoma without evidence of nonteratomatous germ cell components, compatible with “growing teratoma syndrome.”

Discussion

The presented case demonstrates multiple possible rare complications that may develop as a result of unaddressed cryptorchidism. The following is a discussion of the clinical and imaging implications of each of these conditions.
Cryptorchidism and testicular cancer

Cryptorchidism is a congenital disorder in newborn males affecting approximately 3% of all male live births, in which one or both testes fail to descend into the bottom of the scrotum [4]. The undescended testis can be located anywhere along the normal route of descent, including intra-abdominal, inguinal, supra-scrotal, or high scrotal positions [2]. Testicular descent is a complex, multifactorial process which is not fully understood. Cryptorchidism, in many cases, spontaneously resolves during the first year of life.

There are 2 primary concerns for patients with history of cryptorchidism: decreased fertility and increased risk of testicular cancer. Cryptorchidism is a significant risk factor for developing testicular cancer, and is present in 5%-10% of all testicular cancer cases, with a 3-10 times increased risk [3,5]. Patients with intra-abdominally located undescended testes are at particularly high risk [1]. The vast majority (95%) of primary testicular cancers are of germ cell origin, with most cases occurring in young men between the ages of 15 and 35 [6]. About 50% of testicular GCTs are seminomas, and the other 50% are comprised of the nonseminomatous GCTs. Of these, 33% are mixed GCTs, 10% are pure embryonal carcinomas, 4% are teratomas, 1% are yolk sac tumors, and 0.3% are choriocarcinomas [7].

The relationship between cryptorchidism and testicular cancer is not fully understood. One hypothesis includes the possibility of a common hereditary or environmental factor predisposing the testes to both abnormal descent and cancer. A second hypothesis is that an unrelated failure in the mechanism of testicular descent results in an intra-abdominal environment with increased temperature, predisposing to the testis to cancer [5]. More recent studies have also implicated aberrant gonocyte transformation as a potential cause of testicular malignancy [8].
Fig. 3 – FDG-PET statistical mapping analysis compares uptake throughout the brain relative to an age-matched cohort. (A) Fig 3A demonstrates a relative decrease in FDG uptake within the occipital lobe. (B) Fig 3B demonstrates a relative increase in FDG uptake within the cingulate cortex and anterior temporal lobes.

On ultrasound, seminomas are typically hypoechoic and homogenous, and may be somewhat lobular with sharply demarcated borders. Nonseminomatous GCTs on the other hand are often heterogeneous with cystic changes. Mixed GCTs have a variable appearance depending on their composition. For example, those with a teratoma component will likely be more cystic with multiple echogenic foci [9].

The preferred treatment for cryptorchidism is orchiopexy, which should be performed within the first 18 months of life to maximize fertility preservation. Recent studies have demonstrated that pre-pubertal orchiopexy decreases risk of testicular cancer [5]. The risk of testicular cancer increases in a stepwise manner depending on the age at which orchiopexy was performed, with the largest increase occurring around the time of puberty (6-fold increased risk) [10]. Even with timely orchiopexy, patients with history of cryptorchidism still have increased risk of developing cancer; orchiopexy serves a secondary role in that it helps to facilitate early detection through self-examination [5].

Torsion and rupture

Just as with descended testes, an undescended testis can spontaneously undergo torsion. This is rare in modern times due to widespread screening and correction of cryptorchidism. Undescended testes are at increased risk of torsion compared to a normally descended testis, which can be exacerbated by presence of testicular tumor, which acts as a lead-point for torsion. One study estimated the risk of cryptorchid testicular torsion to be 10 times that of normally descended testes [11]. Although very rare, it is not surprising that an intrabdominal testicular GCT may rupture, similar to their far more common ovarian counterparts. GCT rupture can cause significant intrabdominal hemorrhage, and extruded contents may also lead to clinically significant chemical peritonitis [12]. Underlying pedicle torsion as a cause of testicular GCT rupture has been previously reported, as seen in the presented case [13].
Fig. 4 – (A) Coronal contrast-enhanced CT shows interval enlargement and heterogeneity of the pelvic mass with adjacent heterogeneous peritoneal blood products (arrow), consistent with mass rupture. (B) Coronal contrast-enhanced CT demonstrates hemoperitoneum in the upper abdomen (arrows). (C) Axial multiplanar reformat of the previously performed contrast-enhanced CT shows twisting of the mass pedicle from the left spermatic cord (arrow). (D) Coronal multiplanar reformat of the previously performed contrast-enhanced CT shows twisting of the mass pedicle from the left spermatic cord (arrow).

**Growing teratoma syndrome**

Residual metastatic mature teratoma is a common finding in patients who have undergone chemotherapy for metastatic non-seminomatus GCTs. This phenomenon is due to selective chemotherapy resistance of the mature teratoma components compared to the embryonal components. Growing teratoma syndrome is a more uncommon entity, characterized by enlargement of these residual sites of metastatic mature teratoma [14]. Growing teratoma syndrome was first described in 1982 by Logothetis et al., and is characterized by new or growing metastasis during or after chemotherapy, normalization of tumor markers (alpha-fetoprotein, beta hCG), and histologic confirmation of mature teratoma without evidence of embryonal components [15]. These 3 criteria are met in the presented case, confirming the diagnosis of growing teratoma syndrome. In contrast to mature teratomas of the ovary, testicular mature teratomas are considered malignant, as they have similar behavior to teratomas with embryonal components. These lesions are often chemotherapy resistant and may be locally aggressive; for these reasons, surgical resection of these lesions is typically performed [14].

**Anti-N-methyl D-aspartate receptor encephalitis**

Glutamate is an amino acid, and the major excitatory neurotransmitter of the central nervous system (CNS). Glutamate can interact with several postsynaptic neuronal ionotropic and metabotropic receptors, most notably the N-methyl D-aspartate receptor (NMDAR), which plays an important role in neuroplasticity, learning, and memory. Release of glutamate is necessary for normal neuronal function; however, excess levels of glutamate can have detrimental effects including neuronal damage or death due to excitotoxicity [16,17].
Fig. 5 – (A) Gross images display a partially disrupted ovoid mass with attached spermatic cord. (B) When bivalved, the mass reveals a red-brown diffusely hemorrhagic cut surface with solid and cystic components and testicular remnant. (C) Histology sections reveal features of a mature teratoma, including cartilage (right), spindled mesenchymal cells (center) and neuroectodermal (left) cells. (D) There are features of seminoma including nests of large cells with clear cytoplasm and prominent nucleoli, separated by delicate fibrous septae, with admixed lymphocytes in the background (left).

Fig. 6 – Multiple soft tissue nodules and masses are present in the abdomen and pelvis including adjacent to the sigmoid colon (A) and the cecum (B). These soft tissue nodules demonstrate internal calcification.
In anti-NMDAR encephalitis, a type of autoimmune encephalitis, IgG antibodies bind to the NR1 subunit of the NMDARs of the postsynaptic neuron [18–20]. The binding of the antibody to the NR1 subunit causes reversible internalization of the NMDARs within the neurons. Diminished NMDARs on the synapse lead to inhibition of ions passage across the cell membrane [19]. This “drug-like” effect of anti-NMDA receptor antibodies is similar to the mechanism of action of ketamine as a NMDAR uncompetitive antagonist, leading to similar clinical effects [21].

Anti-NMDAR encephalitis disproportionately affects women of child-bearing age because of their association with mature ovarian teratomas, patients with this antibody may not have an associated neoplasm [19,22]. Multiple other tumor types can exhibit cell surface NMDA receptors that trigger the development of NMDAR encephalitis, including small cell carcinoma of the lung, breast cancer, thymic tumors, and testicular GCTs [19].

Clinical symptoms of anti-NMDAR encephalitis are commonly mistaken as psychiatric or substance-induced disorders, and have been grouped into 5 major phases. The prodromal phase can last from 5-14 days, and is characterized by fever, malaise, vomiting, and headache. The psychotic and/or seizure phase begins afterwards, and the patient may experience emotional and behavioral disturbances such as decreased cognitive skills, psychosis, and depression. Patients then transition to the unresponsive phase, when they can appear mute and akinetic. This is followed by a hyperkinetic phase in which autonomic instability will manifest with cardiac arrhythmia, blood pressure and temperature lability, hypoventilation, dyskinesia, and extra-pyramidal signs. Finally, patients undergo a gradual recovery phase [23,24].

Initial brain MR imaging is normal in approximately 50%-77% of patients with anti-NMDAR encephalitis [25,26]. Brain MR abnormalities include regions of inflammation associated with increased T2/FLAIR signal and diffusion restriction, which can be seen in many nonspecific regions of the brain including the medial temporal lobe, hippocampus, basal ganglia, cerebral/cerebellar cortex, and brainstem [22]. FDG-PET/CT may demonstrate increased FDG uptake in regions of inflammation, and decreased uptake which classically preferentially involves the occipital lobe [27].

The diagnosis of NMDAR encephalitis is made by detecting autoantibodies to the anti-NMDA receptor in the CSF and/or serum [18,22]. Treatment includes removal of the tumor (if present), and immunotherapy such as intravenous immunoglobulin, corticosteroids, and plasmapheresis [18,19]. Approximately 66%-80% of patients will recover nearly all baseline neurological function if prompt treatment is initiated, although recovery may take years [19]. Approximately 20% of patients suffer from permanent focal neurological deficits or die from anti NMDAR encephalitis. Ten percent of patients may relapse within 2 years of initial presentation [24].

**Conclusion**

Cryptorchidism is a relatively common and important clinical entity and can lead to an array of downstream complications if it is not corrected in a timely manner, most notably with the development of testicular GCTs. If these masses develop, they are prone to similar complications as their ovarian counterparts, including torsion, rupture, and rarely paraneoplastic anti-NMDA receptor encephalitis. When psychotic and/or neurologic symptoms develop in young patients, it is important to consider NMDAR encephalitis as a cause because it is potentially reversible with prompt treatment.

**Patient consent**

Written, informed consent was obtained from the patient giving permission to publish this article.

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