Testicular Germ Cell Tumors

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Agenda

• **Overview of Testicular Germ Cell Tumors**
  - Brief anatomy of testicle
  - Facts
  - Risk factors
  - Histological subtypes
  - Clinical Presentation

• **Patient Presentation**
  - Index Case
  - Differential Diagnosis
  - Menu of Tests
  - Staging and Prognosis
  - Treatment

• **Companion Cases**

• **Summary**
Overview of the Testicle: Anatomy

Tunica Vaginalis (outer layer)
• Parietal and visceral layer; separated by small amount of fluid
• Testis is covered anteriorly and laterally by visceral layer
• Parietal layer separates testis from scrotal wall

Tunica Albuginea (inner layer)
• Septa divide testicle into lobules (+- 250)
• Each lobule contains coiled seminiferous tubules which converge into straight tubules
• Rete testis → efferent ductules → epididymis → ductus deferens
• The testes are suspended by the spermatic cord within the scrotum
• The average testicle measure 4 x 3 x 2.5 cm, but this is highly variable

Image from http://tcrc.acor.org/testicle.html

Overview of the Testicle: Blood Supply and Lymphatic Drainage

**Blood supply**
- Mainly Testicular arteries
- Collaterals from Cremasteric artery and artery to the Ductus Deferens

**Venous drainage:**
- Right Gonadal vein → IVC
- Left Gonadal vein → Left Renal Vein

**Lymphatic drainage:**
- Follows testicular arteries to paraaortic lymph nodes
- Lymph from scrotum drains to inguinal lymph nodes
Testicular Germ Cell Tumors: Facts

- Most common solid malignancy affecting males between ages 15-34
- 1% of all cancers in men
- 95% of Testicular Cancers are Germ Cell Tumors (GTC)
- White to black incidence of 5:1
- Can present as 1 predominant histologic pattern or a mix of patterns
- Prior to 1970’s accounted for 11% of cancer death in men between 25-34 with a 5-year survival of 64%
- Due to treatment advances it is now one of the most curable of solid neoplasms with a 5-year survival over 90%

Testicular Germ Cell Tumors: Risk factors

- Cryptorchidism (undescended testis)
- Personal or family history of testicular cancer
  - higher RR for brothers than for fathers or sons
- Testicular microlithiasis
- Hypospadias (abnormally located urethral opening)
- Congenital conditions (Klinefelter’s, Down’s)
- Infertility and reduced fertility (causation vs correlation)
- HIV infection (small increase seen in several small studies)
- Perinatal factors (DES exposure previously thought to contribute, but not statistically significant)
- Genetics (candidate genes on chromosome 12p are actively being investigated)
Testicular Germ Cell Tumors: Histological Subtypes

Subdivided in to 2 broad categories for treatment purposes

Pure seminoma (50%)
- Most frequent in 4th decade of life
- Less aggressive than other testicular tumors
- Radio- and chemosensitive $\rightarrow$ favorable prognosis

Nonseminomatous germ cell tumors (NSGCT) (50%)
- Most frequent in 3rd decade of life
- Some subtypes may be more aggressive
- Some subtypes are less radio-and chemosensitive $\rightarrow$ less favorable prognosis

Weinstein MH., Hirsch MS. Anatomy and Pathology of testicular tumors. UptoDate 9/13
Testicular Germ Cell Tumors: Histological Subtypes of NSGCT

Embryonal carcinoma (most undifferentiated)
- Most frequent in 2nd and 3rd decade of life
- More aggressive and less radio- and chemosensitive

Yolk sac tumor
- Infantile form
- 60% of testicular neoplasms in infants

Pure Choriocarcinoma (rare)
- Associated with widely metastatic disease due to hematogenous spread

Teratoma (3 types)
- Dermoid Cyst; Monodermal Teratoma; Teratoma with somatic type malignancy
- Peak incidence in infancy and early childhood
- In children generally benign (pure form); in adults generally malignant (mixed form)

Mixed germ cell tumor
- Most frequent in 3rd decade of life
- 1/3 of GCT

Weinstein MH., Hirsch MS. Anatomy and Pathology of testicular tumors. UptoDate 9/13
Testicular Germ Cell Tumors: Clinical Presentation

- Painless testicular mass is pathognomonic of a primary testicular tumor
  - May be noted incidentally by the patient or sexual partner
- Diffuse testicular pain, swelling, or hardness
- Sharp pain or dull ache in lower abdomen or scrotum

Less commonly patient may present with symptoms caused by metastasis (5%)
- Lumbar back pain from retroperitoneal metastases
- Dyspnea or hemoptysis from pulmonary metastases
- A lump in the neck due to lymph node metastases
- Gynecomastia from increased serum levels of hCG

On Physical Exam the physician should palpate for a mass
- transillumination can further define mass (solid vs. fluid filled)
- Palpate to detect lymphadenopathy, especially inguinal


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• Summary
Our Patient: HPI

- 32M with no PMH presents to OSH with a witnessed new onset Generalized Tonic Clonic seizure for about 20 minutes following headaches for several days.

- At OSH head MRI showed two right frontal lobe lesions.

- Patient received Decadron 10mg and Keppra 1g and was transferred to BIDMC.
Our Patient: Frontal Lobe Lesions on Head MRI

There are 2 mixed signal masses in the right frontal lobe measuring 2.1 x 1.3 cm and 1.8 x 2.0 cm.

There is a homogeneous increase in flair signal consistent with vasogenic edema.
Our Patient: HPI Continued

• At BIDMC patient reported that 2 weeks prior to presentation he had one episode of distinct, sharp, left sided abdominal pain which radiated down to the groin. On palpation of the area after this episode he noticed a mass in the abdominal area, that he had never been aware of before.

• Following that episode he did not experience any other symptoms until his seizure.

• ROS was positive for 85 lbs weight loss, fatigue, migraines, and occasional blurry vision over the last year

• The patient’s family history was non-contributory
Our Patient: Physical Exam

- Large LUQ mass palpable extending into LLQ and left flank
- Left testis significantly enlarged, tense, mildly tender
- Dilated vessels palpable within left spermatic cord, no masses
- Soft, non distended abdomen
- Normal appearing penis
- Testes descended bilaterally
- Right testis and cord normal
- No inguinal lymphadenopathy
Differential Diagnosis of Testicular Tumors

- Germ cell tumor
- Non germ cell tumor
- Metastases
- Lymphoma
- Leukemia
Let’s continue to view the menu of tests available to distinguish between various Testicular Germ Cell Tumors...
Serum Tumor Markers: Utility

• Not recommended for screening of asymptomatic adults for GCTs
• Main utility is for monitoring response to treatment and detecting recurrence
• Can be used for clinical diagnosis, prognosis, and risk stratification of testicular cancer
• 3 tumor markers dominate in terms of use; alpha-fetoprotein (AFP), human chorionic gonadotropin (hCG), and lactate dehydrogenase (LDH)
• Concentrations should be determined before, during, and after treatment and throughout long-term follow up.
• Serum half-life of AFP and hCG are 5-7 days and 30 hours respectively
Serum Tumor Markers: Diagnostic and Prognostic Value

↑AFP
• Restricted to NSGCT (specifically embryonal carcinoma and yolk sac tumor)
• Seen in 40-60% of patients with metastases
• Other conditions with elevated AFP include liver damage, HCC, and other GI cancers

↑beta-hCG
• May be observed in both seminomas and NSGCT
• Seen in 40-60% of patients with metastatic NSGCT, and 15-20% with metastatic seminomas
• False positive hCG includes cross reactivity of antibody with LH and treatment-induced hypogonadism

↑LDH
• Less specific, but independent prognostic value in advanced germ-cell tumors
• Increased in 40-60% of patients with NSGCT and 80% with seminomas

Our Patient: Serum Tumor Markers Values

- AFP: 5.7 (Reference Range 0-8.7)
- LDH: 1435 (Reference Range 94-250)
- hCG: 41246 (<5 = negative; 5-25 = equivocal, >25 = positive)

→ These result may represent a Pure Seminoma or a Non-Seminomatous Germ Cell Tumor
Let’s continue to view the imaging modalities used in the work up of Testicular Germ Cell Tumors...
Scrotal Ultrasound

• Modality of choice in ascertaining the nature of scrotal masses, with a sensitivity of nearly 100%

• Depicts most intratesticular malignancies as focal or diffuse hypoechoic masses in relation to normal testicular echogenicity

• Can conveniently evaluate contralateral testis

• No reliable sonographic criteria to distinguish a malignant from a focal benign intratesticular lesion

→ Therefore, all intratesticular masses should be considered malignant until proven otherwise

• Color Doppler Ultrasound readily displays testicular vascular anatomy
  - not sonographically distinguishable from inflammatory hypervascularity
  - more helpful for infiltrative lesions (lymphoma, leukemia)

Appearance of Various Tumors on Scrotal US

- **Seminoma**
  - typically hypoechoic without calcification or cystic areas
  - margin may be smooth or ill defined

- **Embryonal cell carcinoma**
  - hypoechoic, inhomogenous, and less well circumscribed compared to seminoma
  - 1/3 contain cystic areas

- **Teratoma**
  - anechoic and hyperechoic components
  - produce acoustic shadowing from dense foci (calcification, fibrosis, cartilage)

- **Choriocarcinoma**
  - mixed echogenicity resulting from hemorrhage, necrosis, and calcification.

- **Metastases**
  - may present with areas of increased echogenicity

→ These may be helpful in predicting type of tumor, but are not reliable!
Now that we have a better understanding of the appearance of Germ Cell Tumors on US. Let’s view the US imaging on our patient...
Our Patient: Normal Right Testicle on Scrotal US

Sagittal view of right testis with normal homogenous echotexture throughout. **Testis** and the **Head of the Epididymis** are labeled.
Transverse view shows left testicle is replaced by a large heterogeneous mass with mixed echogenicity measuring 9.6 x 6.4 x 11.2 cm.

There is an anechoic area surrounding part of the left testis compatible with a left hydrocele.

Our Patient: Left Testicular Mass on Scrotal US
Our Patient: Normal Vascularity of Right Testicle on Scrotal Color Doppler US

Sagittal view of right testis with normal homogenous echotexture throughout with normal vascularity. Testis and the Head of the Epididymis are labeled.
Our Patient: Hypervascular Left Testicular Mass on Scrotal Color Doppler US

Transverse view shows left testicle is replaced by a large heterogenous mass with mixed echogenicity measuring 9.6 x 6.4 x 11.2 cm. Here we can see that the heterogenous mass is hypervascular.

There is marked hypervascularity within the heterogeneous mass.
Our patient had a large mass in his left testicle. Let’s discuss the spread of testicular GCTs, and what imaging modalities are used for staging...
Testicular GCT Metastasis

- Metastasize by either the hematogenous or lymphatic route
- Most follow the testicular lymphatic drainage alongside testicular veins to regional lymph node groups
  - Left testicular tumors → left para-aortic nodal group
  - Right testicular tumors → paracaval, precaval, and aortocaval nodes
- Regional lymph node disease can further spread to nonregional lymph node groups
- Distant metastasis via the thoracic duct → left supraclavicular nodes → lungs
- Metastasis to liver, bones, and brain is also possible

Imaging Modalities: Staging

Computed Tomography
• CT abomen/pelvis most common study used for assessing retroperitoneum for metastases
• Reproducible
• Excellent imaging of periaortic and pericaval regions

Plain Film
• CXR may be sufficient to assess pulmonary metastases
• When equivocal → Chest CT

MRI
• Comparable to CT
• Useful in patient in whom iodinated contrast is contraindicated
• Second line for preoperative evaluation of testes when US is inconclusive
• MRI of brain is indicated if suspect brain metastases

Radionuclide Imaging
• FDG-PET has slightly higher sensitivity than CT
• May play a role in f/u of higher stage seminoma after chemotherapy

Bone Scans
• Used in absence of FDG-PET, when bone metastases is suspected
### ACR Appropriateness Criteria for Staging

**Clinical Condition:** Staging of Testicular Malignancy

**Variant 1:** Testis tumor (diagnosed by orchidectomy).

<table>
<thead>
<tr>
<th>Radiologic Procedure</th>
<th>Rating</th>
<th>Comments</th>
<th>KRL</th>
</tr>
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<tbody>
<tr>
<td>CT abdomen and pelvis with contrast</td>
<td>9</td>
<td></td>
<td></td>
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<tr>
<td>X-ray chest</td>
<td>8</td>
<td></td>
<td></td>
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<td>CT chest with contrast</td>
<td>7</td>
<td>Can be used when combined with staging abdomen and pelvis CT with IV contrast. If ordered above (i.e., with the CT abdomen and pelvis examination), without contrast preferred.</td>
<td></td>
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<tr>
<td>CT chest without contrast</td>
<td>7</td>
<td>See statement regarding contrast in text under “Anticipated Exceptions.”</td>
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<tr>
<td>MRI abdomen and pelvis without and with contrast</td>
<td>7</td>
<td></td>
<td></td>
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<tr>
<td>CT abdomen and pelvis without contrast</td>
<td>6</td>
<td>Possibly indicated for follow-up of residual or recurrent seminoma. No clear benefit in initial staging over CT.</td>
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<tr>
<td>MRI abdomen and pelvis without contrast</td>
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<td>FDG-PET/CT whole body</td>
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<td></td>
<td></td>
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<tr>
<td>Tc-99m bone scan whole body</td>
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<td>Variable and usually limited visualization of the retroperitoneum</td>
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<td>US abdomen and retroperitoneum</td>
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<td>Varies</td>
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<td>Lymphangiography abdomen and pelvis inguinal</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>US scrotum</td>
<td>2</td>
<td>Essential for initial diagnosis, usually not useful for staging</td>
<td></td>
</tr>
<tr>
<td>CT abdomen and pelvis without with contrast</td>
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<td>CT chest without with contrast</td>
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<td>X-ray abdomen</td>
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<tr>
<td>X-ray intraosseous urography</td>
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**Rating Scale:** 1-2.5 Usually not appropriate; 4.5-6 May be appropriate; 7-9 Usually appropriate

**Relative Radiation Level:**
Our Patient: Retroperitoneal Mass Encasing Left Renal Artery on CT

CT abdomen shows a large left-sided soft tissue density retroperitoneal lymph node conglomerate measuring 16.5 x 16 cm consistent with metastatic disease from the primary testicular mass.

There is moderate left sided hydronephrosis secondary to mass effect on the left ureter.

The left renal artery is encased by the mass.
Our Patient: Retroperitoneal Mass Encasing Aorta on CT

CT abdomen shows a large left-sided soft tissue density retroperitoneal lymph node conglomerate measuring 16.5 x 16 cm consistent with metastatic disease from the primary testicular mass.

The aorta is encased and displaced anteriorly by the mass.

There is deviation of small and colonic loops of bowel to the right hemiabdomen.

There is mass effect on the IVC.
Our Patient: Retroperitoneal Mass Displacing the Aorta on CT

There is slight displacement of the aorta to the right by the mass.

Coronal reconstruction of CT abdomen/pelvis shows a large left-sided soft tissue density retroperitoneal lymph node conglomerate measuring 16.5 x 16 cm consistent with metastatic disease from the primary testicular mass.
Our Patient: Retroperitoneal Mass Displacing Left Kidney on CT

There is moderate left sided hydronephrosis secondary to mass effect on the left ureter.

The left kidney is displaced superiorly and laterally.

Large left-sided retroperitoneal lymph node conglomerate.
The CT with contrast demonstrates hilar lymphadenopathy with a large high attenuation lymph node within the left hilum, measuring 2.9 x 2.5 cm consistent with pulmonary metastases from the primary testicular mass.
The CT with contrast demonstrates a large high attenuation nodule located within the left lower lobe measuring 3.2 x 2.5 cm consistent with pulmonary metastases from the primary testicular mass.
Let’s discuss our patient’s diagnosis and prognosis....
Our Patient: Course of Hospitalization

- Patient underwent left radical orchiectomy and testicle with spermatic cord were sent to pathology
- Pathology showed tumor invasion of hilar soft tissues, epididymis, and spermatic cord grossly
- Histology consistent with Mixed Germ Cell Tumor composed of:
  - Seminoma (84%)
  - Choriocarcinoma (10%)
  - Embryonal Carcinoma (5%)
  - Yolk Sac Tumor (1%)
  - Teratoma (<1%)
- Patient elected for cryopreservation of his sperm
- Patient was started on chemotherapy regimen consisting of Etoposide, Ifosfamide, and cisplatin (BEP)
- Patient continues to be followed by Urology, Rad-Onc, Gu-Onc, Hem-Onc, Neuro-Onc
# Testicular Tumors: Staging

Our Patient: **T3NXM1S2**

Good risk: 91% 5-year survival rate  
Intermediate Risk: 79% 5-year survival rate  
Poor Risk: 48% 5-year survival rate  

Our Patient: **Poor Risk**
Testicular GCT: Treatment

Treatment will depend on histological type, stage, and risk of recurrence.

Component of treatment include:

**Surgery**
- Radical Orchietomy
- Retroperitoneal lymph node dissection (RPLND)

**Chemotherapy**
Various combinations and amount of cycles dependent on risk of spread and recurrence; some examples of combinations are:
- Bleomycin, Etoposide, Platinol (BEP)
- Taxol, Ifosfamide, Platinol (TIP)
- Taxol, Ifosfamide, Carboplatin, Etoposide (TICE)

**Radiation Therapy**
- External-beam radiation therapy
- No longer commonly used
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• **Companion Cases**

• Summary
Transverse view of right testicle showing a large heterogeneous-appearing mass, predominantly solid with smaller more cystic-appearing areas. The lesion contains areas of calcification. The mass measures 4.0 x 4.0 x 2.7 cm.
Transverse view of right testicle demonstrating a hypoechoic nodule in the mid pole of the right testis measuring 5.6 x 5.7 x 5.7 mm. There are extensive tiny hyperechoic foci consistent in appearance with microlithiasis.
Hypervascular Seminoma on Color Doppler US

Companion Patient 2:

Transverse Color Doppler US of Right Testicle

- hypoechoic nodule in the mid pole of the right testis with increased vascular flow
- hyperechoic foci consistent in appearance with microlithiasis
Transverse view of right testis demonstrating a **large multiseptated predominantly cystic lesion** in the right mid-to-lower testis with internal solid components. There is a **focus of hyperechogenicity** within it with **posterior acoustic shadowing**. It measures 3.9 x 2.5 x 3.8 cm.
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✓ Companion Cases

• Summary
Testicular GCT are the most common malignancy affecting adult men between the ages of 15-34.

The clinical presentation may often be insidious.

Ultrasound is the modality of choice in ascertaining the nature of the testicular mass.

CXR and CT are the best modalities to assess for metastasis.

Prognosis is dependent upon histological type, metastases, and serum markers.

treatment advances have made Testicular Germ Cell Tumors into one of the most curable of solid neoplasms.
References

- Weinstein MH., Hirsch MS.Anatomy and Pathology of testicular tumors. UptoDate 9/13
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