Testicular tumors in children and adolescents

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Outline

- Epidemiology
- Pathology
- Diagnosis
- Clinical course
- Management
- Differences from adults
Introduction

- Tumor registries
  - Prepubertal tumor registry (AAP)
  - Armed Forces Testicular Tumor Registry
  - Children’s Oncology Group
  - UK Children’s study Group

- Prepubertal vs postpubertal:
  Different beasts

Classification

<table>
<thead>
<tr>
<th>Type</th>
<th>Benign</th>
<th>Malignant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germ cell</td>
<td>Teratoma</td>
<td>Yolk sac tumor</td>
</tr>
<tr>
<td></td>
<td>Epidermoid cyst</td>
<td></td>
</tr>
<tr>
<td>Stromal</td>
<td>Leydig cell</td>
<td>Sertoli cell tumor</td>
</tr>
<tr>
<td></td>
<td>Juvenile granulosa cell</td>
<td></td>
</tr>
<tr>
<td></td>
<td>tumor</td>
<td></td>
</tr>
<tr>
<td>Para-testicular</td>
<td>Lipoma, leiomyoma</td>
<td>Rhabdomyosarcoma</td>
</tr>
</tbody>
</table>
Epidemiology

- Prepubertal TT:
  - 1-2% of all pediatric solid tumors
  - 0.5-2 per 100,000
- Age: Median 2y
  - Yolk sac: 13 mo
  - Teratoma: 16 mo
- Mortality 1 per 10 million per year
  - Ross JH; Urology 2009
  - Ross JH et al; JU 2002
  - Alanee S et al; BJU Int 2009

Type of tumors

- Post pubertal: same as adults but rhabdomyosarcoma more prevalent
- Prepubertal:
  - Registries: 60% malignant (yolk sac), 40% benign
  - Recent multi centre studies: 75% benign
  - Selection bias in registries due to under reporting benign lesions?
  - Pohl HG et al JU 2004
  - Metcalfe P et al JU 2003
### Major North American Centers

<table>
<thead>
<tr>
<th>TUMOR TYPE</th>
<th>PERCENTAGE (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>teratoma</td>
<td>50</td>
</tr>
<tr>
<td>Epidermoid cyst</td>
<td>15</td>
</tr>
<tr>
<td>Yolk sac</td>
<td>15</td>
</tr>
<tr>
<td>Jeuvenile granuolsa cell tumor</td>
<td>5</td>
</tr>
<tr>
<td>Leydig cell tumor</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Sertoli cell tumor</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Mixed gonadal stromal cell tumor</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

### Etiology / Genetics

- Teratomas; no Abn
- Yolk sac: Ch 1q deletion, Ch3
- Post pubertal Germ cell tumor: Ch 11,13, 18 Gain 7, 8 and X loss
- Most common: i(12p)
- Risk factors:
  - Environmental
  - Intersex disorders (esp. with Y ch.)
  - 10% tumor by age 20, 6% Ca.in situ
  - Cryptorchidism risk factor for childhood TT?
PATHOLOGY

- Yolk sac tumor (YST)
  - Most common prepubertal malignant tumors
  - Orchiblastoma, endodermal sinus tumor, embryonal adenocarcinoma.
  - Extraembryonic diff. of germ cells

  - Wold et al., Am J Clin Path, 1984

YST

- Epithelial and mesenchymal cells in organoid pattern
- Schiller-Duval bodies
- AFP inclusion bodies
teratoma

- More than one embryologic layers cells
  - Mature
  - immature
    - Immature tissue: neuroepithelium,
    - Generally benign, occasional mx reported
  - malignant
    - YST component
EPIDERMOID CYSTS

- Mono layer teratoma
  - Obrint Mod path
    - 2005
- Differentiated squamous cell lined cysts
- Filled with keratinous debris
- Not associated with ITCGN

Gonadoblastoma

- Benign tumor seen in gonadal dysgenesis
- Germ + stromal cells
Sex-cord stromal tumors

- Juvenile granulosa cell tumor
  - Most common TT of neonates
  - Benign
- Leydig cell
  - Reinke Crystals
  - Benign
  - Hormonally active

Sex cord stromal tumors

- Sertoli cell tumors
  - 10% hormonally active
  - 1/3 genetic syndrome
  - Large cell calcifying variant: benign
  - Uncommonly: malignant: older boys, vascular invasion, high mitotic rates and > 5cm
Intra-tubular Germ Cell Neoplasia (ITGCN)

- CARCINOMA IN SITU
- Common in adolescents and adults with GCT
  - Malignant precursor
- Seen rarely in prepubertal GCT
- Even when seen malignancy markers are lacking (PLAP, C-KIT)
- 1.7% adults with UDT $\rightarrow$ CIS, but rare in prepubertal biopsy
  
  Hadziselimovic et al Uro res 1984

Clinical findings

- Painless mass
- 10% history of hernia, hydrocele
- 15-50% hydrocele in p/e
- Precocious puberty or gynecomastia may be seen in Leydig or Sertoli cell tumor
Diagnosis

- High def u/s + doppler → first step
- No 100% reliable distinguishing features between benign and malignant but:
  - Anechoic Cystic lesions: benign
  - Onion skin appearance: epidermoid cyst
  - Sharp borders, low flow: benign
- evaluate the possibility of testis sparing surgery

Epidermoid cyst
Tumor markers

- HCG: Not useful in prepubertal cases since embryonal ca. and chorioca. are rare.
- AFP: + in 90%-100% of YST
- Pitfalls:
  - Levels are high up to 6-8 mo. age
  - Stable t1/2 achieved by 4 mo. age

Staging

- CT chest / Abdomen
- CT chest / MR abdomen
- GA required for young children → atelectasis → difficulty in dx. Of pulmonary mets
### Children's Oncology Group Staging System for Testicular Germ Cell Tumors

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>I</td>
<td>No disease beyond testis, negative tumor markers post op, if LN &gt; 2 cm → node sampling should be negative</td>
</tr>
<tr>
<td>II</td>
<td>Microscopic residual, elevated markers post op, tumor rupture or scrotal biopsy</td>
</tr>
<tr>
<td>III</td>
<td>+ RP nodes → &gt; 4cm, between 2to 4 cm → bx is needed</td>
</tr>
<tr>
<td>IV</td>
<td>Distant Mx</td>
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### Practical Approach to management

- Management of prepubertal cases are different from post pubertal
- Post pubertal: same principles as adults
Prepubertal testicular mass

- Consider testis sparing surgery:
  - u/s shows adequate amount of normal testis
  - Tumor markers are negative, or below 100ng/ml in infants
  - No evidence of extra-testicular disease
- Intra-op frozen section: if suspicious
  - Sampling errors
    - Elert A. Euro Uro 2002
- Intra-op U/S for deep small lesions

Testis sparing surgery

- Inguinal incision
- Cord is controlled
- Testis is delivered
- Incision of albuginea
- Tumor removal
- Capsular repair
Teratoma

- Generally benign (mature or immature) → no further treatment
  - No association with CIS
  - No mets, local recurrence if resected completely with median F/U to 7 years
    - Shukla AR et al JU 2004
- Rarely may contain foci of YST → usually AFP is elevated
Testicular mass in 1y o. with solitary testis

Epidermoid cysts

- Not associated with CIS or MX
- Surgical excision is curative
YST

- Staging is very important
- RPLND does not have a central role:
  - Mostly stage 1: 70-80%
  - Predominantly pure histology as opposed to mixed histology in adults
  - AFP very reliable in F/U
  - Hematogenous MX is common: 20% lung mx., half with negative RPN
  - RPLND more morbid in children
  - Excellent response to chemo, if relapsing

YST

- Confirmed stage 1 → surveillance
  - Different regimen: CXR, tumor markers, CT/MRI
  - More intense in the first 2 years
- Stage II and above: platinum based chemo
- RPLND: evidence of residual or recurrent disease
- Survival: 6y EFS stage II to IV: 85-100%
- Survival slightly worse for postpubertal patient → mixed germ cell pathology more common (80%)

- Cushing et al J Clin Onc, 2004
Sex cord stromal tumors

- **Juvenile Granulosa cell tumor**
  - Resection (testis sparing) is curative
- **Leydig cell tumor**
  - Resection (testis sparing) is curative
  - Hormonal effects are not reversible
- **Sertoli cell**
  - If histology is suspicious and in older boys → full metastatic work up
  - Testis sparing may be done in younger children.
Paratesticular rhabdomyosarcoma (RMS)

- 5% of “testicular” tumors
- 2 peaks: 3-4 months and 16 y
- 40% have Mx at Dx.
- Arises from mesenchymal tissue
- 90% embryonal variant → better Px
- Distinct pathology → reliable Dx
  - Electron microscopy
  - Immunohistochemistry

Management

- Inguinal orchiectomy
- Scrotal orchiectomy → removal of the cord and partial or total hemiscrotectomy.
- CT for staging:
  - If positive nodes → up to 90% + pathology
  - If negative: 15% false negative rate (IRS IV)
  - 2-3% (German cooperative study)
Role of RPLND

- Full RPLND is morbid with up to 25% serious complication
- Template and Nerve sparing RPLND are good alternatives
- Some studies suggested sampling since this is staging not treatment
- Effective treatment available for nodal disease
  - Ferrari et al. J Clin Onc 2002

Role of RPLND

- IRS IV, Italian and German cooperative study and SIOP studies
  - Relapse free survival of patients over 10 years of age lower than younger boys
  - RPLND should be done in this group for staging purposes
  - If +: intensified chemo with alkylating agent and radiation
  - With current approach overall survival 90%
    - Weiner et al. Semin Ped Surg 2002
Take home message

- Prepubertal tumors even if malignant are approached differently
- There is no place for scrotal approach since malignancy cannot be ruled out based on clinical findings
- If scrotal mass is identified in children referral should be made to a pediatric center