Rhabdomyosarcoma of the genito-urinary organs

Aurore Coulomb

Monday September 9
Rhabdomyosarcoma of the genito-urinary organs

1/ Know the histological prognostic stratification of RMS

2/ Know the specificities of Bladder/Prostate and Paratesticular RMS

3/ Understand the place of Pathology for GU-RMS management
1/ General considerations

✓ Malignant mesenchymal tumour with skeletal muscle differentiation – myogenesis
✓ Children and adolescents > adults
   ✓ 5-8% of malignant tumours in children
   ✓ 3\textsuperscript{d} most common solid tumour in children
   ✓ 2 peaks : 1 month-5y, adolescent 16y
✓ May arise in soft tissue of the GU organs
   ✓ Even in sites without skeletal muscle
Myogenesis

✓ Somite stage
  ✓ Myotome: loose, stellate primitive mesenchyme
  ✓ SHH (notocord)
✓ Myoblast stage
  ✓ Elongated eosinophilic cytoplasm, thick and thin filaments aligned by Z bands
  ✓ PAX3 induces myogenesis via induction of MyoD1 and myogenin
✓ Multinucleated giant cells: fusion of adjacent myocytes
✓ Terminal differentiation: role of innervation
✓ PAX7: initiation of muscle regeneration via satellite cells
Somite stage
Myoblast stage

A. Embryonic
- Primary myogenesis
- Cell fusion

Fetal
- Secondary myogenesis
- Basal lamina assembly
- Innervation/NMU formation
- MTJ formation

Neonatal
- Adult fiber type specification
- Satellite cell niche establishment

Primary myotome
- Primary fibers
- Progenitor migration to limb buds and body wall

Adult
- Homeostasis
- Atrophy/hypertrophy
- Regeneration

B. Embryonic
- Primary myogenesis

Fetal
- Secondary myogenesis

Neonatal
- Adult

Somitic stem cell
- Pax3, Pax7

Fetal stem cell
- Pax7, Myf5, Pax3

Myocytes
- Myog,
- Slow MyHC (Myh7), MyoD,
- Emb. MyHC (Myh3), Nfix,
- Perinatal MyHC (Myh8)
- MyLC1, Acta1, Acta1, AchRy,
- Glut1/2/4, ICaT

Satellite cells
- Pax7,
- Myf5, Pax3
- NCAM1, VCAM1

Myofibers
- Fast MyHC
- Ila (Myh2), Ilb (Myh4), Ilx (Myh1)
- MyLC3, Acta1, AchRc, Glut4, ICaL
# RMS associated familial cancer syndrome

<table>
<thead>
<tr>
<th>Gene</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>NF1</td>
<td>Neurofibromatosis type 1</td>
</tr>
</tbody>
</table>
| RAS/MAPK pathway | Cranio-facio-cutaneo syndrome  
Costello syndrome |
| 11p15 epigenetic anomalies | Beckwith-Weidemann syndrome |
| TP53 | Li Fraumeni |
| Genetic defect in DNA repair via homologous recombination | Fanconi |
| DICER1 | DICER1 predisposition syndrome |
| PTCH | Gorlin syndrome |
| MMR deficiency MLH1, PMS2, MSH2, MSH6 | Lynch syndrome |
| Other factors | Ionizing radiation, myopathy |
RMS localisations

- Head and neck: 40%
- Genito-urinary: 30%
  - Bladder-prostate
  - Paratesticular
- Limbs: 15%
- Others: thorax, abdomen, trunk wall, Bile ducts: 15%
Histological key features

Heterogeneous group: from small round blue cell tumour to highly differentiated RMS

1/ Cross striation on HE
   Striated malignant muscle tumour

2/ Brightly eosinophilic plump pink cytoplasm
   Malignant skeletal muscle
   Don’t forget to perform INI1 to exclude MRT

3/ Immunohistochemistry
   Desmin: cytoplasmic
   Myogenin: nuclear
   MyoD1: nuclear - Spindle cell RMS
Pitfalls

• Entrapped atrophic muscle vs tumoral rhabdomyoblasts
  – May express myogenin and MyoD1

• Aberrant expression
  – Dot like expression of Keratins

• Myogenic markers may be expressed by non-RMS
  – Wilms tumour
  – Other sarcomas: malignant triton tumour, mesenchymal chondrosarcoma....
## 2/ Histological classification

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhabdomyoma</td>
<td>Rare, syndromic No GU involvement</td>
</tr>
<tr>
<td>Embryonal RMS 60%</td>
<td>Classical Smiley Face Botryoid – DICER1 Smiley Face GU tract involve 11p15 LOH, RAS pathway CN aberration No fusion transcript</td>
</tr>
<tr>
<td>Alveolar RMS 20%</td>
<td>80% PAX3/PAX7-FOXO1 20% No fusion</td>
</tr>
<tr>
<td>Spindle cell/sclerosing RMS 5-10%</td>
<td>Fusion NCOA2 or VGGL2 Mutation MyoD1 +/-PIK3CA</td>
</tr>
<tr>
<td>TFCP2-RMS Pleomorphic RMS Unclassified RMS</td>
<td></td>
</tr>
</tbody>
</table>

* Variants
  - PAX3/NCOA1
  - PAX3/NCOA2
  - FOXO1/FGFR1
  - PAX3/FOXO4
  - PAX3-AFX

Variants
  - VGLL2-CITED
  - SRF-VGGL2
  - TEAD1-NCOA2
  - SRF-NCOAV2

WHO 2013-2019
ERMS

11p15 LOH, RAS pathway CN aberration FISH FOXO1 negative

PAX3/PAX7-FOXO1

ARMS

Fusion NCOA2/VGGL2 Mutation MyoD1 +/-PIK3CA

Sc RMS
Rhabdomyosarcoma
European Paediatric Soft Tissue Sarcoma Study Group (EpSSG) stratification 2005

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Subgroups</th>
<th>Pathology</th>
<th>IRS Group</th>
<th>Site</th>
<th>Node Stage</th>
<th>Size &amp; Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Risk</td>
<td>A</td>
<td>Favourable</td>
<td>I</td>
<td>Any</td>
<td>N0</td>
<td>Favourable</td>
</tr>
<tr>
<td></td>
<td>B</td>
<td>Favourable</td>
<td>I</td>
<td>Any</td>
<td>N0</td>
<td>Unfavourable</td>
</tr>
<tr>
<td>Standard Risk</td>
<td>C</td>
<td>Favorable</td>
<td>II, III</td>
<td>Favorable</td>
<td>N0</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>D</td>
<td>Favorable</td>
<td>II, III</td>
<td>Unfavorable</td>
<td>N0</td>
<td>Favourable</td>
</tr>
<tr>
<td>High Risk</td>
<td>E</td>
<td>Favorable</td>
<td>II, III</td>
<td>Unfavorable</td>
<td>N0</td>
<td>Unfavourable</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>Favourable</td>
<td>II, III</td>
<td>Any</td>
<td>N1</td>
<td>Any</td>
</tr>
<tr>
<td></td>
<td>G</td>
<td>Unfavorable</td>
<td>I, II, III</td>
<td>Any</td>
<td>N0</td>
<td>Any</td>
</tr>
<tr>
<td>Very High Risk</td>
<td>H</td>
<td>Unfavorable</td>
<td>II, III</td>
<td>Any</td>
<td>N1</td>
<td>Any</td>
</tr>
</tbody>
</table>

Favourable: ERMS
Unfavourable: ARMS
Genito-Urinary RMS

Bladder/Prostate RMS
- Embryonal RMS 80%
- ARMS rare

Paratesticular RMS
- Spindle cell ERMS
Bladder/prostate RMS

Large mass affecting
- Ouraque
- Bladder dome
- Bladder neck
- Prostate
- Posterior urethra

- Hematuria, dysuria, bladder dysfunction, pain
- Metastasizes to regional lymph nodes, lungs, liver
TDM at diagnosis
M, 5 y
Large suprabladder mass (ouraque)

Fine needle biopsy

Small round cell tumour
No myogenesis

Mitosis
Apoptosis
M, 3y, dysuria, cervix bladder tumour
Endoscopic biopsy
Multimodal treatment strategy

EpSSG protocols

✓ Intensive chemotherapy
  ✓ Regimen VAC
  ✓ Regimen IVA, IVE-CEV
  ✓ 4 courses of chemotherapy
  ✓ It may be more (6 or more courses) in order to facilitate local surgical treatment

✓ Surgery
✓ Brachytherapy, Radiation
Multimodal treatment strategy

At diagnosis

After 3 IVA

After 6 IVA
Bladder/prostate RMS

Partial cystectomy

✓ M, 11y, pelvic mass (ouraque)
✓ FNB: Embryonal RMS
✓ RMS2005 High risk group E
✓ Good response : 4cm
Left prostatectomy + brachytherapy

- Iridium 192
- 2 loops encompassing the prostate
- Low dose rate (5-7 days)
- 60 Gy
Bladder/prostate RMS

✓ Localized RMS: 90%
  ✓ CR: 90%
  ✓ OS 5 year: 70%
  ✓ 20-30% local relapse
    ✓ Early or late recurrences (> 3 ans)

✓ Metastatic disease: poor outcome

✓ Prognostic factors
  ✓ Tumor size > 5 cm
  ✓ Stage
  ✓ Age: <1y or >9 y
  ✓ Alveolar histology
M, 6y, NF1
Posterior bladder ERMS with a posterior thoracic nodule: neurofibroma? Metastasis?
Paratesticular RMS

✓ 7-10% of all GU tumours
✓ Reactional hydrocele
✓ AFP, HCG normal
✓ Delay in diagnosis >10y
  ✓ Large tumour
  ✓ 15% metastatic

2 year old boy
Paratesticular RMS

Diagnosis: US

Enlarged intrascrotal extratesticular mass, abdominal extension

MRI
Paratesticular RMS

Usually inguinal radical orchietomy
Hemi-scrotectomy rare

Lower end of the spermatic cord > epididymis > tunica vaginalis
Testis displaced by the tumour or surrounded by the tumour
M, 6y
Localised right paratesticular mass
Well-circumscribed
Nodular, Lobulated
Firm, grey-white, smooth surface

Primary right orchiectomy using inguinal approach
Microscopy

✓ Spindle RMS
  ✓ Leiomyosarcoma like
  ✓ Cross striation in spindle elements
  ✓ Micro-alveolar pattern
✓ Considered as embryoonnal RMS
✓ Desmin+, myogein+, MyoD1+
M, 16y
Juxta-epididymal mass with bilateral metastatic iliaque lymph nodes
M, 16y
Juxta-epididymal mass with bilateral metastatic iliaque lymph nodes
M, 16y
Juxta-epididymal mass with bilateral metastatic iliaque lymph nodes
Myogenin
Differential diagnosis

• Testicular tumour
  – Yolk sac tumour (AFP +++)

• Paratesticular tumour
  – Fibrous hamartoma of infancy
  – Fibromatosis
  – Melanotic neuroectodermal tumour of infancy MNTI
  – Inflammatory myofibroblastic tumour IMT
  – Lymphangioma/Vascular malformation
Paratesticular RMS

✓ Localised tumour: 60%-80%
✓ Lymphatic dissemination to retroperitoneal lymph nodes
✓ Hematologic dissemination: lung, lymph nodes
✓ Better prognostic localisation
  ✓ 5y OS: 95%
✓ Bad outcome pronostic factors
  ✓ < 1 y or > 10y
  ✓ Unresectable retroperitoneal metastasis
  ✓ Distant metastasis
Take home message

Bladder/Prostate RMS
Embryonal RMS 80%
Classical or botryoid

Paratesticular RMS
Spindle ERMS
Take home message

✓ FOXO1 FISH to exclude an alveolar RMS
✓ INI1 immunostaining mandatory to exclude rhabdoïde tumour
  ✓ Poorly differenciated RMS
  ✓ Even if the tumour is desmine+ et myogénine+
  ✓ Metastatic and refractory forms
✓ Botryoid variant may be associted with DICER (cervix)
The most challenging site in term of functional sequelae
Tailor the treatment to risks factors to maintain or improve survival and decrease morbidity
Bladder function/erectile function/fertility

Take home message

OS 5 year: 70%

Bladder/Prostate RMS

5y OS: 95%

Paratesticular RMS

Complete resection R0
Total orchidectomy with inguinal approach
No biopsy

Multidisciplinary approach including pathologists
Merci