Overview

- Epidemiology & Risk Factors
- Genetics & Novel Markers
- Gender & Age Factors in Gonadal GCT
- IGCNU
- Diagnostically “Problematic” Germ Cell Tumors (GCT)
Testicular Germ Cell Neoplasms
Epidemiology & Risk Factors

- Germ Cell Tumors (GCT) are most common malignancy in men aged 15-44y.
- 500,000 cases Worldwide/8,250 cases in the US (370 death).
- Incidence increases after puberty, peaks in third decade.
- Modal age of NS-GCT is a decade earlier than S-GCT.
- Geographical variation: Life time risk is 0.4-0.7% in US, 1% in Nordic region and least in Asia and Caribbean.
Testicular GC Neoplasms
Epidemiology & Risk Factors

• Steep increase in incidence in US and Northern Europe.

• Decreased incidence in men born during WWII
  - risk determined early in life?

• Risk of invasive GCT parallels prevalence of IGCNU
  - Cryptorchid testis
  - Contralateral testis in GCT pts

• Depletion of IGCNU pool with age.
Abnormal In-utero conditions affect primordial GC?
- Male genitalia abnormalities: Cryptorchidism, Maldescent, Hypospadia
- Gonadal dysgenesis: 45,X/46,XY (10-50% risk)
- Low birth weight
- Older maternal age

Abnormal diff. of primordial GC  ➔  IGCNU  ➔  Invasive GCT
Testicular Neoplasms
Epidemiology & Risk Factors

• Familial Risk: 2% of GCT have familial origin. 8xRR in siblings

• Male infertility: Shared causality with GCT

• Adulthood exposures/factors:
  - Physical activity
  - Socioeconomics
  - Immunosupression

• YST in infants and Spermatocytic Seminoma in older pts: lack association with IGCNU origin from differentiated spermatogonia
Testis
Cryptorchidism

- Incidence: 1-2%.
- IGCNU: 0.4% in cryptorchid testis biopsied at pexy.
- Currently Bx at time of orchiopexy recommended only if karyotypic abnormalities /malformation present.
- 3-5% life time risk (4-7 times RR) for malignancy in affected Testis.
- 2-3 RR in contralateral Testis
- 80 % of GCT are seminomas
Testis
Cryptorchidism

- Orchiopexy even before 2 year of age is not protective from subsequent GCT.
- Comparable stage of GCT at time of presentation in orchiopexy Vs no intervention pts.
- Animal models support link of increased risk of IGCNU in cryptorchid to hormonal environment during pregnancy rather than abdominal location (endocrine disrupters)
- Mother smoking: risk for bilateral cryptorchidism?
- Micro: atrophic tubules, thick BM, leydig cell hyperplasia, microlithiasis, IGCNU.
- Microlithiasis alone not a risk for GCT.
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Over-representation of Chromosome 12p Region:

- Consistently present structural aberration in GCT
- \(i\ (12p)\): present in up to 80% of cases including extratesticular tumors
- \(i\ (12p)\): uniparental origin (disomy)
- Other abnormalities include additional copies of parts of 12p chromosome
- Amplification of 12p11.2-p12.1 region: apoptosis resistance genes such as DAD-R
- \(i\ (12p)\) is rare in IGCNU
- \(i\ (12p)\) is rare in Infantile GCT (YST: -6q; Teratoma: 2N, no karyotypic change)

- FISH or CGH analysis for ip12 can be helpful in DDX of GCT vs Somatic Ca. In extratesticular location.
Testicular GC Neoplasms
Genetics

Therapy Predictive Biomarkers
• DNA damage detection/Apoptosis initiation programs:
  - WT p53 overexpression is associated with chemosensitivity
  - Disturbance in MMR is found in cisplatin refractory seminoma

Epigenetics:
• Genomic Imprinting:
  - In Utero: Erasure of genetic imprinting in Primordial Germ Cell
  - Global Methylation differences between S-GCT and NS-GCT may offer clues to early stages of histogenesis of GCTx
Mixed Model for GCT Development
Suggested by Smiraglia et al. 2002
IN-UTERO

Spermatogonial Stem Cell

PGC with Remethylation Marks

5mC

NS-GCT (Methylated)

IGCNU

5mC

Gametes

PREPUBERTY/ADULT

IGCNU (Methylated)

Proposed Linear Model for GCT Development

Gametes

Sm-GCT

PGC with Methylation Erasure

5mC

Proposed Linear Model for GCT Development
Testicular Germ Cell Neoplasms
Novel Diagnostic Markers

C-kit (CD117):

- Membranous positivity in IGCNU, Seminoma and Embryonal Carcinoma.
- Tyrosine Kinase (TK) receptor.
- Mutations in exons 17 and 11 ? Target of therapy for TKI in refractory seminoma

OCT4 (POU5F1; OCT3)

- Nuclear transcription factor expressed in pleuripotent embryonic and stem cells
- Nuclear staining.
- Positive in IGCNU, seminoma, embryonal carcinoma and germ cell component of gonadoblastoma.
- Greater sensitivity (100%) than c-kit and PLAP including extratesticular seminomas.
- Greatly specific: only 3/3439 TMA “somatic” carcinoma cases were found to be positive (Clear cell RCC, NSCLC)
Podoplanin

- MAB: D2 -40 and M2 A
- Transmembrane mucoprotein.
- Membranous staining.
- Excellent sensitivity for IGCNU and seminoma (diffuse staining in metastatic/extratesticular seminoma)
- Positive in non seminomatous GCT (lower sensitivity)
- Also labels lymphatic endothelium, vascular neoplasms, epithelioid mesothelioma.

Activator protein - 2γ (Ap-2γ)

- Nuclear transcription factor involved in embryonic morphogenesis
- Functionally related to c-kit and PLAP expression.
- Nuclear staining.
- Strong sensitivity for IGCNU, seminoma
- Positive in non seminomatous GCT (lower sensitivity)
- Also expressed in somatic neoplasms: melanoma, breast and ovarian carcinoma.
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<th>IGCNU</th>
<th>CLASSIC SEMINOMA</th>
<th>SPERMATOCYTIC SEMINOMA</th>
<th>EMBRYONAL CARCINOMA</th>
<th>YST</th>
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Modified from Ulbright TM. Mod pathol 2005
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Gonadal Germ Cell Neoplasms

tesicular Vs Ovarian

Ulbright TM. Mod pathol 2005
Incidence/Histologic type:
- GCT account for 98% of testicular but only 1% of all ovarian tumors.
- Majority of male GCT are seminomas and mixed Sem & NS-GCT
- Majority of ovarian GCT are mature teratomas/dermoid cyst (very rare in male)
- Mixed GCT: 1/3 of testicular but only 1% of ovarian GCT

Pure teratomas form 95% of ovarian but only 5% of testicular GCT but are a common component (50%) of mixed testicular GCT

Spontaneous regression is limited to testicular GCT.

Spermatocytic seminoma lacks an ovarian counterpart.
Prepubertal Testicular GCT

Pure YST:
- Most common GCT in children.
- Median age 16 months of age
- 20% present with metastasis (lung and RPLN)
- Age not a factor in prognosis.
- PGX: Stage, AFP levels and Vascular invasion

Pure Teratoma
- Prepubertal testicular teratomas are benign
- Thought to originate from benign GC (diploid)
- 36% of GCT in children
- 2/3 occur in 1-2 year old (some peri-natal)

Other Types
- Mixed GCT Rare in prepuberatal pts.
- Pure Chorionicinoma has poor PGX (12% survival)
Adult Testicular Teratoma

- All postpubertal testicular teratomas in adult males are malignant.
- No prognostic difference between mature or immature elements.
- Both elements originate from other NS-GCT.
- Preteratomatous malignant transformation: Clonal relation to NS-GCT elements.
- Metastasis may differ in histologic type from their testicular primary.

- ONLY In post Rx RPLND, characterizing mature /immature elements is required.
Adult Testicular Teratoma

Teratoma with Somatic-Type Malignancy/Teratoma with Malignant Transformation

- Can occur in testicular or metastatic site.
- Expansile/overgrowth (4x field rule)
- 1/2 are undifferentiated sarcoma
- Rhabdosarcoma, leiomyosarcoma and others.
- PNET
- WT (very rarely)
- Adenocarcinoma, SCCa.

- Some share ip12 with GCT origin others show DZ specific genetic change (11;22 etc…)
- PGX: poor in metastatic site, ? not affected in testicular primary
- Rx: Do not respond to GCT Rx. Surgery and corresponding type specific Rx
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Intratubular Germ Cell Neoplasm Unclassified
IGCNU

- **Incidence:**
  - 1% incidence in testicular biopsies taken as part of Infertility W/U
  - Cryptorchid testis (0.4-2%)
  - up to 25% of testis in Gonadal Dysgenesis pts
  - IGCNU present in association with the majority (80%) of invasive testicular GCT cases of adults
  - GCT pts: 5% IGCNU in contralateral testicular biopsy

- **Significance:**
  IGCNU risk of progression to invasive GCT: 50% in 5 years (infertility and contralateral testis data)

Management: XRT, organ preserving resection, surveillance
Intratubular Germ Cell Neoplasm Unclassified
IGCNU

- DDX:
  - Intratubular seminoma
  - Intratubular spermatocytic seminoma
  - Spermatogenic arrest
  - Prepubertal spermatogonia (giant spermatogonia)

- IHC:
  - PLAP(+), C-kit (+), OCT3/4 (+)

- IGCNU can extend via pagetoid spread to rete testis and epididymis
- Microinvasion
IGCNU in Rete
IGCNU in Rete
IGCNU in Rete Mimicking Emb Ca
Sertoli Cell-Only Mimicking IGCNU
Prepubertal Testis Mimicking IGCNU
Intratubular Emb Ca
Intratubular Seminoma
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Germ Cell Tumors

Classic Seminoma

- Sheets of clear cells, well defined cytoplasmic borders, “squared-off” central large nuclei, amphophilic nucleoli, fibrous bands, granulomatous-lymphocytic host reaction.
- IHC: PLAP(+), C-kit (+), OCT3/4 (+), AE1/AE3(-).

- "Anaplastic" seminoma:
  - Terminology is now generally discouraged.
  - No Prognostic or Rx implications.
  - Poor fixation can lead to plasmocytic or "anaplastic" morphology.

- True focal transformation into an embryonal carcinoma component can be confirmed by a contrasting IHC staining pattern (AE1/AE3 + & CD30 +).
- MSKCC group: seminoma with atypia?
Seminoma

“Problematic” Variants

• **Intertubular (Interstitial) Seminoma:**
  - can be underdiagnosed as orchitis.
  - grossly non palpable.
  - discovered during infertility W/U.
  - can be obscured by the host response or admixture with Leydig cells.
  - identifying an interstitial seminoma component will lead to a more accurate GCT size estimates for staging.

• **Microcystic Seminoma:**
  - Edema?
  - may mimic YST
  - lined by polygonal rather than flattened cells; exfoliated cells; inflammatory response
  - IHC panel: C-kit+, OCT3/4+, AFP-, AE1/AE3 -
Seminoma

“Problematic” Variants

• **Tubular Seminoma:**
  - Can mimic Sertoli cell tumor
  - IHC panel: C-kit +, OCT3/4 +, Inhibin -

• **Seminoma with prominent syncitiotrophoblast:**
  - 5% of classic seminoma have scattered syncitiotrophoblasts.
  - When clustered (adjacent to areas of hemorrhage) may mimic a component of choriocarcinoma.
  - Lack of an admixed cytotrophoblastic component.
  - Only clinical relevance: help explain an associated hCG levels/hormonal manifestations
Germ Cell Tumors
Spermatocytic Seminoma

Clinical Features:

- Older patients (average age: sixth decade), rare before 30 years of age.
- Occurs only in testicular location.
- No association with cryptorchidism.
- No ovarian counterpart.
- EXCELLENT prognosis.
- Rx: orchiectomy ONLY

- Aggressive behavior seen only in rare cases with associated “sarcomatous” component.
Germ Cell Tumors
Spermatocytic Seminoma

Histopathology

- Hallmark: cytologic polymorphism/round nuclear shape
- Three cell types: small, intermediate and large
- “spiremic” filamentous chromatin pattern.
- Can have brisk mitotic activity.
- Lack IGCNU component or lymphogranulomatous host response
- No other non-seminomatous GCT component.
- Rare examples with focal areas of a more monotonous large cells may raise DDX of Embryonal Ca.
- IHC: PLAP (absent to scant); OCT3/4 -; C-kit +/-; AE1/AE3-; CD30 -
Germ Cell Tumors
Spermatocytic Seminoma

Histopathology

- Spermatocytic Seminoma with sarcomatous component:
  - very rare occurrence (12 cases)
  - undifferentiated sarcoma
  - metastasis in 50% of cases
  - DDX: malignant transformation in other GCT
Germ Cell Tumors
Spermatocytic Seminoma

Looijenga LH et al. Cancer Res. 2006:

- Genomic analysis: karyotyping; SKI; array CGH and gene expression profiling.
- Spermatocytic Seminoma expressed markers specific to *prophase meiosis I* while Classic Sem. expressed stem cell markers such as OCT3/4 and CD133
- Support a “primary spermatocyte” origin for spermatocytic seminoma
- Chromosome 9 gains was the only consistently present karyotypic abnormality in S.Sem
- *DMRT1*: a male-specific transcriptional regulator on chromosome 9 likely candidate gene involved in S. Sem pathogenesis
Embryonal Carcinoma

- **Histology:** solid sheets, tubular-papillary architecture, primitive cells with indistinct cell borders, marked nuclear atypia.
- **IHC:** AE1/AE3 (+), CD30 (+), C-kit (+/-), OCT3/4 (+), PLAP (+), AFP (+/-).
- **Differentiating papillary areas of Emb. Ca. from YST:** Cytologic features less primitive in YST.
- **In extratesticular location (e.g. mediastinum)** DDX with metastatic adenocarcinoma. IHC: EMA (-), OCT3/4 (+), CD30 (+) is helpful.
- **PGX:** lymphovascular invasion. Percentage of embryonal in mixed GCT predictive of stage II (opposite of YST and Teratoma %)
Emb Ca

YST
Choriocarcinoma

- Present in 8% of mixed GCT
- Very rare in pure form (1% of GCT)
- **Histology:** Plexiform admixture of syncitiotrophoblasts, cytotrophoblasts and intermediate trophoblasts.
- **DDX:** “syncitiotrophobalst only” elements associated with seminoma or mixed GCT IS NOT CONSIDERED a choriocarcinoma component.
- **IMHX:** hCG (+), CK (+), EMA (+/-), PLAP (+/-). Intermediate cells HPL (+)

- **PGX:**
  - presence of a minor element of choriocarcinoma in mixed GCT DOES NOT AFFECT prognosis.
  - pure choriocarcinoma usually presents with advanced stage & high hCG levels → worse prognosis.
“Burnt-out” GCT

• Spontaneous regression.
• Most frequently occurs in choriocarcinoma but also in seminoma (responsible for most of cases) and embryonal ca.
• Can led to GCTx presenting as extratesticular metastasis with no clinically evident testicular primary
• **Histology:** Scar with inflammation, “ghost hyalinized tubules”, intratubular calcifications, hematoxyline bodies, may have residual partially viable tumor, IGCNU.
THANK YOU !!!!