Testicular Microlithiasis (TM): A Review
“What to do with a Sack of Gravel?”

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Why Microlithiasis?

Outline for TM
- History
- Classification
- Epidemiology
- Histopathology
- Association with Testis Ca
  - ITGCN
  - GCC
  - Literature
- Other Associations
- Bottom Line

What Campbell’s 8th Edition Says:

Volume III, Page 2499
“Testicular microlithiasis (TM) has been reported in association with testicular tumors. It has been noted rarely in children. Recommendations have been made for noninvasive ultrasound follow-up until adult age”.

(Snell: Campbell’s urology, 8th ed., Copyright © 2002)

“Snow Storm” Testis

- Bilateral TM
- Edmonton in July
Thought to result from degenerating cells in the seminiferous tubules. Associated with cryptorchidism, infertility, Klinefelter syndrome, testicular infarction, alveolar microlithiasis, and numerous other conditions. 

Exact premalignant potential of this condition is unknown. Subject of much speculation.
Epidemiology: New Prospective Data

- Peterson 2001, Tacoma n=1504
  - (15-35 yo asymptomatic healthy volunteers)
  - 5.6% TM
- Middleton 2002, St. Louis n=1079
  - (15-92 yo presenting for U/S)
  - 18.1% (3.7% Classic; 14.4% Limited)

Epidemiology of TM

- More Common in Kids (Hobarth 1992)
  - 1:2100 Adults
  - 1:618 Boys
- Most Common in Black Men (Peterson 2001)
  - Black (14.1%): Low incidence of Ca Testis
  - Hispanic (8.5%)
  - Asian (5.6%)
  - White (4.2%)
  - GCT highest in White People of Northern European Descent

Epidemiology

- Progression to GCT?
  - 5 Case Reports
  - 48 month median time (10 months – 11 years)
- GCT
  - Concurrent TM 40-45% (Hobarth 1992, Backus 1994, Bach 2001)
  - Usually Focal and Irregular

Under the Microscope: Histology

- Hematoxylin Bodies
- Laminated Microcalcifications
- Histopathology

- What is it?
  - Intratubular Deposits
  - Calcified cores of cellular debris and glycoprotein
    - Hydroxyapatite (Calcium Phosphate)
    - De Jong, 2004, Rotterdam, Raman Spectroscopy, n=6
  - Surrounded by concentric layers of stratified collagen
  - Surrounded by Glycogen if GCT

Histopathology

- Pathophysiology (Vegni-Talluri 1980)
  - Breakage of BM of Seminiferous Tubule
  - Precipitation of Glycoprotein
  - Failure of Sertoli Cells to Phagocytize degenerating cells
ITGCN with testicular microliths

Microcalcification (Ca) surrounded by cellular debris within the seminiferous tubules (arrows).

Intratesticular Calcifications

- Classification (Renshaw 1998, Boston)
  1. True Ossification
  2. Hematoxylin Bodies
     - Amorphous Dystrophic
     - Rare, Rapid Cell Turnover
     - GCT and “Burned Out Tumors”
  3. Laminated / Psammomatous Calcifications
     - Correspond to TM

Intratesticular Calcifications

Cannot Differentiate between Hematoxylin Bodies and Laminated Calcifications on U/S

Radiologic Correlation?
- Backus 1994
  45% Correlation (10 / 22)
- Derogee 2001
  60% Correlation (17 / 28)

TM and Testis Ca?

ITGCN (CIS) & TM
Association with ITGCN (CIS)

- Precursor for all GCT except Spermatocytic Seminoma
- 50% of ITGCN progresses to GCT within 5 years
- 0.3 – 0.8% Prevalence
- Atrophy - 46% CIS

Association with ITGCN (CIS)

- No Prospective Data
- Early Case Reports
  - Hx of Contralateral GCT with TM
- Incidence of Contralateral ITGCN (CIS) with Testis GCT 4.5 – 22%
- Incidence of Bilateral GCT 2-3%
  - Synchronous and Metachronous

Association with ITGCN (CIS)

- Holm 2003, Copenhagen
  - N = 68 with GCT for Sperm Cryopreservation
  - Routine Contralateral Bx
  - 5 / 68 (7.4%) TM on U/S
  - 7 / 68 (10.3%) ITGCN (CIS)
- De Gouveia Brazao 2004, Netherlands
  - N = 263 Infertile Men
  - 53 / 263 (20%) TM
  - 23 unilateral TM: No CIS or Tumor
  - 30 Bilateral TM: 6 (20%) ITGCN (CIS)
Association with GCT: Retrospectoscope

- Relative Risk: 2 - 20
  - ??? Overestimation
  - Missing Isolated Cases of TM
  - Testis Ca
  - Annual Incidence 3 / 100 000

Association with GCT: Retrospectoscope

- Pre-Ultrasound
  - Ikinger 1982, Mammography on Post Orchiectomy Specimens
    - 74% of GCT had TM
    - 8% of Benign had TM
  - Renshaw 1998, autopsy data
    - 40% of GCT had Laminated TM

Association with GCT: Retrospectoscope

- Ganem 1999, North Carolina
  - 22 / 1100 (2%) TM
    - 8 / 22 (36%) Ca Testis
  - Cast 2000, UK (Largest Cohort)
    - 33 / 4892 (0.68%) TM
    - 7 / 33 (21%) Ca Testis

Association with GCT: Retrospectoscope

- Bach 2001, MSKCC (Tertiary Center Bias)
  - 48 / 528 (9%) TM
    - 13 / 48 (27%) Ca Testis
  - Derogee 2001, Netherlands
    - 63 / 1535 (4.1%) TM
    - 29 / 63 (46%) Ca Testis

Association with GCT

- Simultaneous / Concurrent Diagnosis
  - ??? Chicken vs. Egg

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<th>Number of patients with tumor</th>
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Association with GCT: Retrospectoscope

- All Preselected Patients undergoing U/S for Symptoms or Physical Exam Abnormality

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Association with GCT:
Progression
- 5 case reports of TM resulting in Ca
- Average Age: 27
- Median Time: 48 months

Progression to GCT:
U/S Follow up
- Furness 1998, Chicago
  - Multi-institutional, Pediatrics (Mean Age 12.3 yrs)
  - N = 26 TM
  - 28 month mean F/U
    - No Development of Tumor
- Ganem 1999, North Carolina
  - N = 9 TM
  - 31 month mean F/U
    - No Development of Tumor

Progression to GCT:
U/S Follow up
- Skyrme 2000, Newport, UK
  - N = 34 / 2215 (1.4%) TM
  - 41 month mean F/U
    - No Development of Tumor
- Bennett 2001, St Louis
  - N = 72 TM (Largest F/U Series)
  - 45 month mean F/U
    - No Development of Tumor

Progression to GCT:
U/S Follow up
- Derogee 2001, Netherlands
  - N = 31 TM
  - 61.8 month median F/U
    - 1 Patient developed Mixed GCT (Seminoma and Teratoma) @ 35 months
    - Hx: Contralateral Embryonal 10 yrs
    - Previously and Bilateral UDT !!!!!!!

Progression to GCT:
U/S Follow up
- Leenen 2002, Germany
  - Pediatrics (age 6-18 yrs)
  - 16 / 850 (1.9%) TM
    - 4 / 16 had simultaneous Testis tumors
      - (Chorio, Metastatic Germ Cell, Sertoli Cell x 2)
    - 5 / 16 w/o Tumor
      - Followed for 6 years
      - No Tumor Development

Association with GCT:
Scenarios
- 3 Groups
  1. TM and Ipsilateral Tumor
  2. TM and Contralateral Tumor
  3. TM with No Tumor (Isolated TM) *****
**Prospective Data**

- **Association with GCT: Prospective Data**
  - Peterson 2001, Madigan Army Center, Tacoma, Washington
  - N = 1504 (No Ca Risk Factors)
  - Volunteer Army Reserve Officers (18-35 yrs)
    - 5.6% had TM (84 / 1504)
    - 3 developed Ca Testis, None had TM

- **TM Race Distribution**
  - Testis Ca: Whites >> Blacks

- **TM Geographic Distribution**
  - Testis Ca - Lowest in Southeastern US

- **Association with GCT: Prospective Data**
  - Middleton 2002, St. Louis
    - Classified into Classic TM and Limited TM
    - N = 1079, Referred for U/S
    - Ages 15 – 92

- **Association with GCT: Prospective Data**
  - Triggers for U/S (Screening Bias)
    - Orchalgia 48%
    - Palpable Mass 25%
    - Scrotal Enlargement 20%
    - Infertility 5%
    - Tumor History 3%
    - 15 / 1079 (1.4%) Ca Testis
Association with GCT: Prospective Data

- 195 / 1079 (18.1%) had TM
  - 40 (3.7%) Classic TM
  - Tumor 3/40 (8%)
- 155 (14.4%) Limited TM
  - Tumor 9/155 (5.8%)
- No Difference between CTM and LTM (P=0.72)
- No TM = 884 / 1079
  - 3 (0.3%) had Tumor
  - Difference between TM and No TM (P=0.001)

Association with GCT: Symptomatic

- Ringdahl JU November 2004, Missouri
  - Symptomatic Men 17-45 yrs, n= 160
    - Symptoms - Pain / Swelling
    - TM = 12 (8%)
      - 4 / 12 (33%) GCT
    - No TM = 148
      - 2 / 148 (2%) GCT w/o TM
    - RR = 36.5

Association with GCT: Risk Factors for GCT

- Contralateral Testis Tumor (1-5% Risk)
  - Bach 2003, MSKCC
    - Prior Orchiectomy with U/S of Solitary Testis
    - N = 156
      - 23 / 156 (15%) TM
      - 8 / 156 (5%) recurrence of Ca
        - (+) TM: 5 / 23 (22%) Ca Testis
        - (-) TM: 3 / 133 (2%) Ca Testis
  - Independent Predictor?
Screening for Ca Testis

- TSE (Pocket Pool) vs. U/S
  - Teach TSE and do regularly
  - U/S: earlier detection?
  - Testis Biopsy? Tumor Markers?

Impact on Survival?
- High Cure rate of Ca Testis regardless of Stage

Inform Patients about Association
- Stratify Risk Factors

**Recommendations / Suggestions**

Suggested follow-up for patients with TM
- No Risk Factor(s) for Testicular Cancer
  1. Self Testicular Exam
  2. Annual Physical Exam by PCP
  3. Follow-up as needed with Urologist (per symptoms, PE and season for initial ultrasound)
- Risk Factor(s) for Testicular Cancer
  1. Self Testicular Exam
  2. Annual Physical Exam by Urologist/PCP
  3. Annual Ultrasound

**Other Associations and TM**

- Infertility
  - Kessans 1994: 1.3%
  - Azzopardi 1996: 2.8%
  - Pierik 1999: 0.9%
  - Ganem 1999: 23%
  - Thomas 2000: 6.2%
  - Von Eckardstein 2001: 2.3%
  - De Gouveia Brazoa 2004: 20%

- Cryptorchidism
  - Renshaw 1998: 50%
  - Dell’Acqua 1999: 33%
  - Khan 2000
  - Leenen 2002: 50%

- Torsion
  - Ganem 1999: 14%
Other Associations
- Klinefelter’s (47 XXY)
  - Aizenstein 1997
  - High Risk of Extragonadal (Mediastinal) GCTs (8%)
- Down’s (Trisomy 21)
  - Guzman Martinez-Valls, 2003
  - ? Risk of Testis GCT (Satge 1997, Cancer)
- Intersex
  - Frush 1996

Bottom Line: Argument Against Association
- 90% of TM
  - No tumor at presentation
  - No Interval Development
  - Those that did Develop Ca
    - Underlying Risk Factors Present
- Tacoma Study
  - Opposite Race Distribution and Geographic Distribution

Bottom Line
- All Screening and F/U Regimes Vary Widely
  - No Consensus
- ? F/U for UDT / Infertility / Contralateral Tumor / CIS
- Assess Risk Factors then Make Decision

Bottom Line
- If Asymptomatic and No Risk Factors
  - Teach TSE and Follow PRN
- If Risk factors for Ca Testis present with TM
  - Teach TSE w/ Yearly Hx and Px with U/S PRN
- Still NO Good Evidence to Follow Everybody

July’s New PGY-1