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

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UBC Urology Grand Rounds
February 16, 2005

Why Microlithiasis?

Outline for TM

- History
- Classification
- Epidemiology
- Histopathology
- Association with Testis Ca
  - ITGCN
  - GCT
    - Literature
- Other Associations
- Bottom Line

What Campbell's 8th Edition Says:

Volume III, Page 2499

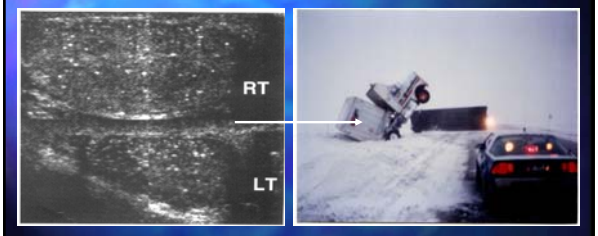
"Testicular microlithiasis (TM) has been reported in association with testicular tumors.

It has been noted rarely in children.

Recommendations have been made for noninvasive ultrasound follow-up until adult age".

(Walsh: Campbell's urology, 8th ed., Copyright © 2002)

"Snow Storm" Testis



• Bilateral TM

• Edmonton in July

Grainger & Allison's Diagnostic Radiology: A Textbook of Medical Imaging, 4th ed., Copyright © 2001

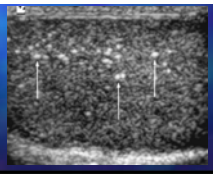
- Thought to result from **degenerating cells in the seminiferous tubules**
- Association with **cryptorchidism, infertility, Klinefelter's syndrome, testicular infarction**, **alveolar microlithiasis**, and numerous other conditions
- Exact **premalignant potential** of this condition is **unknown**
- Subject of much **speculation**
- **Regardless** of their presenting **symptoms** are **followed** up by annual US studies until the age of **50** years

History

- 1st Described by Priebe & Garrett 1970
  - Pelvic X-ray of 4 yo for Pharyngitis
- Nistal 1979
  - Autopsy Series: 1 / 2100 (0.05%)
  - Testis Biopsy: 1 / 1260 (0.08%)
- U/S appearance 1st described by Doherty 1987
  - 23 yo UDT

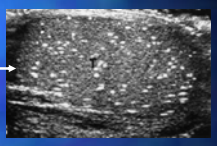
U/S Definition

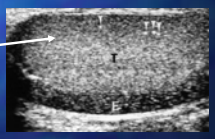
Ultrasound diagnosis of TM
Greater than 5 calcifications per image field
Calcifications less than 2 mm in diameter
Diffuse in nature
No acoustic shadowing
No loss of testicular shape or volume



Classification

- Backus 1994
- Classic TM
  - 5 or more Echogenic Foci on at least 1 U/S Image
- Limited TM
  - < 5 Echogenic Foci





DDx

- Orchitis
- Scar
- Fibrosis
- Granuloma
- Sarcoidosis
- Infarction
- S/P Chemo and EBRTx

Epidemiology

- 0.6 – 9% of Testicular Ultrasounds
  - Higher in Infertility (1.5 – 2.8%), UDT (6.7%) and Klinefelter's (XXY)
  - Majority Bilateral
  - True Prevalence ????
  - Early Studies had Lower Incidences
  - Higher Frequency U/S transducers (7-10 MHz)
  - Increased Reporting due to Recognition

Epidemiology: New Prospective Data

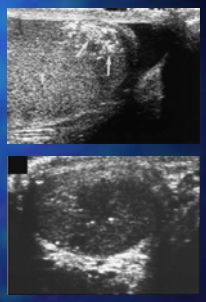
- Peterson 2001, Tacoma n=1504 (15-35 yo asymptomatic healthy volunteers)
  - 5.6% TM
- Middleton 2002, St. Louis n=1079 (15-92 yo presenting for U/S)
  - 18.1% (3.7% Classic; 14.4% Limited)

Epidemiology of TM

- More Common in Kids (Hobarth 1992)
  - 1:2100 Adults
  - 1:618 Boys
  - 1:15 Boys with UDT
- 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



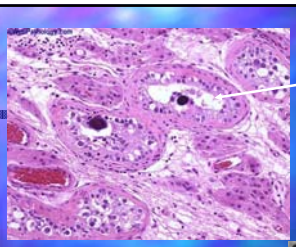
Under the Microscope: Histology

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

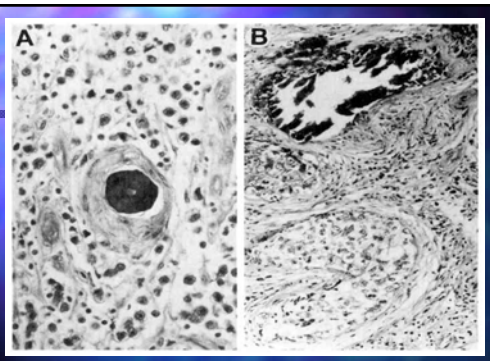


ITGCN with testicular microliths

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

Intratesticular Calcifications

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



A: ***Laminated calcification*** surrounded by seminoma
B: ***Hematoxylin body***, consisting of amorphous calcific debris within seminiferous tubule

Intratesticular Calcifications

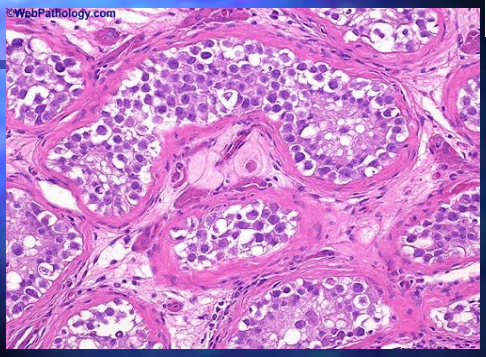
- **Cannot** Differentiate between Hematoxylin Bodies and Laminated Calcifications on U/S
- Radiologic Correlation?
  - Backus 1994
    - 45% Correlation (10 / 22)
  - Derogee 2001
    - 60% Correlation (17 / 28)

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)

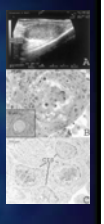
- No Prospective Data
- Early Case Reports
  - Parra 1996; Kaveggia 1996; Wegner 1998
  - Hx of Contralateral GCT with TM
- Incidence of Contralateral ITGCN (CIS) with Testis GCT 4.5 – 22%
- Incidence of Bilateral GCT 2-3%
  - Synchronous and Metachronous

Association with ITGCN (CIS)

- Bach 2001, MSKCC
  - N = 48 TM of 528 U/S
    - 8 / 48 (17%) ITGCN (CIS)
    - 29 / 480 (6%) ITGCN w/o TM

Association with ITGCN (CIS)

- Holm 2003, Copenhagen
  - N = 64 with GCT for Sperm Cryopreservation
    - Routine Contralateral Bx
    - 9 / 64 (14%) TM on U/S
      - 7 / 9 (78%) 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)



Germ Cell Tumors & TM

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
  - 8% in 480 had Ca Testis w/o TM
- Derogee 2001, Netherlands
  - 63 / 1535 (4.1%) TM
    - 29 / 63 (46%) Ca Testis

Association with GCT

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

Association between TM and testis cancer

Studies	TM prevalence	Number of pts with TM	Percentage of TM pts with cancer	Number of testis cancer pts	Percentage of testis cancer pts with TM	Comments
Bach [17]	9%	48	27%	43	12%	8% without TM had tumors
Middleton [15]	3.70%	40	8%	15	20%	2.9% with tumor history
Derogee [37]	4.60%	63	46%	60	48%	0.02% without TM had tumor
Cast [11]	0.68%	33	21%	54	12.50%	Used computerized word search
Peterson [16]	5.60%	84	4%	—	—	Asymptomatic Population
Ganem [9]	2%	22	36%	—	—	23% of patients were infertile
Ikinger [12]	—	32	80%	43	74%	28% of TM were solitary
Bennett [33]	—	39	18%	—	—	No tumors on follow up (mean 45 months)
Backus [27]	—	42	40%	—	—	14% with history of tumor

Association with GCT: Retrospectoscope

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

Association with GCT: Progression

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

Development of ipsilateral testicular cancer with TM history

Case report	Year	Age	Duration of known TM	Testis cancer type	Tumor risk factors
Salfer et al. [5]	1990	32	Right TM for 14 months	Embryonal cell carcinoma	Cryptorchidism
McNeil et al. [28]	1995	17	Bilateral TM for 6 years	Left testis sex tumor	None
Winter et al. [30]	1996	21	Left TM for 3 years	Metastatic left mixed GCT	None
Frush et al. [29]	1996	25	Left TM for 16 months	Metastatic left mixed GCT	None
Golash et al. [31]	2000	47	Bilateral TM for 6 months	Right seminoma CIS	Left atrophic testicle

- 2 of 5 known Risk Factors for Ca

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

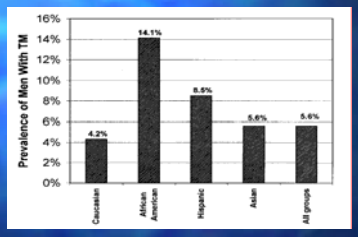
- 3 Groups
  1. TM and Ipsilateral Tumor
  2. TM and Contralateral Tumor
  3. TM with No Tumor (Isolated TM) ******

Prospective Data

Association with GCT: Prospective Data

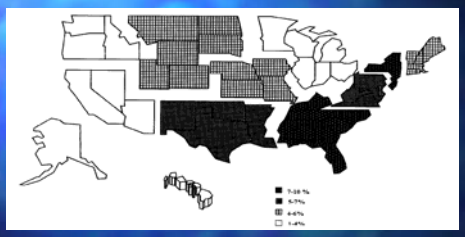
- Peterson 2001, Madigan Army Center, Tacoma, Washington
  - N = 1504 (No Ca Risk Factors)
  - Volunteer Army Reserve Officers (18-35 yrs)
    - 5.6% had TM (84 / 1504)
    - 3 developed Ca Testis, None had TM

TM Race Distribution



- Testis Ca: Whites >> Blacks

TM Geographic Distribution



- Testis Ca – Lowest in Southeastern US

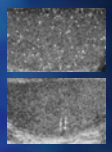
Association with GCT: Prospective Data

- 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)

Symptomatic with TM

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

Contralateral Tumor with TM

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?

Should We Screen for Ca Testis ?

Screening for Ca Testis

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

Screening for Ca Testis

- Impact on Survival?
  - High Cure rate of Ca Testis regardless of Stage
- Inform Pateints about Association
- Stratify Risk Factors

Risk factors for testicular tumors

Cryptorchidism
Atrophy
Infertility
Intratubular germ cell neoplasia (IGN)
Gonadal dysgenesis
Contralateral testicular tumor
Exogenous estrogen administration

Recommendations / Suggestions

Suggested follow-up for patients with TM

A. 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 reason for initial ultrasound)

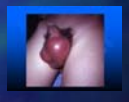
B. Risk Factor(s) for Testicular Cancer
1. Self Testicular Exam
2. Annual Physical Exam by Urologist/PCP
3. Annual Ultrasound

Other Associations and TM

Other Associations

- Infertility
  - Kessaris 1994: 1.3%
  - Aizenstein 1998: 2.8%
  - **Pierik 1999: 0.9%**
  - **Ganem 1999: 23%**
  - Thomas 2000: 6.2%
  - Von Eckardstein 2001: 2.3%
  - De Gouveia Brazoa 2004: 20%

Other Associations



- 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 Concensus
- ? 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