Intratubular Germ Cell Neoplasia of the Testis

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Clinical scenario

A 33 years old man has bilateral testicular biopsies to investigate infertility. The testicular biopsies reveal intratubular germ cell neoplasia (ITGCN) with some areas of spermatogenesis.

Discuss the pathological features and the clinical presentations of ITGCN. What advice would you offer this patient?
Introduction

• ITGCN – intratubular germ cell neoplasia of testis is synonymous with:
  – Carcinoma in situ (CIS) – phasing out
  – Testicular intraepithelial neoplasia (TIN)\(^1\)
  – Intratubular germ cell neoplasia, unclassified (IGCNU)\(^2\)

• A precursor germ cell tumour of testis except:
  – Spermatocytic seminoma
  – Yolk sac tumour
  – Mature teratoma

• AJCC classification: pTis N0 M0 S0

Risk MC, Masterson TA. Ind J Urol 2010

2. NCCN Guidelines Testicular Cancer 2014
Epidemiology of ITGCN

• ITGCN commonly associated with testicular germ cell tumour (GCT)
  – 5-8% GCT has ITGCN in contra-lateral testis
  – Up to 98% of seminoma and non-seminoma specimens have ITGCN
  – 82% primary GCT has surrounding ITGCN

Risk MC, Masterson TA. Ind J Urol 2010

• 1% of infertile men have ITGCN

Dieckmann KP, Skakkebaek NE. Int J Cancer 1999

• Incidence bilateral ITGCN: 1 – 5% general population


• Risk of invasive cancer: after diagnosis of ITGCN, at 3 years (40%), at 5 years (50%) and at 7 years (70%)

• Risk factors: similar to GCT
  – Cryptorchidism - incidence of ITGCN: 2-4%
  – Infertility – incidence of ITGCN: 2.2%
  – contralateral GCT – incidence of ITGCN: 5%
  – Ambiguous genitalia – 25%

Bazzi WM et al. Urol Ann 2011
ITGCN to Invasive Tumour

Fig. 13-12  Follow-up of patients with intratubular germ cell neoplasia of the unclassified type on biopsy. Approximately 90% have invasive tumor after 7 years. (Data from Skakkebaek NE, Berthelsen JG, Visfeldt J. Clinical aspects of testicular carcinoma-in-situ. Int J Androl 1981;4[Suppl]:153-162.)
A new model for testicular neoplasm?

Pathological Features (1)

• Why has ITGCN replaced carcinoma *in situ*?
  
  – Advances in immunohistochemistry
  – No epithelial structures recognised in ITGCN
  – ITGCN cells not positive for epithelial markers
  – Cells are in seminiferous tubules, located at basement membrane (intact)

Bazzi WM et al. Urol Ann 2011
Pathological Features (2)

Gross
• Testis: unremarkable, atrophic or fibrotic

Microscopic
• Large, intratubular, gonocyte-like cells
• Large nuclei and prominent nucleoli
• Abundant cytoplasmic glycogen (98%)
• ‘fried egg’ appearance
• Spermatogenesis reduced or absent at affected seminiferous tubules
• Sertoli cells may be displaced luminally
• Patchy cellular distribution

Dieckmann KP, Skakkebaek NE. Int J Cancer 1999

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Pathological Features (3)

• Stains with OCT-4 on testicular biopsy
  – Identifies 20% more ITGCN than H&E stain
• Other stains: Placental Alkaline Phosphatase (cytoplasmic membrane), CD 117, NANOG
• Bouin’s or Stieve’s fixative, not formalin
• Other immunohistochemical stains:
  • M2A, 49-3F, NANO, AP-2γ, c-kit


• Progression of ITGCN to GCT. Events:
  – loss of PTEN
  – p18 gene expression
  – induction of cyclin E

Risk MC, Masterson TA. Ind J Urol 2010
Testicular Biopsy Stains (L to R): Placental Alkaline Phosphatase, OCT-4, CD 117
Clinical Presentation

• Asymptomatic
• Incidental
  – During investigation for infertility - histopathologic
    • Bilateral testicular biopsies
  – Work-up for unilateral testicular cancer
    • Controversial to biopsy contra-lateral testis
      – **For**: High risk patients – atrophic testis (<12 ml), cryptorchidism, poor spermatogenesis (Johnson score 1 – 3), < 30 years old.

      – **Against**: Low incidence of ITGCN and metachronous GCT in contra-lateral testis, morbidity of biopsy, low stage metachronous GCT

  Albers P, et al. EAU 2014
Management Issues

Risk Reduction Measures. Options:
- Radiotherapy
- ‘Prophylactic’ Bilateral Orchidectomy
- Partial Orchidectomy
- Chemotherapy
- Watchful waiting

Issues
- Residual fertility
- Androgen insufficiency
- Psychological impact
Risk Reduction Measure (1)

• Radiotherapy (RTx)
  – No studies on bilateral testicular ITGCN
  – Studies on ipsilateral GCT and contralateral ITGCN or solitary testis ITGCN scenario are extrapolated:
    • After orchidectomy, RTx to contralateral testis...
      – eradicates ITGCN cells, prevents invasive cancer developing
      – non-dividing and Leydig cells survive (to a certain extent)
      – causes higher risk of infertility (Sertoli cells not radio-resistant)
      – close follow-up needed up to 5 years (repeat biopsies/US)
  • Dose: 16 to 20 Grays in divided doses (2 Gray fractions)
  • Durability: resolution of ITGCN up to 2 years
  • Before RTx, patient should be counseled on issues of infertility, Leydig cell dysfunction (androgen insufficiency), impaired testosterone production long-term

Risk MC, Masterson TA. Ind J Urol 2010
Albers P, et al. EAU 2014
Risk Reduction Measure (2)

• **Chemotherapy**
  – Germ cells are chemo-sensitive
  – Platinum-based chemotherapy agents effect on ITGCN is unpredictable:
    • German study: cysplatin+etoposide+bleomycin to 11 pts with ITGCN, 7 had cancers at 8.8mths follow-up
      - Kleinschmidt K et al. Oncology 2009
    • Dutch study: reduced incidence of contra-lateral testicular cancer from platinum based chemotherapy
    • Frequent recurrences post-chemotherapy – 21% at 5 years and 42% at 10 years
      - Ulbright TM, Roth LM. Diagnostic Surgical Pathology. Raven Press, NY, 1994
Risk Reduction Measure (3)

- **Orchidectomy**
  - Most-definitive method of risk reduction of cancer
  - Concomitancy of GCT with ITGCN: 80-90%
  - Partial orchidectomy
    - Concept popularised by Weissbach for testicular GCT
    - Conditions for partial orchidectomy: organ-confined tumours <2cm, away from testicular vasculature, involving <30% testicular volume, with negative margin and histologically undetected ITGCN during intraoperative biopsy
    - Hence, partial orchidectomy is not practical for bilateral ITGCN

Bazzi WM et al. Urol Ann 2011; 3:115-8
Orchidectomy and Fertility

• **Is fertility/paternity of concern?**
  – No: total bilateral orchidectomy. Issues:
    • Absolute infertility
    • Androgen insufficiency - testosterone replacement
  – Yes: is there viable spermatozoa?
    ➢ Yes: conceive first (delay-to-therapy)
    ➢ Probable: sperm cryopreservation, assisted reproduction
    ➢ No: adoption
  – Delay-to-therapy issues:
    • Cumulative risk of invasive cancer
    • Regular follow-up and self-examination

• **Post orchidectomy**
  – Testicular prosthesis
Risk Reduction Measure (4)

• Watchful waiting

  – No guidelines
  – Minimal indications – eg. paternity
  – Cumulative risk of invasive cancer developing with time
  – Compliant with regular follow-up, self testicular-examination, repeated ultrasound and/or biopsy

Risk MC, Masterson TA. Ind J Urol 2010
Clinical scenario

A 33 years old man has bilateral testicular biopsies to investigate infertility. The testicular biopsies reveal intratubular germ cell neoplasia (ITGCN) with some areas of spermatogenesis.

Discuss the pathological features and the clinical presentations of ITGCN. What advice would you offer this patient?
Clinical Advice (1)

Diagnosis

- Bilateral ITGCN is rare
- Entity is strongly associated with GCT (80%)
- ITGCN progresses to GCT with time
- ITGCN and GCT share the same risk factors i.e. infertility

- Options of risk reduction measures to be given to patient
Clinical Advice (2)

Risk Reduction Measure

Watchful waiting (WW) in view of testicular biopsy revealing areas of spermatogenesis

- Patient already infertile thus needs assisted reproductive techniques
- Histological spermatogenesis assessment: Johnson Score at least 8 required for fertility treatment to work
- Sperm retrieval (TESE/PESA/MESA or TESA)
- Cryopreservation of viable spermatozoa
- Assisted conception: IUI, IVF and ICSI (less sperm needed)

WW may buy time (young patient) to confront issues of hypogonadism and psychological impact of orchidectomy

But WW carries cumulative risk of invasive cancer developing with time
Clinical Advice (3)

Risk Reduction Measure

– Radiation therapy (to preserve testes)
  • Limited data on bilateral ITGCN
  • Durability proven for short-term
  • Active surveillance for at least 5 years
    – Repeated biopsies and ultrasound
    – Biopsy complications 3–20%
    – Psychological impact
    – May avoid orchidectomy and hypogonadism
    – but testosterone production reduces in the long term
Risk Reduction Measures

- Chemotherapy (to preserve testes)
  - Durability is unpredictable
  - Side-effects
  - Not recommended

- Orchidectomy
  - Partial bilateral: not recommended as data exist only for unilateral testicular cancer with absence of ITGCN
  - Total bilateral: most effective in eradicating cancer risk
    - Testosterone replacement
    - Cosmetically acceptable testicular prosthesis
Conclusions

• ITGCN is rare but strongly and progressively associated with GCT

• In the absence of concomitant invasive cancer, fertility/paternity is a crucial factor in the selection of risk reduction measures

• Radiotherapy to testes is the most durable testes-preserving measure if followed by surveillance

• Total bilateral orchidectomy is most effective in eliminating testicular cancer risk
Conclusions

• Watchful waiting does not delay the development of invasive cancer but allows time for completion of family, and delays the effect of androgen insufficiency

• There is limited data to recommend chemotherapy upfront for ITGCN in the absence of invasive cancer

• Risk reduction measures should be individualised to enable a patient to make informed decisions