Intratubular germ cell neoplasm

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Scenario

• 33 years old man has bilateral testicular biopsy to investigate infertility. Testicular biopsy revealed intratubular germ cell neoplasm (ITGCN) with some area of spermatogenesis.

• Discuss the pathological features and the clinical implications of ITGCN.

• What advice would you offer this patient?
Intratubular germ cell tumor, (ITGCN)

– aka= TIN (testicular intra- epith neoplasia)/ CA in situ
– Is the PRECURSOR of all invasive germ cells tumor
– EXCEPT spermatocytic seminoma and infantile/prepubertal germcell tumor
– So what ?
  • 50% probability of progression to GCT over 5 yrs
  • 70% cumulative probability of developing Ca in 7 yrs
FIG. 47-2. Diagram of testicular germ cell tumor histogenesis. Note the derivation of the pediatric tumors, spermatocytic seminoma, and dermoid and epidermoid cyst independent of IGCCU. Also note the key role of seminoma in giving rise to other types of tumor. Abbreviations: Ca, carcinoma; IGCCU, intratubular germ cell neoplasia, unclassified; SS, spermatocytic seminoma; SynT, syncytiotrophoblast cells.
• ITGCN is morphologically and immunohistochemically similar to seminoma cells
  – This has led to the hypothesis that seminoma is the direct derivative of ITGCN and a common pathway in the development of all other GCTs
Pathological features ITGCNU

- Testes: USUALLY normal size but can be small
- Histology:
  1. Characterized by malignant germ cells lining seminiferous tubules containing Sertoli cells in a single row with nuclear pleomorphism with intact basement membrane.
  2. characterized by large primitive atypical cells that are usually twice the size of normal germ cells, having clear cytoplasm and irregular prominent nucleoli
  3. lie along the thickened basement membrane of atrophic seminiferous tubules or may replace the entire tubules
  4. Tubules are of smaller diameter than normal, with thickened walls, and show reduced or absent spermatogenesis.
  5. normal germ cells are not stained with periodic acid–Schiff (PAS), this stain may help to distinguish IGCN cells from normal cells
Intratubular germ cell neoplasia, showing large atypical germ cells lying along the basement membrane of atrophic seminiferous tubules.
Immunoprofile

- Most ITGCN cells stain for **placental-like alkaline phosphatase (PLAP)**
  - an enzyme that in addition to ITGCN is present in embryonal carcinoma, seminoma, and several other GCTs but is usually absent in normal germ cells
- Also positive for c-Kit (CD117) and p53
- OCT3/4, also known as POU5F1, is a recently recognized marker for GCTs
  - indicator for the presence of IGCNU, seminoma, and/or embryonal carcinoma
  - Doesn’t raise any specific tumour markers!
Prevalence and associations

(European consensus on diagnosis and treatment of germ cell cancer: a report of the European Germ Cell Cancer Consensus Group (EGCCCG)

- In gen pop, the overall incidence = 0.8% (1%)
- Contralateral involvement = 5-10%
- If small testicular volume (<12ml) and pt is <40 yrs old, contralateral involvement = 34%
- Risk factors for dev of ITGCN:
  - UDT (3%)
  - Extragonadal GCT (40)
  - 45XO karyotype
  - Subfertility (0.4-1.1%)

Role of contralateral biopsy

- Biopsy of the contralateral testis should be offered to high-risk patients for contralateral TIN if:
  - Testicular volume of less than 12 mL,
  - History of cryptorchidism,
  - Poor spermatogenesis (Johnsen Score 1-3).

- Yield of contralateral biopsy is 9% for TIN & 2.5% of testicular tumor (EAU 2012)

- Biopsies to identify TIN must be preserved in Stieve's or Bouin's solution (not in formalin!)

- A contralateral biopsy is not necessary for patients older than 40 years.
- A double biopsy is preferred to increase sensitivity
- Negative biopsy does not exclude tumor in future
Biopsy in pts post chemo

(European consensus on diagnosis and treatment of germ cell cancer: a report of the European Germ Cell Cancer Consensus Group (EGCCCG))

• Since all patients with extragonadal germ cell cancer will receive platin-based chemotherapy which will eliminate a substantial percentage of TIN, a routinely performed bilateral testicular biopsy is not recommended.

• Nevertheless, if a biopsy is planned in patients with a higher risk for TIN following an extragonadal germ cell tumour, this should be preferably performed prior to chemotherapy.

• If performed thereafter, testicular biopsy may be considered not earlier than 6 months after the completion of chemotherapy.
Management & Counselling

• Spontaneous regression of IGCNU generally DOES NOT occur.
• Controversy in regard to the management

• Options: surveillance, radiotherapy or orchidectomy => rendering pts anorchic and reliant on testosterone replacement. Need to discuss with patient and partner(s).

• If ITGCN diagnosed and the contralateral testis is healthy; option of mx: orchidectomy or surveillance (with a risk of 50% in 5 yrs to dev CA)

• For men who haven’t completed family – advice to complete family via natural method or assisted contraception.
• Close surveillance programme -> regular self P/E and annual u/s testis
• Dxt => total of 20 gy delivered at a single 2 Gy doses over 5 days per week.
  • Adequate to eliminate all foci of ITGCN, but high chances of losing Leydig cell fx
  • Hence, require regular f/up for serum testos level
  • some authorities treatment of choice in bilateral ITGCN
  • leads to permanent infertility, BUT has the benefit of preserving hormonal function of the testis
  • Frozen sperm storage must be offered.
• Study showed 16Gy not sufficient to eradicate all foci of ITGCN
  – Classen J et al ‘ Radiotherapy with 16Gy may fail to eradicate testicular intraepith neoplasm : German testicular Cancer Study Gp. Br J Cancer 2003; 88:828-31
• **Orchidectomy** –
  – (bilateral) – long term testos replacement and loss of fertility
  – provides the highest success rate and perhaps is the therapy of choice in unilateral IGCNU

• **Role of Chemotherapy??**
  – yes ...not routinely used unless otherwise indicated
**European consensus on diagnosis and treatment of germ cell cancer: a report of the European Germ Cell Cancer Consensus Group (EGCCCG): Treatment of testicular intraepithelial neoplasia (TIN)**

**TIN in contralateral testis or in case of organ preserving surgery**
- If fertility should be maintained ⇒ delay definitive treatment by surveillance until resolution of fertility issue, followed by active treatment or further surveillance.
- If fertility not relevant ⇒ irradiation 20 Gy (2 Gy, 5×/week)

- **TIN in patients without gonadal tumour (incidental diagnosis, e.g. by biopsy for infertility or extragonadal germ cell tumour)**
  - Orchietectomy to be preferred over irradiation (potential damage of contralateral not affected testis by scattered radiation)

- **TIN in patients receiving chemotherapy (either as adjuvant treatment or for advanced or extragonadal disease)**
  - Since chemotherapy eradicates TIN in two-thirds of patients with TIN prior to chemotherapy, definitive treatment for TIN only if TIN is diagnosed at (re)biopsy after chemotherapy (re-biopsy not mandatory).