

## Non-germ cell tumours of the testis

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## Testis: non-germ cell tumours

- Sex cord-stromal tumours
- Haemolymphoid neoplasms
- Other neoplasms
- Tumour-like conditions
- Metastases



## Testis: sex cord-stromal tumours

- Leydig cell tumour
- Sertoli cell tumour, NOS
- Sclerosing Sertoli cell tumour
- Large cell calcifying Sertoli cell tumour
- Granulosa cell tumour, adult-type
- Juvenile granulosa cell tumour
- Fibroma
- Brenner tumour
- Sertoli-Leydig cell tumours (exceptionally rare in testis)
- Sex cord-stromal tumour, unclassified
- Mixed germ cell-sex cord stromal tumour
  - gonadoblastoma
  - unclassified (some may be sex cord stromal tumours with entrapped germ cells – see Ulbright *et al.*, 2000)
  - collision tumour



## Leydig cell tumour



## Differential diagnosis of Leydig cell tumour

- Testicular tumour of adrenogenital syndrome (TTAGS) (especially in a child/young adult)
- Leydig cell hyperplasia (<5mm)
- Large cell calcifying Sertoli cell tumour
- Sertoli cell tumour
- Seminoma (rare cases with cytoplasmic clearing)
- Mixed sex cord stromal tumours
- Sex cord stromal tumour unclassified
- Metastasis e.g. melanoma



## TTAGS

- Multifocal/bilateral lesions
- Seen in patients with congenital adrenal hyperplasia
- 21 hydroxylase deficiency most common
- Elevated serum ACTH
- Benign lesion treated with steroids; partial orchidectomy reserved for steroid unresponsive cases
- Fibrous bands; lipofuscin pigment ++; nuclear pleomorphism but no mitosis



### Histopathological and immunophenotypic features of testicular tumour of adrenogenital syndrome

Wang Z *et al. Histopathology* 2011;58:1013-18

- TTAGS did not contain Reinke's crystals, had thicker fibrous bands and were often bilateral
- All 6 TTAGS tested were diffusely and strongly positive for CD56 (Leydig cell tumours were negative or showed focal weak +ve)
- Androgen receptor was positive in Leydig cell tumour in 6/7 cases but negative in all TTAGS



### Immunohistochemistry of testicular Leydig cell tumour

#### McCluggage *et al*

- 20 cases
- Inhibin (15/16)
- CAM 5.2 (7/16)
- Vimentin (14/16)
- S100 protein (10/16)
- Desmin (2/16)

#### Amin, Young, Scully

- 12 cases
- Inhibin (12/12)
- CAM 5.2 (5/12)  
dot-like in 20%
- Vimentin (11/12)
- S100 protein (2/12)
- EMA (0/12)



### Kim I, Young RH, Scully RE (1985)

- 40 cases Leydig cell tumour
- Follow-up available for 30 cases
- 5 were malignant
- Size (all cases) 0.5 - 10cm, mean 3cm
- 2/40 arose in cryptorchid testis
- Mean age 46.5 years (range 2-90 yrs)



### Non-progressive vs. malignant Leydig cell tumours (1)

#### Non-progressive

- Mean age 41 years
- \*Smaller size (<5cm)  
mean 2.7cm
- \*Absence of infiltrative margin
- \*Absent lymphovascular invasion

#### Malignant

- Mean age 67
- \*Larger size (>5cm)  
mean 6.9cm
- \*Infiltrative margin
- \*Lymphovascular invasion present



### Non-progressive vs. malignant Leydig cell tumours (2)

#### Non-progressive

- \*Necrosis absent
- \*MF<3/10HPF
- Marked cytological atypia
- [All had low MIB-1 index (0-2%)]
- [Most were diploid by flow cytometry]
- [All p53 negative]

#### Malignant

- \*Necrosis present
- \*MF>3/10HPF
- Minimal cytological atypia
- [Most had high MIB-1 index 20-50%]
- [Aneuploid by flow cytometry]
- [p53 over expression]



### \*Histological criteria of Kim, Young and Scully associated with malignancy

- Size >5cm
- Infiltrative margins
- Lymphovascular invasion
- Mitoses >3/10HPF
- Necrosis

All 5 of their malignant cases satisfied 4 or more criteria  
In series of McCluggage *et al.* 2 malignant cases satisfied 5 criteria and 2 satisfied 3 criteria



### 32 Leydig cell tumours (Cheville and Sebo, 1998)

	<u>Non-Progressive</u>	<u>Malignant</u>
Infiltrative margin*	0%	67%
Necrosis*	4%	83%
MF>5/10HPF*	12%	100%
Cytological atypia >3-4*	19%	100%
Vasc Inv*	8%	50%
Size>5cm	12%	17%



### Metastatic Leydig cell tumour (based on 26 cases)

- Sites in descending order of frequency - regional lymph nodes, lung, liver, bone, kidney, other
- Metastases present at diagnosis in 22% malignant cases
- Metastases within 1 year of diagnosis 19%
- >1 year from diagnosis in 59% (up to 10 years from diagnosis)
- Median survival 2 years for patients with metastasis



### Variant appearances in testicular Leydig cell tumour

- Nested pattern
- Pseudoglandular pattern
- Trabecular pattern
- Cord-like pattern
- Spindle cell/sarcomatoid areas
- Small cells
- Microcystic areas resembling yolk sac tumour
- Stromal hyalinisation, myxoid change or oedema
- Stromal calcification/ossification [exceptional cases]
- Cytoplasmic clearing due to lipid (can mimic seminoma focally)
- Adipose metaplasia



### Typical profile of Leydig cell tumour

#### Positive

- Inhibin
- Melan A
- Steroidogenic factor-1 (SF-1)
- Calretinin
- CAM 5.2 (dot-like), or -ve
- Synaptophysin (-/+)

#### Negative

- OCT3/4
- Chromogranin
- PLAP
- S100
- EMA
- SALL-4



### Sarcomatoid Leydig cell tumour of testis

Richmond I et al. *Histopathology* 1995;27:578-80



### Leydig cell tumors of the testis with unusual features

Ulbright et al. *AM J Surg Pathol* 2002;26:1424-33

- 19 cases
- 12 had adipose differentiation (3 of these showed psammomatous calcification with ossification in 2)
- 8 had spindle cell growth (spindle cell morphology *per se* was not associated with a malignant course, only adverse if pleomorphic spindle cell areas present)
- Presence of typical Leydig cell areas distinguishes Leydig cell tumour with spindle/sarcomatoid areas from sex cord-stromal tumour, unclassified (which does not contain typical Leydig cell areas)



## Sertoli cell tumour, NOS



## Immunohistochemistry of Sertoli cell tumour, NOS

- Variable from case to case, some similarity to Leydig cell tumour but less often inhibin positive and more often cytokeratin positive
- May be negative for multiple markers for sex cord stromal tumour in some cases



## Features described/variant features in testicular Sertoli cell tumour, NOS

- Solid/hollow tubules/trabeculae/cords
- Diffuse/solid pattern (sheets of Sertoli cells – can be confused with seminoma) NB Rare seminomas have a tubular growth pattern which can mimic Sertoli cell tumour
- Cystic pattern (can mimic yolk sac tumour)
- Retiform areas
- Palisading, simulating Verocay bodies
- Grooved nuclei (occasional cases)
- Cytoplasmic vacuolation (due to lipid)
- Cytoplasmic eosinophilia
- Prominent stromal sclerosis/hyalinisation
- Stromal calcification in rare cases
- Ectatic blood vessels



## Sclerosing Sertoli cell tumour



## Large cell calcifying Sertoli cell tumour



## Clinical History

- 10 year old boy
- Presented with precocious puberty and breast enlargement
- 6 months later complained of testicular pain and found to have bilateral irregular enlarged testes
- Bilateral testicular biopsies performed



## Follow-up

- Treated with aromatase inhibitors and cyproterone acetate
- 2 years after presentation had bilateral breast reductions for gynaecomastia
- Remains well on endocrine follow-up
- However, found to have a mutation within the regulatory unit of protein kinase A – confirming Carney's complex



## Clinical and molecular genetics of Carney complex

Sandirini F and Stratakis C, *Mol Genet Metab* 2003;78:83-92; Rothenbuhler and Stratakis C *Best Pract Res Clin Endocrinol Metab* 2010;24:389-99

- Lentiginos, cardiac myxomas, endocrine abnormalities, schwannomas. Autosomal dominant inheritance.
- Significant clinical heterogeneity
- Mapped to 2p16 and 17q22-24
- Gene for protein kinase A type I- $\alpha$  regulatory subunit (*PPRKAR1A*) mapped to 17q
- Gene shows mutations in almost half of Carney's complex patients
- Carney's complex is the first human disease linked to mutations in one of the subunits of the PKA enzyme, a critical component of numerous cellular signalling systems



## Differential diagnosis of large cell calcifying Sertoli cell tumour

- Leydig cell tumour
- Sertoli cell tumour, NOS
- [Metastatic carcinoma]
- [Metastatic melanoma]



## Features favouring large cell calcifying Sertoli cell tumour in differential diagnosis with Leydig cell tumour

- Bilateral/multifocal distribution
- Associated syndromes
- Strong cytokeratin and/or S100 positivity
- Presence of neutrophils in many cases of large cell calcifying Sertoli cell tumour



## Large cell calcifying Sertoli cell tumour

- Carney's syndrome
- Peutz-Jegher's syndrome

[Tumours are often bilateral and usually benign in these conditions, though extremely rare malignancy has been recorded; malignancy is less rare (approx. 20% cases) in unilateral solitary tumours]

Patients with Peutz-Jegher's syndrome may instead have intratubular large cell hyalinising Sertoli cell neoplasia of the testis see Ulbright *et al. Am J Surg Pathol* 2007;31:827-35 [always benign]



## Granulosa cell tumour

- adult-type
- juvenile



### Architectural features which may be encountered in adult granulosa cell tumour

- Solid
- Microcystic
- Microfollicular
- Gyriform
- Insular
- Trabecular
- Spindle cell



- Fibroma
- Brenner tumour
- Sertoli-Leydig cell tumours (exceptionally rare in testis)
- Unclassified
- Mixed germ cell-sex cord stromal tumour
  - gonadoblastoma
  - unclassified (some may be sex cord stromal tumours with entrapped germ cells – see Ulbright *et al.*, 2000)
- collision tumour



### Sex cord-stromal tumour, unclassified



### Differential diagnosis

- Sertoli cell tumour
- Sclerosing Sertoli cell tumour
- Granulosa cell tumour
- Sarcoma (primary/metastatic)
- 'Testicular gonadal stromal tumour'/fibroma
- Metastatic carcinoma
- Metastatic melanoma
- Leydig cell tumour (sarcomatoid)



### Gonadoblastoma

- Young patients (<20 yrs)
- Occurs in patient with abnormal dysgenetic gonads
- XY gonadal dysgenesis or X0-XY mosaicism
- 80% phenotypically female; 20% phenotypically male
- Invasive germ cell tumour, usually seminoma may develop
- Bilateral gonadectomy recommended



### Sex cord-stromal tumour, unclassified

- Unclassified sex cord-stromal tumours of testis are rare
- There is often a prominent spindle cell component with partial or incomplete differentiation towards Sertoli cell and/or granulosa cell components
- Areas of classical Leydig cell tumour are not usually a feature
- Sertoli cell tumour, NOS and granulosa cell tumour are the major differential diagnoses
- Ongoing studies with better delineation of the spectrum of such tumours is required



### Sex cord-stromal tumours of testis: summary of typical immunophenotype

- The immunophenotype of sex cord-stromal tumours of testis is quite variable
- Leydig cell tumours and large cell calcifying Sertoli cell tumours are consistently positive for inhibin, Sertoli cell tumour and unclassified sex cord stromal tumour less consistently positive
- A variety of other markers, including steroidogenic factor-1 (SF-1), melan-A (MART-1), S100, calretinin, and sometimes alpha-SMA, can be expressed in sex cord-stromal tumours, though HMB45 is consistently negative.
- EMA is usually negative.
- Cytokeratins are frequently expressed in Sertoli cell tumour, NOS and in some unclassified sex cord-stromal tumours; they also expressed, though less frequently in some Leydig cell tumours.



### Prognosis (sex cord stromal tumours, testis)

- 10% Leydig cell and 10% Sertoli cell tumours have malignant behaviour according to literature, though this is historical data and tumours often present when much smaller today, so incidence of malignancy very likely to be lower now
- ? 20% of sex cord-stromal tumour unclassified have malignant behaviour in adults (contemporary cases likely to be <20%); malignant behaviour less common in children, and especially rare <10 years age



### Adverse histological prognostic features for sex-cord stromal tumours of testis

- Large size (>50mm)
- Infiltrative margins
- Lymphovascular invasion
- Tumour necrosis
- Mitotic index >3/10HPF (Leydig cell tumours) >5/10HPF (Sertoli cell tumours)

[behaviour can be difficult to predict and no feature is absolute.  
Cheville *et al.*, 1998 found neither MIB-1 index nor ploidy added to prognostication ]



### Tumour-like conditions

- Sertoli cell nodules ('Pick's adenoma')
- Testicular 'tumour' of adrenogenital syndrome (TTAGS) [bilateral/multifocal involvement; history; look for large cells with abundant lipochrome pigment; abundant dense connective tissue septa]
- Leydig cell hyperplasia
- Inflammatory myofibroblastic tumour
- Sperm granuloma
- Adrenal rests
- Splenic-gonadal fusion
- Sclerosing lipogranuloma
- Malakoplakia
- Granulomatous orchitis



### Haemolymphoid neoplasms

- Malignant lymphoma  
    commonest is primary testicular diffuse large B cell lymphoma which often involves unusual sites (e.g. CNS, skin, lung)
- Plasmacytoma (primary or secondary to myeloma)
- Leukaemia (common sanctuary site)



### Other neoplasms

- Sarcoma
- Carcinoid tumour
- Benign tumours



## Testicular sarcoma

- Pure, primary (various subtypes)
- Arising from:
  - teratomas
  - spermatocytic seminoma
  - Leydig cell tumour
- Metastatic

[Sarcomas are more common in the paratestis/spermatic cord e.g. liposarcoma [the most frequent in adults], which may be dedifferentiated; leiomyosarcoma; rhabdomyosarcoma in children/adolescents]



## Reports of unusual spindle cell 'testicular gonadal stromal tumours'

- Evans and Glick 1977 "Unusual gonadal stromal tumour"
- Greco *et al.*, 1984 "Testicular stromal tumor with myofilaments"
- Meittinen *et al.*, 1986 "Testicular stromal tumour with epithelial differentiation"
- Nistal *et al.*, 1996 "Fusocellular gonadal stromal tumour of the testis with epithelial and myoid differentiation (myofibroblastoma)"
- Weidner 1991 "Myoid gonadal stromal tumours with epithelial differentiation (testicular myoepithelioma?)"



## Testicular carcinoid tumour

- Primary
  - pure
  - component of teratoma
- Metastatic



## Metastases



## Paratesticular tumours

- Adenomatoid tumour
- Rhabdomyosarcoma (children/adolescents)
- Malignant mesothelioma of tunica vaginalis
- Liposarcoma of spermatic cord (sclerosing variant of well differentiated liposarcoma more common than at other sites; dedifferentiated elements can also cause diagnostic difficulty)
- Leiomyosarcoma
- Mullerian epithelial tumours (serous, endometrioid, mucinous, clear cell, Brenner tumour)
- Rete testis adenoma; adenocarcinoma
- Cystadenoma of the epididymis (clear cell type, associated with VHL syndrome)



## Adenocarcinoma of the rete testis

Skailies GE *et al.* *Histopathology* 1998;10:401-3





## Adenocarcinoma of rete testis

- Absence of primary tumour elsewhere
- Tumour centred on testicular hilum
- Transition from non-neoplastic rete
- Incompatible with other testicular/paratesticular tumour
- Papillary serous adenocarcinoma and malignant mesothelioma excluded by immunohistochemistry

