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Commentary

# Of Age and Distinct-Adult Granulosa Cell Tumour Testis

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Adult granulosa cell tumour of testis emerges as a sex cord stromal tumour recapitulating granulosa cells of ovarian Graafian follicles. The exceptionally discerned, low grade sex cord stromal tumour is associated with an indolent clinical course. Nearly 10% tumours may display a potential for malignant metamorphosis.

Commonly, tumefaction displays cogent architectural patterns as diffuse, solid, insular or spindle shaped cells. The pathognomonic Call-Exner bodies articulating a component of micro-follicular pattern are infrequently discerned.

Characteristically, tumour cells display uniform, spherical to ovoid nuclei with conspicuous, longitudinal nuclear grooves. In contrast to ovarian variant, few lesions may depict FOXL2 genetic mutations.

Preponderantly incriminating the testicular parenchyma, adult granulosa cell tumour is an exceptionally encountered tumefaction representing < 0.5% of sex cord stromal tumours [1,2].

Mean age of disease emergence is 40 years and the neoplasm may appear within 14 years to 87 years [1,2].

Of obscure aetiology, testicular adult granulosa cell tumour is derived from constituent granulosa cells. Pre-eminently, FOXL2 is a granulosa cell expressed gene which contributes to regulation of cellular proliferation and genesis of the neoplasm [1,2].

Additionally, missense mutation 402C → G, C134W induces dysregulation of genetic expression with consequently augmented cellular proliferation and decimation of apoptosis.

In contrast to ovarian neoplasms, few instances (~40%) of testicular adult granulosa cell tumours manifest with FOXL2 C134W (c.402C > G) genetic mutation [1,2].

Testicular adult granulosa cell tumour manifests with unilateral testicular tumefaction or swelling. Typically, neoplasm is devoid of clinical symptoms concurrent with endocrine features as gynecomastia or decreased libido. However, specific endocrine features may emerge in ~20% instances [2,3].

Grossly, a well circumscribed, predominantly solid, lobulated neoplasm of magnitude between 0.5 centimetres to 6.0 centimetres and mean tumour magnitude of 2.8 centimetres is encountered. Occasionally, tumefaction is solid and cystic. Features as infiltrative tumour perimeter, extra-testicular involvement, focal haemorrhage and necrosis are exceptionally discerned and frequently associated with aggressive biological behaviour [2,3].

Upon microscopy, low power magnification exhibits a characteristic nodular or lobulated neoplastic countenance.

High power magnification expounds tumour cells incorporated with variable, eosinophilic cytoplasm, uniform, spherical to ovoid nuclei with prominent, longitudinal nuclear grooves and indistinct cellular outline. Commonly, diffuse, solid, insular and spindle shaped cellular configurations are observed [3,4]:

- Insular pattern exhibits nests of tumour cells circumscribed by fibrous tissue stroma.
- Spindle shaped cellular pattern is constituted of sheets of fusiform cells.
- Cellular cords or a trabecular pattern articulating regular or irregular, thin cords or thick columns of neoplastic cells.
- Water silk or gyriform pattern delineating interweaving cords and undulating columns of tumour cells.
- Micro-follicular pattern demonstrating innumerable, miniature spaces imbued with hyalinised, basement membrane substance or eosinophilic fluid, thereby configuring the characteristic Call-Exner bodies.
- Herringbone or fascicular pattern displaying spindle shaped cells embedded within a fibro-collagenous stroma.
- Pseudo-papillary pattern enunciating tumour cells encompassing fibro-vascular cores.
- Palisading pattern exemplifying tumour cells with a parallel arrangement, simulating a 'fence'.
- Luteinized pattern wherein tumour cells are pervaded with abundant, clear to eosinophilic cytoplasm and spherical nuclei.

Notwithstanding, diffuse or solid sheets of spherical cells may be discerned [3,4].

Tumour cell component is intermingled within variable quantities of fibro-collagenous or oedematous stroma.

Mitotic activity varies from 0 to 18 mitosis per 10 high power fields or exhibits a mean count of 4.9 mitosis per 10 high power fields. Thus, mitotic figures appear non concurrent with prognostic outcomes [3,4].

Tumefaction may expound foci of haemorrhage or hemosiderin pigment deposition. Focal necrosis or lymphatic and vascular invasion representing as features of aggressive biological behaviour are infrequently observed.

Tumour cells may infiltrate between seminiferous tubules with incrimination of rete testis and tunica albuginea. Para-testicular or extra-testicular soft tissue is infrequently implicated [3,4].

| **Sex cord/Stromal Tumours** |
|---|
| Leydig cell tumour |
| Malignant Leydig cell tumour |
| Sertoli cell tumour |
| Malignant Sertoli cell tumour |
| Large cell calcifying Sertoli cell tumour |
| Intra-tubular large cell hyalinising Sertoli cell neoplasia |
| Granulosa cell tumour |
| Adult type |
| Juvenile type |
| Thecoma/fibroma group of tumours |
| Other sex cord gonadal/stromal tumours |

| |
|---|
| Mixed |
| Unclassified |
| Tumours containing germ cell and sex cord/gonadal stromal component |
| Gonadoblastoma |
| **Miscellaneous non specific stromal cell tumours** |
| Ovarian epithelial tumours |
| Tumours of collecting ducts and rete testis |
| Adenoma |
| Carcinoma |
| **Tumours of paratesticular structures** |
| Adenomatoid tumour |
| Mesothelioma(epithelioid/biphasic) |
| Epididymal tumours |
| Cystadenoma of epididymis |
| Papillary cystadenoma |
| Adenocarcinoma of the epididymis |
| Mesenchymal tumours of spermatic cord and testicular adnexa |

***Table 1:*** *World health organization of testicular tumours [3].*

| Gene | Variant | Location | Frequency |
|---|---|---|---|
| FOXL2 | C134W | Exon 1 | 8% |
| TERT | c.-124C>T | - | 25% |
| CDKN2A | E87Gfs*24 | Exon 2 | 2% |
| TP53 | S183* | Exon 5 | 5% |
| H3F3A | K28R | Exon 2 | 35% |

***Table 2:*** *Genomic analysis of testicular adult granulosa cell tumour [4].*

Adult granulosa cell tumour appears immune reactive to inhibin A, vimentin, calretinin, CD99, smooth muscle actin (SMA), S100 protein or FOXL2.

Tumour cells appear immune non reactive to epithelial membrane antigen (EMA), human melanoma black antigen 45 (HMB45), desmin, OCT3/4, SALL4, β catenin, cytokeratin or melan A [5,6].

Testicular adult granulosa cell tumour requires segregation from neoplasms as juvenile granulosa cell tumour, Leydig cell tumour, Sertoli cell tumour, fibrothecoma, sex cord stromal tumour, unclassified or sex cord stromal tumour, mixed [5,6].

Upon imaging or ultrasonography, non specific features or a testicular tumefaction may be expounded. Additionally, a characteristic well demarcated, hypoechoic tumefaction intermingled with hyperechoic zones and focal calcification is observed. Cogent histopathological assessment may categorically detect the neoplasm.

Testicular adult granulosa cell tumour appears devoid of elevation of specific serum makers.

Radical orchiectomy appears curative for testicular adult granulosa cell tumour. Besides, testis sparing surgical procedures or wedge excision may be beneficially employed for eradicating miniature, benign neoplasms [5,6].

Retroperitoneal lymph node dissection or platinum based chemotherapy with agents as bleomycin, etoposide or cisplatin appears advantageous for alleviating neoplasms delineating distant metastasis. Exceptionally, therapy with tyrosine kinase inhibitors as pazopanib is associated with partial response [5,6].

Majority (~90%) neoplasms appear benign wherein ~10% tumours exhibit possible malignant metamorphosis.

Morphological features commonly associated with aggressive biological behaviour emerge as:

- Lymphatic and vascular neoplastic invasion.
- Infiltrative tumour perimeter.
- Extra-testicular tumour incrimination.
- Tumour magnitude > 4 centimetres [5,6].

Morphological features associated with possible malignant metamorphosis appear as:

- Moderate or marked nuclear atypia.
- Occurrence of tumour necrosis.
- > 5 mitotic figures per 10 high power fields.
- Concurrence with hormonal manifestations as gynaecomastia [5,6].

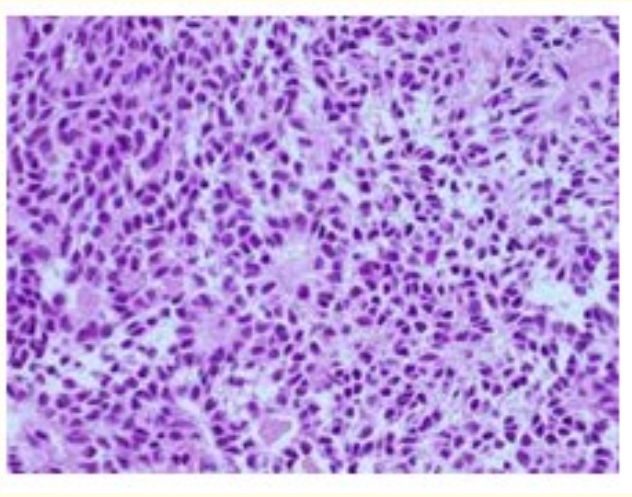

***Figure 1:*** *Adult granulosa cell tumour delineating cellular aggregates pervaded with variable, eosinophilic cytoplasm, spherical nuclei, longitudinal nuclear grooves and indistinct cellular outline [7].*

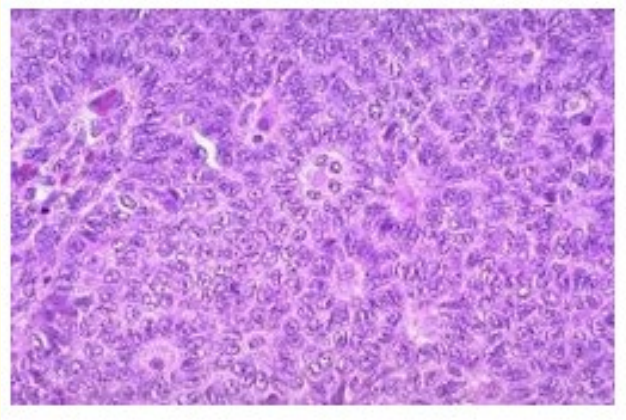

***Figure 2:*** *Adult granulosa cell tumour demonstrating cellular nests incorporated with variable, eosinophilic cytoplasm, spherical nuclei, longitudinal nuclear grooves and indistinct cell outline. Intervening stroma is minimally fibrotic [8].*

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7. Image 1 Courtesy: BMJ case reports.
8. Image 2 Courtesy: Pathology Apps.

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