ONCOLOGY/RECONSTRUCTION
MINI-REVIEW

Adult-type granulosa cell tumour of the testis: Report of a case and review of the literature

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KEYWORDS
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ABBREVIATIONS
GCT, granulosa cell tumour; AGCTT, adult-type GCT of the testis; T2WI, T2 weighted imaging; CD, cluster of differentiation

Abstract Granulosa cell tumours (GCTs) can be either juvenile or adult type, and more commonly occur in the ovaries. Adult-type GCTs of the testis (AGCTT) are very rare and only 46 cases have previously been reported. We report here on a 48-year-old Filipino man with a left testicular AGCTT, which measured 1.2 × 1.2 × 1.0 cm. He underwent radical orchidectomy with postoperative surveillance for 1 year, which included computed tomography with oral intravenous contrast and clinical examinations, which have been unremarkable. The previously reported AGCTTs were briefly reviewed.

Background Sex cord-stromal tumours of the gonads are numerous including thecomas, fibromas, Sertoli, Leydig, Sertoli-Leydig cell, and granulosa cell tumours (GCTs) [1]. GCTs are divided into two different types: juvenile and adult [2]. The juvenile type commonly occurs in
the first 6 months of life [3]. The adult type is very rare and can occur at any time after puberty. Only 46 cases of adult-type GCT of the testis (AGCTT) have been reported to date [1–36]. Many morphological, clinical, and immunohistochemical characteristics have been identified that help in the diagnosis of AGCTT.

AGCTT presents clinically as a slow, painless enlargement over a variable period of time in > 50% of cases [4–6]. The mean (range) age at diagnosis is 47 (12–77) years [4,7]. Erectile dysfunction, gynaecomastia, and decreased libido may also be present [5,7]. AGCTTs typically have a solid, well-circumscribed, lobular mass.
that may have a fibrous pseudocapsule in gross morphological analysis.

Some AGCTTs have the potential for distant metastases and thus poor outcomes, but otherwise they are non-functioning, slow growing, and most often benign [4,8]. A relatively long survival period was found in patients with metastases to regional lymph nodes; however, deaths occurring at few months to a few years after metastases have occurred in patients that have distant metastasis and who exhibited rapid disease progression [8]. The retroperitoneal lymph nodes are the most common metastatic region, but lung, liver, and bone metastases have also been reported [8–10]. Recent evidence indicates that ≈20% of cases of AGCTT are malignant; however, factors predictive of malignancy have yet to be well defined due to the very limited number of cases.

Case report

A 48-year-old man presented with the complaint of mild pain in his left testis. He denied dysuria, urethral discharge, back pain, abdominal pain, or recent illness. There was no personal or family history of genitourinary disease and his past medical history was not significant. There had been no previous abdominal or genitourinary surgeries and he was a non-smoker. His vital signs were within normal limits and a physical examination was remarkable for tenderness and swelling in the left testis, with a small hard mass at the lower pole on palpation of the left testicle, and the right testicle was unremarkable. Other pertinent findings included the absence of cervical, supraclavicular, or inguinal lymphadenopathy, gynaecomastia, urethral discharge, or scrotal swelling. Abdominal examination revealed no masses or tenderness.

Urine analysis showed no red blood corpuscles, leucocytes, or protein, and was negative for nitrite and leucocyte esterase. Serum tumour markers included lactate dehydrogenase measuring 197 IU/L, serum α1-fetoprotein measuring 2 ng/mL, and plasma β human chorionic gonadotrophin measuring <0.50 IU/mL. Testicular ultrasonography (US) revealed a left testis measuring 3.9 × 1.4 cm with a cystic lesion of 1.2 × 1.2 × 1.0 cm towards its lower pole, with coarse internal echoes, and the wall showed mild irregularity (Fig. 1).

Contrast-enhanced MRI of the pelvis revealed a well-defined left intra-testicular focal lesion (1.2 × 1.2 × 1.0 cm) at the infero-posterior aspect of the testis, which had a low signal on T2 weighted imaging (T2WI), and low to iso-intense on T1WI. There was a central high signal on T2WI, suggestive of fluid (necrosis). The tunica albuginea was infiltrated in a small area in the posterior aspect of the lesion to the near-by epididymis (Fig. 2).
The patient agreed to an orchidectomy after his initial diagnosis and a radical orchidectomy was performed with no complications.

Gross appearance of the specimen revealed a testis with a lower pole well-circumscribed solid mass measuring $1.2 \times 1.2 \times 1.0$ cm. The mass had a fleshy and homogenous cut surface (Fig. 3). Microscopic evaluation revealed an encapsulated well-circumscribed nodule consisting of micro follicles, cords and solid sheets of tumour cells. The cells appeared elongated with scanty cytoplasm and pale ovoid nuclei. The nuclei had longitudinal grooves giving them a coffee bean-like appearance (Fig. 4). Very few mitotic figures could be seen. There was no evidence of haemorrhage, necrosis, sarcomatous differentiation or other germ cell elements.

Immunohistochemistry was applied, the tumour cells were strongly positive for vimentin, inhibin (Fig. 5),

| Case | Age, years | Testis Signs and duration, years | Endocrine symptoms | Size, cm | Follow-up, years | Source |
|------|------------|---------------------------------|--------------------|----------|------------------|--------|
| 1    | 35         | Right 15                        | Gynaecomastia      | 9        | 8.5 NED          | Laskowski [14] |
| 2    | 21         | Left 1                          | Gynaecomastia      | Microscopic Autopsy finding | NED | Cohen and Diamond [15] |
| 3    | 53         | Right 1                         | Gynaecomastia      | > 10     | NS               | Massachusetts General Hospital [16] |
| 4    | 52         | Right 5                         | None              | 13       | NS               | Melicow [17] |
| 5    | 41         | Left 8                         | Gynaecomastia      | 10.1     | 0.42 DOD         | Mostofi et al. [18] |
| 6    | 53         | Right 2                         | Gynaecomastia      | 10       | 17 NED           | Marshall et al. [19] |
| 7    | 44         | Right Few months                | None              | 3.5      | 3 NED            | Talerman [20] |
| 8    | 41         | Right NS                        | None              | 1.8      | NS               | Gaylis et al. [21] |
| 9    | 83         | Left NS                         | None              | NS DOC   | Dite et al. [22] |
| 10   | 61         | Right 0.17                      | None              | 5        | 2 NED            | Nistal et al. [23] |
| 11   | 26         | Left 0.58                       | Gynaecomastia      | 10       | 14 NED           | Matoska et al. [12] |
| 12   | NS         | NS                              | NS                | NS NS    | NED              | Sasano et al. [24] |
| 13   | 42         | Left NS                         | None              | NS AWD   | Monobe and Manabe [25] |
| 14   | 57         | Right 10                        | None              | 2.5      | 3 years DOC      | Jimenez-Quintero et al. [11] |
| 15   | 55         | Left Not known                  | None              | 1.3      | NS               | Jimenez-Quintero et al. [11] |
| 16   | 60         | Left Many years                 | None              | 7        | 11.17 DOD        | Jimenez-Quintero et al. [11] |
| 17   | 39         | Left 2                          | None              | 4        | 3 NED            | Jimenez-Quintero et al. [11] |
| 18   | 16         | Left Incidental                 | None              | 1.8      | 0.33 NED         | Jimenez-Quintero et al. [11] |
| 19   | 29         | Right Incidental                | None              | 7.5      | 1.17 AWD         | Jimenez-Quintero et al. [11] |
| 20   | 76         | Left Incidental                 | None              | 0.7      | 0.08 NED         | Jimenez-Quintero et al. [11] |
| 21   | NS         | NS                              | NS                | NS NS    | NED              | Renshaw et al. [26] |
| 22   | NS         | NS                              | NS                | NS NS    | NED              | Renshaw et al. [26] |
| 23   | NS         | NS                              | NS                | NS NS    | NED              | Renshaw et al. [26] |
| 24   | NS         | NS                              | NS                | NS NS    | NED              | Renshaw et al. [26] |
| 25   | NS         | NS                              | NS                | NS NS    | NED              | Renshaw et al. [26] |
| 26   | NS         | NS                              | NS                | NS NS    | NED              | Renshaw et al. [26] |
| 27   | 51         | Left 0.17                       | Incidental        | 7        | 1.08 NED         | Morgan and Brame [27] |
| 28   | 48         | Right 3                         | None              | 5        | 0.58 NED         | Al-Bozom et al. [28] |
| 29   | 54         | Left Incidental                 | None              | NS NS    | NED              | Wang et al. [29] |
| 30   | 33         | NS Incidental                   | None              | 1        | NS               | Guzzo et al. [30] |
| 31   | 51         | Left Incidental                 | None              | NS 6 AWD | Suppiah et al. [9] |
| 32   | 59         | Left 2                          | None              | 15       | 4 NED            | Hisano et al. [31] |
| 33   | 32         | Left Incidental                 | None              | 1.98     | NS               | Arzola et al. [32] |
| 34   | 77         | Left Incidental                 | None              | 4        | NS               | Lopez [33] |
| 35   | 45         | Right Months                    | None              | 6.5      | 2 NED            | Ditonno et al. [6] |
| 36   | 5         | Left 5                          | None              | 10       | NS               | Gupta et al. [4] |
| 37   | 55         | NS Lung metastases              | None              | NS NS    | NED              | Hammerich et al. [8] |
| 38   | 28         | Left Incidental                 | None              | 2.6      | NS               | Song et al. [34] |
| 39   | 21         | Left Incidental                 | None              | 1        | 2 NED            | Hanson and Ambaye [5] |
| 40   | 77         | Right NS                        | NS                | 2.5      | NS               | Lima et al. [1] |
| 41   | 22         | Left NS                         | NS                | 1        | NS               | Lima et al. [1] |
| 42   | 40         | Left NS                         | NS                | 2.1      | NS               | Lima et al. [1] |
| 43   | 78         | Left Incidental                 | None              | 13       | 1.92 NED         | Schubert et al. [35] |
| 44   | 37         | Left Incidental                 | None              | 4.2      | 2 NED            | Miliaras et al. [2] |
| 45   | 22         | Left 0.75                       | None              | 4.6      | NS               | Tanner et al. [36] |
| 46   | 48         | Left 0.25                       | None              | 2        | 1 NED            | Present case |

NS, not specified; NED, no evidence of disease; DOD, dead of disease; AWD, alive with disease; DOC, death from other cause.
calretinin, and cluster of differentiation 99 (CD99). Focal staining for smooth muscle actin, desmin, and cytokeratin (AE1/AE3) was seen. The tumour cells were negative for placental alkaline phosphatase, stem cell marker Oct-3/4, Sal-like protein 4, synaptophysin, chromogranin, and CD117.

Given the histopathological findings, as well as the immunohistochemistry, the patient was diagnosed with AGCTT. The 1-year postoperative surveillance, including CT with oral i.v. contrast and clinical examinations, has been unremarkable.

Discussion

The adult-type GCT is extremely rare in the testis, Schubert et al. [35] have found 43 cases in the literature [1–36] and we were able to find three more recent cases in PubMed (Table 1) [2,36]. However, in most of the reports these tumours are only the object of immunohistochemical or cytogenetic investigations; thus, the clinical data are missing partially [5,11,22,24]. The initial treatment for all reported cases was radical or inguinal orchidectomy [11,8]. There is no evidence to support additional therapy in patients with a disease clinically confined to the testicle. Dissection of the retroperitoneal lymph nodes should be considered with pathology suggestive of malignant features or if small-volume metastatic disease is present. If performed, it should be immediately after the orchidectomy. A very poor prognosis is expected for patients with unresectable metastatic, widespread disease [6]. There is no consensus about the treatment for metastatic disease, which may include chemotherapy [11,8] and/or radiation therapy [12]. In the reported cases of AGCTT, three were treated with chemotherapy. One received cisplatin and doxorubicin 121 months after initial diagnosis and died from disease 13 months later. The next was treated with retroperitoneal lymph node dissection followed by one cycle of etoposide, had a recurrence treated with radical inguinal lymphadenectomy and radiation therapy; and was alive 2 months after the last therapy. The last patient received six cycles of BEP (bleomycin, etoposide, cisplatin) followed by metastasectomy of the right lung and was alive at 39 months after initial diagnosis. Interestingly, Harrison et al. [13] reported an advanced AGCTT partially responding to an angiogenesis inhibitor after initially resisting cytotoxic chemotherapy. Their patient enrolled in a phase I study of pazopanib (GW-786034, GlaxoSmithKline), an oral multitargeted receptor tyrosine kinase inhibitor of vascular endothelial growth factor receptor-1, -2, and -3; platelet-derived growth factor receptor-β; and c-kit. He was treated at the recommended phase II dose (800 mg by mouth daily) and tolerated this therapy well, and ≈32 months after his initial diagnosis the patient died from his disease.

Jimenez-Quintero et al. [11] suggested that haemorrhage, a necrosis size of >7.0 cm, and presence of lymphovascular invasion, might be indicative of malignancy because these characteristics were present in the malignant cases they identified. In a recent attempt to find variables for malignancy prediction, Hanson and Ambaye [5] evaluated laterality, patient age, presence of gynaecomastia, presence of mitoses, necrosis, and tumour size. Of the variables analysed, only a tumour size of >5.0 cm showed statistical significance.

US of the abdomen and testis, coupled with clinical examination, may be sufficient in cases thought to have low malignant potential [11]. More extensive follow-up may be warranted with larger tumours or tumours deemed to be aggressive. A follow-up protocol suggested is an abdominal and testicular US along with chest X-ray, with a CT of the abdomen and pelvis every 6 months. The duration of follow-up is not well-defined; however, long-term follow-up is mandatory because metastasis has been found after 10 years of treatment [6].

Conclusion

Further reporting every case of AGCTT, to allow thorough analysis, is necessary to identify factors that can reliably predict tumour behaviour and to optimise methods of diagnosis and treatment together with classic means of follow-up.

Long-term follow-up with a sufficient number of cases may be needed to define optimal treatment options for patients with this rare tumour.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflicts of interests

The authors declare that they have no competing interests.

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