SHORT REPORT

Giant Sertoli cell nodule of the testis: distinction from other Sertoli cell lesions

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The case of a 33-year-old man with a clinically suspected testicular neoplasm is reported here. The radical orchidectomy specimen showed a sharply demarcated, firm, yellow-white 1-cm nodule beneath the tunica albuginea at the upper pole. Microscopical examination showed the encapsulated nodule to be composed of tubules lined by immature Sertoli cells with interspersed spermatogonia and an interwoven network of hyalinised basement membrane having foci of calcification. Immunohistochemical studies verified the fetal phenotype of the Sertoli cells and the non-neoplastic nature of the germ cell component. Except for the large size, the findings were identical to those of a Sertoli cell nodule—a typically microscopic, unencapsulated lesion commonly detected in cryptorchid testes. The term “giant Sertoli cell nodule” is used for this unique, hitherto undescribed lesion and its distinction from other Sertoli cell lesions of the testis is considered here.

Sertoli cell tumours represent only about 1% of testicular neoplasms^{1,2} and are, almost by definition, sex cord tumours that form defined tubular structures.^{1–4} A minority of cases are malignant and can be prospectively recognised by well-defined criteria.^{4,5} A Sertoli cell nodule, on the other hand, “consists of coiled tubules lined by immature Sertoli cells” and “are [is] commonly encountered in undescended testes”.⁶ Most Sertoli cell nodules are microscopic lesions that may contain spermatogonia^{1,2} and have no malignant potential. We present a unique case of a testicular Sertoli cell lesion that had all of the usual findings of a Sertoli cell nodule but which formed a grossly evident testicular mass at clinical presentation.

CASE REPORT

A 33-year-old Caucasian man, father of two healthy girls, 8 and 4 years old, reported to his general physician a 3-month history of a painless, right testicular firmness. There was no history of cryptorchidism. The patient was referred to a urologist, and clinical evaluation confirmed medial firmness of the right testis. On ultrasound examination this lesion was hyperechogenic. Because of a suspected germ cell tumour, a right-sided radical orchidectomy as well as a contralateral testicular biopsy were performed.

RESULTS

We received a radical orchidectomy specimen, consisting of a bisected testis, 3.8 cm × 3.0 cm × 2.5 cm, with attached epididymis and spermatic cord. The cut surface showed a 1.0 cm × 0.7 cm × 0.7 cm sharply demarcated, firm, yellow-white nodule located beneath the tunica albuginea at the upper pole (fig 1A,B). Microscopical examination showed this nodule to be composed of numerous tightly packed tubules containing three elements: (1) elongated,

immature-appearing Sertoli cells with round or oval nuclei and indistinct cytoplasm; (2) interspersed spermatogonia with clear cytoplasm, distinct borders and large, round nuclei having slightly granular chromatin; and (3) interspersed deposits of eosinophilic, periodic acid Schiff-positive, laminated basement membrane matrix, sometimes with central calcification (fig 1B–D). This nodule was separated from the surrounding parenchyma by a mostly thin fibrovascular capsule (fig 1C). The adjacent seminiferous tubules showed intact spermatogenesis without any evidence of intratubular or invasive germ cell neoplasia. Interestingly, there was a second, microscopic nodule near the rete testis that showed the same features as the large nodule. Immunohistochemical analysis showed reactivity against inhibin, calretinin, vimentin and CAM 5.2 (cytokeratins 8 and 18; fig 1E) and negativity for cytokeratin 8 in the immature Sertoli cells. The spermatogonia were immunoreactive with NY-ESO-1 (a cancer-testis antigen) and negative for placental-like alkaline phosphatase (fig 1F). The matrix component showed strong positivity for anti-collagen-IV.

The left testicular biopsy was unremarkable and showed no evidence of intratubular or invasive germ cell neoplasia. The patient was well and without evidence of disease 2½ years after the orchidectomy.

DISCUSSION

The Sertoli cell lesion in this case has all of the expected microscopical and immunohistochemical findings of a Sertoli cell nodule, which we and others consider a localised “hyperplasia” of immature Sertoli cells within pre-existing seminiferous tubules. Sertoli cell nodules often, but not always, occur in maldescended testes.⁷ As in our case, they are composed of small, often compressed tubules lined by immature, fetal-type Sertoli cells with scant cytoplasm, with the tubules also typically containing scattered, non-neoplastic spermatogonia and globular deposits of basement membrane, which may develop laminated foci of calcification.^{1,2,7,8} They are usually microscopic but are occasionally visible grossly as white nodules a few millimetres in diameter.¹ Synonyms include “nodules of immature tubules”, “tubular adenoma”, “Pick’s adenoma” or even “Sertoli cell adenoma”,⁶ although we believe the last term is best restricted to the hamartomatous lesions seen in the androgen insensitivity syndrome (see below). Our immunohistochemistry studies showed positivity for vimentin and focal staining for cytokeratin 18 in the tubular lining cells, indicating an immature Sertoli cell phenotype,^{9–11} as expected in a Sertoli cell nodule. Although vimentin and cytokeratin 18 are coexpressed in embryonic Sertoli cells, cytokeratin 18 is progressively down regulated and completely absent from the 20th gestational week.¹¹ The associated spermatogonia were immunoreactive for NY-ESO-1, which is expressed in prenatal germ cells, spermatogonia and intratubular germ cell neoplasia unclassified,¹² although the latter was excluded morphologically as well as by absent reactivity for

Figure 1 (A) Orchidectomy specimen showing a sharply demarcated yellow-white nodule, 1 cm in diameter, beneath the tunica albuginea at the upper pole ($\times 2.5$). (B) Low-power view showing the relationship of the nodule with the surrounding testicular parenchyma. A thin capsule surrounds a proliferation composed of tubules and an anastomosing matrical network. (C) Medium magnification. The encapsulated nodule is made up of eosinophilic matrix and solid, compressed tubules. The cells are mostly small, with round to elongated hyperchromatic nuclei ($\times 100$). (D) High magnification identifies the round to oval cells as immature Sertoli cells, as well as a second cellular component of spermatogonia with abundant clear cytoplasm ($\times 400$). (E) Focal expression of cytokeratins 8 and 18 (CAM 5.2) in the immature Sertoli cells. (F) The spermatogonia show no immunoreactivity for placental-like alkaline phosphatase.

placental-like alkaline phosphatase. An additional, microscopic Sertoli cell nodule near the rete testis further supports our diagnosis as these cell nodules are frequently multifocal.

Several neoplastic Sertoli cell lesions merit consideration in the differential diagnosis. Sertoli cell tumours of the testis mostly belong in the "Not Otherwise Specified" category.⁴ Their cells do not have a fetal phenotype, and they do not have a prominent internalised basement membrane component. When they contain germ cells, it is secondary to incorporation of non-neoplastic elements into the tumour, typically representing a focal finding at the periphery and occurring in clusters that usually lack a perceptible intratubular location.⁶ The tubular distribution of regularly occurring, residual germ cells in our case is a strong argument against a Sertoli cell tumour. The sclerosing variant is characterised by a prominent collagenous background.¹³ It may contain focal entrapped non-neoplastic tubules, lined by immature Sertoli cells and germ cells, but a mixture of immature Sertoli cells and non-neoplastic germ cells throughout the lesion is not seen. Furthermore, the stroma is sclerotic and not an accumulation of basal membrane substance. The large-cell calcifying Sertoli cell tumour, on the other hand, is characterised by polygonal cells with abundant

eosinophilic cytoplasm and relatively large nuclei with prominent nucleoli. The myxoid to fibrous stroma often has scattered, large, irregularly shaped islands of calcification.⁵ Gonadoblastoma, another neoplasm considered in the differential diagnosis, has a nested arrangement of large atypical germ cells, similar to seminoma cells, and small cells resembling immature Sertoli cells and granulosa cells.¹⁴ Furthermore, it is most commonly seen in mixed gonadal dysgenesis. Our patient, however, was phenotypically male, with no evidence of mixed gonadal dysgenesis or an inherited syndrome, and the Sertoli cell lesion contained only non-neoplastic germ cells, as supported by their positivity for NY-ESO-1 and negativity for placental-like alkaline phosphatase. The germ cell-sex cord/gonadal stromal tumour, unclassified, differs from gonadoblastoma in having a combination of neoplastic germ cells and neoplastic sex cord-stromal elements arranged in a diffuse pattern.¹⁴ By definition its germ cells are neoplastic, unlike those identified in our case; the sex cord elements have not had a fetal phenotype, nor has basement membrane been found as a prominent component of this tumour. These tumours are vanishingly rare and remain a controversial entity with respect to their distinction from sex cord-stromal tumours with entrapped germ cells.

Take-home messages

- Not all distinct nodules in the testis are neoplastic.
- Not all Sertoli cell lesions are neoplastic.
- Sertoli cell nodules can be macroscopic.
- Sertoli cell lesions should be investigated for a combination of immature/fetal Sertoli cells and non-neoplastic germ cells to diagnose Sertoli cell nodules.

The Sertoli cell lesions of the androgen insensitivity (testicular feminisation) syndrome bear some resemblance to our case, but are not realistic diagnostic considerations as our patient was phenotypically male with no evidence of intersexuality and had fathered two children. One Sertoli cell lesion of the androgen insensitivity syndrome is considered a hamartoma, represented by multiple testicular nodules composed of tubules lined by immature Sertoli cells and also having few spermatogonia.¹⁵ However, prominent Leydig cells and a spindle-cell, ovarian-type stroma are found in most of these cases, in contrast with their absence in our case. The Sertoli cell adenoma of the androgen insensitivity syndrome is composed of a pure proliferation of Sertoli cell-lined tubules and has a greater resemblance to our case, but lacks the prominent basement membrane deposits and germ cell component.¹⁵

In conclusion, we describe a clinically and grossly evident testicular nodule that had an identical composition to a Sertoli cell nodule except for its large size. For this unique, hitherto undescribed lesion we propose the term "giant Sertoli cell nodule".

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REFERENCES

- 1 Young RH, Scully RE. *Testicular tumors*. Chicago: ASCP Press, 1990.
- 2 Ulbright TM, Amin MB, Young RH. Tumors of the testis, adnexa, spermatic cord, and scrotum. In: Rosai J, ed. *Atlas of tumor pathology*. Washington, DC: Armed Forces Institute of Pathology, 1999.
- 3 Sesterhenn IA, Jacobsen GK, Chevillat J, et al. Sex cord/gonadal stromal tumors. In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA, eds. *World Health Organization classification of tumours: tumours of the urinary system and male genital organs*. Lyon: IARC Press, 2004:250–8.
- 4 Young RH, Koelliker DD, Scully RE. Sertoli cell tumors of the testis, not otherwise specified: a clinicopathologic analysis of 60 cases. *Am J Surg Pathol* 1998;**22**:709–21.
- 5 Kratzner SS, Ulbright TM, Talamon A, et al. Large cell calcifying Sertoli cell tumor of the testis: contrasting features of six malignant and six benign tumors and a review of the literature. *Am J Surg Pathol* 1997;**21**:1271–80.
- 6 Mostofi FK, Sesterhenn IA. *World Health Organization international histological classification of tumours: histological typing of testis tumours*. Berlin: Springer-Verlag, 1998.
- 7 Hedinger CE, Huber R, Weber E. Frequency of so-called hypoplastic or dysgenetic zones in scrotal and otherwise normal human testis. *Virchows Arch Pathol Anat Physiol Klin Med* 1967;**342**:165–8.
- 8 Stalker AL, Hendry WT. Hyperplasia and neoplasia of the Sertoli cell. *J Pathol Bacteriol* 1952;**64**:161–8.
- 9 Costa MJ, Morris RJ, Wilson R, et al. Utility of immunohistochemistry in distinguishing ovarian sertoli-stromal cell tumors from carcinosarcomas. *Hum Pathol* 1992;**23**:787–97.
- 10 McCluggage WG, Shanks JH, Whiteside C, et al. Immunohistochemical study of testicular sex cord-stromal tumors, including staining with anti-inhibin antibody. *Am J Surg Pathol* 1998;**22**:615–19.
- 11 Franke FE, Pauls K, Rey R, et al. Differentiation markers of Sertoli cells and germ cells in fetal and early postnatal human testis. *Anat Embryol* 2004;**209**:169–77.
- 12 Satie AP, Rajpert-De Meyts E, Spagnoli GC, et al. The cancer-testis gene, NY-ESO-1, is expressed in normal fetal and adult testes and in spermatocytic seminomas and testicular carcinoma in situ. *Lab Invest* 2002;**82**:775–80.
- 13 Zukerberg LR, Young RH, Scully RE. Sclerosing Sertoli cell tumor of the testis. A report of 10 cases. *Am J Surg Pathol* 1991;**15**:829–34.
- 14 Ulbright TM. Tumours containing both germ cell and sex cord/gonadal stromal elements. In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA, eds. *World Health Organization classification of tumours: tumours of the urinary system and male genital organs*. Lyon: IARC Press, 2004:259–60.
- 15 Rutgers JL, Scully RE. The androgen insensitivity syndrome (testicular feminization): a clinicopathologic study of 43 cases. *Int J Gynecol Pathol* 1991;**10**:126–44.