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■ CASE STUDY ■

Large Cell Calcifying Sertoli Cell Tumor of the Testis: A Case Study and Review of the Literature

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A 24-year-old man was admitted due to an incidentally detected mass in his left testis, which showed radiopaque calcification on plain X-ray film. Left orchiectomy was performed, and the resected testis contained a well-demarcated, hard mass measuring 1.1 cm. Histological analysis revealed that the tumor was composed of neoplastic cells, fibrotic stroma, and laminated or irregularly shaped calcific bodies. The individual cells had abundant eosinophilic or clear cytoplasm with round nuclei, each of which contained one or two conspicuous nucleoli. They were arranged in cords, trabeculae, clusters, and diffuse sheets. There were several foci of intra-tubular growth patterns, with thickening of the basal lamina. Immunohistochemically, the neoplastic cells were positive for S-100 protein and vimentin, focally positive for inhibin alpha, and negative for cytokeratin, CD10, and Melan-A. In addition to reporting this rare case, we also review the relevant literature regarding large cell calcifying Sertoli cell tumors.

Key Words: Testis; Sertoli cell tumor; Immunohistochemistry

Sertoli cell tumors represent about 1% of all testicular tumors. These testicular Sertoli cell tumors are further categorized as a large cell calcifying Sertoli cell tumor (LCCSCT), a sclerosing Sertoli cell tumor or a Sertoli cell tumor not otherwise specified. Proppe and Scully[1] described the first reported case of LCCSCT in 1980; overall 61 cases have been reported through 2005.[2] LCCSCTs are frequently associated with Carney complex (CNC) or Peutz-Jeghers syndrome (PJS). Herein, we report a case of LCCSCT, which is the first occurring in Korea, to our knowledge, and shows unusual presentation, without any clinical signs of CNC or PJS.

CASE REPORT

A 24-year-old man was admitted to The Armed Forces Capital Hospital to investigate a left testicular mass, which had been incidentally detected in a plain radiograph taken for lower back pain (Fig. 1). There were no clinical signs of CNC or PJS. A left orchiectomy was performed, whereupon the testis was found to contain a 1.1-cm, well-demarcated, stony hard mass. On a cut section, this lesion had a grey-brown area with, whitish calcific changes and was confined to the testis (Fig. 2).

Microscopically, the tumor was composed of neoplastic cells, fibrotic stroma, and laminated or irregularly shaped calcific bodies, containing focal ossification. The tumor cells had abundant eosinophilic or clear cytoplasm, and were arranged in cords, trabeculae, clusters, and diffuse sheets (Fig. 3). An intratubular growth pattern was also apparent, along with thickening of the basal lamina of these tubules, and intratubular microcalcification (IMC) at the periphery (Fig. 4). The nuclei were round with one or two conspicuous nucleoli, and showed moderate degree of nuclear pleomorphism. No mitotic figures, ne-

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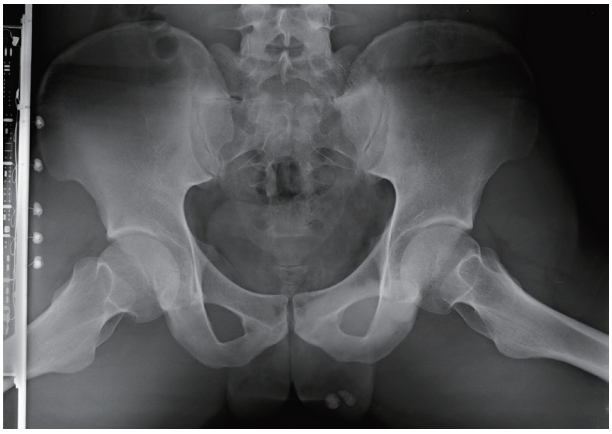

Fig. 1. Radiologic finding. The plain radiograph shows a round shaped calcification in the left testis.

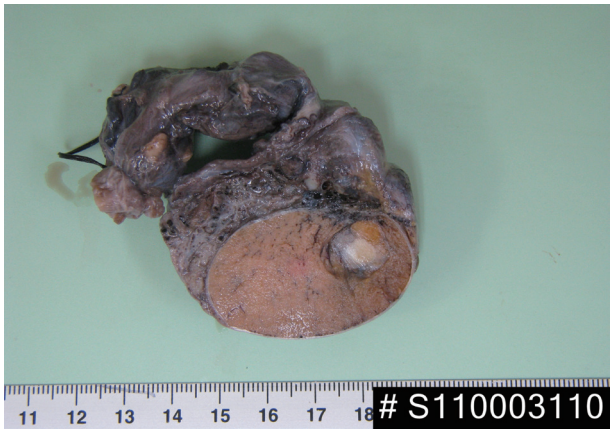

Fig. 2. Gross finding. The lesion has a gray-brown area, with whitish calcification changes, and is confined to the testis.

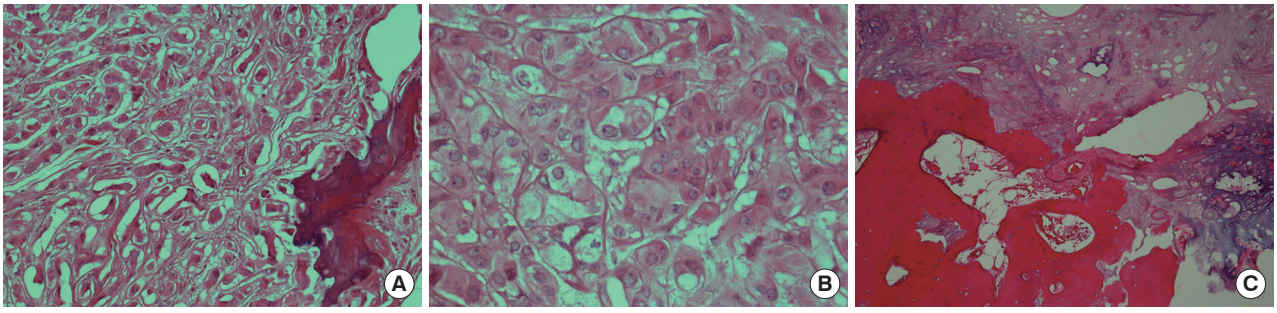

Fig. 3. Microscopic findings in tumor cells. (A) Most of the tumor cells are arranged in cords and clusters. (B) They have abundant eosinophilic cytoplasm with round nuclei and conspicuous nucleoli. (C) There is an irregularly shaped calcification with focal ossification.

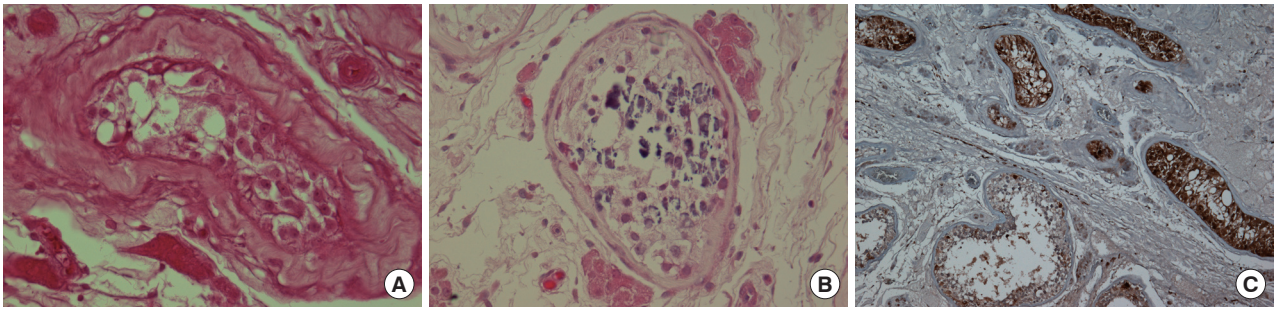

Fig. 4. Microscopic findings of intratubular growth patterns. There are several foci of intratubular growth patterns with thickening of the basement membrane (A) and intratubular calcification (B). (C) The intratubular lesions (upper) demonstrate diffuse positivity for S-100 protein, compared to normal seminiferous tubules (lower).

crosis, Reinke crystalloids, or lipofuscin pigment were present, and the fibrotic stroma appeared benign.

Immunohistochemically, neoplastic cells were diffusely positive for S-100 protein (ready-to-use, anti-S-100 polyclonal antibody, Dako, Glostrup, Denmark), vimentin (ready-to-use, anti-vimentin monoclonal antibody, clone VIM 3B4, Dako), focally and weakly positive for inhibin alpha (ready-to-use, anti-inhibin alpha monoclonal antibody, clone R1, Dako) (Fig. 5) but negative for cytokeratin (ready-to-use, anti-cytokeratin monoclonal antibody, clone AE1/AE3, Dako), CD10 (ready-to-use, anti-CD10 monoclonal antibody, clone 56C6, Dako), and Melan-A (ready-to-use, anti-melan-A monoclonal antibody, clone A103, Dako).

DISCUSSION

LCCSCTs originating from Sertoli cells are most commonly seen in patients younger than 20 years old. They are usually be-

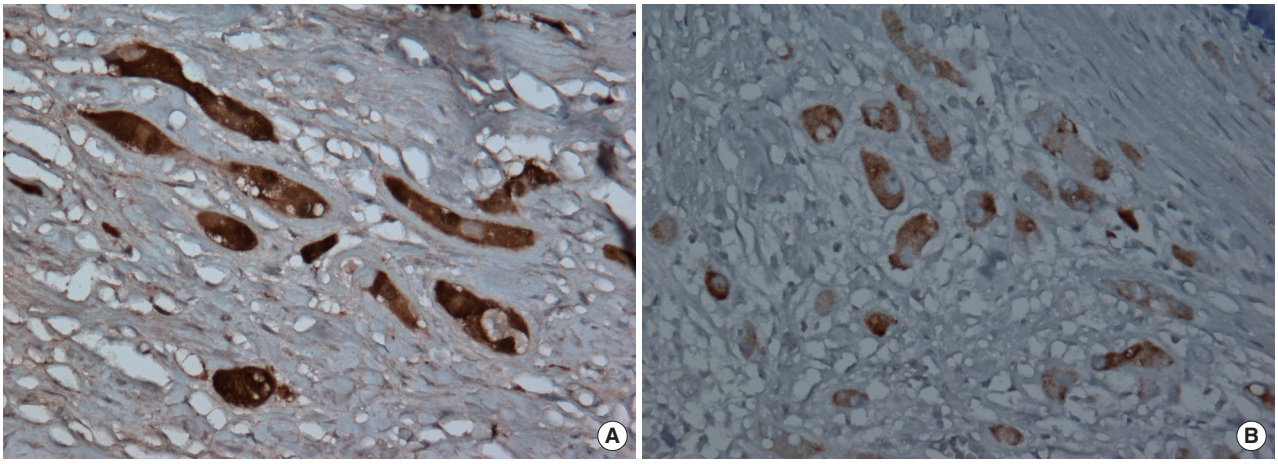

Fig. 5. Immunohistochemical findings of tumor cells. The neoplastic cells are positive for S-100 protein (A) and positive for inhibin alpha (B).

nign, especially when occurring concurrently with endocrine over-activity. These tumors are related to multiple neoplasia syndrome, and PJS and CNC are present in 40% of reported cases.[3] PJS is a rare autosomal-dominant syndrome, presenting at a median age of 11 years, with multiple hamartomatous polyps in the gastrointestinal tract and mucocutaneous hyperpigmentation. About 50% of patients with this syndrome have a mutation in the *LKB1/STK11* gene, but otherwise, the mechanism of LCCSCT pathogenesis in individuals with PJS remains unclear.

CNC is also an autosomal-dominant mutation, with two or more clinical manifestations, including spotty skin pigmentation, cardiac myxoma, cutaneous or mucosal myxoma, myxomatosis of the breast, primary pigmented nodular adrenocortical disease, acromegaly with growth hormone-producing adenoma, LCCSCT, thyroid carcinoma, psammomatous melanotic schwannoma, blue nevus, ductal adenoma of breast, and osteochondromyxoma. Approximately 45% to 80% of individuals with CNC have inactivating mutations of the *PRKAR1A* gene. Around 50% of male patients with CNC develop a LCCSCT, but as with PJS, the mechanism of LCCSCT pathogenesis in men with CNC remains unclear.

It has been reported that about 17% of LCCSCTs are malignant.[4] Malignant LCCSCTs are more frequently present in older patients (with a reported range of 28 to 73 years), and are usually unifocal or unilateral lesions, greater than four cm in size, characterized by more than three mitoses per 10 high power fields, noteworthy nuclear atypia, necrosis, lymphovascular invasion and extratesticular growth.[4,5] The present case was a unilateral tumor, with moderate nuclear pleomorphism, but tumor recurrence was only detected eight months postoperatively.

An intratubular growth pattern, with hyalinization of the tubular basement membrane is a very useful diagnostic feature of LCCSCT, and is present in around 50% of all LCCSCTs,[6] although it remains unclear whether the intratubular lesion is neoplastic or not.[7] The tumor in the present case showed several foci of intratubular growth patterns, at the periphery of the tumor. Without this pattern, the differential diagnosis from Leydig cell tumor (LCT) may be problematic, since LCTs often have unusual features, including adipose differentiation, calcification with ossification, and spindle-shaped tumor cells.[8] It may be impossible to differentiate LCCSCT, from LCT with calcification, without performing immunohistochemical studies.

Sato *et al*.[2] reported that LCCSCT is positive for CD10 and Melan-A, with a patchy pattern in the cytoplasm, whilst LCT shows a diffuse pattern. Furthermore, at an ultra-structural level the mitochondria often aggregate in the perinuclear area in a LCCSCT, whilst LCTs have mitochondria dispersed throughout the cytoplasm. The tumor, however, in this present case did not show any immunoreactivity for CD10 or Melan-A. Although this is unusual, it is not without precedent, as Petersson *et al*.[9] have also described a CD10 and Melan-A negative LCCSCT. This discrepancy, however, should be addressed by a further study of more cases.

Tanaka *et al*.[10] reported that the S-100 beta isoform is an useful marker, as it is present in LCCSCT, but not in LCT. This is particularly noteworthy because S-100 is a calcium-binding protein and is potentially related to calcification.[2] Thus, the immunoreactivity of S-100 beta in LCT with calcification needs to be further evaluated. The lesion in the present case also showed focal and weakly positive staining for inhibin alpha in tumor cells, but negative staining in normal Sertoli and Leydig cells,

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probably because of decalcification.

The present case also showed several IMC foci in the tubules, which contained several germ cells (Fig. 4B), although there was no IMC in the tubules with intratubular Sertoli cell proliferation. Venara *et al*.[7] reported that IMC was absent from most seminiferous tubules with intratubular Sertoli cell proliferation. The possible association between IMC and malignant tumors of the testis has been discussed previously by Furness *et al*.[11] who suggested that IMC may be another sign of testicular dysfunction. Its apparent association with malignancy may be a result of selection bias.[11] Thus, it remains unclear whether IMC is a premalignant condition; and therefore, long-term follow-up is required.

In conclusion, our case of LCCSCT is a rare and distinctive entity and presents a diagnostic challenge for pathologists. We hope that the present report will help in future diagnostic and treatment decisions.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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