Sex Cord Stromal Tumors of the Ovary in Children: 
A Clinicopathological Report From the Italian TREP Project

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Background. Ovarian sex-cord stromal tumors (SCST) are rare in childhood and include a variety of neoplasms with different clinical features and biologic behavior. Aim of the analysis was to report the clinical findings and treatment results of a series of patients with SCST of the ovary, registered in a multi-institutional Italian network on rare tumors in children and adolescent between 2000 and 2009.

Methods. Data on 23 patients, 5–176 months old, from 13 Centers were reviewed. All patients were grouped on the basis of the results of the first surgical approach, according to the Children Oncology Group staging system. A cisplatin based chemotherapy was recommended in patients with a localized disease, who had undergone an incomplete excision/inital biopsy, and in case of metastatic spread. Results. A frequent symptom was abdominal pain; 9/23 cases had signs of hormonal secretion and two patients were hospitalized for acute pain following ovarian torsion. Twelve patients had a Juvenile–Granulosa Cell tumor, six a Sertoli–Leydig Cell tumor, three a Fibrothecoma, and two a Sclerosing-Stromal tumor. Twenty-one patients maintained the complete remission (follow-up: 9–91 months), 2 with a ST II Sertoli–Leydig Cell tumor relapsed and one of them died. Immunohistochemical studies could be done in 10 cases.

Conclusions. Complete resection and histology were important prognostic factors; in our series the Sertoli–Leydig Cell tumor was the most aggressive variety. Hormonal signs (precocious puberty, telarca, menarche) were common in younger patients and led to an early diagnosis. Cisplatin based chemotherapy seemed to be effective for locally advanced tumors.

Key words: adolescents; children; ovarian tumors; sex cord-stromal tumors

INTRODUCTION

Ovarian sex cord stromal tumors (SCST) are very rare in childhood. They include a heterogeneous group of neoplasms developing from nongerminative tissue, with different clinical features and biologic behavior, and account for 5–12% of all pediatric ovarian neoplasms [1,2].

Two main groups of SCST are generally considered on the basis of their histology and secretory pattern: the Granulosa–Theca Cell tumors and the Sertoli–Leydig Cell tumors (SLCT). The Granulosa–Theca Cell tumors represent the largest subgroup (7–8%); although they can occur in women of any age, the typical form of the first two decades of life is the Juvenile Granulosa Cells tumor (JGCT). JGCT is frequently characterized by hormonal symptoms (isosexual precocity or virilization) and has a less aggressive behavior than that of adult type. In most cases, the disease is localized, as demonstrated in a large study of Young et al. [3]. The SLCT, also known as arrenoblastomas, constitute a less frequent subgroup, representing 1–2% of all ovarian tumors, and are characterized by huge size and frequent malignant course. About 40% produces male hormones, causing virilization, which may be used as clinical markers. The aggressive behavior is usually related to the histological retiform subtype. Other less frequent histotypes (fibrothecoma, sclerosing stromal tumor) with a general benign behavior may also occur in children [4,5].

Since 2000, the ovarian SCSTs have been registered within the TREP project (Tumori Rari in Età Pediatrica), an Italian multi-institutional network dedicated to very rare tumors in children and adolescents, which was launched under the auspices of the Italian Association of Pediatric Oncology (AIEOP) and the Italian Society of Pediatric Surgeons (SICP). The clinical-pathological findings and therapeutic results observed in the patients registered are here described, with the purposes to evaluate the efficacy of our clinical approach and contribute with our data to better know these rare entities.

MATERIALS AND METHODS

All patients included in this analysis were registered into the TREP Study [6]. According to the TREP Study guidelines, patients with a suspected SCST of the ovary had to be evaluated with abdominal ultrasound (US), abdominal CT scan or MRI and chest X-ray. Serum levels of α-fetoprotein (AFP) and Human Chorionic Gonadotropin (β-HCG) were required to exclude secreting Germ Cell Tumors (GCT), and an accurate hormonal diagnostic work-up (17-hydroxyprogesterone, estrogens, FSH, LH, prolactin, testoster- one, androstenedione, DHEA-S) was recommended whenever endocrinologic abnormalities were found.

Therapeutic guidelines were similar to those recommended by the Italian Study for GCT [7]. Primary surgical excision of the mass with ovariectomy or adnectomy (ovariosalpingectomy), including intraoperative staging manoeuvres, was recommended only when a complete and non-mutilating procedure was feasible;

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Sex Cord Stromal Ovarian Tumors in Children

TABLE I. COG Staging System Adopted in the TREP Project for Ovarian Sex Cord Stromal Tumors

<table>
<thead>
<tr>
<th>Stage</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Disease limited to the ovary and completely excised; negative peritoneal washing. No clinical, surgical, or histologic evidence of disease extending beyond the ovary and tumoral markers and/or hormonal levels in range after surgery</td>
</tr>
<tr>
<td>Stage II</td>
<td>Microscopic residuals, spillage, or nodes affected by disease (&lt;2 cm); negative peritoneal washing. Tumoral markers positive or negative</td>
</tr>
<tr>
<td>Stage III</td>
<td>Microscopic residuals or initial biopsy only; local invasion (omentum, bowel, bladder); positive peritoneal washing; nodes affected (&gt;2 cm). Tumoral markers positive or negative</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Distant metastases. Negative or positive markers</td>
</tr>
<tr>
<td>Hidden disease</td>
<td>Stage I but tumoral markers persistently out of normal range after a complete surgery</td>
</tr>
</tbody>
</table>

Clinical and therapeutic information were obtained prospectively through special forms sent to the Centers, and completed by the physicians in charge for every patient; however, for the purposes of this analysis, the records of all cases were also centrally reviewed. The informed consent was obtained for all patients enrolled into the study.

All cases were grouped according to the Children Oncology Group (COG) staging system (Table I). The PEB regimen (cisplatin 25 mg/m² days 1–4, etoposide 100 mg/m² days 1–4, bleomycin 15 mg/m² day 2) was recommended in patients with localized disease who had undergone an incomplete excision or initial biopsy, and in case of metastatic spread. Three courses were suggested for ST II patients, four courses for ST III and ST IV [11,12].

A revision of the histological specimens by pathologists of the TREP panel was highly recommended. Hematoxylin-Eosin (HE) stained slides, paraffin blocks, and/or unstained sections were requested. All available HE stained sections and immunostains were reviewed, and the tumors were categorized using standard criteria according to the current WHO classification [13]. The immunohistochemical panel included the classic markers Pancytokeratin (MNF116), Vimentin, Inhibin, and WT1, recently identified as markers of SCST [14,15].

RESULTS

Clinical Findings and Surgical Treatment

Between January 2000 and July 2009, 23 patients (age 5–176 months, median 110), with ovarian SCST were enrolled from 13 Italian Centers.

The clinical features of the patients and the treatment results are reported in Table II. A common symptom was abdominal pain (12 patients) which was the only symptom in 5, and associated with palpable mass in 3, fever in 3, constipation in 2, vomiting in 2, and polliakiuria in 1. Three patients were hospitalized for an acute abdomen due to ovarian torsion in 2 and spontaneous rupture of the mass in 1. Nine out of 23 cases had signs of hormonal secretion: precocious telarca (7), pubarche (2) and menarche (3), leucorrhea (2), and amenorrhoea (1), variably associated with palpable mass, pain or fever. In two patients the tumor was an occasional finding at US performed for other reasons.

Serologic investigations were performed in 22 patients: AFP was slightly increased in 6 (range 17–76 μg/L), β-estradiol in 4, CA 125 in 4, CA 19.9, progesterone, LH and FSH in 2, testosterone and NSE in 1 respectively. Twenty patients underwent US, 17 CT scan, and an MRI was performed in 5: the characteristics of the lesions at imaging were variable, with solid and cystic areas in 12 cases, with solid aspect in 7.

Nineteen out of 23 patients underwent a primary surgical excision (Table II): adnectomy was done in 12 patients and the ovariectomy in 7. In two children, an initial biopsy was followed, by complete adnectomy and ovariectomy after 1 and 5 days respectively. One patient, initially treated with tumor enucleation, underwent adnectomy, due to suspected residual disease at histological evaluation, and one with bilateral synchronous tumor underwent adnectomy on the left and tumorectomy of the contralateral tumor.

In five patients, a biopsy of enlarged regional nodes was performed during the procedure: only in 1 with peritoneal spread, the nodes were positive (case #15). The biopsy of the contralateral ovary was performed in 2/22 cases with unilateral tumor, and in both, the histological examination excluded presence of disease.

A minimally invasive approach was performed in four cases: in one for the initial biopsy, in one for the ovariectomy, in one for the adnectomy after an incomplete excision, and in one case it was utilized to remove a metachronous contralateral tumor (adnectomy).

At macroscopic evaluation the maximum diameter of the mass ranged from 3 to 24 cm (mean value 13 cm). Nineteen patients out of 23 were grouped as ST I, 3 as ST II (spontaneous rupture with hemoperitoneum 1, intra-operative spillage and microscopic residuals after surgery 2) and 1 as ST IV (diffuse peritoneal spread and lymph nodes involvement).

Pathological and Immunohistochemical Findings

Macroscopic features were obtained from the original reports. The histological review confirmed the initial diagnosis in all cases but one which was originally interpreted as JGCT, while the following central review confirmed a diagnosis of SLCT-id (case #13). The series included: 12 JGCT, 6 SLCT, 3 Fibrothecomas/Theca Cell tumors, and 2 Stromal Sclerosing tumors.

Juvenile Granulosa Cell tumors ranged widely in diameter (from 3 to 23 cm) and appeared macroscopically as yellowish, nodular lesions. Cysts were present in five cases. The microscopic examination showed well circumscribed lesions, characterized by sheets of round to slightly elongated cells, with round nuclei, lacking the typical nuclear groove of adult GCT and eosinophilic cytoplasm. In case #10, wide areas of necrosis were seen, as well as scattered atypical cells. Mitotic index was often intermediate or high (range: 1–21 mitoses per 10 HPF).

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TABLE II. Clinical Features and Treatment of 23 Patients With SCST the Ovary Registered in the TREP Study

<table>
<thead>
<tr>
<th>Age (m)</th>
<th>Side</th>
<th>Symptoms</th>
<th>Surgical approach</th>
<th>Histology</th>
<th>Stage</th>
<th>CT</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (75)</td>
<td>R</td>
<td>Talarca, precocious menarche</td>
<td>Adnectomy</td>
<td>JGCT</td>
<td>I</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>2 (24)</td>
<td>L</td>
<td>Precocious puberty</td>
<td>Adnectomy</td>
<td>JGCT</td>
<td>I</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>3 (49)</td>
<td>L</td>
<td>Talarca, pubarche</td>
<td>Ovariectomy</td>
<td>JGCT</td>
<td>I</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>4 (118)</td>
<td>L</td>
<td>Abdominal pain, fever</td>
<td>Biopsy and ovariectomy</td>
<td>JGCT</td>
<td>I</td>
<td>Yes</td>
<td>CR</td>
</tr>
<tr>
<td>5 (167)</td>
<td>R</td>
<td>Abdominal pain, mass</td>
<td>Adnectomy</td>
<td>JGCT</td>
<td>I</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>6 (42)</td>
<td>L</td>
<td>Mass, precocious menarche, talarca</td>
<td>Adnectomy</td>
<td>JGCT</td>
<td>I</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>7 (66)</td>
<td>L</td>
<td>Talarca, leucorrhea</td>
<td>Adnectomy</td>
<td>JGCT</td>
<td>I</td>
<td>Yes</td>
<td>CR</td>
</tr>
<tr>
<td>8 (148)</td>
<td>L</td>
<td>Pain, fever, amenorrhoea</td>
<td>Adnectomy</td>
<td>JGCT</td>
<td>I</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>9 (110)</td>
<td>L</td>
<td>Pain, constipation, pollakiuria and mass</td>
<td>Ovariectomy</td>
<td>JGCT</td>
<td>I</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>10 (40)</td>
<td>R</td>
<td>Abdominal pain, fever</td>
<td>Adnectomy</td>
<td>JGCT</td>
<td>II</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>11 (7)</td>
<td>L</td>
<td>Pubarche, talarca</td>
<td>Ovariectomy</td>
<td>JGCT</td>
<td>I</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>12 (31)</td>
<td>R</td>
<td>Menarche, leucorrhea</td>
<td>Adnectomy</td>
<td>JGCT</td>
<td>I</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>13 (176)</td>
<td>L</td>
<td>Abdominal pain</td>
<td>Adnectomy</td>
<td>SLCT-id</td>
<td>I</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>14 (118)</td>
<td>L</td>
<td>Constipation, pain, mass and fever</td>
<td>Biopsy and adnectomy</td>
<td>SLCT with retiform pattern</td>
<td>II</td>
<td>Yes</td>
<td>DODa</td>
</tr>
<tr>
<td>15 (144)</td>
<td>L</td>
<td>Abdominal pain</td>
<td>Biopsy and adnectomy</td>
<td>SLCT with retiform pattern</td>
<td>IV</td>
<td>Yes</td>
<td>CR</td>
</tr>
<tr>
<td>16 (168)</td>
<td>R</td>
<td>Occasional diagnosis</td>
<td>Adnectomy</td>
<td>SLCT-id</td>
<td>I</td>
<td>No</td>
<td>2b CR</td>
</tr>
<tr>
<td>17 (40)</td>
<td>L</td>
<td>Abdominal pain</td>
<td>Incomplete enucleation and adnectomy</td>
<td>SLCT-id with retiform pattern</td>
<td>II</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>18 (102)</td>
<td>L</td>
<td>Talarca</td>
<td>Ovariectomy</td>
<td>SCT with annular tubules</td>
<td>I</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>19 (59)</td>
<td>L</td>
<td>Abdominal pain</td>
<td>Ovariectomy</td>
<td>Fibrothecoma</td>
<td>I</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>20 (175)</td>
<td>R</td>
<td>Fever, inappetence</td>
<td>Adnectomy</td>
<td>Fibrothecoma</td>
<td>I</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>21 (154)</td>
<td>R</td>
<td>Abdominal pain, vomiting</td>
<td>Ovariectomy</td>
<td>Fibrothecoma</td>
<td>I</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>22 (72)</td>
<td>R</td>
<td>Constipation, mass</td>
<td>Ovariectomy</td>
<td>Sclerosing stromal tumor</td>
<td>I</td>
<td>No</td>
<td>CR</td>
</tr>
<tr>
<td>23 (133)</td>
<td>Bil</td>
<td>Pain, vomiting, and constipation</td>
<td>Adnectomy + R enucleation</td>
<td>Sclerosing stromal tumor (bil. synchronous)</td>
<td>I</td>
<td>No</td>
<td>CR</td>
</tr>
</tbody>
</table>

CT = chemotherapy; m = months; L = left; R = right; Bil = bilateral; JGCT = juvenile granulosa cell tumor; SLCT = Sertoli–Leydig cell tumor; SLCT-id = Sertoli–Leydig cell tumor immediately differentiated; SCT = Sertoli cell tumor; Adnectomy = ovariosalpingectomy; CR = complete remission; HE = heterologous elements; DOD = died of disease. aRelapse in the lung and in contralateral ovary: a biopsy showed rhabdomyosarcomatous component. bRelapse in the contralateral ovary treated with adnectomy: bilateral metachronous tumor at histology.

Many SLCT were large in size (range: 3.3–18 cm), with yellow areas, and those showing a Leydig cell component were darker. Histologically, cases #15 and #17 were characterized by a network of branching slit-like tubules and cysts lined by epithelial cells with hyperchromatic nuclei and amphophilic cytoplasm. Solid sheets were also found. Case #14 was characterized by a sarcomatous component resembling fibrosarcoma; in this case, the local relapse in the contralateral ovary showed a prevalent sarcomatous component with associated focal areas of rhabdomyosarcomatous differentiation. Case #18 was a Sertoli Cell Tumor (SCT), with annular tubules containing a central hyaline body basement membrane material, without any Leydig element.

Fibrothecomas were large, white-yellowish masses mostly solid but with focal cystic features. The size ranged from 8 to 24 cm. Microscopically they were characterized by elongated cells with clear cytoplasm, bland oval nuclei, and occasional lutein cells. Mitoses were absent in all cases.

The two sclerosing stromal tumors (one bilateral) showed cellular pseudo-lobules with blood vessels in a typical hemangiopericytomatosus stroma surrounded by fibroblast and rounded cells often vacuolated with eccentric nuclei and clear cytoplasm with signet ring-like features. Mitoses were absent. Immunohistochemical investigations were performed in 10/23 cases (Table III). WT-1 was shown to be expressed positive in 3 SLCT and 1 JGCT, Inhibin, in 8, Vimentin in 8, and Pancytokeratin (MNF116) in 3.

Further Therapy and Outcome

Chemotherapy (CT) was delivered in 4/23 cases and was administered cautiously in two patients with ST I JGCT because of tumor size (11 cm × 10 cm × 5.5 cm in a 4-year-old female, and 22 cm × 10 cm × 12 cm in a 10-year-old patient, respectively), in 1/3 ST II patient (SLCT) and in the ST IV patient (SLCT). The other two patients with ST II disease did not receive CT, by physician decision (JGCT) and by parental refusal (SLCT-id) respectively.

Twenty-one patients are alive in first complete remission (CR) with a mean follow-up of 27 months (range 9–91 months); one female with ST I SLCT obtained the second CR after removal of a metachronous controlateral SLCT, that occurred 24 months after the first operation (bilateral adnectomy); another female with a ST II SLCT died because of progressive disease after metastatic relapse (controlateral ovary and lung) after CT treatment.

DISCUSSION

Ovarian sex cord-stromal tumors are a heterogeneous group of neoplasms which are rarely encountered in a daily Pediatric Surgery and Pediatric Oncology practice. They are characterized by various clinical features with often increase of hormonal secretion and different behavior. What it is known about these tumors derives essentially from few case reports concerning a particular histotype.
or series including patients observed in long periods of time [11,16,17], and definite guidelines for their treatment, especially in case of advanced disease, do not exist. A recent prospective study on ovarian SCST in children and adolescents offers some diagnostic and therapeutic suggestions on the basis of their clinical and histological assessment [11].

Our analysis includes 23 patients, observed over 9 years and 7 months, and enrolled on a multicentric study for very rare pediatric tumors. It might be hypothesized that some cases, especially those observed in teenagers, could not be registered, since these patients are mostly treated in Gynecology and Oncology Centers, explaining the tendency to under-report their number, as recently demonstrated by Pastore et al. [18].

Concerning the clinical characteristics, the most common symptom in our series was abdominal pain with or without abdominal mass. The endocrinologic symptoms were more common in younger and prepubertal females, with a median age of 42 months, but while they were present in 66% in JGCT, in accordance with other reports, in SLCT, these data was lower then expected (16%) [11,16,19]. The presence of hormonal signs may address the diagnostic work-up, makes more possible an early diagnosis [20], and the further surgical approach.

Inhibin-b has recently obtained consideration as a serum marker either at diagnosis and during the follow-up of adult SCST, especially Granulosa Cell tumors [21]. However elevated Inhibin-b levels were observed also in adult epithelial ovarian cancer, particularly in the mucinous variety [21–24]. Its evaluation is recommended also in children [25,26].

As expected, JGCTs were the most frequent histotype. The clinical presentation was comparable with that reported in literature [11,16]. All had early stages at diagnosis and excellent outcome after surgery, including those with huge tumors. We did not observe cases with advanced disease, as described by other authors [11,17,27], and also those tumors with high mitotic index (HMI), normally associated with a more aggressive behavior [17,28], had a favorable clinical course.

SLCTs occurred in older patients (mean age 125 months) and the majority did not have endocrine manifestations. In this group only one patient with ST II disease, due to intraoperative rupture of the tumor, died of disease: the tumor, characterized by heterologous elements, known to be associated with a more aggressive behavior relapsed 12 months after the first operation, and the histological examination showed a predominant rhabdomyosarcomatous component.

As previously reported [16,29,30], the aggressiveness of SLCTs is higher in tumors with retiform pattern and/or heterologous elements. These features suggest a possible malignant behavior and the necessity of a more aggressive treatment. In the largest series published to date on 164 SLCT, the outcome seemed to correlate with both stage and histological differentiation [31].

Fibrothecomas and Sclerosing Stromal tumors are benign tumors, very uncommon in children: an appropriate treatment must be managed preserving patients’ fertility and avoiding extended surgical procedures [5], but the rarity of this entities and the clinical similarities with other SCSTs keep this purpose very difficult to achieve. In our series, 3/23 patients had a fibrothecoma and all are free of disease after surgery; 2 had a Sclerosing Stromal tumor (one bilateral and synchronous), even more rarely observed (less than 30 cases are reported in literature [5,16,32]). No further therapy was delivered after the complete excision. The first patient was lost to follow-up and the other is alive and free of disease at 12 months after diagnosis.

The extension of the surgical excision for ovarian SCSTs is still debated. Most authors are in favor of the ovariectomy and recommend the adnectomy when the salpinx is adherent and/or suspected to be involved; others support a sparing surgery, especially in small and well encapsulated lesions, followed by the ovariectomy, if necessary, on the basis of the histological results. Our therapeutic strategy has generally not favored a sparing surgery, as well as laparoscopic approach, to avoid incomplete excision or tumor spillage. Minimally invasive procedures have been recently accepted in patients with small tumors. Several authors underline that a complete surgery is sufficient to avoid recurrence and allow a complete remission independently from the histological features [20].

The histological diagnosis of SCST may be difficult, especially for those SLCTs which can display a wide morphologic variation. In our experience, immunostaines were helpful to exclude other diagnoses. Immunohistochemical detection for Inhibin, observed in all

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**TABLE III. Pathological Findings and Outcome in 10 Patients With Immunohistochemical Investigations**

<table>
<thead>
<tr>
<th>Case #</th>
<th>Stage</th>
<th>Histology</th>
<th>MI</th>
<th>Inh</th>
<th>Vim</th>
<th>MNF-116</th>
<th>WT-1</th>
<th>D2-40</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>II</td>
<td>JGCT</td>
<td>H</td>
<td>++</td>
<td>Neg</td>
<td>++</td>
<td>Neg</td>
<td>Neg</td>
<td>CR</td>
</tr>
<tr>
<td>11</td>
<td>I</td>
<td>JGCT</td>
<td>H</td>
<td>++</td>
<td>+++</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>CR</td>
</tr>
<tr>
<td>12</td>
<td>I</td>
<td>JGCT</td>
<td>L</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>Neg</td>
<td>CR</td>
</tr>
<tr>
<td>14</td>
<td>II</td>
<td>SLCT-id with retiform pattern and HE</td>
<td>H</td>
<td>+*</td>
<td>Neg</td>
<td>Neg</td>
<td>+§</td>
<td>Neg</td>
<td>DOD</td>
</tr>
<tr>
<td>15</td>
<td>IV</td>
<td>SLCT with retiform pattern</td>
<td>H</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>CR</td>
</tr>
<tr>
<td>16</td>
<td>I</td>
<td>SLCT-id</td>
<td>H</td>
<td>+*</td>
<td>+++</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>2nd CR</td>
</tr>
<tr>
<td>17</td>
<td>I</td>
<td>SLCT-id with retiform pattern</td>
<td>L</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
<td>Neg</td>
<td>CR</td>
</tr>
<tr>
<td>18</td>
<td>I</td>
<td>SCT with annular tubules</td>
<td>L</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>Neg</td>
<td>CR</td>
</tr>
<tr>
<td>20</td>
<td>I</td>
<td>Fibrothecoma</td>
<td>L</td>
<td>Neg</td>
<td>/+</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>CR</td>
</tr>
<tr>
<td>22</td>
<td>I</td>
<td>Sclerosing stromal tumor</td>
<td>L</td>
<td>Neg</td>
<td>+++</td>
<td>Neg</td>
<td>Neg</td>
<td>Neg</td>
<td>CR</td>
</tr>
</tbody>
</table>

JGCT, juvenile granulosa cell tumor; SLCT, Sertoli–Leydig cell tumor; SLCT-id, Sertoli–Leydig tumor intermediately differentiated; SCT, Sertoli cell tumor; Inh, Inhibin; Vim, Vimentin; MNF-116, Pancytokeratin; WT-1, Wilms tumor protein 1; D2-40, Podoplanin; MI, mitotic index; H, >10 mitoses/10 HPF; L, <10 mitoses/10 HPF; +++, positive staining in scattered cells; +++, positive staining >50%; +++, diffusely positive staining; +*, positive staining only in Sertoli cells; +§, positive staining only in rhabdomyoblastic cells.

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SLCTs, led to exclude the diagnosis of GCT. Fibrothecomas and Sclerosing Stromal tumors, as expected, were negative for Inhibin. WT-1 resulted to be seldom positive in SLCT and JGCT and not found and is of primary importance in term of a complete resection is possible when an abdominal mass or hormonal signs are expressed in the other patients, whereas it has been described as a valid marker in SCSTs, especially in SCL/SLCT [33–35] but also in JGCT [35,36] and in thecoma/SST group [35,37].

In our study patients were evaluated and treated prospectively in different centers according to common recommendations. These tumors have to be considered in the differential diagnosis with GCT also when hormonal signs are not present. An early diagnosis is possible when an abdominal mass or hormonal signs are found and is of primary importance in term of a complete resection without any other treatment. In our series all patients who underwent an initial complete excision were cured, independent of the size of the tumor.

A cisplatin-based chemotherapy was useful in patients with residual disease after surgery or metastatic spread; however, the optimal role of chemotherapy is still to be defined and larger series are necessary to make conclusions. International cooperation would likely improve our knowledge on these tumors in term of clinical findings and histopathology characteristics.

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