J. Cell. Mol. Med. Vol 7, No 4, 2003 pp. 461-471

Sertoli-Leydig cell tumor - a rare androgen secreting ovarian tumor in postmenopausal women

Case report and review of literature

Ancuta Gheorghisan-Galateanu [a] *, Simona Fica [b], Dana Cristina Terzea [c], Andra Caragheorgheopol [d], V. Horhoianu [e]

[a] *Department of Cellular and Molecular Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[b] *Department of Endocrinology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[c] *Department of Morphology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[d] *Laboratory of Hormonology, Institute of Endocrinology "C. I. Parhon", Bucharest, Romania*
[e] *Department of Gynecology, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*

Received: August 30, 2003; Accepted: October 6, 2003

Abstract

Sertoli-Leydig cell tumors (SLCT) constitute only 1-0.5% of all primary ovarian neoplasms. We report a SLCT in a postmenopausal woman aged 69 years. The physical examination revealed severe hirsutism. Basal hormonal evaluation showed high plasma testosterone and estradiol values, with suppressed plasma gonadotropins. Computer tomograph scan revealed a right ovarian tumor mass of 4,3/3 cm, confirming an androgen secreting ovarian tumor. The histopathological and immunocytochemical examination established the diagnosis of well differentiated Sertoli-Leydig cell tumor. The tumor was positive for cytokeratin KL 1 and S-100 protein and, in isolated tumor cells, positive for alpha-fetoprotein. Postsurgical evolution was favorable; controls after 6 months and 3,5 years showed marked reduction of hirsutism, normal plasma testosterone values and gonadotropins in normal postmenopausal range. We discuss the complex aspects of etiology and pathogenesis, the clinical and hormonal settings, the role of immunocytochemical markers in diagnosis, as well as the therapy and the prognostic features of this ovarian tumor.

Keywords: androgen secreting ovarian tumor - Sertoli-Leydig cell tumor - postmenopause - diagnosis - pathogenesis

Introduction

The Sertoli-Leydig cell tumor (SLCT) or arrhenoblastoma is a rare ovarian tumor (0,1-0,5%) of unknown pathogenesis, occurring more frequently in women of reproductive age (78%). Some cases are discovered during pregnancy and only a few in childhood and in postmenopausal women.

It is generally a benign tumor which originates from the ovarian stromal sex cords [1], with a mixed tissue structure resembling the Sertoli and Leydig testicular cells. SLCT is a androgen secreting ovarian tumor (androblastoma). Recent studies

* Correspondence to: Ancuta GHEORGHISAN-GALATEANU
"Carol Davila" University,
8 Eroilor Sanitari Blvd., 76241 Bucharest, Romania.
Tel./Fax: +40(0)21 312 4855,
E-mail: agheorghisan@hotmail.com

showed that the lack of estrogen signal in the adult ovaries induces follicle transdifferentiation to structures resembling seminiferous tubules of the testis. These data suggest a possible role of the steroid environment in the development of a SLCT in the ovary. SLCT is associated with secondary amenorrhea and in 2/3 of cases with hirsutism and other signs of virilization. In 50% of the cases, SLCT does not have endocrine manifestations. The tumor cells of SLCT secrete steroids similarly to the ovarian theca cells, hormonal profile being dominated by high plasma testosterone values. This fact may be a support for the development of the Sertoli tumor cells in SLCT from preexisting granulosa cells. The main ways in diagnosis of SLCT are routine pathology and immunocytochemistry, both of them having a great prognostic value. The therapy and prognosis of SLCT depend on the age, stadialization of the tumor and the degree of differentiation. We describe a case of SLCT in a postmenopausal woman and discuss the complex aspects of etiology and pathogenesis, the clinical and hormonal settings, the role of immunocytochemical markers in diagnosis, as well as the therapy and the prognostic features of this unique ovarian tumor.

Case report

A 69- year-old female patient was diagnosed for the first time in 1997, at the age of 63, with hirsutism of recent onset (10 years after menopause) and rapidly progressing. The medical history of the patient consists of two thyroidectomies at the age of 44, and respectively 61 ys (at the time of examination receiving L-thyroxine 100 μg daily, , which maintained a normal TSH (3 mU/L), with a family history of nodular goiter affecting both male (brother) and female (mother), hypertension, dyslipidemia, and NIDDM controlled with diet. At that time she had major signs of virilization - hirsutism (facial, lip, breast, abdomen) (Fig. 1) and deepening of the voice. The testosterone was high, with low for menopausal age gonadotropins. Adrenal excretion of urinary 17 ketosteroids (9,15 mg/24h) and 17 hydroxisteroids (10,3 mg/24h) was normal, and decreased after low dose dexamethasone test at 5,88 and 2,38 mg/24h, respectively. Hormonal values are presented in Table 1.

The gynecological examination and pelvic ultrasound revealed endometrial hyperplasia and a right ovary of 3/2 cm. The diagnosis was of androgen secreting ovarian tumor, confirmed by CT examination - a right ovarian tumoral mass with the dimensions of 4.3/3 cm (Fig. 2). The adrenal glands had a normal aspect both by ultrasound and CT. A hysterectomy with bilateral oophorectomy was performed, followed by postsurgical safety cobaltotherapy.

The histopathological (Fig. 3-7) and immunocytochemical (Fig. 8-14) examination of the tumor established the diagnosis of well differentiated SLCT and cystic endometrial hyperplasia.

The postsurgical evolution was favorable; follow up after 6 months and 3.5 years showed a marked reduction of hirsutism, normal plasma testosterone values and gonadotropins in the normal postmenopausal range (Table 1).

Table 1 Case P.N. Hormonal profile before and after the surgical cure.

Evaluation	Testosterone	Testosterone	FSH	LH	E2
	ng/ml	ng/ml	mUI/ml	mUI/ml	pg/ml
	baseline	after DXM			
Before	8.65	5.21	8.09	2.31	53.72
After 6 mo	0.54	-	92.8	48.38	13.48
After 3.5 y.	0.69	-	86.77	25.76	-

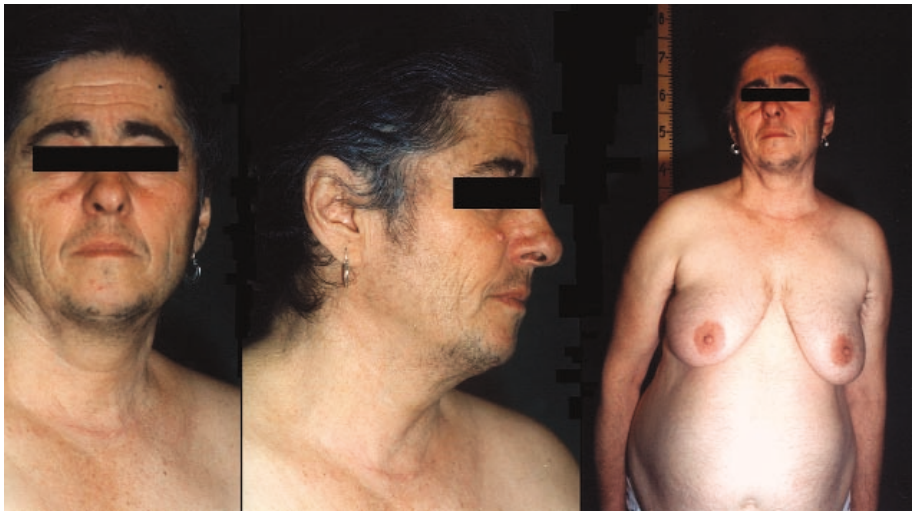


Fig. 1 Case P.N. Female patient with rapidly progressing hirsutism of recent onset.

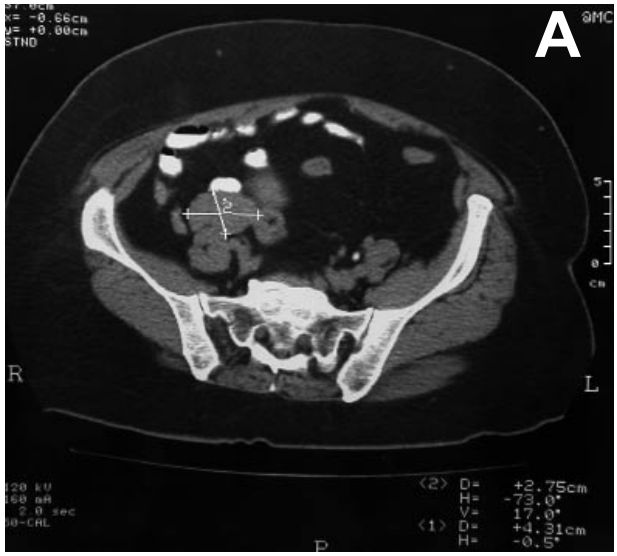
Discussion

This case report illustrates several points relevant for the clinical, histopathological and immunocytochemical aspects of SLCT.

Although the peak incidence of SLCT is during the reproductive period of the woman, this case shows a rare situation of an androgen secreting ovarian tumor- SLCT - after menopause. Irrespective of the age of onset, the clinical findings of severe, rapid virilization are frequently associated with a tumor source of androgens, SLCT being the most frequent cause of virilizing ovarian tumor. The virilizing effects of the tumor were most probably caused by accumulation of testosterone due to deficiency in enzymes transforming testosterone to 17-ketosteroids or aromatization to estrogens [2]. SLCT requires a differential diagnosis with other origins of hyperandrogenemia (drugs induced androgenization, Cushing's syndrome, neoplasms of the adrenal, other neoplasms of the ovary, pituitary adenoma, adrenal hyperplasia, polycystic ovary syndrome, several systemic conditions) [3].

The histogenesis of SLCT is still a matter of controversies, with 3 hypotheses for the origin of the tumoral tissue [4]:

- residual sex cords from the indifferent primitive gonad, originating in the coelomic tissue



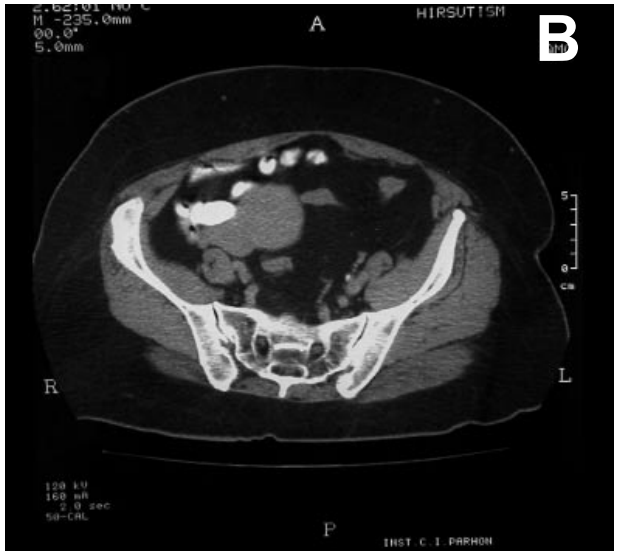


Fig. 2 A, B. Case P.N. Axial CT examination. A right ovarian tumoral mass (see markers).

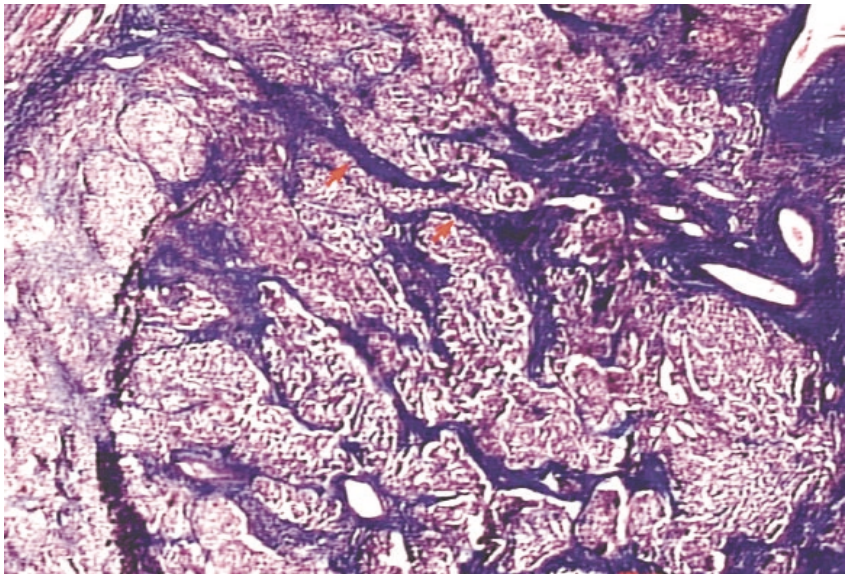


Fig. 3 Case P.N. SLCT- well differentiated. Ovarian tumoral mass is compartmented in pseudolobules by connective tissue septa, rich in collagen fibers Col HEA x40.

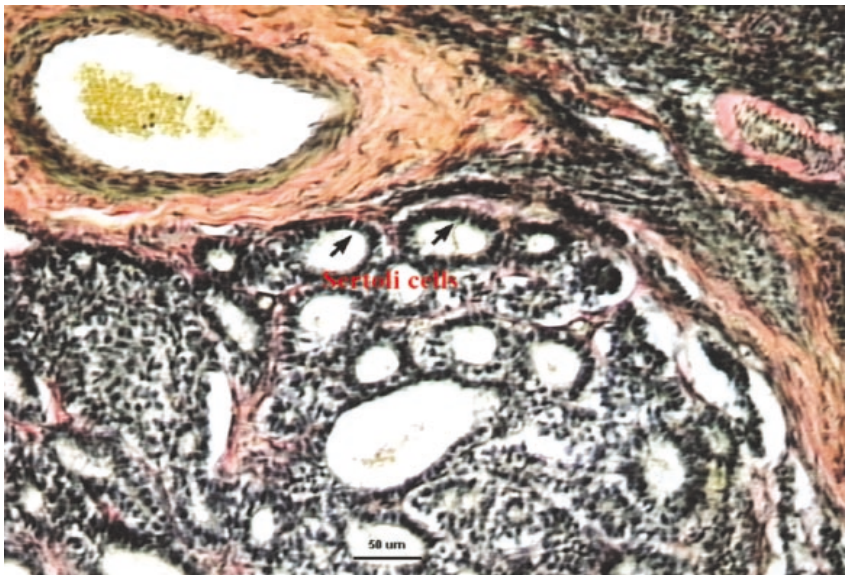


Fig. 4 Case P.N. SLCT- well differentiated. Compact anastomosing cords and small tubules embedded within a fibrous stroma. Col van Gieson x100.

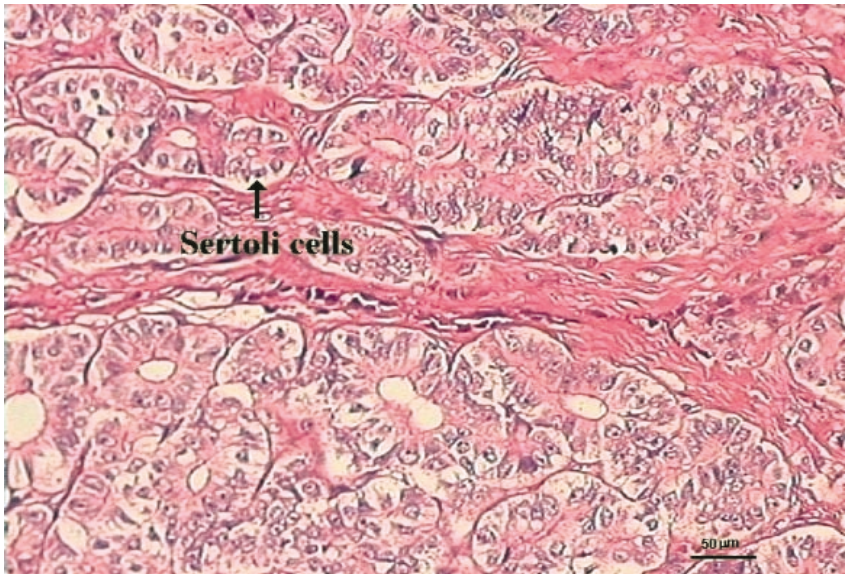


Fig. 5 CaseP.N. SLCT-well differentiated. Cords, nests and tubules of tumoral Sertoli cells are present in the tumoral mass. Col HE x200.

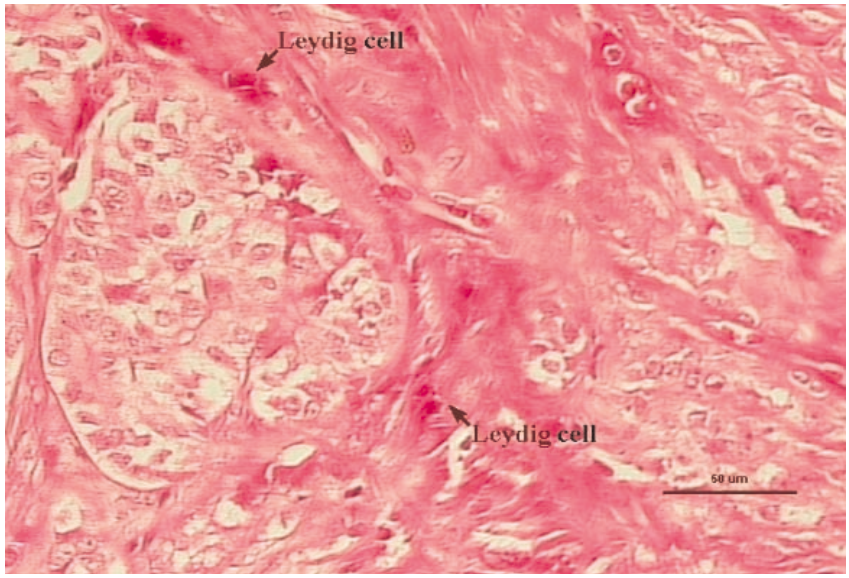


Fig. 6 Case P.N. SLCT-well differentiated. In stroma, next the tumoral Sertoli cells, a small number of tumoral Leydig cells Col HE x400.

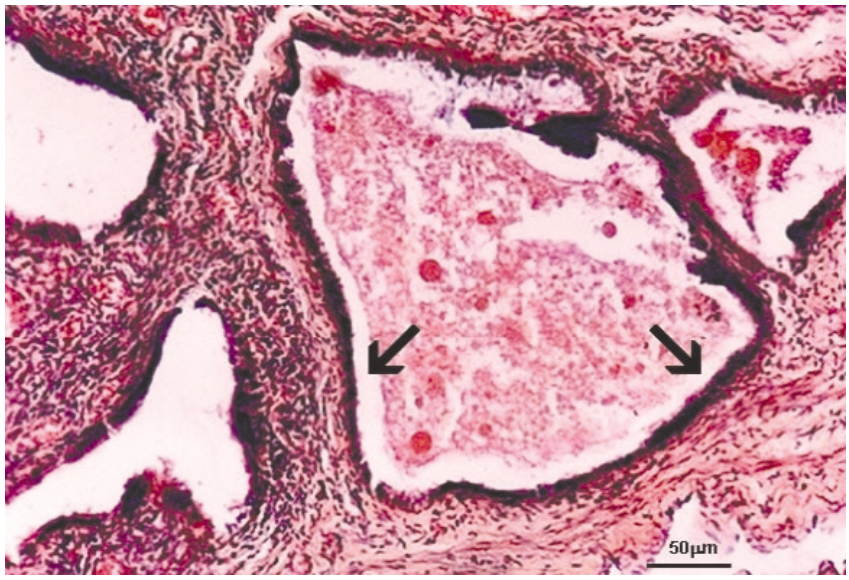


Fig. 7 Case P.N. SLCT-well differentiated. Cystic endometrial hyperplasia. Col HE x100.

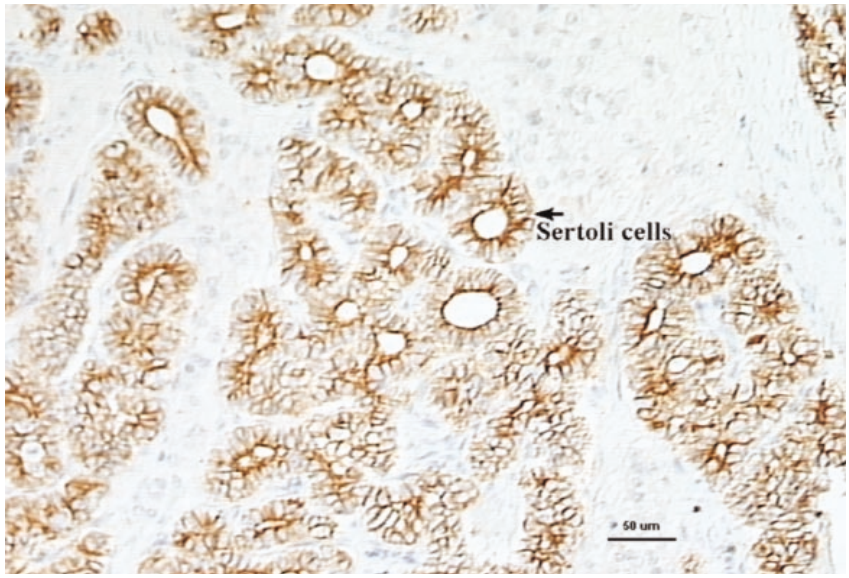


Fig. 8 Case P.N. SLCT-well differentiated. The areas with tumoral Sertoli cells are positive for cytokeratin KL 1 x100.

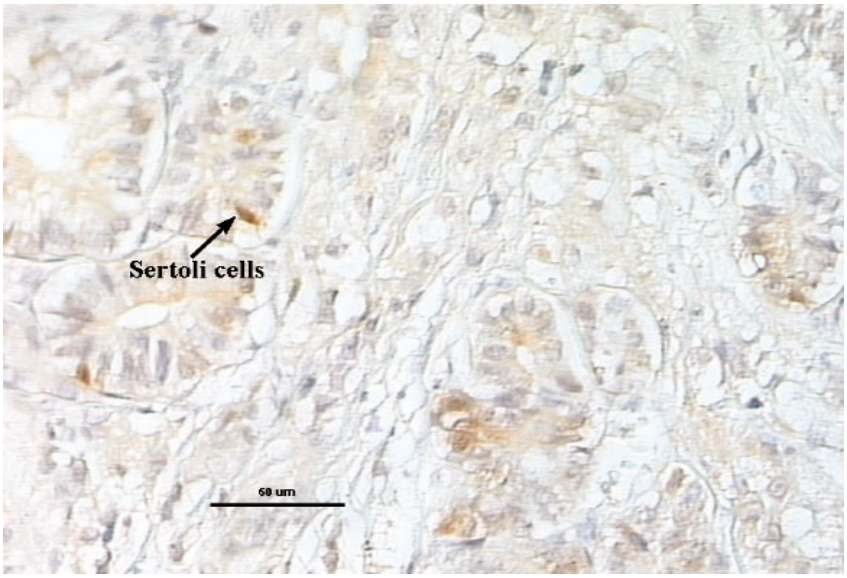


Fig. 9 Case P.N. SLCT-well differentiated. The areas with tumoral Sertoli cells are positive for S-100 protein x200.

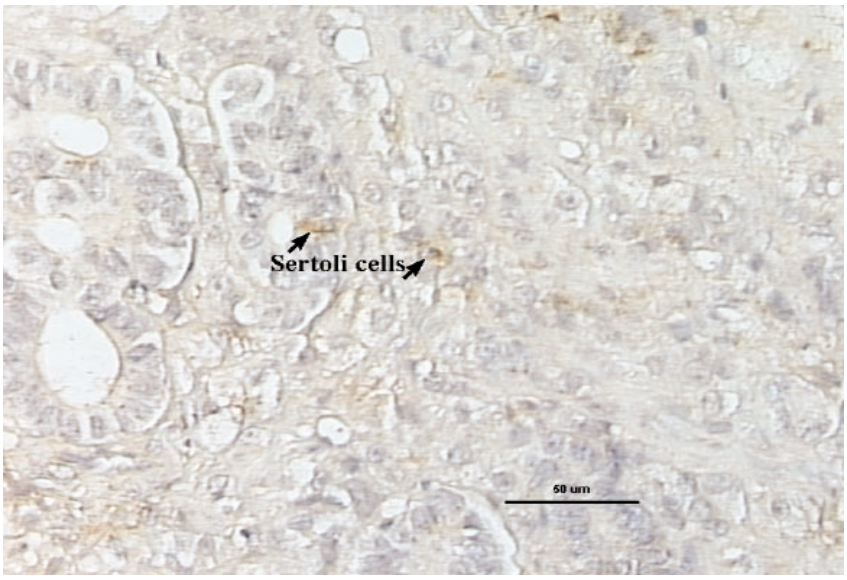


Fig. 10 Case P.N. SLCT-well differentiated. AFP1 is positive in isolated tumoral cells x200.

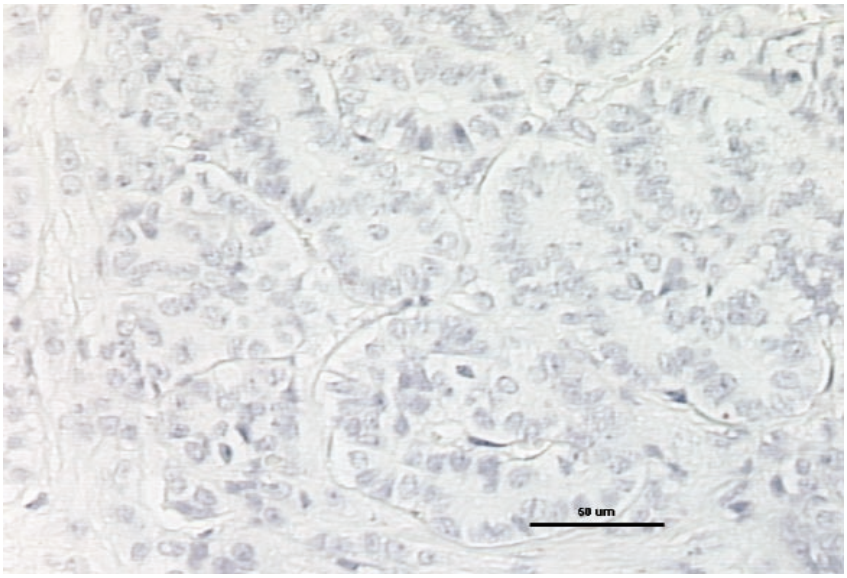


Fig. 11 Case P.N. SLCT-well differentiated. The areas with tumoral Sertoli cells are negative for CEA1 x200.

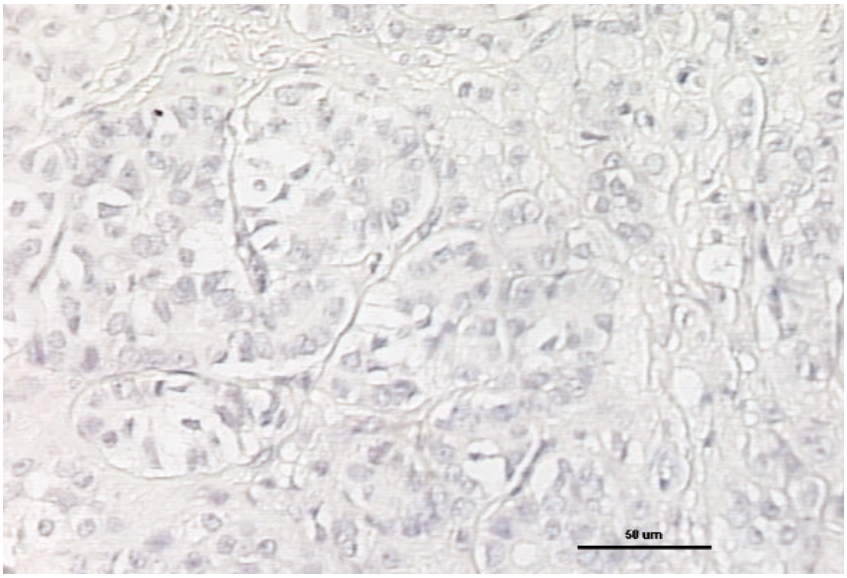


Fig. 12 Case P.N. SLCT-well differentiated. The areas with tumoral Sertoli cells are negative for EMA 1 x200.

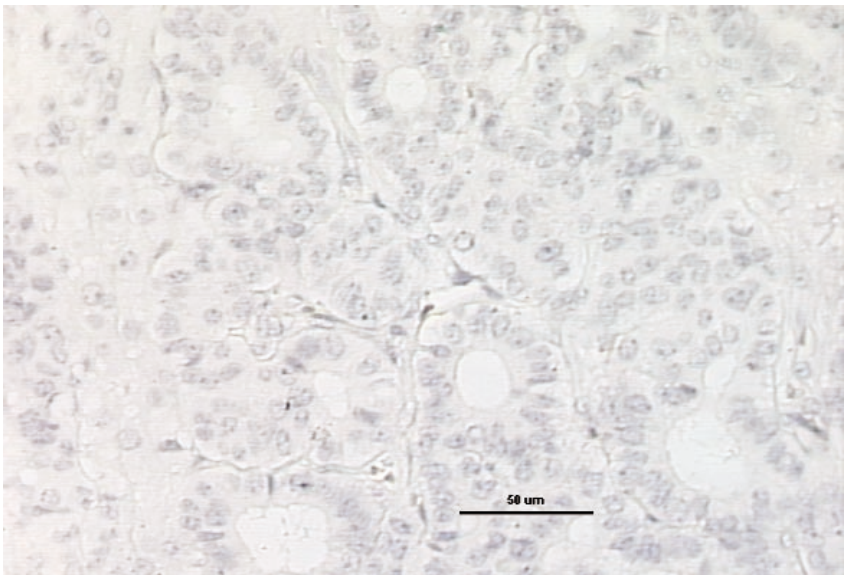


Fig. 13 Case P.N. SLCT-well differentiated. The areas with tumoral Sertoli cells are negative for CA125 x200.

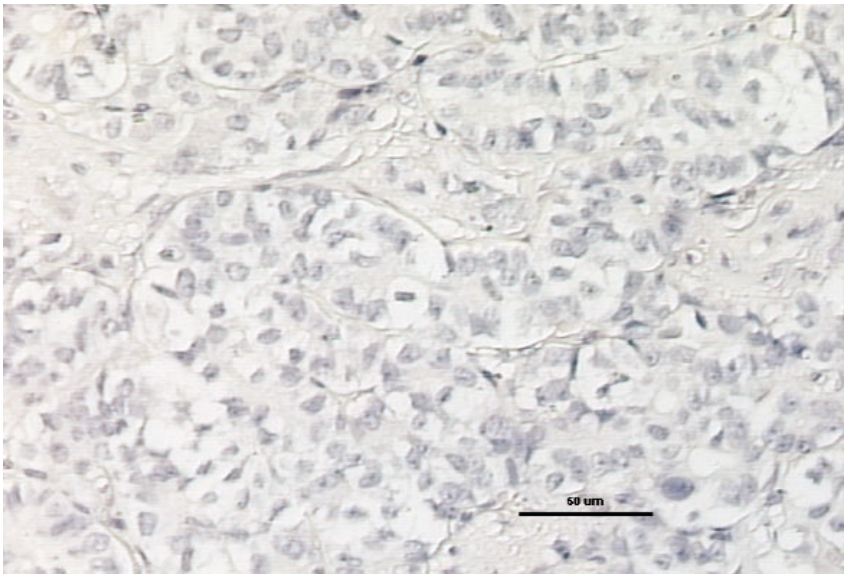


Fig. 14 Case P.N. SLCT- well differentiated.The areas with tumoral Sertoli cells are negative for Fapl 1 x200.

- mesenchymal cells of the cortical and medullar primitive gonad (undifferentiated multipotent endocrine stroma)
- primitive ovarian medulla from the mesonephric mesenchyme

In most cases it is accepted that the tumor originates from the ovarian stroma in ovotestis [5]. The mammalian sex determination and differentiation of the gonads is under the control of the sex-determining gene, Sry, on the chromosome Y. Recent studies suggest that the differentiation of somatic cells in the ovary is influenced by their estrogen environment [6]. The lack of estrogen signal in the adult ovaries induces follicle transdifferentiation to structures resembling seminiferous tubules of the testis, with Sertoli-like cells and expression of the Müllerian inhibiting substance [7]. These data suggest a possible role of the steroid environment in the ovarian transdifferentiatin and oncogenesis. These considerations can be discussed in the presented case, related to diagnostic in postmenopause and its specific hormonal features.

Electronmicroscopy studies have shown that tumor Sertoli cells resemble more ovarian granulose cells, than testicular Leydig cells. Tumoral Leydig cells had a typical ultrastructure of steroid - producing cells. Stimulation of these cells by HMG-HCG did not show significant changes in their activity, suggesting that production of androgens by tumor Leydig cells is independent on gonadotropins [8]. The demonstration that Leydig cells from SLCT are polyclonal suggests that their origin is nonneoplastic [9]. Also, both tumor cell types (Sertoli and Leydig) are positive for sex chromatin, indicating that their origin is more likely from specialized ovarian stromal cells [10].

Genetic studies suggest a possible involvement of the transcription factor GATA 4 in the tumorigenetic process or in the progression of SLCT, this factor being identified in tumoral Sertoli and Leydig cells [11]. There is a possible association of SLCT with sex chromosome abnormalities; it was report one case of SLCT with X chromosome mosaicism (45X/46XX/47XXX) [12] and one case of female karyotype with Y-chromosomal material insertion into chromosome 1 in an ovarian Sertoli-Leydig cell tumor with endometrioid-like yolk sac tumor [13]. In our case the chromosomal analysis revealed a 46,XX karyotype. This results of genetic studies show the need of new methods for the diagnosis and genetic investigations in the families were such cases have been reported based on molecular and cytogenetic models.

Studies *in vitro* have shown that cells of SLCT can secrete steroids similarly to the ovarian theca cells (dehydroepiandrosterone, androstenedione, testosterone, 17-hydroxy progesterone), but lacking aromatization. Determination of hormone levels indicates that, although both the D_4 and D_5 pathways are involved, the D_4 pathways is probably dominant in androgen biosynthesis [14]. There is no correlation between the degree of tumor differentiation and the testosterone level. The excessive testosterone production appears to have a little effect on the plasma level of sex steroid binding globulin, since these levels are similar before and after removal of the tumor [15]. ACTH test induces slight changes in androgen secretion, dexamethasone test decreases androstendione and dehydroepiandrosterone, whereas testosterone levels are only partially suppressed, while HCG test stimulates testosterone and androstendione production. Supressed gonadotropin levels did not respond to LHRH stimulation [16]. The suppressing effect of LHRH-agonist on the secretion of testosterone suggest that LH-RH receptors are present in the tumor cells of SLCT. This finding shows that the treatment with LHRH agonist may be beneficial in patients with androgen secreting metastatic ovarian tumors [17]. Some cases of SLCT can be associated with a high production of estrogens or progesterone. It was suggested that the excessive secretion of estrogens might have originate in the hypertrophy tecal tissue found in tumoral gonad rather than in the tumor itself [18]. Some authors reported cases with increased production of inhibin [19] and alpha-fetoprotein (in tumors with areas of hepatocytic differentiation) [20].

In our case the hormonal profile is dominated by the high plasma testosterone values and suppressed gonadotropins. The hormonal profile of the case presented also included: normal plasma estradiol, but relatively high for the postmenopausal age and normal urinary 17 ketosteroids. The estrogenic stimulation of the uterus in our case, in a postmenopausal woman with no hormonal replacement therapy, could be the result of peripheral androgen aromatization to estrogens, rather than the direct tumoral secretion of estradiol.

SLCT are dysembrional tumors - benign or malignant tumors originating from residual embryonic cells, capable of tissue differentiation, or rarely "sarcomas" - malignant tumors originating from the connective tissue [21]. The tumor tissue has a variable proportion of Sertoli, Leydig and stromal cells. The Leydig cells are an inconstant feature and have a low mitotic index [22].

Pathology and immunocytochemistry are basic tools for diagnosing the type of SLCT, having also a prognostic value.

Sertoli-Leydig cell tumors are classified in five histological types, which have different prognoses: well differentiated, of intermediate differentiation, poorly differentiated, with a retiform component and with heterologous elements (gastrointestinal-type epithelium, hepatocytes, skeletal muscle or cartilage) [23].

Immunohistochemistry is useful in distinguishing SLCT from other tumors that they may resemble. The immunocytochemical characterization of SLTC reveals positive stains of the Sertoli and Leydig cells for testosterone and estradiol [24]. Testosterone synthesis take place predominantly in the tumor Leydig cells, but also to a small extent in the tumor Sertoli cells [25]. The areas with tumor Sertoli cells are positive for keratins and vimentin, and negative for epithelial membrane antigen (EMA), placenta-like alkaline phosphatase (PLAP), carcinoembryonic antigen (CEA), CA 19.9, CA 125 or S-100 protein [26]. The tumor Leydig cells have negative reactivity for keratins and show positive immunoreactivity for vimentin and for alpha-inhibin (in 91% of cases) [27]. The association of positive staining for alpha-inhibin and negative staining for EMA supports the diagnosis of a stromal sex cords tumor [28]. These results show that the inhibin immunostaining may be useful in the differential diagnosis, but inhibin negativity does not exclude a diagnosis of sex cord tumor [29]. It were reported cases with positive alpha-fetoprotein (AFP) in SLCT with hepatocytic differentiation [30]. In the last years it has been described that relaxin-like factor, a new member of the insulin-like growth factor family, is a marker for normal Leydig cells in the human postpubertal testis [31]. In this context investigations of the expression of relaxin-like factor in ovarian Sertoli-Leydig cell tumors must be considered.

In our case the tumor cells are positive for cytokeratin KL1 and S-100 protein, while AFP 1 was positive in isolated tumoral cells. For the differential diagnosis of SLCT with other ovarian tumors (especially adenocarcinomas) we have used immunostaining for CEA 1, EMA 1, CA 125 and PLAP, in all situation the tumoral cells having a negative immunoreactivity.

The ultrasound examination of the ovaries is the first choice diagnostic procedure. In cases of small tumors, undetected by ultrasound imaging techniques, the diagnosis is sustained by the high testosterone values in samples from the ovarian veins (selective catheterization) [32]. In our patient it was possible to identify the ovarian tumor with pelvic ultrasound, due to its dimensions.

In over 90% of cases the tumor is unilateral (usually in the left ovary) located in the ovarian medulla, sometimes multifocal. Our case presented with a right ovarian tumor of 4.3/3 cm. SLCTs are solid tumors, with dimensions that correlate with the degree of differentiation- well differentiated tumors are under 0.5 cm, while poorly differentiated tumors can reach up to 10-15 cm. SLCTs under 5 cm are usually benign [33].

Rarely, SLCT can be associated with other tumor-like mucynous cystadenoma [34], cervical sarcoma [35], ovarian serous cystadenoma [36], endometrial carcinoma, or polycystic ovaries [37].

Relapses after surgical treatment of SLCT were reported in 33% of the cases. They are more common in poorly differentiated tumors [38]. SLCT is a tumor with a low incidence of malignancy. Metastases are commonly observed in the omentum, the abdominal lymph nodes and in the liver. A rare case was reported with a metastasis in the frontal sinus [39].

To establish the prognosis in a female patient with SLCT, the evaluation of telomerase activity (a ribonucleoprotein that protects chromosomes from degradation and end-to-end fusions by maintaining telomere length) was proposed because it is considered that telomerase activation is a primarily step in carcinogenesis. Recent studies showed the link between telomerase activity and the bad prognosis in some patients with sex cord-stromal tumors of the ovary [40]. Despite this, telomerase activity cannot be use as a predictive factor in the evaluation of malignant sex cord-stromal tumors of the ovary, some aggressive tumors being associated with negative telomerase [41]. Also, a few studies indicate that in SLCT a simple numeric chromoso-

mal abnormality, for example trisomy 8, may be associated with a malignant phenotype [42].

The therapy and prognosis of SLCT depend on the age, stage of the tumor and the degree of differentiation. In young women the therapy of choice is unilateral surgical removal of the ovary and the salpinx, while older patients benefit from bilateral castration with hysterectomy, as was performed in our case. After the surgical treatment, plasma testosterone values decreased rapidly, but the signs of virilization regressed slowly. Some cases can benefit from adjuvant therapy with GnRH analogs [43]. In cases with positive staining for alpha-fetoprotein or poorly differentiated tumors with metastases, adjuvant chemotherapy with bleomycin, etoposide and cysplatine or vincristine, actinomycine and cyclophosphamide showed beneficial short term results [44]. Postoperative monitorizing of SLCT consisted in periodic plasma determinations of testosterone and inhibin.

The present study shows a particular case of SLCT, due to its postmenopausal onset, with remarkably favorable evolution after the surgical treatment. The histological form of SLCT (well differentiated) has a low recurrence rate and a good prognosis. The patient is under frequent medical controls; 5 years after surgery there was no evidence of recurrence. The correct precocious diagnosis with histological characterization of cell differentiation and immunochemistry is essential for the evolutive potential of SLCT, the risks of metastases and the impact on the rate of survival.

The medical history of pathological association between SLCT and thyroid disease, in our case, might suggest the existence of a new specific type of endocrine complex disease genetically determined.

References

1. **Montella L.,** Virilizing ovarian tumors: arrhenoblastoma, *Rass. Int. Clin. Ter.*, **52**:732-738, 1972
2. **Maschler I., Weidenfeld J., Fleischer B., Ehrenfeld E.N., Finkelstein M.,** Steroidogenesis in a virilizing ovarian tumor, *Clin. Endocrinol.*, **4**: 427-436, 1975
3. **Fleckenstein G., Sattler B., Hinney B., Wuttke W., Osmers R., Emons G.,** Androblastoma of the ovary: clinical, diagnostic and histopthologic features, *Onkologie,* **24**: 286-291, 2001
4. **Young R., Clement P.B., Scully R.E.,** The ovary. In: Diagnostic Surgical Pathology, Sternberg S.S., ed., Raven Press, New York, 1989, pp.1687-1690
5. **Tanaka Y.O., Ide Y., Nishida M., Nishide K., Tsunoda H., Kajitani M., Itai Y.,** Ovarian tumor with functioning stroma, *Comput. Med. Imaging Graph.,* **26**: 193-197, 2002
6. **Britt K.L., Findlay J.K.,** Regulation of the phenotype of ovarian somatic cells by estrogen, *Mol. Cel. Endocrinol.*, **202**: 11-17, 2003
7. **Couse J.F., Curtis Hewitt S., Bunch D.O., Sar M., Walker V.R., Davis B.J., Korach K.S.**, Postnatal sex reversal of the ovaries in mice lacking estrogen receptors a and b, *Science*, **286**: 2328-2331, 1999
8. **Mandurino S., Mazzei C.,** A case of ovarian arrhenoblastoma, *Arch. Sci. Med.*, **139:** 139-142, 1982
9. **Takekawa Y., Kimura M., Sakakibara R., Yoshii R., Ato M., Nemoto N., Sakurai I.,** Immunohistochemical study of Sertoli-stromal cell tumor; comparison between the tumor arising from the gonad of a testicular feminization syndrome bearing patient and from ovaries of non-bearing patients, *Rinsho. Byori.*, **47**:1070-1074, 1999
10. **O'Hern T.M., Neubecker R.D.,** Arrhenoblastoma of the ovary, *Obste. Gynecol.,* **19**: 758-770, 1962
11. **Ketola I., Pentikainen V., Vaskivuo T., Ilvesmaki V, Herva R., Dunkel L., Tapanainen J.S., Toppari J., Heikinheimo M.,** Expression of transcription factor GATA-4 during human testicular development and diseas, *J. Clin. Endocrinol. Metab.,* **85**: 3925-3931, 2000
12. **Hitosugi M., Matsuoka Y., Irimajiri S., Fukuda J.,** Sertoli-Leydig cell tumour complicated by X chromosomal mosaicism, *Clin. Endocrinol.,* **47**: 619-622, 1997
13. **De Giorgi U., Turci D., Crisanti E., Cantu M.G., Cappelini A., Marangolo M.,** Ovarian Sertoli-Leydig cell tumor, endometrioid-like yolk sac tumor, and Y-chromosomal material, *Oncology*, **64**: 370-3, 2003
14. **Stegner H-E., Lisboa B.P.,** Steroid metabolism in an androblastoma (Sertoli-Leydig cell tumor). A histopathological and biochemical study, *Int. J. Gynecol. Pathol.,* **2**: 410-425, 1984
15. **Fleetwood J.A., Watson M.J., Wastell H.J., Weddell A.,** Hormone studies in a case of virilisation due to ovarian tumor, *Ann. Clin. Biochem.*, **22**: 498-501, 1985
16. **Tita P., Spina A., Briguglia G., Magro A., Gallo D., Finocchiaro C., Padova G., Pezzino V.,** Clinical features and hormonal characteristics in a case of ovarian arrhenoblastoma, *J. Endocrinol. Invest.,* **19**: 484-487, 1996
17. **Viollier E.H., Young D.S.,** What is your diagnosis? Arrhenoblastoma, *Schweiz. Rundsch. Med. Prax.*, **71**: 205-206, 1982
18. **Graham C.E., McClure H.M.,** Sertoli-Leydig cell tumor in a chimpanzee, *Lab. Anim. Sci.*, **26**: 948-950, 1976
19. **Kommoss F., Oliva E., Bhan A.K., Young R.H., Scully R.E.,** Inhibin expression in ovarian tumors and tumor-like lesions: an immunohistochemical study, *Mod. Pathol.,* **11**: 656-664, 1998
20. **Singh Z.N., Singh M.K., Chopra P.** Sertoli Leydig cell tumor with malignant heterologous elements and raised alpha-fetoprotein: a case report, *J. Obstet. Gynaecol. Res.,* **22**: 595-598, 1996

21. **Aboud E.,** A review of granulosa cell tumours and thecomas of the ovary, *Arch. Gynecol. Obstet.,* **259**: 161-165, 1997
22. **Mooney E.E., Man Y.G., Bratthauer G.L., Tavassoli F.A.,** Evidence that Leydig cells in Sertoli-Leydig cell tumors have a reactive rather than a neoplastic profile, *Cancer,* **86**: 2312-2319, 1999
23. **Young R.H.,** Sertoli-Leydig cell tumors of the ovary: Review with emphasis on historical aspects and unusual variants, *Int. J. Gynecol. Pathol.*, **12**:141-147, 1993
24. **Kurman R.J., Andrade D., Goebelsmann U., Taylor C.R.,** An immunohistological study of steroid localization in Sertoli-Leydig tumors of the ovary and testis, *Cancer,* **42**: 1772-1783, 1978
25. **Haider S.G., Pickartz H., Freundl G., Passia D.,** Demonstration of hydroxisteroid dehydrogenases and testosterone in the Sertoli-Leydig cell tumor (androblastoma) tissue of the human ovary: an enzyme histochemical and immunohistochemical study, *Acta Anat.*, **121**:170-173, 1985
26. **Costa M.J., Morris R.J., Wilson R., Judd R.** Utility of immunohistochemistry in distinguishing ovarian Sertoli stromal cell tumors from carcinosarcomas, *Hum. Pathol.,* **23**: 787-797, 1992
27. **Costa M.J., Ames P.F., Walls J., Roth L.M.** Inhibin immunohistochemistry applied to ovarian neoplasms: a novel, effective, diagnostic tool, *Hum. Pathol.,* **28**: 1247-1254, 1997
28. **Riopel M.A., Perlman E.J., Seidman J.D., Kurman R.J., Sherman M.E.,** Inhibin and epithelial membrane antigen immunohistochemistry assist in the diagnosis of sex cord-stromal tumors and provide clus to the histogenesis of hypercalcemic small cell carcinomas, *Int. J. Gynecol. Pathol.,* **17**: 46-53, 1998
29. **Kommoss F., Oliva E., Bhan A.K., Young R.H., Scully R.E.,** Inhibin expression in ovarian tumors and tumor-like lesions: an immunohistochemical study, *Mod. Pathol.*, **11**: 656-664, 1998
30. **Mooney E.E., Nogales F.F., Tavassoli F.A.** Hepatocytic differentiation in retiform Sertoli-Leydig cell tumors: distinguishing a heterologous element from Leydig cells, *Hum. Pathol.,* **30**: 611-617, 1999
31. **Klonisch T., Hombach-Klonisch S., Buchmann J, Fischer B., Bergmann M., Steger K,** Relaxin-like factor expression in a human ovarian Sertoli-Leydig cell tumor, *Fertil. Steril.*, **72**:546-568, 1999
32. **Inoue Y., Kamura T., Okuma A., Shigematsu T., Amada S., Ogata R., Koga M., Nozaki M., Nakano H.,** Efficacy of selective venous sampling to localize a small ovarian androgen-producing tumor, *J. Obstet. Gynaecol. Res.,* **25**: 231-236, 1999
33. **Lantzsch T., Stoerer S., Lawrenz K., Buchmann J., Strauss H.G., Koelbl H.,** Sertoli-Leydig cell tumor, *Arch. Gynecol. Obstet.,* **264**: 206-208, 2001
34. **Yang S.W., Cho M.Y., Jung S.H., Lee K.G., Cha D.S., Kim K.R.,** Mucinous cystadenoma coexisting with stromal tumor with minor sex-cord elements of the ovary: a case report, *J. Korean. Med. Sci.,* **16**: 237-240, 2001
35. **Golbang P., Khan A., Scurry J., MacIsaac I., Planner R.,** Cervical sarcoma botryoides and ovarian Sertoli-Leydig cell tumor, *Gynecol. Oncol.,* **67**: 102-106, 1997
36. **Seo E.J., Kwon H.J., Shim S.I.** Ovarian serous cystadenoma associated with Sertoli-Leydig cell tumor-a case report, *J. Korean. Med. Sci.,* **11**: 84-87, 1996
37. **Spremovic-Radjenovic S, Radosavljevic A, Petkovic S, Matijasevic S., Cvetkovic M., Lazovic G., Popovic V.,** The polycystic ovary syndrome associated with ovarian tumor, *Srp. Arh. Celok. Lek.,* **125**: 375-377, 1997
38. **Latthe P., Shafi M.I., Rollason T.P.,** Recurrence of Sertoli-Leydig cell tumor in controlateral ovary. Case report and review of literature, *Eur. J. Gynaecol. Oncol.,* **21** : 62-63, 2000
39. **Campisi P., Cheski P.,** Metastatic Sertoli-Leydig cell ovarian cancer manifested as a frontal sinus mass, *J. Otolaryngol.,* **27**: 361-362, 1998
40. **Dowdy S.C., O'Kane D.J., Keeney G.L., Boyd J, Podratz K.C.**, Telomerase activity in sex cord-stromal tumors of the ovary, *Gynecol. Oncol.*, **82**: 257-260, 2001
41. **Zheng P.S., Iwasaka T., Yamasaki F., Ouchida M., Yokoyama M., Nakao Y., Fukuda K., Matsuyama T., Sugimori H.**, Telomerase activity in gynecologic tumors, *Gynecol. Oncol.*, **64**: 171-175, 1997
42. **Manegold E., Tietze L., Günther K., Fleischer A., Amo-Takyi B.K., Schröder W., Handt S.**, Trisomy 8 as sole karyotypic aberration in an ovarian metastasizing Sertoli-Leydig cell tumor, *Hum. Pathol.*, **32**: 559-562, 2001
43. **Chao H.T., Wang P.H., Lin H.D.,** Gonadotropin-releasing hormone-agonist as a neoadjuvant therapy for Sertoli-Leydig cell tumors of the ovary, *Int. J. Gynaecol. Obstet.,* **66**: 189-190, 1999
44. **Gershenson D.M., Morris M., Burke T.W., Levenback C., Matthews C.M., Wharton J.T.,** Treatment of poor-prognosis sex cord-stromal tumors of the ovary with the combination of bleomycin, etoposide, and cisplatin, *Obstet. Gynecol.,* **87**: 527-531, 1996