Sclerosing stromal tumor of the ovary: A case report and review of the literature

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Summary

Sclerosing stromal ovarian tumor is an extremely rare neoplasm occurring predominantly in the second and third decades of life. It presents most often with non-specific symptoms. We describe a new case occurring in a young woman presenting with infertility and irregular menses. Ultrasound examination showed a left heterogenous ovarian mass without focal calcifications. Histological features included a pseudolobular pattern with focal areas of sclerosis, prominent vascularity and a two-cell population of spindled and polygonal cells. Immunohistochemical analysis for actin, vimentin, laminin, vascular epidermal growth factor (VEGF), oestrogen and progesterone receptors using formalin-fixed and paraffin-embedded materials showed predominant positivity for a-smooth muscle actin and consistent positivity for laminin and vimentin. The epidermal VEGF demonstrated rich tumor vascularity. Oestrogen and progesterone receptors were not expressed, suggesting hormonally independent development. Menstrual cycle disturbances, however, were corrected following extirpation of the tumor, indicating some endocrine involvement. In addition, the patient became pregnant ten months after the operation. The differential diagnosis is discussed.

Key words: Sclerosing stromal tumor; Ovarian tumor; Ultrasound picture; Histochemistry; Immunohistochemistry; Oestrogen receptors; Progesterone receptors; A-smooth muscle actin; Lamin; Vimentin; Vascular epidermal growth factor (VEGF).

Introduction

Sclerosing stromal tumor (SST) of the ovary is a rare benign neoplasm which most often presents with non-specific symptoms [1]. It was first described by Chalvardjian and Scully [2] in 1973 and by Damjanov *et al.* [3] in 1975 as a distinctive subtype of other ovarian sex cord stromal tumors (fibromas, thecomas, fibrothecomas and lipid-steroid cell tumors). Chalvardjian and Scully [2] chose this term because of the characteristic feature of the cellular areas of the tumor to undergo collagenous sclerosis.

According to Tang and Liu, six percent of ovarian stromal tumors are sclerosing [4]. Since the first description of this entity less than 100 cases have been described in the literature [1, 5, 6, 7].

In this report we have documented a new case of a sclerosing stromal tumor of the ovary (SST). In addition, we discuss its clinical, pathological, histochemical and immunohistochemical features as well as its ultrasound picture and differential diagnosis.

Case Report

The patient was a 21-year-old white female, gravida I, para 0, with a history of an induced abortion three years earlier. Her menarche had been at age thirteen. Apart from a history of secondary infertility for three years, which was the main reason that the patient came for a gynaecologic examination, she had had irregular menses for the previous three years. The general examination did not reveal abnormalities. The patient did not have any sign of virilization. External and internal gynaecological findings where all within normal limits except the palpatory finding of a mass in the left adnexa. A pregnancy test was negative. Ultrasound examination showed a 6x4.5x3.5 cm left ovarian mass with mixed heterogeneity without focal calcifications (Figure 1). No fluid was observed in the pouch of Douglas. The body of the uterus, the uterine cavity and the cervix appeared normal. The right ovary was normal in shape and echotexture. The patient was referred for surgery. All routine preoperative haematological, biochemical tests, serum CA125 and chest X-ray were within normal limits. The 17-ß-oestradiol, progesterone and testosterone serum levels were not determined before or after the operation. At operation the patient was found to have the left ovary replaced by the tumor mass. The right ovary and other pelvic organs were normal without adhesions or presence of endometriosis. No ascites was seen. A methylin blue test showed both tubes to be patent. Tumor enucleation was performed and the postoperative course was uneventful. On follow-up three months after the operation her menstrual cycle disturbance had been corrected. In addition, the patient became pregnant ten months after the extirpation of the tumor.

Methods

Tissue sections for histologic study were fixed in 10% formalin and embedded in paraffin; 1 μm sections were used for histological diagnosis, histochemical and immunohistochemical staining. An ultrastructural study was performed using formalin-fixed materials. A histochemical study was performed using the Gomori, Sudan and PAS stain. Immunohistochemistry was studied with the indirect immunoperoxidase method. Formalin-fixed and paraffin-embedded, unstained sections were examined for the presence of vimentin (VIM; Dako, Denmark; monoclonal antibody), a-muscle-specific actin (MSA, Immunon, Pittsburgh, PA; monoclonal antibody), laminin (LAM, Biomakor, Israel; monoclonal antibody), vascular epidermal growth factor (VEGF, Dako, Denmark; polyclonal antibody), oestrogen receptors (Immunon, Pittsburgh; monoclonal antibody) and progesterone receptors (Immunon, Pittsburgh; monoclonal antibody). The following dilutions of primary antibodies were used: vimentin,

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1:10; a-muscle-specific actin, stock dilution; laminin, 1:1000; vascular epidermal growth factor, 1:120; oestrogen receptors, stock dilution; and progesterone receptors, stock dilution.

Pathology

Gross examination

The outer surface of the mass was smooth and glistening. The cut surface was grayish white with yellowish areas and predominantly solid with gritty nodules. Several small cysts (up to 5 mm in diameter) filled with serous fluid were present underneath the surface.

Light microscopic findings

Histologically, the tumor had the typical appearance of a sclerosing stromal tumor of the ovary as described by Chalvardjian and Scully. Low-power examination of the tumor revealed the pseudolobular pattern with cellular areas separated by less cellular loose oedematous or dense acellular sclerosing areas (Figure 2). Higher power examination of the cellular areas revealed a mixture of spindle-shaped (Figure 3) and larger polygonal eosinophilic or clear epithelial-like cells (Figure 4). The spindle-shaped cells had a single nucleus and moderate cytoplasm. In many areas, the larger polygonal cells had peripherally placed nuclei resembling signet-ring cells, which can suggest the diagnosis of Krukenberg tumor (Figure 4). The nuclei of both types of cells were uniformly bland, with limited mitotic activity. The hypocellular areas consisted either of haphazardly arranged coarse collagen bands or of oedematous loose stroma with few spindle-shaped cells. The tumor, especially in the cellular areas, was characterized by numerous branching vascular spaces of various sizes with an hemangiopericytoma-like pattern locally (Figure 5).

Histochemical and immunohistochemical findings

Histochemical individual cells were surrounded by a fine meshwork of reticulin fibres (Gomori stain). The polygonal eosinophilic or clear epithelial-like cells as well as the signet-ring cells contained lipid droplets (Sudan stain) (Figure 6). They did not contain mucin (Alcian blue/PAS stain).

Immunohistochemically, a number of spindle-shaped fibroblastic cells and polygonal clear epithelial-like cells were predominantly positive for a-smooth muscle actin (Figures 7, 8, 9). Vimentin was consistently demonstrated in almost all the tumor cells (Figure 10). The vascular epidermal growth factor demonstrated the rich vascularity of the tumor (Figure 11) but was not expressed in the tumor cells. A remarkable observation was the strong positivity for laminin in the cellular areas of the tumor (Figure 12). Regarding oestrogen and progesterone receptors, the tumor cells were negative for both.

Discussion

Sclerosing stromal tumors of the ovary are most common in the second and third decades of life and are usually unilateral and solid, as in our case; rarely they are bilateral [8] or predominantly cystic [9, 10].

Sclerosing stromal tumors of the ovary present most often with non-specific symptoms such as a swelling in the lower abdomen [7] and abdominal ache or pain [1, 11, 12]. The presence of ascites is rare even with large tumors [1, 13].

Chalvardjian and Scully [2] considered the sclerosing stromal tumor of the ovary as a nonfunctioning tumor. However, Damjanov *et al.* [2] provided biochemical evidence of hormonal production of this tumor, which was further confirmed by subsequent reports. When steroidogenesis occurs it is usually oestrogenic [4, 14, 15, 16]. Androgens are secreted rarely [8, 17, 18, 19], and oestrogens and androgens even less often [2, 20, 21]. Androgen producing tumors have, however, been reported in pregnant women [8, 19]. As regards the hormonal function of other sex cord stromal tumors, it is always absent in fibromas, while in thecomas it is typically oestrogenic, and in lipid-steroid cell tumors it is androgenic [5].

The manifestations of sclerosing stromal tumors of the ovary can include precocious puberty [5], irregular menstruation (menorrhagia, menometrorrhagia, polymenorrhoea and prolonged menstruation) [3, 6, 11, 13, 18, 22], transient amenorrhoea [18] and infertility [20]. In elderly patients, postmenopausal bleeding can also be a presenting symptom [14, 23], and associations with endometrial hyperplasia or adenocarcinoma have been reported as well [24].

Although these clinical findings are suggestive of hormonal activity in sclerosing stromal tumors of the ovary, unequivocal hormonal production has not been demonstrated by measurement of 17-ß-oestradiol, progesterone or testosterone pre- or postoperatively [25]. Clear hormonal activity has only been demonstrated in pregnant women [8, 17, 19].

In our case the clinical features of secondary infertility and irregular menses could be considered as evidence of oestrogenic activity, however a biochemical evaluation of the hormonal status was not carried out. In the literature, menstrual cycle disturbances are usually corrected following surgical extirpation of the tumor, as also happened with our patient [18, 20, 26]. Moreover, our case and some reports of pregnancy following excision of the tumor [20] suggest that endocrine activity in some patients may cause infertility, perhaps the result of anovulation due to the secretion of steroids.

To date, all sclerosing stromal tumors reported have been benign. Nonetheless, cytogenetic study of one case [12] revealed monosomy of chromosome 16 and a more aggressive histology which the authors considered consistent with a low-grade malignancy. However, neither recurrence nor metastasis were described in that case [12]. Rarely, sclerosing stromal tumors of the ovary are associated with complications such as endometrial carcinoma of the uterus, resulting in a less favorable prognosis [24]. As regards the behavior of the other sex cord stromal tumors, it has been benign for fibromas and thecomas but often malignant for lipid-steroid cell tumors [5].

Sclerosing stromal tumor of the ovary mimics several neoplastic ovarian lesions in morphology. The differential diagnosis of sclerosing stromal tumor is based on the gross variegation and the microscopic appearance of the cellular pseudolobulation, the focal oedema, the prominent vascularity, the two cell types, and the absence of hyalinised plaque [1, 5].

Gross variegation is absent in thecomas, fibromas and steroid cell tumors. Pseudolobulation and prominent vascularity are rare in thecoma, fibroma and lipid-steroid cell tumors, while in fibroma and thecoma hyaline pla-

Fig. 1

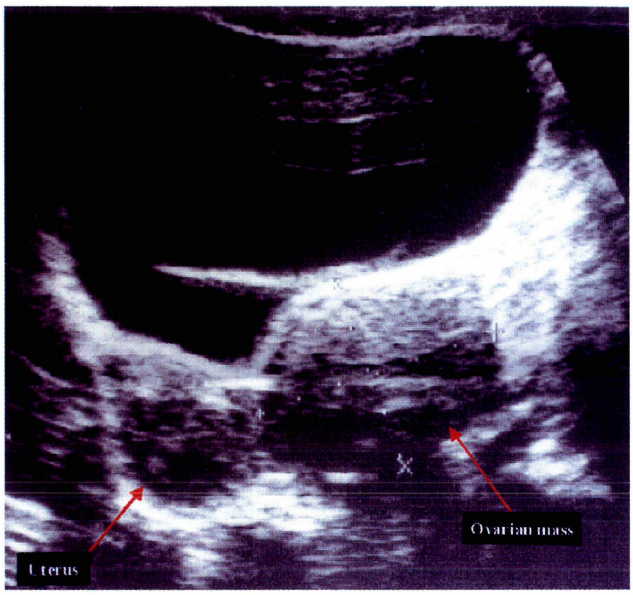
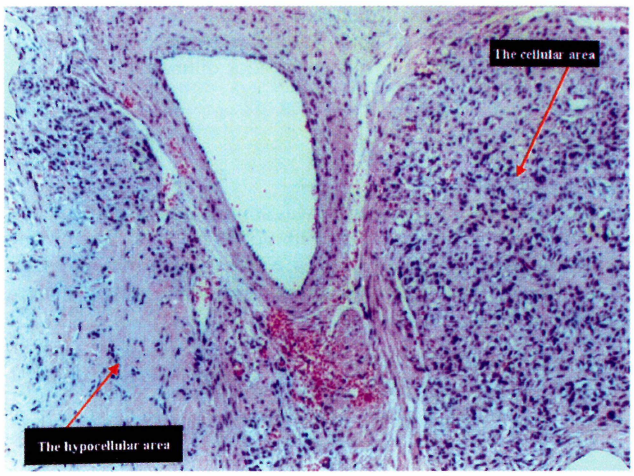


Fig. 2



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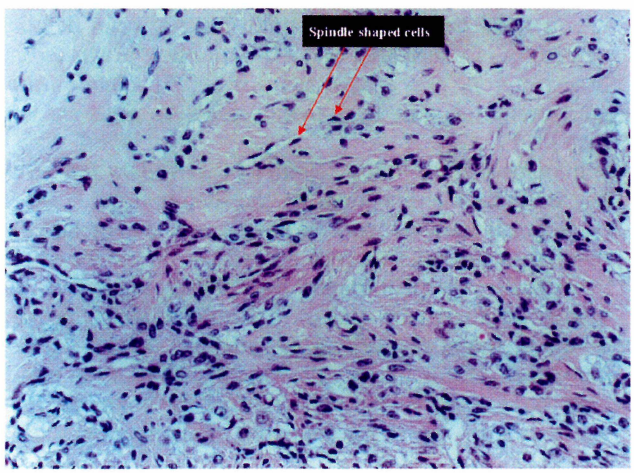

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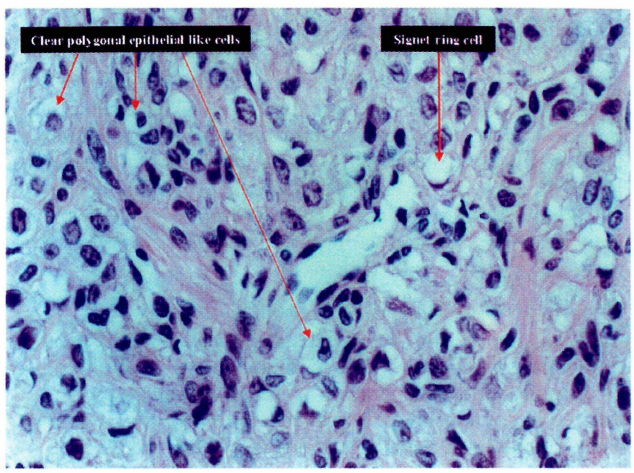

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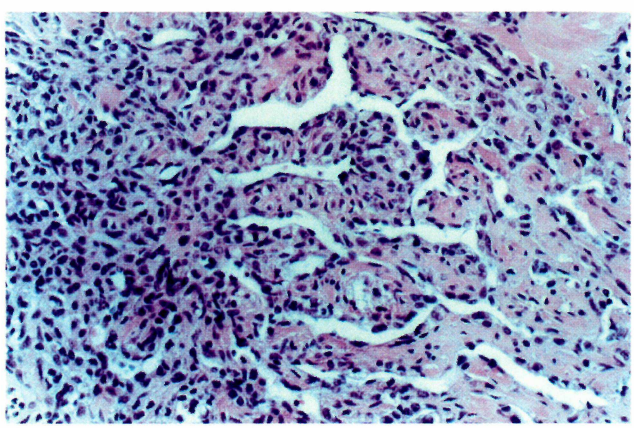

Fig. 6

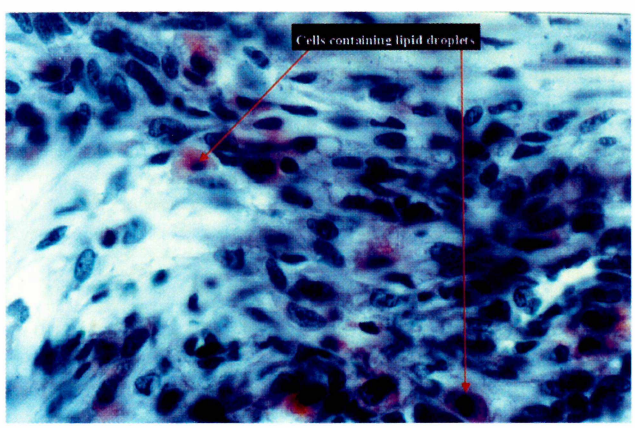

Figure 1. — Abdominal ultrasound scan showing a 6x4.5x3.5 cm left ovarian mass with mixed heterogeneity.
Figure 2. — Pseudolobular pattern with clear distinction between cellular and stromal areas (H&E, x 100).
Figure 3. — Spindle cells in the collagenous stroma (H&E, x 200).
Figure 4. — Cellular area with clumped, polygonal cells, some with vacuolated cytoplasm. Also, signet ring-like cells are noted (H&E, x 400).
Figure 5. — Prominent vascularity with an hemangiopericytoma-like pattern (H&E, x 400).
Figure 6. — Polygonal eosinophilic or clear epithelial-like cells as well as signet-ring cells containing lipid droplets (Sudan stain x 400).

Fig. 7

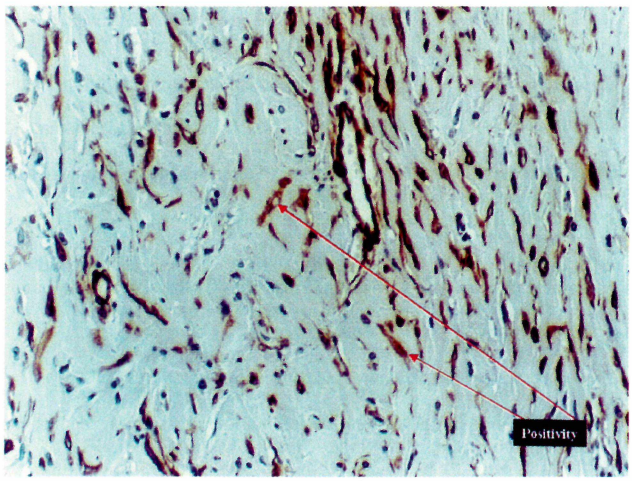

Fig. 8

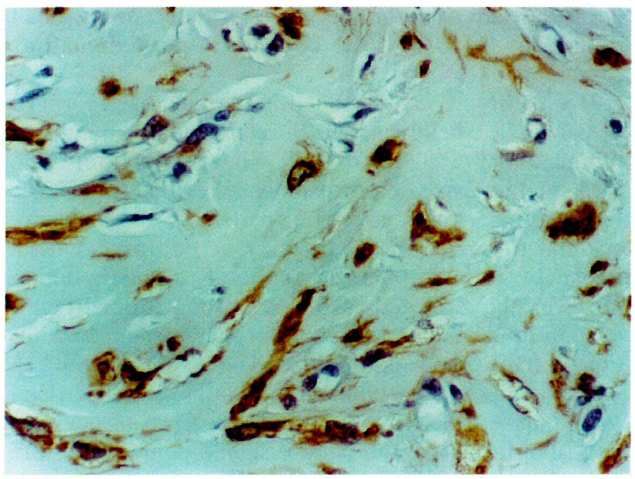

Fig. 9

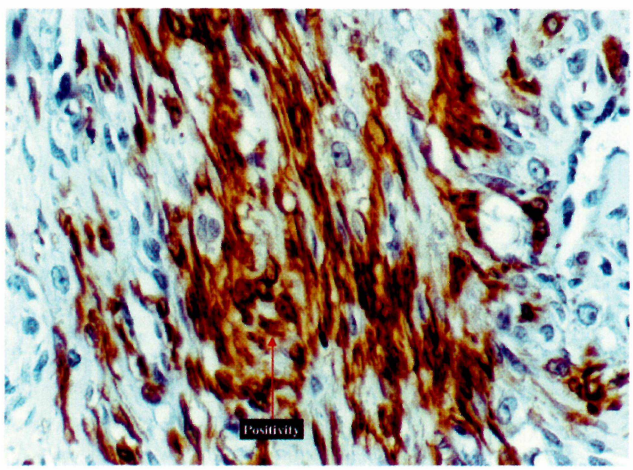

Fig. 10

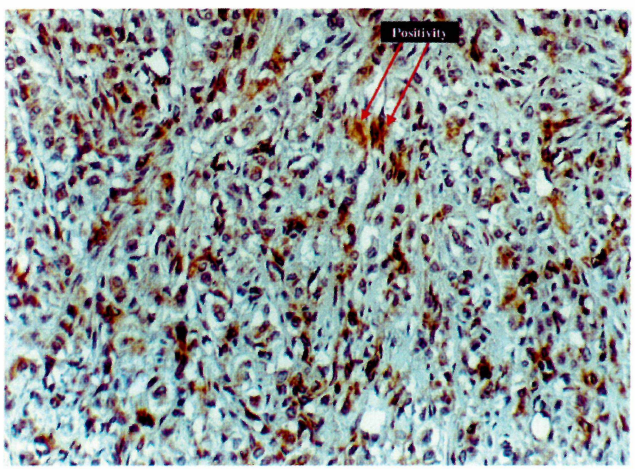

Fig. 11

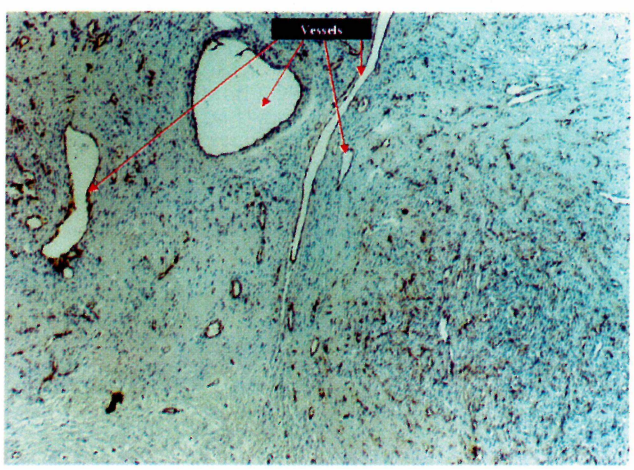

Fig. 12

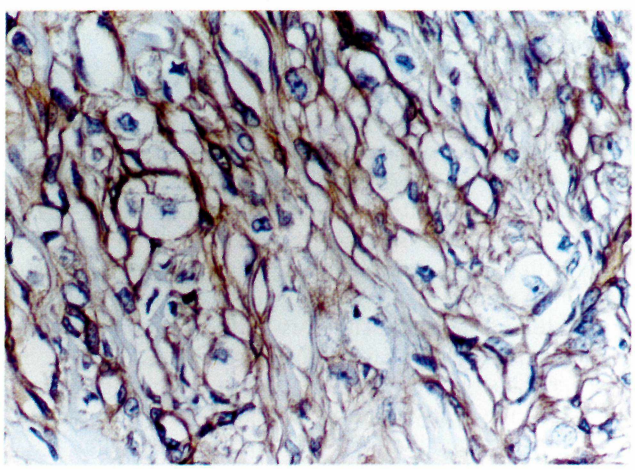

Figure 7. — Predominant positivity for a-smooth muscle actin (x 200).
Figure 8. — Positivity of spindle cells for a-smooth muscle actin (x 400).
Figure 9. — Positivity of epithelial-like cells for a-smooth muscle actin (x 400).
Figure 10. — Positivity for vimentin in the tumor cells (x 200).
Figure 11. — Demonstration of the rich vascularity of the tumor with vascular epidermal growth factor (VEGF) (x 100).
Figure 12. — Strong positivity for laminin in the cellular areas of the tumor (x 400).

queas they are common. In contrast to sclerosing stromal tumors of the ovary, the oedema in an oedematous fibroma is diffuse [7].

Two cell types can be found in the luteinized form of thecoma [5]. The lutein cells in sclerosing stromal tumor of the ovary are vacuolated, whereas in luteinized thecoma they have dense eosinophilic cytoplasm [7, 21]. Furthermore, the signet-ring cells of the sclerosing stromal tumor of the ovary may be confused with a Krukenberg tumor. In contrast to the Krukenberg tumor, however, the clear cells of the sclerosing stromal tumor contain lipids and are negative for mucin stain. In addition, in the Krukenberg tumor nuclear atypia is noted [1].

Sclerosing stromal tumor may also have a superficial resemblance to leiomyoma, but the absence of intersecting fibre fascicles in the tumor should point away from this diagnosis [5]. Prominent SST vascularity may suggest haemangiopericytoma [1, 21]. Massive oedema of the ovary can occur in young women but in sclerosing stromal tumor of the ovary, oedema is zonal and there is also microscopic heterogeneity [1].

Immunohistochemical studies of SSTs have revealed positive vimentin [19], desmin [19, 27], a-muscle-specific actin [27, 28] and negative cytokeratine stains in the tumor cells [1]. The results of our immunohistochemistry showed predominant positivity for a-smooth muscle actin and consistent positivity for vimentin. An intense distribution of laminin was detected between the tumor cells, especially in the cellular areas, a fact that has not been mentioned in the literature. In contrast, laminin has not been detected in thecomas, but it had a similar pattern of distribution between the theca interal and external cells of growing follicles, and it also presented in the basement membrane between granulosa-theca cells. The presence of laminin has to be further investigated to determine if a relationship exists with the histogenesis of ovarian stromal sclerosing tumor.

In our patient although hormonal activity was clinically indicated, oestrogen and progesterone receptors were not expressed. The expression of progesterone receptors seems to be unusual in sclerosing stromal tumors of the ovary, although Liftschitz-Mercel *et al.* [29] described a case with intense nuclear staining for progesterone receptors. Nonetheless, the usual absence of oestrogen and progesterone receptors suggests hormonally independent development of the majority of these tumors.

In conclusion, this is a new case of sclerosing stromal tumor of the ovary, a rare distinctive benign tumor. Its histology, histochemistry and immunohistochemistry suggest that its development is independent of hormones, yet symptoms indicate some level of endocrine involvement.

Finally, further investigation is warranted regarding the relationship between laminin and SST histogenesis.

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