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

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ABSTRACT

Sclerosing stromal tumours are rare benign ovarian neoplasms of the sex cord stromal that occur predominantly in the second and third decades of life. To date, 208 cases have been recorded in the literature. Most patients have menstrual irregularities and pelvic pain. Infertility and virilisation have also been described. In this article, histopathological features and differential diagnosis of the benign sclerosing stromal tumour were described together with the literature data. It is imperative to consider the differential diagnosis of a sclerosing stromal tumour of the ovary in a young woman with an ovarian tumour. A combination of morphological, immunohistochemical, radiological and clinical findings is needed in differentiating the tumour from thecoma, fibroma/fibrosarcoma, lipoid tumours and Krukenberg tumour.

Key words: Ovary, pelvic pain, sclerosing stromal tumours

INTRODUCTION

Sclerosing stromal tumour (SST), which were defined by Chalvardjan and Scully in 1973 for the first time, is an extremely rare ovarian sex cord stromal tumour with distinctive pathological features and benign nature.¹ Since it was first described by Chavarjian and Scully, fewer than 200 cases have been described in the literature. Most patients are young, with 70% of whom being between 14 and 29 years.² The most frequent presenting complaint is menstrual irregularity and pelvic pain. Macroscopically, they are usually observed as solid and typically unilateral tumours. SST is usually hormonally inactive, but it has been reported that some cases are related to pregnancy and androgenic symptoms.³

Awareness of such entity is crucial because of its histopathologic similarity with other neoplastic and non-neoplastic lesions of the ovary. SST should be distinguished from malignant tumours, but it is difficult to diagnose before surgery by imaging studies. It used to be diagnosed by pathological examination during surgery or after surgery. In this study, the case of ovarian sclerosing stromal tumour is described and its clinicopathologic and immunohistochemical features are reviewed together with the literature data.

CASE REPORT

A 25-year-old woman was presented with pelvic pain during the last 4 months. Physical examination revealed a large, palpable abdomino-pelvic mass. There was no unusual symptoms such as hypermenorrhoea, menstrual irregularities and virilisation. Ultrasound examination showed a 15 cm heterogeneous left ovarian tumour consisting of predominantly solid tissue with several loculated cysts. Laboratory tests including tumour markers and serum hormonal assays were normal in case. The patient underwent laparotomical left oophorectomy and showed a normal uterus and right ovary with the left ovary replaced by a solid mass. Ascites was not present. On gross inspection, the removed left ovarian mass measured 15 × 14 × 13 cm. The mass was grey-white in color and had a smooth and well-encapsulated surface. The cut surface was a mostly solid and slightly oedematous [Figure 1]. The mass was described as benign by frozen analysis. The histologic features included a pseudolobular pattern with widespread areas of sclerosis and a two-cell population of spindle and round cells. Haemangiopericytoma-like vessels, myxoid to fibrotic stroma and focal cystic change were noted. Mitoses and necrosis were absent. Immunohistochemical studies showed positive inhibin [Figure 2]. The final diagnosis was that of sclerosing stromal tumour of the ovary. Post-operative recovery was uneventful.
**DISCUSSION**

SST is attributable to theca cell-fibrous tumour subtypes of ovarian sex cord-stromal tumour from WHO-2003 classification that is distinctive clinical, pathologic and radiological features, which differentiates it from other stromal tumours. The aetiology of SSTs is unknown. Based on the ultrastructural features, SSTs were thought to arise from pluripotent immature stromal cells of the ovarian cortex. However, SST has been proposed to stem from the perifollicular myoid stromal cells that are normally present in the theca externa. The vascular, sclerotic and edematous stromal changes are constant features of these tumours and relate to the local elaboration of some vascular permeability and growth factors like vascular endothelial growth factor (VEGF). On the other hand, Ismail et al. suggested that endocrine milieu might be responsible for the morphology of SST and they may be developed from preexisting ovarian fibromas.

In the literature, reports of ovarian SSTs are rare. We undertook a MEDLINE® search using keywords ovarian neoplasms and sclerosing stromal tumour to obtain reports on this tumour in the English literature and then extended the search to related reports listed in their references. Until 2003, 114 cases had been reported by Peng et al. We concluded that up to the writing of this paper, a total of 208 cases had been reported and cases identified between 2003 and 2014 were summarised in Table 1.

Ovarian SST occurs more commonly during the second to third decades of life with an average age of occurrence of 25, 9 years (4-73 years) and most of the reported cases have been unilateral. Bilateral SST was depicted in only four cases. The most common signs and symptoms are a palpable pelvic mass, menstural irregularity, pelvic pain and non-specific symptoms related to the ovarian mass and our patient is complained of pelvic pain. Tumour size varies from 1cm to 31cm in diameter. Elevated serum CA125 level and/or ascites were depicted in some cases. Meigs’ syndrome associated with SST of the ovary has been described in four cases.

Sclerosing stromal tumour with an ovarian torsion has been described in two cases.

Sclerosing stromal tumours were reported in which the inactive tumours did not represent endocrine clinical symptoms. However, currently according to several reports, it is the active tumour that produce hormones (estrogenic or androgenic). These tumours synthesised dehydroepiandrosterone and that when steroidogenesis occurred, which caused irregular menses, amenorrhoea, infertility, precocious puberty and virilisation. Endometrial hyperplasia concomittent with SST have also been described which might indicate a status of excessive hormone production. Other authors have documented elevated levels of both estrogenic and androgenic hormones that were corrected after surgery. In several patients with irregular menses, normal menses following the excision of the tumour was noticed. To date, 9 cases of virilising SST of the ovary have been described in the literature and three of the reported virilising SST were diagnosed during pregnancy [Table 2]. A virilising SST of the ovary in a young woman with Mc Cune Albright Synrome was reported in 2013 by Boussaid K et al. In this case, neither hormonal activity nor virilisation was observed. Sclerosing stromal tumours are rarely seen together with pregnancies; only 15 reports of sclerosing stromal tumour of the ovary during pregnancy have been presented [Table 3].

SST can not predict its presence preoperatively on the basis of clinical and ultrasonographic findings alone. It is difficult to distinguish SST consisting of solid and cystic areas from ovarian malignancies on the basis of radiological and macroscopic examination, as these tumours additionally appear very vascular giving the impression of malignant...
### Table 1: Overview of all case reports on SST between 2003-2014

| Case no and article | Age | Side | Clinic and symptom | CA-125 | Tumour size (cm) | Gross appearance | Immunohistochemical staining |
|---------------------|-----|------|-------------------|--------|-----------------|-----------------|-----------------------------|
| Peng HH et al., 2003 | 24  | Left | IM                | High   | 8.4             | Solid           | SMA(+), vimentin(+), PR(+)  |
| Kim JY et al., 2003 (3 cases) | 16  | Left | IM                | Normal | 6               | Solid           | SMA(+), vimentin(+)         |
|                     | 26  | Left | IM                | Normal | 6               | Solid           |                             |
|                     | 39  | Left | IM, pelvic pain   | Normal | 5.5             | Cyst            | SMA(+), CA125(-), S100(-), desmin(-) |
| Kuscu E et al., 2003 | 34  | Right| Pelvic pain, hirsutism, IM | Normal | 12.5            | Solid           | SMA(+), CK(-), S100(-), desmin(-) |
| Yerli H et al., 2003 | 34  | Right| Amenorrhoea, hirsutism | Normal | 10              | Solid-cystic    | Inhibin(+), vimentin(+), SMA(-), CK(-), ER(-), PR(-) |
| Deval B et al., 2003 | 29  | Right| Pregnancy         | Normal | 4.5             | Solid-cystic    |                             |
| Huang SC et al., 2003 | 31  | Right| Pregnancy         | High   | 14              | Cyst            |                             |
| Calabrese M et al., 2004 | 30 | Right| Meigs' syndrome | Normal | 19              | Solid-cystic    |                             |
| Bildirici K et al., 2004 | 17 | Right| Pregnancy         | Normal | 7               | Solid-cystic    |                             |
| Gurbuz A et al., 2004 | 21  | Left | IM                | Normal | 5,5             | Cyst            | SMA(+), CK(-), S100(-), desmin(-) |
| Akbulut M et al., 2004 | 17  | Right| IM, pelvic pain   | Normal | 10              | Solid-cystic    |                             |
| Bouraouis et al., 2004 (3 cases) | 15, 25, 56 | Right | IM                | Normal | 6-14            | Solid-cystic    | ER(-), Inhibin 4 cases (+); calretinin, SMA, PR 3 cases (+) |
| Akyildiz EU et al., 2004 (3 cases) | 23, 24, 28 | Right | IM                | Normal | 10              | Solid-cystic    |                             |
| Mathur SR et al., 2004 (4 cases) | — | — | — | — | — | — |                             |
| Kostopoulou E et al., 2004 (3 cases) | — | — | — | — | — | — |                             |
| Kurt G et al., 2004 (6 cases) | 16-24 | Right| Pelvic pain, pregnancy (2) | Normal | 6-14            | Solid-cystic    | CA125(-)                  |
| Popovska S et al., 2005 | 26  | Mean | All case unilateral | IM    | Mean 10         | Solid-cystic    |                             |
| Pai RR et al., 2005 (4 cases) | Mean 22,2 | Right| IM, pelvic pain   | Normal | 6               | Solid-cystic    | SMA(+), CD99(+), desmin(-), S-100(-), EMA(-), CD34 (+) |
| Pai R et al., 2005 (4 cases) | Mean 22 | Right| Abdominal distention | High   | 20              | Solid-cystic    |                             |
| Arora R et al., 2008 | 25  | Left | Abdominal pain    | 6      | Solid-cystic    | SMA(+), CD99(+), desmin(-), S-100(-), EMA(-), CD34 (+) |
| Chang W et al., 2006 | 11  | Bilateral | IM                | Normal | Left 8,5        | Solid-cystic    | SMA (+)                    |
| Sen N et al., 2006 | 25  | Left | Abdominal distention | Normal | 4.5             | Solid           |                             |
| Jung NH et al. 2006 | 50  | Right| Meigs' syndrome   | High   | 18              | Solid-cystic    | Vimentin(+), reticulin(+), calretinin (+), CD34(-), SMA(-), S-100(-), inhibin (-) |
| Darghouth CL. et al., 2007 | 15  | Right| Polymenorrhagia   | Normal | 6               | Solid           |                             |
| Sharma M et al., 2007 (2 cases) | 19  | Left | Abdominal pain    | Normal | 6               | Solid-cystic    | SMA (+)                    |
| Iravanloo G et al., 2008 | 25  | Left | Pelvic pain, IM   | Normal | 23              | Solid           |                             |
| Ergeneli MH et al., 2008 | 11  | Left | Pelvic pain, IM   | Normal | 23              | Solid           |                             |
| Ismail SI et al., 2010 (Continued) | (Continued) | Left | Pelvic pain, IM   | Normal | 23              | Solid           |                             |
Table 1: (Continued)

| Case no and article       | Age | Side | Clinic and symptom         | CA-125 | Tumour size (cm) | Gross apperance | Immunohistochemical staining |
|---------------------------|-----|------|-----------------------------|--------|------------------|-----------------|-----------------------------|
| Park SM et al., 2011      | 11  | Left | Hirsutism                   | 9      | Solid            |                 | Vimentin(+), SMA(+), inhibin(+), S100(-), CK(-) |
| Liou JH et al., 2011      | 18  | Right| IM, pelvic pain, Meigs’ Syndrome | High    | 16,5             | Solid           | Inhibin (+), Ca-125 (-), CK(-) |
| Dilbaz B et al., 2011     | 14  | Right| Pelvic pain                 | Normal  | 7                | Solid           | —                            |
| Akbulut M et al., 2011    | 73  | Left | Ovarian torsion             |        | 14               | Solid-cystic    | Calretinin(+), inhibin(+), ER(+), PR(+), CK 7(-), CD34(-), vimentin(-), SMA(-), S100(-), chromogranin(-), sinaptophysin(-) |
| Banik T et al., 2012 (3 cases) | 19 | Left | IM, abdominal pain          | 5      | Solid            |                 | Inhibin(+), CK(-), vimentin(-), SMA(-), desmin(-), EMA(-) |
|                          | 21  | Right| IM                           |        | 12               | Solid-cystic    | SMA(+)             |
|                          | 18  | Right| Abdominal pain              | High   | 8,5              | Solid           | Inhibin(+), desmin(-), Vimentin(+), calretinin(+), inhibin(+), PR(2), SMA(+), ER(+), EMA(+), CK 7(-), CK 20(-), AFP(-) |
| Chung CP et al., 2012     | 59  | Left | IM                           | 1,5    | Solid            |                 | Vimentin(+), inhibin(+), desmin(-), Vimentin(+), calretinin(+), inhibin(+), PR(+), SMA(+), ER(+), EMA(+), CK 7(-), CK 20(-), AFP(-) |
| Khanna M et al., 2012     | 32  | Right| IM, pelvic pain              | High   | 16               | Solid-cystic    | SMA(+)             |
| Suraweera P et al., 2012  | 33  | Right| Hirsutism, Virilisation      | Normal  | 6                | Solid-cystic    | Vimentin(+), inhibin(+), desmin(-), Vimentin(+), calretinin(+), inhibin(+), PR(+), SMA(+), ER(+), EMA(+), CK 7(-), CK 20(-), AFP(-) |
| Foteder V et al., 2012    | 23  | Right| Abdominal pain, IM           | High   | 4,7              | Solid-cystic    | —                            |
| Duzcu SE et al., 2012     | 17  |      |                              | Normal  |                  | Solid           | —                            |
| Kim D et al., 2012        | 26  | Right| Pregnancy                   | High   | 6,5              | Solid           | —                            |
| Mahadevappa A et al., 2012| 16  | Left | IM, pelvic pain, Meigs’ Syndrome | High   | 17               | Solid           | —                            |
| Sayilgan AT et al., 2012  | 19  | Right| Pelvic pain                  | High   | 10               | Solid           | Vimentin(+), SMA(+), CA125(+), CD34(-), CD99(-), CD100(-), EMA(-), VEGF(-), PLAP(-), CK(-), PAS(-) |
| Parlagkumus HA et al., 2013|  24 | Right| Pelvic pain                  | Normal  | 2                | Solid           | Inhibin(+), calretinin(+), vimentin(+), SMA(+), ER(+), PR(+), CD34(+), desmin(-), CK(-), EMA(-) |
| Boussaid K et al., 2013   | 24  | Left | McCune Albright syndrome, hirsutism, acne, amenorrhoea |         |                  | Solid           | Inhibin(+), vimentin(+), CK(-), WT1(+) |
| Limaiem F et al., 2013 (2 cases) | 16 | Left | Pelvic pain                  | Normal  |                  | Solid           | SMA(+), inhibin(+), vimentin(+), cytokeratin(-) |
|                          | 45  | Right| Pelvic pain                  | Normal  |                  | Solid-cystic    | SMA(+), inhibin(+), vimentin(+), CK(-) |
| Kutuk MS et al., 2013      | 18-25 | Right| Pregnancy (3), IM (2), abdominal discomfort (2) | All cases normal | 6-12 | Solid, Solid-cystic | Vimentin, SMA, desmin, inhibin, calretinin, PR all cases (+), ER, CK, CK 7(-), all cases (-), c-kit, melan-A 4 cases (+), CD10-3 cases (+) |
| Kaygusuz EI et al., 2013 (7 cases) | 18-25 | Left | Pregnancy (2), IM, pelvic pain, laparoscopic excision (2) | All cases normal | 6-12 | Solid, Solid-cystic | Vimentin, SMA, desmin, inhibin, calretinin, PR all cases (+), ER, CK, CK 7(-), all cases (-), c-kit, melan-A 4 cases (+), CD10-3 cases (+) |
| Amal Abd. 2014            | 19  | Right| IM, pelvic pain              | High   | 8,6              | Solid-cystic    | Calretinin(+), inhibin(+) |
| Liang YF et al., 2014      | 25  | Right| Ectopic pregnancy           | High   | 5                | Solid-cystic    | CD34(+), desmin(+), SMA(+), CD33(-), S-100(-), ER(+), PR(-) |

EMA – Epithelial membrane antigen; CK – Cytokeratin; SMA – Smooth muscle actin; ER – Estrogen receptors; PR – Progesterone receptors; IM – Irregular menstruation

tumours. Ultrasonography is useful for distinguishing between cystic and solid masses, but can be undetermined in lesion characterisation, such that a differential diagnosis from malignant ovarian neoplasms is not always possible.
Ultrasonography and computed tomography findings of SST show an increased peripheral vascular as seen in malignant tumours. Magnetic resonance imaging findings include typical signal patterns such as hypointense nodules, hyperintense stroma, lobulation, strong enhancement with gadolinium and a peripheral hypointense rim are present.\textsuperscript{18} The distinct histopathological appearance and immunohistochemistry of SST are important in aiding diagnosis.

Characteristic histological finding of the SST of ovary is the pseudolobular pattern that is formed by the cellular nodules that are separated from each other by hypocellular, oedematous and collagenous stroma. The characteristic pathological findings of the SST of ovary were observed both macroscopically and microscopically in all the cases reported in literature.

Several immunohistochemical markers of the sex-cord stromal tumours were studied in SST. Immunohistochemical analysis for inhibin, smooth muscle actin (SMA), vimentin, estrogen receptors (ER) and progesterone receptors (PR) using formalin-fixed and paraffin-embedded materials showed predominant positivity for a SMA, consistent positivity for inhibin and vimentin, and negativity for S-100 protein and epithelial markers, suggesting a stromal origin of the SST.\textsuperscript{16,19}

Inhibin has been shown to be a useful marker for ovarian sex cord stromal tumours. Inhibin is a specific, but less sensitive marker than calretinin in the diagnosis of ovarian sex cord-stromal tumours. In addition, a correlation was observed between the calretinin and α-inhibin expressions and the luteinisation level of tumour cells.\textsuperscript{19} Also, inhibin and calretinin have been shown to be more sensitive and specific marker than CD99, A103 (melan-A), CD10 and WT-1 for ovarian sex cord stromal tumours.\textsuperscript{19} CD34 stains the endothelium of often dilated and branching vascular architecture and clearly distinguishes SST from thecoma and fibroma. αGST positivity within scattered cells appears to be useful in the distinction of SST from diffuse staining thecomas and no staining fibromas.\textsuperscript{21} Lifschitz-Mercer \textit{et al.}, proved that PR stained positively in SST cells.\textsuperscript{22} Kostopoulou E \textit{et al.}, defined that a positivity for ER beta was observed in a significantly larger number of cells than that for ER alpha.\textsuperscript{23} In addition, three copies of chromosome 12 in 13-21\% of all examined SSTs tumour cells was reported using fluorescence \textit{in situ} hybridisation (FISH) analysis.\textsuperscript{6} One researcher described a patient with SST with monosomy of chromosome 16.\textsuperscript{24} Although many studies showed variable immunohistochemical analysis.

### Table 3: Sclerosing stromal tumour (SST) of the ovary during pregnancy in the literature

| Case          | Age | Side  | Clinic and symptom | CA-125 | Tumour size (cm) | Gross appearance     |
|---------------|-----|-------|--------------------|--------|------------------|----------------------|
| Tiltman, 1985 | 18  | Right | Pregnancy          |        | 20               | Cystic               |
| Tiltman, 1985 | 32  | Right | Pregnancy          | 4      | 4                | Solid                |
| Ismail \textit{et al.}, 1990 | 29  | Bilateral | Pregnancy, virilisation | R 14; L 10,5 | 3 | Solid               |
| Cashel \textit{et al.}, 1991 | 27  | Left  | Pregnancy, virilisation |        | 50               | Solid                |
| Duska LR \textit{et al.}, 1998 | 31  | Right | Pregnancy          | 3      | Cystic           | Solid-cystic         |
| Huang SC \textit{et al.}, 2003 | 30  | Right | Pregnancy, pelvic pain | High   | 14               | Cyst                 |
| Calabrese \textit{et al.} 2004 | 21  | Right | Pregnancy          | 7      | Solid            |                      |
| Gurbuz A \textit{et al.}, 2004 | 16-24 | Right | Pregnancy (2 cases) | 6-14 (mean 11) | Solid-cystic       |                      |
| Kurt \textit{et al.}, 2004 | 19  | Right | Pregnancy          |       | 6,5              | Solid                |
| (126 cases pregnant) | 3 | Left  | Pregnancy          |       | 6               | Solid                |
| Kim D \textit{et al.}, 2012 | 19  | Right | Pregnancy          | 5      | Solid            |                      |
| Kaygosuz EI \textit{et al.}, 2013 | 21  | Right | Pregnancy          | 8,5    | Solid            |                      |
| Kaygosuz EI \textit{et al.}, 2013 | 19  | Right | Pregnancy          | 6      | Solid-cystic     |                      |
| Liang YF \textit{et al.}, 2014 | 25  | Right | Ectopic pregnancy | 50     | 50               | Solid-cystic         |
for sclerosing stromal tumours, a predominant positivity for inhibin, calretinin, smooth muscle actin and vimentin is a well-known immunohistochemical panel suggesting a stromal origin of the SST.

In conclusion, the patient's young age (generally, the second or third decade of life), the unilaterality of the tumour and the characteristic macroscopic and histopathological appearance of the tumour are essential characteristics for the diagnosis of SST of the ovary. SST is a very rare tumour but tumour markers, hormone tests and ultrasonography, in addition to MRI should be performed when the women are under the age of 30 and the visual inspection reveals 5 cm or more of a solid tumour. Frozen biopsies should also be performed during surgery. The distinct histopathological appearance and immunohistochemistry of SST are important in aiding diagnosis. All cases were diagnosed as benign except for one patient with low-grade malignancy reported in 1990. Surgical resection of the tumour is curative since to date, no local or distant recurrences have been reported in literature. A combination of morphological, immunohistochemical, radiological and clinical findings is needed in differentiating the tumour from thecoma, fibroma/fibrosarcoma, lipid tumours and Krukenberg tumour.

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