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CORRESPONDENCE

Signet-Ring Stromal Tumor of the Ovary: Report of a Case and Review of the Literature

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Abstract Signet-ring stromal tumor of the ovary is extremely rare, with only ten cases reported in the literature. We report on a case of signet-ring stromal tumor of the left ovary in a 54-year-old woman who presented with abdominal discomfort. Histologically, the tumor was composed of an admixture of spindle and round cells which contained a large cytoplasmic vacuole which displaced the nucleus, creating a signet-ring appearance. Numerous cells showed intracytoplasmic hyaline globules. Immunohistochemically, the tumor cells showed positivity for vimentin, actin, inhibin, and calretinin, thus confirming the ovarian stromal origin of the neoplasm. The patient remains free of disease one year and 9 months after surgery. Signet-ring tumor of the ovary is a rare variant of benign ovarian stromal neoplasm and should be distinguished from metastatic mucin-secreting signet-ring adenocarcinoma.

Keywords Calretinin · Inhibin · Ovary · Sex cord-stromal tumor · Signet-ring stromal tumor

Introduction

Signet-ring stromal tumor is an exceedingly rare type of ovarian tumor with only ten previously reported cases in the literature [1–6]. Microscopically, this ovarian neoplasm is characterized by a proliferation of stromal spindle-shaped cells merged with rounded cells containing eccentric nuclei and single vacuoles, resembling signet-ring cells. The signet-ring cells may either be diffuse or represent a focal change in an otherwise typical fibroma.

Herein, we report on a case of signet-ring stromal tumor of the ovary with description of the immunohistochemical findings. A brief review of the previously reported cases is presented, and the main differential diagnosis of this rare entity is discussed.

Case Report

A 54-year-old woman, gravida 2, para 2, presented with a 3-month history of low abdominal discomfort. There was no relevant medical or family history. Pelvic examination revealed a palpable mass located at the left hemiabdomen. Ultrasound examination showed a 5×4.5 cm left-sided ovarian mass with mainly solid components. No significant ascites was present. Serum CEA, CA125 and CA 19.9 levels were within normal limits. The patient subsequently underwent a laparoscopic bilateral salpingo-oophorectomy. She has been followed up regularly, and was alive and free of disease for 1 year and 9 months after surgery.

Materials and Methods

The surgical specimen was fixed in 10% buffered formalin and embedded in paraffin. Four-micrometer thick sections were then stained with hematoxylin and eosin, periodic acid-Schiff (PAS) with and without diastase digestion,

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Masson trichrome, and reticulin. Formalin-fixed, unembedded samples were stained with Oil-red-O.

Conventional immunohistochemistry was performed on 4-μm sections of formalin-fixed, paraffin-embedded tissues. The following antibodies were used: vimentin (clone 3B4, 1:200, Progen BioTechnik GmbH, Heidelberg, Germany), high- and low-molecular-weight cytokeratin (clone AE1/AE3, 1:50, Progen BioTechnik GmbH), epithelial membrane antigen (EMA) (clone E29, 1:50, Dako, Glostrup, Denmark), carcinoembryonic antigen (CEA; clone 12-140-10, 1:50, Novocastra Laboratories Ltd, Newcastle Upon Tyne, UK), muscle-specific actin (clone HHF35, 1:100, Dako), α-inhibin (clone R1, 1:100, Dako), calretinin (clone DAK-Calret 1, 1:100, Dako), and Ki-67 monoclonal antibody (clone MIB1, Dako, dil. 1:100).

Pathologic Findings

Gross Findings

The ovarian tumor was solid and measured 5.5×5×3 cm. Its outer surface was smooth and glistening. Sectioning revealed a yellowish soft-to-firm solid tumor (Fig. 1a). No cystic, hemorrhagic or necrotic areas were noted. A thin rim of ovarian parenchyma was present at the periphery of the tumor. The right ovary and the fallopian tubes were unremarkable.

Microscopic Findings

Histological examination revealed a circumscribed but unencapsulated tumor surrounded by a rim of normal ovarian stroma of varying thickness. The tumor was composed of an admixture of spindle and round cells. Spindle cells showed elongated nuclei, nonvacuolated cytoplasm and were arranged in fascicles. The round cells contained a large single cytoplasmic vacuole which compressed and displaced the nucleus, creating a typical signet-ring appearance (Fig. 1b). The nuclei had a slightly irregular contour, an open chromatin pattern and they varied only slightly in size. Many of the round cells contained multiple intracytoplasmic eosinophilic globules (Fig. 1c). No mitotic figures were seen. The signet-ring cells were irregularly scattered through the neoplasm. Clear vacuoles were negative for PAS with and without diastase digestion. They were also negative for lipid stains, such as Oil-red-O. The eosinophilic intracytoplasmic globules stained intensely with Masson trichrome, and very lightly with PAS. Reticulin stain showed a delicate network of fibers investing the signet-ring cells as well as the surrounding fibrous stromal cells (Fig. 1d). Necrosis and desmoplasia were absent. Immunohistochemically, the tumor cells showed diffuse immunoreactivity for vimentin (Fig. 2a) and actin (Fig. 2b), and focal staining for α-inhibin (Fig. 2c) and calretinin (Fig. 2d) except in their vacuoles and eosinophilic globules. The signet-ring cells

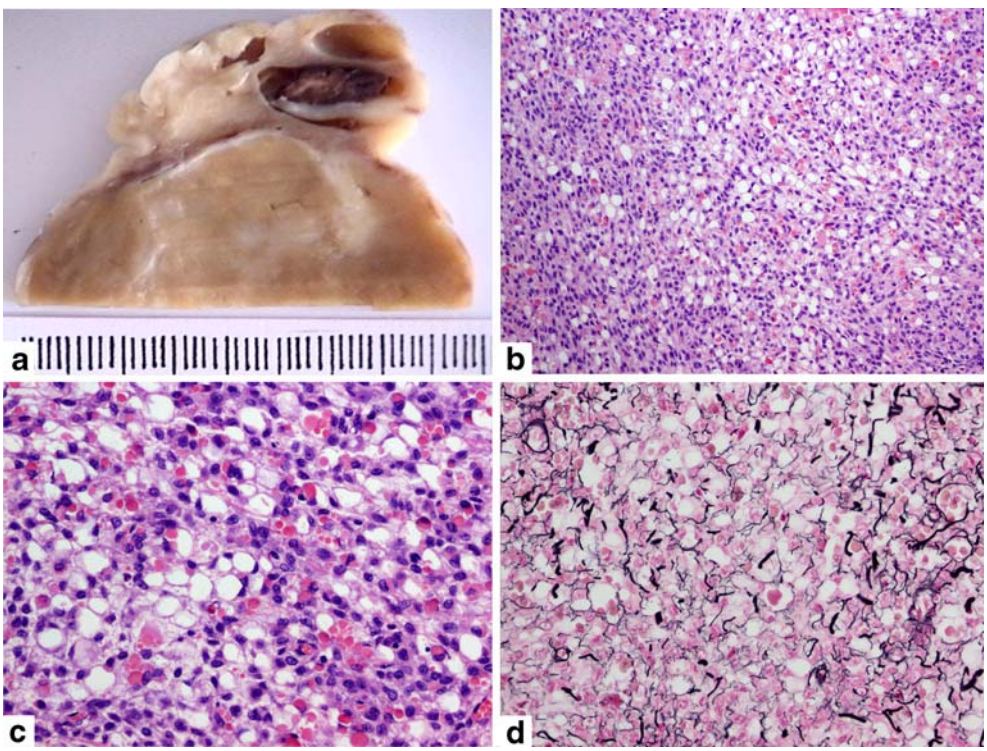

Fig. 1 Signet-ring stromal tumor of the ovary. **a** Cut surface of the surgical specimen showing a yellowish solid tumor, **b** numerous tumor cells showing a signet-ring appearance (hematoxylin and eosin, ×100), **c** signet-ring cells with their cytoplasms replaced by a clear vacuole that has pushed the nucleus to the periphery of the cell. Note the presence of abundant intracytoplasmic hyaline globules (hematoxylin and eosin, ×200), **d** reticulin stain show fibers surrounding individual cells (×200)

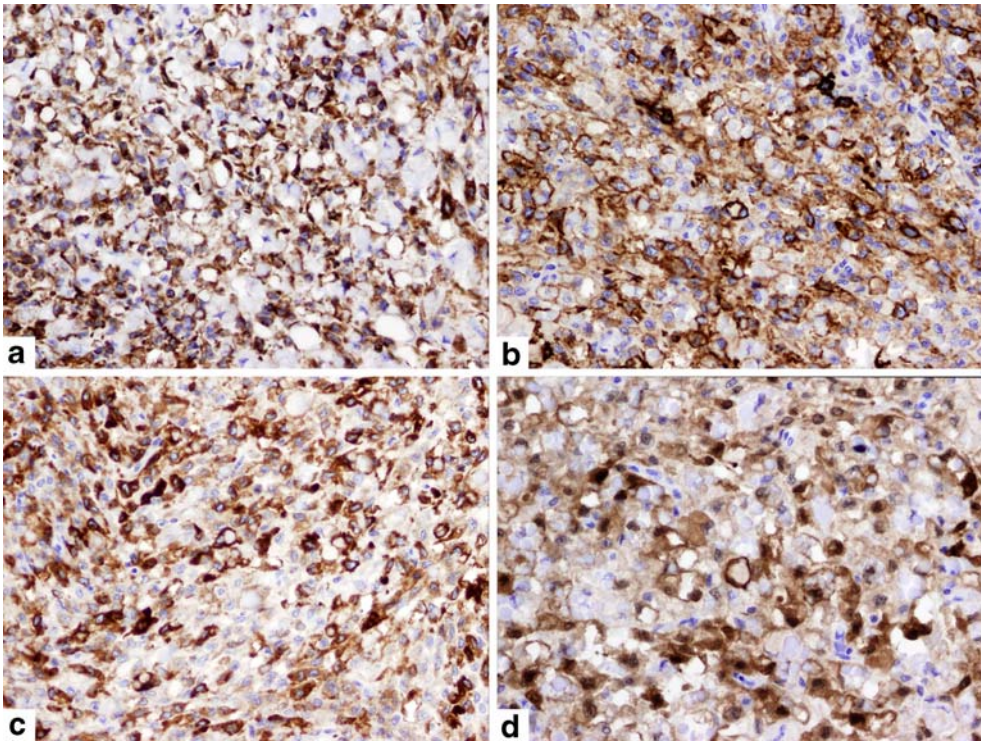

Fig. 2 Immunohistochemical findings in signet-ring stromal tumor of the ovary. **a** Diffuse strong positive staining for vimentin (×200), **b** signet-ring cells are positive for actin (×200), **c** α-inhibin expression in the tumor cells (×200), **d** calretinin is expressed in signet-ring cells of the tumor (×200)

were negative for cytokeratins, epithelial membrane antigen (EMA), and carcinoembryonic antigen (CEA). Proliferation index (Ki67) was lower than 1%. Cytologic examination of peritoneal washing was negative for tumor cells.

Discussion

Signet-ring stromal tumor of the ovary is a rare non-functioning distinctive stromal neoplasm that occurs in adults and is characterized by a proliferation of stromal and signet-ring cells. To date, only ten cases have been reported in the literature [1–6]. Ramzy [1] first described this unique signet-ring type of ovarian tumor in 1976 and concluded that the cell type was of stromal origin. All the tumors reported so far occurred in adults and presented with an unilateral ovarian mass with no known hormone effects or obvious ascites. The patients previously reported had a mean age of 49.8 years, and a range between 21 and 83 years of age. Abdominal pain was the most frequent presenting symptom. Grossly, there was considerably variation in the size range of the tumors (2.5 to 13 cm) with a mean size of 7.6 cm. Most tumors showed a solid appearance, with occasional cystic and hemorrhagic spaces.

Table 1 Summary of findings in signet-ring stromal tumor of the ovary

Source	Age	Symptoms	Side	Size (cm)	Macroscopic appearance	Treatment	Follow-up
Ramzy (1976) [1]	28	Abdominal pain	Right	8	Solid	TAH, right SO	NED, 1.3 years
Suarez et al. (1993) [2]	50	Abdominal pain	Left	9	Solid	Left oophorectomy	NED, 2.2 years
Dickersin et al. (1995) [3]	21	NA	NA	5	Solid-hemorrhagic	NA	NED, 2 years
	78	NA	NA	8.5	Solid-cystic	NA	NED, 1.6 years
	83	NA	NA	8.9	Solid	NA	NED, 2 months
Cashell et al. (2000) [4]	52	Weight loss	Left	2.5	Solid	TAH, BSO	NED, 2 years
Su et al. (2003) [5]	76	Abdominal pain	Left	5	Solid	BSO	NED, 1.4 years
Vang et al. (2004) [6]	34[a]	Pelvic mass	Left	13	NA	TAH, BSO	NED, 17.4 years
	35	Pelvic mass	Right	3.5	NA	Right oophorectomy	NED, 4.7 years
	41	Abdominal pain	Right	13	NA	TAH, BSO	NED, 1 month
Present case	54	Abdominal pain	Left	5.5	Solid	BSO	NED, 1.9 years

TAH total hysterectomy, *BSO* bilateral salpingo-oophorectomy, *NED* no evidence of disease, *NA* not available/reported
[a] This case has been previously reported by Dickersin et al. [3].

All patients were alive and free of disease at last follow-up. Recently, a signet-ring stromal tumor of the ovary occurring in association with a benign Brenner tumor has been reported [4]. The clinical details and follow-up of these cases are summarized in Table 1.

Microscopically, two types of morphologic patterns can be found in signet-ring stromal tumor of the ovary: a diffuse growth of signet-ring cells and an intermixture of signet-ring cells with spindle cells. Hyaline bodies are present in some tumors, as occurred in our case. Stains for lipid and mucin are negative. Ultrastructural studies have shown that in some cases the vacuoles result from diffuse edema of the cytoplasmic matrix, in other cases from swelling of the mitochondria, and in still others from cytoplasmic pseudoinclusions of edematous extracellular matrix [2–5].

In previous studies, calretinin and inhibin have been found to be a sensitive marker for ovarian sex cord-stromal tumors [7, 8]. However, the results of the immunohistochemical analysis for inhibin in signet-ring stromal tumor of the ovary have been contradictory. Cashell et al. [4] reported positive immunoreactivity against α-inhibin in their case, whereas Vang et al. [6] did not find α-inhibin positivity in the three neoplasms they analyzed. In our case, α-inhibin and calretinin were positive in the tumor cells, confirming the ovarian stromal origin of the neoplasm.

The most important differential diagnosis of signet-ring stromal tumor of the ovary is metastatic mucin-secreting signet-ring adenocarcinoma (Krukenberg tumor) [6]. The macroscopic features of the signet-ring stromal tumor are somewhat similar to those of the Krukenberg tumor, but a gelatinous appearance favours the later. Multinodularity is another feature of metastatic tumors involving the ovary, and is therefore more frequently seen in Krukenberg tumor. Unlike most Krukenberg tumors, signet-ring stromal tumors are unilateral. Histologically, both of these entities are composed of cells largely filled by vacuoles. The signet-ring stromal tumor, however, lacks the pleomorphism, mitotic activity, and the hyperchromatic nuclei of Krukenberg tumor. Despite the histologic similarity of signet-ring stromal tumor of the ovary with Krukenberg tumor, additional evidence of epithelial differentiation, such as tubular glands, nests or cords of cells can be found at least focally in the vast majority of Krukenberg tumors. In contrast, epithelial structures are not found in signet-ring stromal tumor of the ovary and are therefore a useful discriminating feature. Additionally, the negative histochemical reactions of the signet ring cells for PAS and mucicarmine and the negative immunohistochemical reactions to cytokeratins and EMA are strong evidence against a metastatic origin. The presence of nonlipid signet-ring cells admixed with fibromatous areas is the primary characteristic separating signet-ring stromal tumor from other ovarian sex cord-stromal tumors, in which the cells are positive for lipid stain. Occasionally, the sclerosing stromal tumor of the ovary may contain a few signet-ring-like cells. However, the signet-ring stromal tumor lacks the pseudolobulation, lipid-rich cells, and prominent vascularity of sclerosing stromal tumor.

In conclusion, signet-ring stromal tumor should be considered a morphologically distinctive type of benign ovarian stromal tumor, which may cause problems in the differential diagnosis of metastatic signet-ring cell tumors of gastrointestinal origin (Krukenberg tumor). It remains to be established whether the signet-ring cells represent a true neoplasm or a non-specific reactive change of stromal cells to an unknown injury.

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References

1. Ramzy I (1976) Signet-ring stromal tumor of ovary. Histochemical, light, and electron microscopic study. Cancer 38:166–172
2. Suarez A, Palacios J, Burgos E et al (1993) Signet-ring stromal tumor of the ovary: a histochemical, immunohistochemical and ultrastructural study. Virchows Arch A Pathol Anat 422:333–366
3. Dickersin GR, Young RH, Scully RE (1995) Signet-ring stromal and related tumors of the ovary. Ultrastruct Pathol 19:401–419
4. Cashell AW, Jerome WG, Flores E (2000) Signet ring stromal tumor of the ovary occurring in conjunction with Brenner tumor. Gynecol Oncol 77:323–326
5. Su RM, Chang KC, Chou CY (2003) Signet-ring stromal tumor of the ovary: a case report. Int J Gynecol Cancer 13:90–93
6. Vang R, Bague S, Tavassoli FA et al (2003) Signet-ring stromal tumor of the ovary: clinicopathologic analysis and comparison with Krukenberg tumor. Int J Gynecol Pathol 23:45–51
7. Deavers MT, Malpica A, Liu J et al (2003) Ovarian sex cord-stromal tumors: an immunohistochemical study including comparison of calretinin and inhibin. Mod Pathol 16:584–590
8. McCluggage WG, Maxwell P (2001) Immunohistochemical staining for calretinin is useful in the diagnosis of ovarian sex cord-stromal tumors. Histopathology 38:403–408