

Sclerosing stromal tumor of the ovary

An ultrastructural study and review of the literature to evaluate hormonal function

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Sclerosing stromal tumor of the ovary is a rare benign neoplasm. Usually regarded as nonfunctional, some of these tumors have been associated with endocrine manifestations that suggest steroid hormone production by the tumor. In this report, the ultrastructural features of a typical sclerosing stromal tumor are analyzed. The electronoptic features of the neoplastic cells include abundant rough endoplasmic reticulum, prominent Golgi structures, and lipid droplets. Mitochondria had lamellar cristae, and smooth endoplasmic reticulum was sparse. These findings do not substantiate steroidogenic activity of the neoplastic cells in this case.

Index term: Ovarian neoplasms

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Sclerosing stromal tumor is a rare neoplasm of the ovary initially described in a report of 10 cases by Chalvardjian and Scully in 1973.¹ Although 74 examples have been mentioned in the literature, only 44 cases have been reported in detail.¹⁻¹⁷ These histologically distinctive stromal tumors occur predominantly in the second and third decades of life. Although sometimes associated with menstrual irregularities or endometrial hyperplasia and rarely with infertility, they are not usually classified as functional tumors. In

a small number of cases, biochemical or immunohistochemical evidence suggesting hormone production by the tumor has been presented.^{2,6,8,9,13}

Electron microscopy of steroidogenic cells usually shows characteristic cytoplasmic organelles. To date, ultrastructural studies have been reported in only four cases.^{2,6-8} In this study, we report a typical sclerosing stromal tumor and analyze its ultrastructural features. A brief review of the literature on ovarian sclerosing stromal tumors with emphasis on reported endocrine manifestations is presented.

Case report

The patient was a 35-year-old woman who had had Crohn's disease of the small intestine for 14 years. Her clinical course had been complicated by multiple surgical procedures for fistulas and abscesses. Menarche was at age 14 years, and she had regular menses. A pregnancy at age 23 years was complicated by a large retroperitoneal abscess, and the infant was stillborn at seven months gestation. The patient subsequently carried two pregnancies to term without complications. She returned to The Cleveland Clinic Foundation with symptoms of Crohn's disease and intermittent bowel obstruction and underwent a laparotomy for lysis of adhesions. At operation, a left ovarian mass was unexpectedly found, and a left oophorectomy was done. Her postoperative course was unremarkable.

Materials and methods

Tissue for light microscopy was fixed in Hollande's solution, routinely processed, and em-

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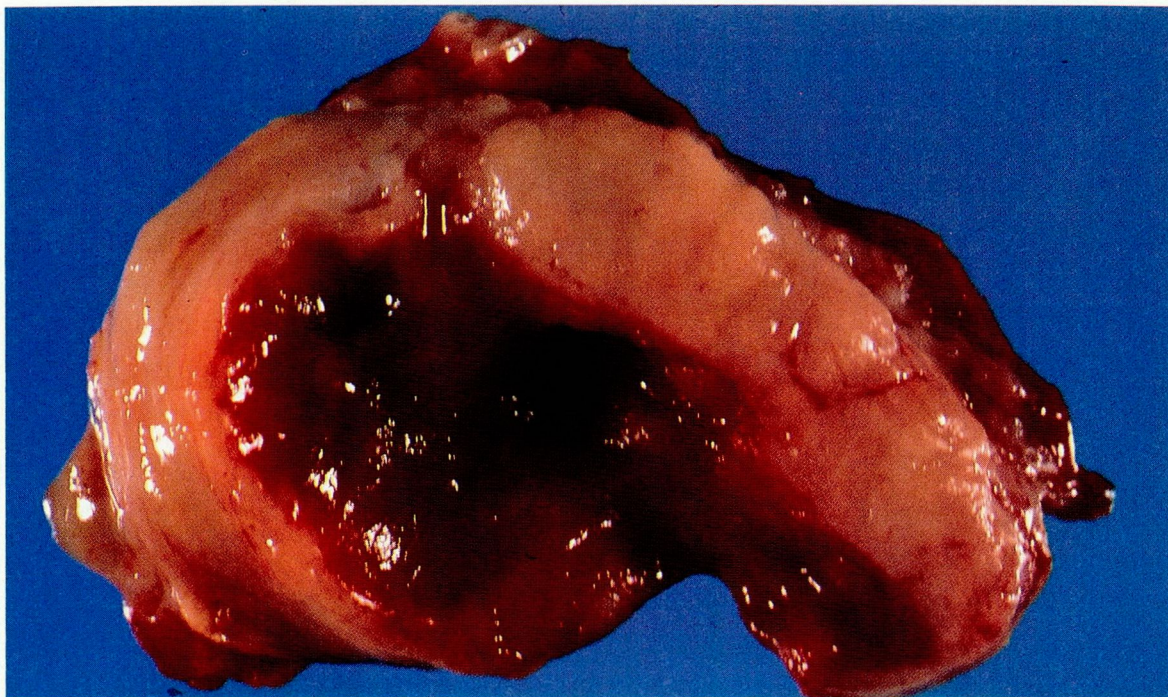


Fig. 1. Gross appearance of cut surface of ovarian sclerosing stromal tumor. The tumor is tan and sharply demarcated with a central area of cystic degeneration.

bedded in paraffin. Histologic preparations were stained with hematoxylin and eosin and with periodic acid-Schiff reagent with and without predigestion with diastase. Fresh-frozen tissue was sectioned with a cryostat and stained with oil red O for detection of neutral lipid deposits.

For electron microscopy, 1-mm³ pieces of the fresh tumor were promptly fixed in 0.1 mol/L cacodylate-buffered 3.75% glutaraldehyde containing 6% sucrose, postfixed in cacodylate-buffered 1% osmium tetroxide, and embedded in Spurr resin. Ultrathin sections were stained in uranyl acetate and lead citrate and examined under a Phillips 400T electron microscope.

Pathologic findings

The left ovarian tumor weighed 50 g and measured 6.2 × 5.0 × 3.0 cm. The outer surface was nodular. The cut surface consisted of a lobulated, tan, firm tumor measuring 5.0 × 3.0 × 2.0 cm (Fig. 1). The tumor was sharply demarcated at its periphery. An irregularly shaped cyst 3.0 cm in greatest dimension filled with clear to slightly hemorrhagic fluid was in the center.

Microscopically, the ovarian mass had the typical features of a sclerosing stromal tumor.¹ The tumor was composed of cellular lobules or "pseudolobules" separated by edematous hypocellular zones in some areas and sclerotic bands in others (Fig. 2). Within the lobules were plump epithe-

lioid cells with vesicular nuclei and prominent nucleoli and pale-staining or clear cytoplasm (Fig. 3). Some cells contained cytoplasmic vacuoles. Spindled cells resembling fibroblasts were also present and were admixed with the epithelioid cells. Portions of the tumor were densely collagenous and hyalinized. There was a prominent vascular network in both the cellular and edematous areas. Neither mitotic figures nor cytologic atypia were present. Oil red O stains demonstrated the presence of neutral lipid in the epithelioid cells. None of the cells contained glycogen or neutral mucin deposits.

Electron microscopic examination showed polygonal-to-spindled tumor cells surrounded by large bundles of collagen. The cells were well preserved, and their ultrastructural features were easily evaluated (Figs. 4,5). No specialized intercellular junctions were identified. The cells had abundant cytoplasm. Nuclei were round to oval with occasional deep indentations. Nucleoli were prominent. The cytoplasmic organelles consisted of mitochondria with lamellar cristae, abundant rough endoplasmic reticulum, rare short segments of smooth endoplasmic reticulum, and dense lysosomes. The amount of lipid varied. Some cells had no lipid or only one or two lipid droplets. In other cells, numerous lipid droplets almost filled the cytoplasm. The Golgi apparatus was prominent and was associated with numerous

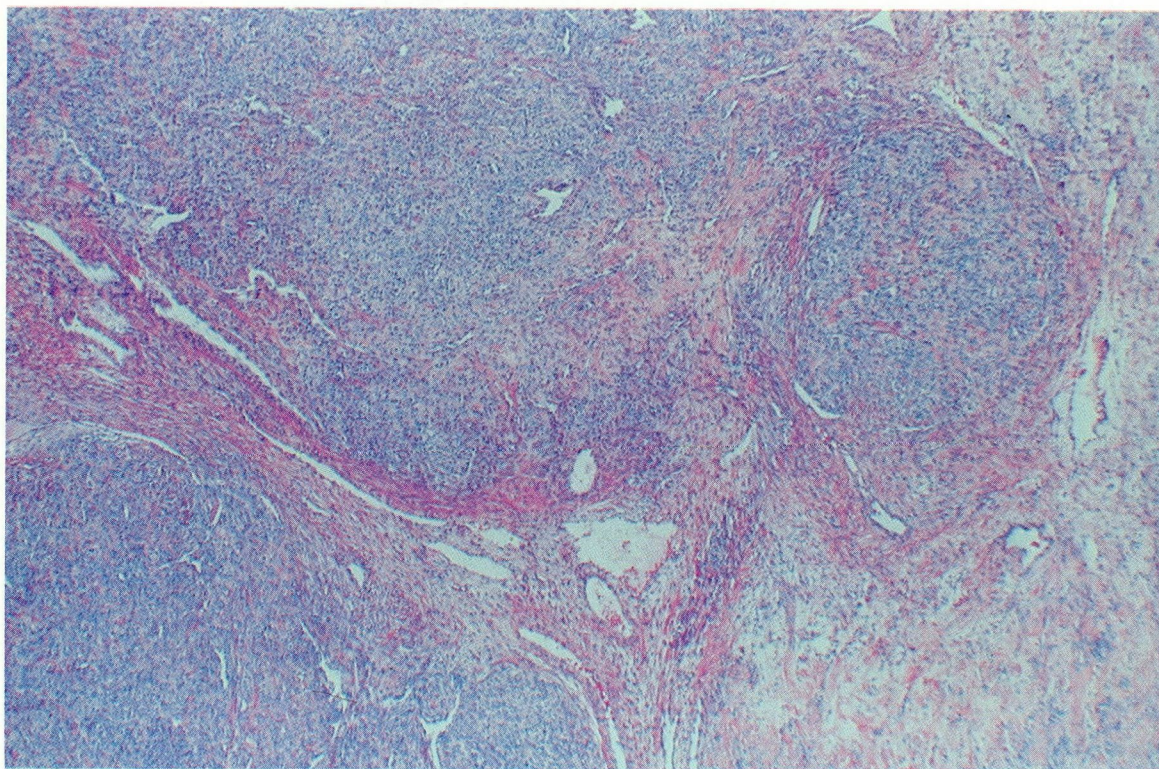


Fig. 2. The tumor consists of cellular lobules separated by edematous hypocellular zones.

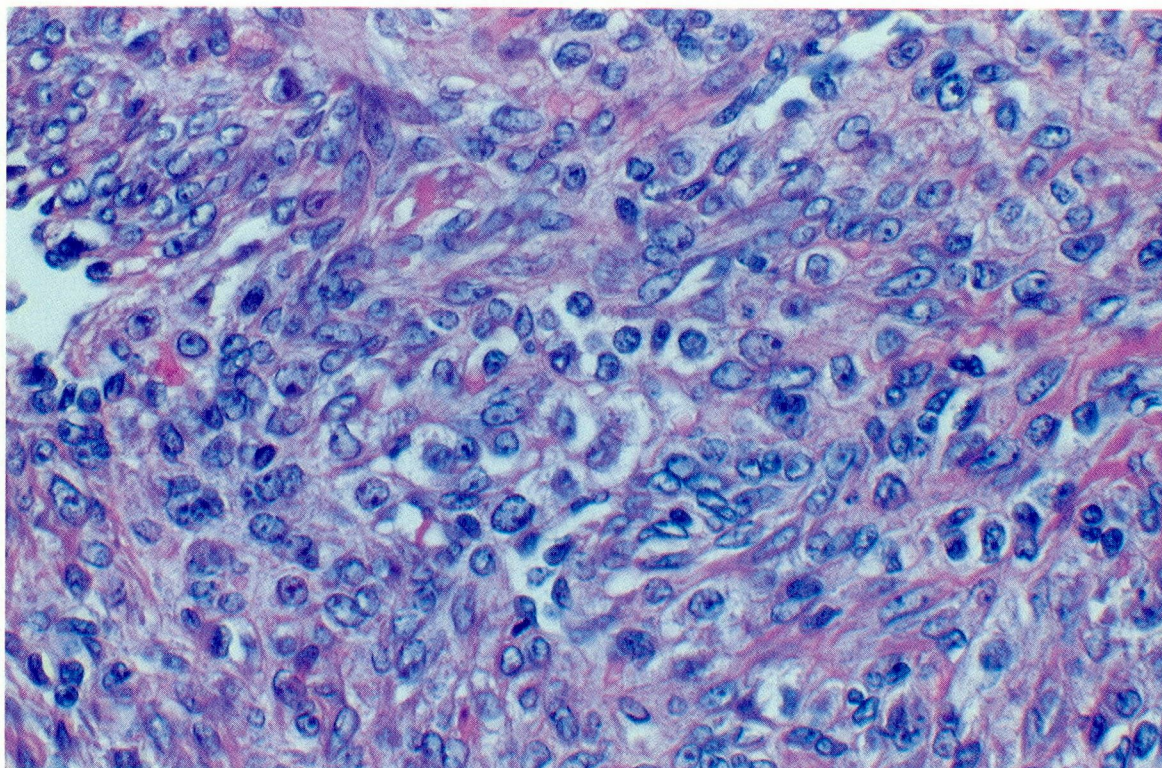


Fig. 3. High magnification of cells within lobules. The neoplastic cells have an epithelioid configuration with abundant pale or vacuolated cytoplasm. Spindle-shaped cells were prominent in other areas of the tumor.

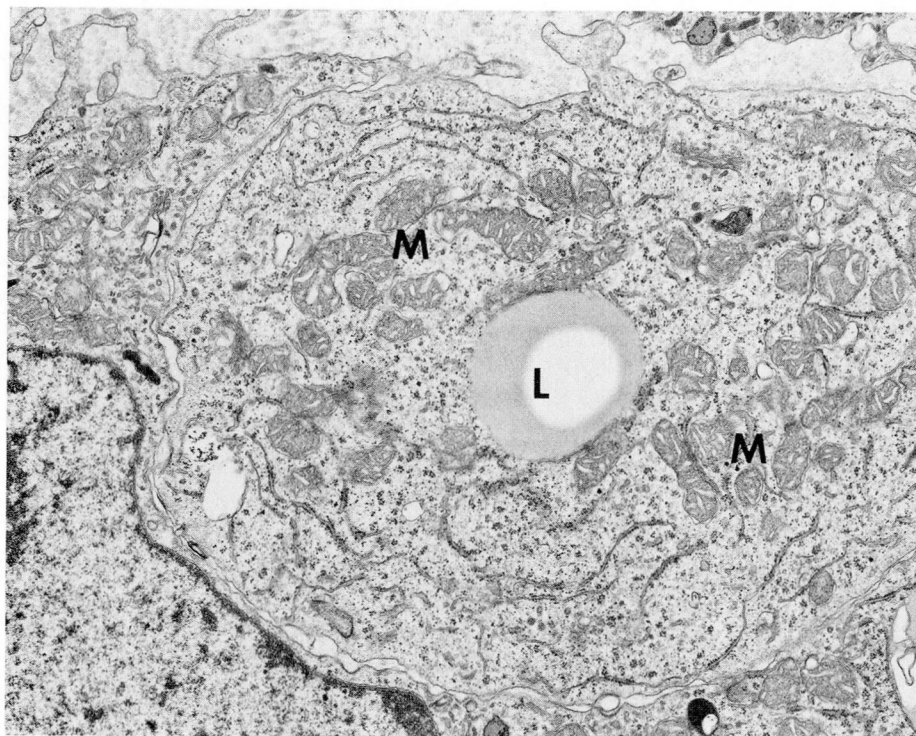


Fig. 4. Electron micrograph of tumor cell. Within the cytoplasm are numerous mitochondria with lamellar cristae (M), a lipid droplet (L) and lengths of rough endoplasmic reticulum. A portion of the nucleus is in the lower left corner.

small vesicles. The more spindled cells with little or no lipid resembled fibroblasts.

Discussion

Since Chalvardjian and Scully's¹ original description of sclerosing stromal tumor in 1972, 44 cases have been reported in detail.²⁻¹⁶ Although these patients ranged in age from 12 to 63 years, 75% were less than 30 years old. The most common presenting symptoms were menstrual irregularities (50%) and pelvic pain (27%). Four of the five reported patients who were over 50 years old presented with postmenopausal bleeding. Although three women presented with infertility, which resolved after removal of the tumor,^{3,4,6} three women were pregnant at the time the ovarian mass was discovered.^{9,13} In three of the reported cases,^{3,8,13} the tumor was an incidental finding, as in our patient.

All tumors have been clinically benign. After postoperative follow-up periods of one month to 10 years, there have not been any recurrences or metastases. An immature teratoma developed in the opposite ovary of one patient 18 months after removal of a sclerosing stromal tumor combined with a small mature teratoma (dermoid cyst).¹⁵

All of the reported tumors were unilateral, 28 occurring in the right ovary and 16 in the left. Tumor size ranged from 1.5 cm to 20.0 cm. Although the tumors were predominantly solid, most also contained multiple small cysts or a single large cyst. The solid areas were firm, nodular, and grey-white with tan-yellow areas. Often, a thin rim of compressed ovary could be seen at the periphery of the sharply circumscribed tumor.

Endocrine activity of sclerosing stromal tumors has been documented in only a small number of cases. Damjanov et al² measured estrogenic and androgenic hormones in 24-hour urine samples collected before removal of a sclerosing stromal tumor and 14 days postoperatively. Elevated levels of 17-ketosteroids, androgens, and estriol were found with normal levels after removal of the tumor.² Ho Yuen et al⁶ measured intraoperative and postoperative serum hormone levels in a patient with a sclerosing stromal tumor who presented with chronic anovulation. In this patient, serum levels of testosterone, estradiol, and progesterone fell after removal of the tumor.⁶ Martinelli et al⁸ demonstrated a drop in serum testosterone and androstenedione levels postoperatively in a patient with amenorrhea associated

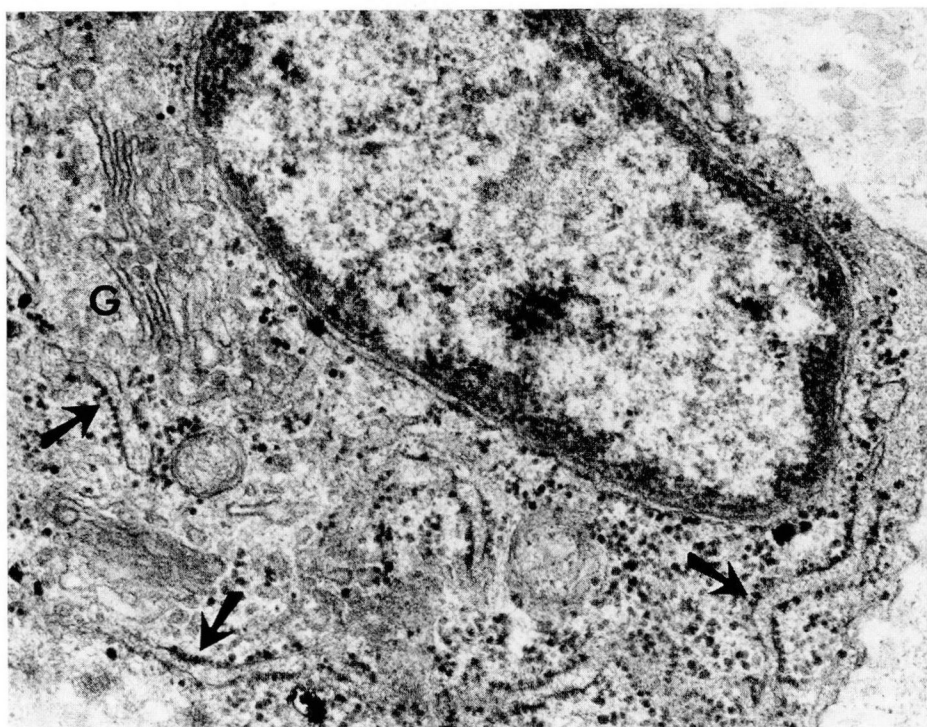


Fig. 5. Electron micrograph of another tumor cell. Prominent Golgi apparatus (G) and abundant rough endoplasmic reticulum (arrows) are apparent.

with a sclerosing stromal tumor. Quinn et al⁹ reported a drop in serum androgen and estrogen levels after removal of a sclerosing stromal tumor found during operation for an ectopic pregnancy. The hormonal findings in that patient were regarded as evidence of androgenic function of the tumor, although the associated pregnancy complicated interpretation of the results.

Cytoplasmic lipid in tumor cells is nonspecific but is often present in ovarian steroid cells and functioning ovarian tumors. Tiltman¹³ demonstrated positive immunohistochemical staining for ligandin in the lipid-containing tumor cells. Ligandin, a cytosol protein found in many tissues, has the ability to bind a wide range of organic ions, including corticosteroids and steroid hormone metabolites.¹⁸ Tiltman^{13,18} reported antiligandin localization in granulosa and thecal cells of the human ovary and indicated such immunoreactivity was useful in demonstrating steroid-producing cells in the ovary and within ovarian neoplasms.

Attempts at immunohistochemical staining of sclerosing stromal tumors for specific steroid hormones have yielded variable results. Martinelli et al⁸ reported positive immunostaining for androgens in a minority of tumor cells in one patient

who also had elevated serum levels of testosterone and androstenedione; two other tumors did not contain immunoreactive cells. Tiltman¹³ was unable to show localization of steroid hormones by immunohistochemistry in his series of three ligandin-positive sclerosing stromal tumors.

In the four reported ultrastructural studies of sclerosing stromal tumor, some evidence of steroidogenesis by the tumor cells has been described. Steroid-producing cells typically contain lipid droplets, abundant smooth endoplasmic reticulum, and mitochondria with tubular cristae. Abundant tubular or vesicular smooth endoplasmic reticulum, lipid droplets, and mitochondria with tubulovesicular cristae were found in tumor cells of one apparently androgenic tumor reported by Martinelli et al.⁸ Some smooth endoplasmic reticulum was found in two other functioning tumors^{2,6} but not in another.⁷ In these three cases, the mitochondrial cristae were either not described (two cases)^{6,7} or were lamellar rather than tubular (one case).²

In our patient, there was no evidence of hormonal function. Because the tumor was clinically unsuspected before operation, serum hormone levels were not measured. Ultrastructurally, the tumor cells contained lipid droplets, mitochon-

dria with lamellar cristae, prominent Golgi structures, and abundant rough endoplasmic reticulum, but only a small amount of smooth endoplasmic reticulum. These electronoptic features suggest that the tumor was synthetically active, but the cells appeared to have been producing protein substances rather than steroids.

In summary, electron microscopy has only rarely revealed morphologic features of steroidogenic activity in ovarian sclerosing stromal tumors. Of the five tumors that have now been examined, only one has had ultrastructural features characteristic of steroid-type cells.⁸ Moreover, that patient also had hypomenorrhea and serum hormonal levels indicating androgenic function by the tumor. Further ultrastructural and hormonal studies of clinically functional and nonfunctional tumors need to be performed to better characterize the hormonal potential of sclerosing stromal tumors.

Addendum

After this manuscript was submitted for publication, a case of sclerosing stromal tumor has been reported from Japan, and six other Japanese cases have been mentioned.¹⁹ An abstract describing ultrastructural findings in two cases from Italy has also been published.²⁰

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