Signet Ring Stromal Cell Tumor
A Legitimate (Benign) Mimic of Krukenberg Tumor

Ryan DeCoste, MD; Saul L. Offman, MD, FRCPC

● Signet ring stromal cell tumor is a rare, benign ovarian neoplasm thought to arise from ovarian stromal cells. The pathophysiology of these tumors is poorly understood. They present in women in a wide age range, often with nonspecific symptoms including lower abdominal or pelvic pain. Their morphologic appearance raises a critical differential diagnosis of Krukenberg tumor, an aggressive malignancy with significant implications for patient management. For this reason, it is important for the pathologist to be aware of signet ring stromal cell tumor and its differentiating features, including useful histochemical and immunohistochemical ancillary tests. These tumors are curable with surgical excision, and there have been no recurrences or metastases among reported cases.


Signet ring stromal cell tumor (SRSCT) is a rare ovarian neoplasm first described by Ramzy1 in 1976. These tumors are considered benign; however, their microscopic appearance raises a differential diagnosis that includes Krukenberg tumor. Krukenberg tumors are ovarian metastases, most commonly originating from gastrointestinal adenocarcinomas, often exhibiting signet ring cell morphology.1 This raises a crucial diagnostic challenge with significant clinical implications for prognosis and patient management. Thus, pathologist knowledge of SRSCT is imperative to avoid misclassification. In this short review, we describe important findings and distinguishing features seen in reported cases of this rare but clinically relevant neoplasm.

CLINICAL FEATURES

Signet ring stromal cell tumors have occurred in premenopausal and postmenopausal women (ages 21–83), often presenting with pelvic or lower abdominal pain, with or without a clinically detectable pelvic mass. Signet ring stromal cell tumors have also been discovered through investigation of dysfunctional uterine bleeding and incidentally on abdominopelvic imaging. The first described case was found in association with pelvic inflammatory disease and hirsutism; however, the androgenic effects persisted after resection, suggesting they did not relate to the ovarian tumor. No additional evidence of endocrine effects has been reported. Tumors are almost always unilateral and confined to the ovary, although one case with bilaterality and adhesions to other intraperitoneal structures has been described. Preoperative serum tumor markers, including carcinoembryonic antigen, CA 125, CA 19–9, and, in one case, squamous cell carcinoma antigen, have been within normal limits.1–9

GROSS AND MICROSCOPIC FINDINGS

Signet ring stromal cell tumors range from 3.0 to 13.0 cm. They are circumscribed, solid, gray-tan, white, brown, or yellow tumors with variable firmness. They may have small areas of hemorrhage, necrosis, or cystic change. Less commonly, the tumors may appear multinodular or less circumscribed. A rim of compressed ovarian parenchyma may be seen peripheral to the tumor, and the serosa of the ovary is typically smooth with no evidence of surface involvement.1–3,9

Microscopically, SRSCTs are composed of cells with a signet ring–like appearance, most frequently with a single cytoplasmic vacuole displacing the nucleus eccentrically (Figure 1). The vacuoles are typically clear, but may contain faint pink material. The constituent cells proliferate in a background of ovarian stromal cells, with reticular fibers surrounding individual cells. No gland, nest, or cord formation is seen. Nuclei are generally bland, with smooth contours, uniform chromatin, and often a single nucleolus (Figure 2). Mitoses are rare; however, one case has been described with up to 16 mitoses per 10 high power fields.4,9 There may or may not be a fibroma-like stromal component, composed of bland spindle cells in a fascicular or storiform pattern, intermixed with the signet ring cell component. Intracytoplasmic and extracellular eosinophilic globules have been described in several cases, nearly all with fibromalike areas (Figure 3). The stroma may also contain edema, hemosiderin, foamy histiocytes, and collagen strands between tumor cells. Tumors may or may not be encapsulated.1–10

Electron microscopy on select cases has shown a lack of basement membrane or intercellular junctions associated with tumor cells. The structure of cytoplasmic vacuoles has varied in description, however, several cases have contained a single pseudoinclusion or hydropic vacuole containing extracellular matrix.5,8,11,12

Accepted for publication July 20, 2017.
From the Division of Anatomical Pathology, Dalhousie University, and Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada.
The authors have no relevant financial interest in the products or companies described in this article.
Corresponding author: Saul L. Offman, MD, FRCPC, Mackenzie Bldg, 7th Floor, Room 738, 5788 University Ave, Halifax, NS, Canada B3H 1V8 (email: saul.offman@nshealth.ca).
ANCILLARY TESTING

Immunohistochemistry (IHC) reveals expression of vimentin, but not cytokeratins, epithelial membrane antigen, carcinoembryonic antigen, desmin, \( \alpha \)-fetoprotein, \( \alpha_1 \)-antitrypsin, type 4 collagen, caldesmon, S100, Melan-A, synaptophysin, chromogranin, CD99, estrogen receptor, androgen receptor, or testosterone. Reports have described variable expression of CD10, inhibin, \( \alpha \) smooth muscle actin, CD56, progesterone receptor, and steroidogenic factor 1. Immunoassays for steroid receptor coactivator 1, \( \beta \)-catenin, and cyclin D1 were reported as positive in one case. Ki-67 index is typically less than 1%.3–12

Cytoplasmic vacuoles in SRSCT are negative for periodic acid–Schiff (PAS), Alcian blue, Hale colloidal iron, Sudan III, oil red O, and Nile blue.3–9,12 Eosinophilic globules, when present, stain with Masson trichrome and \( \alpha_1 \)-antitrypsin and lightly with PAS (Figure 3), but not with hemoglobin or glycophorin C stains. However, globules have been reported to resemble degenerating erythrocytes or lysosomes on electron microscopy.3,4,8 Silver or reticulin stains can highlight the reticulin fibers surrounding individual tumor cells.3,7,8

PATHOGENESIS

Signet ring stromal cell tumors are thought to be of ovarian mesenchymal origin. Supporting features include the presence of reticular fibers surrounding individual cells, the absence of associated basement membrane material or intercellular junctions, and the IHC profile of described cases.3,4,12 In addition, variably vacuolated, bland spindle cells have been noted in background ovarian stroma or fibroma-like areas in SRSCT, and may represent a continuum in the development of signet ring cells from stromal cells.5,11,12 Although this tumor has been referred to as signet ring (cell) stromal tumor, more recently Roth and Ramzy11,12 proposed signet ring stromal cell tumor as a more appropriate name to highlight the suspected stromal cell origin of these neoplasms. Furthermore, Roth and Ramzy11,12 propose distinguishing SRSCTs with and without fibroma-like areas, postulating that the former arise within a fibroma whereas the latter arise directly from ovarian stroma. When this distinction is made, the age range in which tumors without a fibroma-like component occur narrows significantly to 21 to 42 years.

The mechanism of signet ring cell development is not well understood. Histochemical stains reveal that the cytoplasmic vacuoles in SRSCT do not contain mucins, glycogen, or lipid.1–8 Electron microscopy findings have, in many cases, revealed a single hydropic pseudoinclusion of extracellular matrix with eccentric displacement of the nucleus.4,5,8,11,12 Recently, Kopczynski et al10 described a case of SRSCT in a 79-year-old woman in which they used next-generation sequencing to screen the tumor for a panel of 50 oncogenes and tumor suppressor genes. Their case contained a deletion in exon 3 of \( \text{CTNNB1} \), encoding the glycogen serine kinase 3\( \beta \) phosphorylation region of \( \beta \)-catenin. This would result in errors in \( \beta \)-catenin degradation and subsequent activation of the Wnt pathway. Their IHC findings correlated with this description, including strong nuclear and cytoplasmic expression of \( \beta \)-catenin and nuclear expression of cyclin D1. In addition, they noted a missense mutation of unknown significance in the Janus kinase 3 (\( \text{JAK3} \)) gene.10 Additional investigations are required to confirm the reproducibility and significance of these findings.

DIFFERENTIAL DIAGNOSIS

The most crucial differential diagnosis is between SRSCT and Krukenberg tumor. Additional differential diagnoses include carcinoïd tumors, as well as primary ovarian signet ring cell carcinomas and other mucinous epithelial neoplasms.3–9 Roth and Ramzy11,12 and others4,13 have also described sclerosing stromal tumor or thecoma with signet
ring cell transformation and ovarian epithelial or granulosa cell tumors with signet ring cell change in the nonneoplastic stroma.

Krukenberg tumors are more likely to be bilateral or multinodular or to exhibit extraordinary extension. In addition, in contrast to SRSCT, they typically contain pleomorphic nuclei and conspicuous mitoses, and may form glands, nests, or cords. The cytoplasmic vacuoles contain mucin, which can be highlighted with PAS, Alcian blue, or mucicarmine stains. Krukenberg tumors express cytokeratins, epithelial membrane antigen, and carcinoembryonic antigen, but not vimentin, on IHC. This differential could be particularly problematic at the time of intraoperative frozen section, secondary to freezing artifact and lack of available ancillary testing. Clinical correlation and communication with the surgical team is particularly crucial in this setting to avoid misclassification. Similar to Krukenberg tumor, primary ovarian mucinous neoplasms express epithelial IHC markers and contain intracytoplasmic mucin, and many have atypical to overtly malignant cytologic features. Goblet cell carcinoid tumors may also contain signet ring-like cells, but these contain PAS-positive material and will express neuroendocrine and epithelial markers. Primary ovarian carcinoid tumors also tend to occur in association with a mature teratoma.1,3,5,6

Signet ring cell change in the stroma of Brenner tumor and serous cystadenofibroma has been described. Readily identifiable components of the primary surface-epithelial lesion can be used to establish the diagnosis. These signet ring cells tend to express both vimentin and SMA.11,13

Signet ring cell change in other ovarian sex cord–stromal neoplasms, such as fibroma, thecoma, or luteinized granulosa cell tumor, tends to develop from luteinized cells, and thus the cytoplasmic vacuoles contain lipid, which can be highlighted with histochemical stains. Sclerosing stromal tumor may contain signet ring–like cells, but also exhibits pseudolobular architecture, sclerosis, and hemangiopericytoma-like vasculature, as well as expression of SMA and inhibin, which are not consistently expressed among reported SRSCTs.1,3,5,8,12 The microcystic spaces in microcystic stromal tumor may also be confused for signet ring cell change. This recently described entity has also exhibited CTNNB1 mutation in 2 cases, but tends to be a larger mass-forming lesion with macrocystic and microcystic spaces, hemorrhage, and expression of CD10 and Wilms tumor 1 in addition to vimentin.9,10 A further discussion of more rare differential diagnoses is available from Roth and Ramzy.11,12

It has been suggested that at a minimum, an IHC panel of PAS with diastase, vimentin, and a pan-cytokeratin or epithelial membrane antigen should be included in evaluating signet ring cell tumors of the ovary. Furthermore, epithelial membrane antigen may be preferable to a pan-cytokeratin, as cytokeratins may be expressed in adult granulosa cell tumors, in which a case of signet ring cell transformation has been reported.1,3,7,11,12

**TREATMENT AND PROGNOSIS**

Reported cases have been treated by oophorectomy, with or without salpingectomy and total abdominal hysterectomy.8 Follow-up periods ranging from 2 months to 17 years have documented no recurrences or distant metastases.4,6

**CONCLUSIONS**

Signet ring stromal cell tumor of the ovary is a rare benign neoplasm with a clinically relevant differential diagnosis of Krukenberg tumor. For this reason, pathologist knowledge of this entity is crucial to avoid misclassification with potential serious implications for patient management. Histochemistry and IHC are useful adjuncts to separate relevant differential diagnoses. The underlying pathophysiology is not well understood, but next-generation sequencing has been used in one recent case, paving the way to a better understanding of the molecular basis of these tumors. In all reported cases, follow-up has shown no recurrences or metastases, pointing to the benign clinical behavior of this entity.