Small-Cell Carcinoma of the Ovary of Hypercalcemic Type (Malignant Rhabdoid Tumor of the Ovary)

A Review with Recent Developments on Pathogenesis

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KEYWORDS

• Ovary • Small cell carcinoma of hypercalcemic type • *SMARCA4* • Immunohistochemistry • Molecular genetics • Mutation

Key points

- Small-cell carcinoma of the ovary of hypercalcemic type (SCCOHT) is a highly malignant and aggressive tumor and represents the most common undifferentiated ovarian malignancy to occur in women younger than 40 years.
- SCCOHT is characterized by deleterious germline or somatic mutations in a single gene, *SMARCA4*, in almost all cases.
- Given the striking morphologic and molecular similarities between SCCOHT and atypical teratoid/malignant rhabdoid tumor, it is clear that SCCOHT is a malignancy of mesenchymal differentiation and a form of ovarian malignant rhabdoid tumor.
- SMARCA4 (BRG1) immunohistochemistry is useful in the diagnosis of SCCOHT because there is loss of nuclear immunoreactivity in this neoplasm but retention of staining in mimics.

ABSTRACT

Small-cell carcinoma of the ovary of hypercalcemic type (SCCOHT) is a highly malignant and aggressive tumor and is the most common undifferentiated ovarian malignancy to occur in women younger than 40. SCCOHT is characterized by deleterious germline or somatic mutations in *SMARCA4*. Given the striking morphologic and molecular similarities between SCCOHT and atypical teratoid/malignant rhabdoid tumor, we propose this should be reflected in a nomenclature change and that SCCOHT be renamed malignant rhabdoid tumor of the ovary. SMARCA4 (BRG1) immunohistochemistry is useful in diagnosis because there is loss of nuclear immunoreactivity in SCCOHT but retention of staining in mimics.

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OVERVIEW AND HISTORY OF THE DISEASE

Small-cell carcinoma of the ovary of hypercalcemic type (SCCOHT) is a highly malignant undifferentiated ovarian malignancy that was initially described in 1979 by Robert E. Scully.[1] It was characterized by (1) the dominant appearance of small, hyperchromatic cells with brisk mitotic activity, (2) an early age of onset, and (3) the presence of hypercalcemia.[2] Initially, this was considered to most likely represent an epithelial malignancy (carcinoma), although an epithelial histogenesis was never proven, and the term SCCOHT was used to distinguish this type of small-cell "carcinoma" from the neuroendocrine or pulmonary type, which it can resemble.[2,3] The differential diagnosis of SCCOHT may be wide (discussed later) and, along with microscopy, immunohistochemical studies may be necessary to distinguish it from other ovarian neoplasms, although up until recently there has been no specific marker of SCCOHT.

In a seminal study of 150 cases, the mean age at diagnosis was 23.9 years, and 62% of the patients had preoperative hypercalcaemia.[4] Half of the tumors contained a component of large cells with abundant eosinophilic cytoplasm, the so-called "large-cell variant of SCCOHT." Among several interesting features, each of the 23 cases studied by flow cytometry in this study were diploid, an unusual feature for a highly malignant neoplasm.[4] Until recently, the histogenesis of SCCOHT has remained elusive; epithelial, sex cord, germ cell, and neuroendocrine differentiation has been speculated but none proven. Moreover, the underlying molecular events in SCCOHT also were not known until recently, despite the description of a further 250 cases in the English literature and a detailed immunohistochemical study of a series of 15 cases.[5]

In this review, we discuss the clinical and pathologic aspects of SCCOHT, including the differential diagnosis. We also review exciting new data regarding the molecular events underlying this enigmatic neoplasm and present evidence that SCCOHT is a mesenchymal malignancy and a form of ovarian malignant rhabdoid tumor. We propose that this should be reflected in a nomenclature change and that SCCOHT be renamed malignant rhabdoid tumor of the ovary (**Box 1**).

CLINICAL PRESENTATION AND OUTCOME

Although rare, SCCOHT is the most common undifferentiated ovarian malignancy to occur in women younger than 40.[4] Patients are generally diagnosed in their second or third decade of life (peak between 18 and 30 years), although SCCOHT has been seen in a girl as young as 14 months and a woman as old as 47 years.[4,6–8] Occasional familial cases have been reported.[9,10] The symptoms are usually nonspecific and those related to an abdominal or pelvic mass, but in one-third of cases the patient presents with signs or symptoms of hypercalcemia; as already discussed, approximately two-thirds of patients have increased serum calcium. More than half of patients have extraovarian disease at presentation; this usually comprises local spread to the abdomen and pelvis, but occasionally there is hematogenous spread to distant sites.

SCCOHT has a very poor prognosis, with a 33% survival rate when diagnosed at an early stage and a much more dismal prognosis with advanced

Box 1
Key features of small-cell carcinoma of the ovary of hypercalcemic type (SCCOHT)

Clinical

- Patient is typically younger than 50
- Patient may or may not have serum hypercalcemia

Genetic

- 1 Germline *SMARCA4* mutation + 1 somatic mutation or Loss of Heterozygosity (LOH) in the tumor, affecting the other allele
- 1 Somatic *SMARCA4* mutation + LOH in the tumor, affecting the other allele
- Biallelic somatic *SMARCA4* mutations

Histologic

- Typically small cells with scant cytoplasm but there may be a minor, predominant or exclusive component of large cells with abundant eosinophilic cytoplasm and a rhabdoid appearance
- Loss of SMARCA4/BRG1 nuclear staining by immunohistochemistry