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Review Article

Small cell cancers of the female genital tract: Molecular and clinical aspects

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HIGHLIGHTS

- Small cell carcinomas of the gynecologic tract are rare, aggressive malignancies.
- Small cell carcinoma of the ovary, hypercalcemic type has a germline genetic component.
- Understanding the molecular features will improve diagnosis and expand treatments.

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ABSTRACT

Objective. Extra-pulmonary small cell carcinomas of the gynecologic tract (EPSCC-GTs) are a rare group of aggressive malignancies associated with poor prognoses and limited treatment options. Here, we review the clinical and molecular aspects of EPSCC-GTs and discuss how understanding their molecular features can assist in their diagnosis and the identification of novel effective treatments.

Methods. We searched PubMed and Scopus for articles using the following keywords: "small cell carcinoma" in combination with "neuroendocrine", "ovary", "vagina", "fallopian tube", "vulva", "endometrium", "uterus", "cervix", or "gynecologic". Articles were limited to those published in English from January 1984 to October 2017.

Results. EPSCC-GTs account for 2% of all gynecologic malignancies. The molecular features of EPSCC-GTs are largely understudied and unknown, with the exception of small cell carcinoma (SCC) of the ovary, hypercalcemic type (SCCOHT) and SCC of the cervix (SCCC). In nearly all cases, SCCOHT displays mutation in a single gene, *SMARCA4*, a member of the SWI/SNF chromatin remodeling complex. The loss of expression of the SWI/SNF protein SMARCA2 is another feature of SCCOHT. Dual negative staining for SMARCA2 and SMARCA4 is specific for SCCOHT and is generally used by gynecologic pathologists for the accurate diagnosis of this malignancy. Mutational analysis of SCCC has shown alterations in *PIK3CA*, *KRAS* and *TP53*, of which the last is the most common, although other actionable mutations have been identified. The molecular features of other EPSCC-GTs are largely unknown.

Conclusions. Due to their rarity, the majority of EPSCC-GTs are understudied and poorly understood. As demonstrated in the case of SCCOHT, unraveling the mutational profiles of these tumors can lead to improved diagnosis and the identification of novel therapeutic targets.

Contents

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1. Introduction

Small cell carcinomas (SCCs) are rare, very aggressive malignancies. Up to 95% of all SCCs are found in the lung [1]. The morphologic features of SCCs have been described in sites outside of the lung as well, and these extra-pulmonary small cell carcinomas (EPSCCs) have been found to arise from nearly every organ in the body [2–4]. The majority of SCCs, pulmonary and extra-pulmonary, are neuroendocrine carcinomas. EPSCCs are most commonly found in the gastrointestinal (~30%) and genitourinary (~20%) systems [4].

EPSCCs of the gynecologic tract (EPSCC-GTs) account for approximately 2% of all gynecologic malignancies, and their histopathological and clinical characteristics have been reviewed in detail [5,6]. The exact origin of EPSCC-GT is largely unknown; however, primary tumors have been found in the ovary, endometrium, vagina, vulva, and most frequently, the cervix. The management of these tumors often includes surgery, radiation, and chemotherapy. Chemotherapy regimens for the treatment of EPSCC-GT are very similar to those for SCC of the lung [7]. The prognosis for EPSCC-GT is dismal, as these aggressive malignancies are associated with frequent recurrence and poor overall survival (OS). Due to the rarity of these diseases, the biology and molecular landscape of EPSCC-GTs are understudied and poorly understood.

In the current era of advancement in genomics technology, cancer molecular profiling has emerged as a crucial strategy for diagnosis and management, particularly for identifying better treatment options. This review focuses on the molecular and clinical aspects of EPSCC-GTs, as well as the benefits of understanding the biology and molecular features of these diseases.

1.1. Small cell carcinoma of the ovary

There are two types of SCC of the ovary (SCCO) – small cell carcinoma of the ovary, pulmonary type (SCCOPT) and small cell carcinoma of the ovary, hypercalcemic type (SCCOHT). Of all the EPSCC-GTs discussed in this review, SCCOHT is the only subtype that does not belong to the family of neuroendocrine tumors. Both SCCO subtypes are extremely aggressive, with limited treatment options and poor OS. Due to the rarity of these diseases, there are no guideline-based recommendations on standard treatment; however, patients with SCCO are usually treated with surgery followed by chemotherapy. Despite upfront responses, drug resistance and recurrence frequently occur, and survival rates are poor.

SCCOPT and SCCOHT have distinct clinical, pathological, and histological features [8–11]. SCCOPT is diagnosed at a mean age of 51, while SCCOHT occurs in much younger women, with a mean age at diagnosis of 24 years. SCCOPT shows characteristics typical of small cell neuroendocrine carcinomas, such as inconspicuous nucleoli, dispersed chromatin and nuclear molding, whereas SCCOHT has prominent nucleoli, clumped chromatin, and is characterized by the presence of larger cells in approximately half of cases. Patients with SCCOHT almost exclusively present with unilateral disease, while half of patients with SCCOPT present with bilateral disease [9,12]. Approximately two thirds of patients with SCCOHT are also hypercalcemic compared to none of the patients with SCCOPT. SCCOPTs, compared with SCCOHTs, are more often positive for chromogranin A (~53% vs. 9.5%, respectively). The majority of SCCOHTs stain positive for vimentin (~94%); only one SCCOPT case has demonstrated positivity for vimentin [10]. Recent studies have identified the unique molecular features of SCCOHT; it has been characterized as a *SMARCA4*-mutated monogenic disease, but also harbors other epigenetic alterations [13–19]. Identifying these features was crucial in establishing new standards in the diagnosis of these tumors and in distinguishing SCCOHT from SCCOPT and other EPSCC-GTs.

1.1.1. Small cell carcinoma of the ovary, pulmonary type

1.1.1.1. Clinicopathological features. SCCOPT typically presents in women aged 22 to 85 years, with a mean age at diagnosis of 51 years [8–10]. Tumors range in size (4 to 25 cm in greatest dimension) and are predominantly solid with some cystic components. Half of all patients with SCCOPT present with bilateral disease. In one case series, International Federation of Gynecology and Obstetrics (FIGO) stage at diagnosis was I, II, and III in 50%, 10% and 40% of cases, respectively. The majority of SCCOPTs are associated with surface epithelial tumors, which suggests they are probably of surface epithelial-stromal origin [8]. The histological features of SCCOPT are almost indistinguishable from those of SCC of the lung. Also, there are a number of reported cases of metastatic SCCO with sites of origin that include the intestine, thymus, and skin [20]. Therefore, it is extremely important to properly diagnose an SCCO and assess whether it is a metastatic or primary SCCOPT tumor. In addition to the above described histology, SCCOPT also features spindle-shaped cells with scanty cytoplasm, sheets of nucleoli, closely packed nests, and islands [21]. In addition to chromogranin A, SCCOPT also stains positive for other markers typical of neuroendocrine cells, such as neuron-specific enolase (NSE), CD56, and synaptophysin.

1.1.1.2. Molecular features. The biology and molecular features of SCCOPT have not been thoroughly studied, and to our knowledge, there is only one limited report suggesting that some SCCOPTs have alterations in *TP53* and *BRCA2* [22]. In their report, a *TP53* mutation was present in 1 of 4 patients, and a *BRCA2* mutation in 1 of 2 [22]. While the reported *TP53* mutation is likely oncogenic (H179V), the alteration in *BRCA2* (S1733F) does not seem to be a pathogenic mutation. According to the cBioPortal (www.cbioportal.org), within cases included in The Cancer Genome Atlas, the serine 1733 (S1733) is not within any significant BRCA2 domain, and it has not been reported in any other cancer. Also,

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