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Review

Small cell carcinoma of the gynecologic tract: A multifaceted spectrum of lesions

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HIGHLIGHTS

- Small cell carcinoma of the gynecologic tract is a rare disease, with the uterine cervix being the most common site.
- Gynecologic small cell carcinomas resemble the pulmonary counterpart, however it is unknown whether they share similar constellations of genetic alterations.
- Although small cell carcinomas of the gynecologic tract seem to be associated with distinct risk factors, they have similar morphologies.

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ABSTRACT

Objective. Small cell carcinoma (SmCC) of the female genital tract constitutes a diagnostic and clinical challenge given its rarity and the lack of standardized therapeutic approaches. Here we review the morphological, clinical and molecular features of gynecologic SmCCs and discuss potential areas for future research.

Methods. Data for this review article were identified by searches of PubMed, EMBASE and the Internet using the search terms "small cell carcinoma" or "neuroendocrine carcinoma" and "gynecologic", "uterine cervix", "cervix", "uterus", "endometrium", "ovary", "vagina", "fallopian tube" or "vulva", and research articles published in English between 1972 and February 2014 were included.

Results. SmCCs arising from different organs within the gynecologic tract share the same histopathologic characteristics, which closely resemble those of small cell lung carcinoma. The expression of at least one immunohistochemical neuroendocrine marker is a common finding. The uterine cervix is the most frequent site of SmCC in the female genital tract. HPV infection seems to play a role in the development of cervical SmCC but not in cancers of other gynecologic sites. FIGO stage is an established prognostic factor, in particular in SCCs of the cervix. Irrespective of the site, SmCCs of the gynecologic tract display an aggressive clinical behavior with few reported long-term survivors. The therapeutic management includes surgery, radiotherapy and chemotherapy.

Conclusions. Despite the potential differences in etiology and risk factors, SmCCs from different sites of the gynecologic tract have similar morphologic appearances and clinical behavior. Recent genomic analyses of small cell carcinoma of the lung have revealed potential driver genomic alterations. We posit that the comprehensive genomic characterization of gynecologic SmCCs may lead to the identification of markers that result in an improvement of diagnostic reproducibility of SmCCs of the gynecologic tract, and of molecular aberrations that may be exploited therapeutically in subgroups of the disease.

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Introduction

Small cell carcinoma (SmCC) is a neuroendocrine tumor that is most frequently found in the lung with pulmonary SmCC accounting for 95% of all SmCCs [1]. Extrapulmonary SmCC (EPSmCC) has been reported in almost every organ, although its incidence is extremely low ranging from approximately 0.1 to 0.4% in the US [2]. Interestingly, irrespective of the organ of origin, SmCCs display similar morphological features, which closely resemble those of the pulmonary counterpart. EPSmCCs have an aggressive clinical behavior whether in pure form or in conjunction with other histologic types of cancer. Given their pathological resemblance, treatment approaches for patients with pulmonary and extrapulmonary SmCCs are often similar [3,4].

The origin of EPSmCCs is controversial. It was assumed that these neoplasms arise from neuroendocrine cells in the Amine Precursor Uptake and Decarboxylation (APUD) system [2,5]. To date, however, it is thought that the origin of EPSmCCs is either a totipotent stem cell capable of differentiating into a variety of cell types, or that elements of SmCC arise as a late-stage phenomenon in the genetic progression of carcinomas [2]. The gynecologic tract is one of the extrapulmonary systems where EPSmCCs occur more frequently, representing up to 2% of all gynecologic malignancies [3,4]. Reported gynecologic sites include the cervix, but also the endometrium, ovary, fallopian tube, vagina and vulva.

Here we review the morphological, immunohistochemical and molecular features and the clinical management of gynecologic SmCCs. Furthermore, we discuss the potential impact of genomic characterization of SmCCs on our understanding of the disease and improvement of therapeutic approaches for patients with gynecologic SmCCs.

Small cell carcinoma of the uterine cervix

The uterine cervix is the most common gynecologic tract site involved by SmCCs, accounting for 0.9% of invasive cervical carcinomas [6]. Small cell carcinoma of the cervix (SmCCx) was first described by Albores-Saavedra et al. in 1972 [7], and since then case reports as well as case series have been published.

Histopathologic features

Cervical neuroendocrine tumors are classified similar to the pulmonary counterparts: carcinoid tumor, atypical carcinoid tumor, large cell neuroendocrine carcinoma and SmCCx [8,9]. SmCCx is defined as a malignant epithelial tumor consisting of small cells with scant cytoplasm, ill-defined cell borders with common nuclear molding, finely granular nuclear chromatin, and absent or inconspicuous nucleoli (Fig. 1A, B). Nuclei can be round, ovoid or spindled. Architectural patterns shared with other neuroendocrine tumors include nesting, trabeculae, peripheral palisading, and rosette formation and sheet-like growth is also common. Numerous mitotic figures and extensive necrosis are common features. SmCCx are by definition of high histologic grade [8]. Lymph-vascular space involvement is frequently observed, and neurosecretory granules can be seen upon ultrastructural examination [10–12]. SmCCx often coexists with squamous cell carcinoma (SqCC) or adenocarcinoma (AdC). Depending on the series analyzed and the selection criteria employed, between 11% and 64% of SmCCx cases present as admixed histology [13,14].

Immunohistochemical features

Although neuroendocrine immunohistochemical markers are frequently used to support the diagnosis of SmCCx, neither the uterine cervix workgroup [8] nor the current World Health Organization (WHO) classification [9] consider their assessment required. In fact, the expression of neuroendocrine markers may be focal and their interpretation challenging due to common crush artifacts, particularly in biopsy specimens. It is not uncommon, however, that positivity of at least one neuroendocrine marker is used as a selection criterion in studies on SmCCx [15–18]. Chromogranin A (CgA), synaptophysin (SYN) and neuron-specific enolase (NSE) are the most frequently used markers for immunohistochemical detection of neuroendocrine differentiation (Fig. 1C). Other neuroendocrine markers include Leu7 (CD57) and CD56. Staining for the presence of argyrophilia has also been performed to demonstrate neuroendocrine differentiation. The reported expression of neuroendocrine markers in SmCCx ranges from 33% to 100% (see Supplementary Table 1).

Immunohistochemical studies have further revealed that 33–84% of SmCCx cases exhibit diffuse nuclear positivity for thyroid transcription factor-1 (TTF-1) [19–22], and the majority of cases show diffuse nuclear and cytoplasmic p16 positivity (Fig. 1D) [17,19,20]. In contrast to broad-spectrum cytokeratins, which generally show reactivity in SmCCx, CK7 and CK20 expression is observed in only a small subset of cases [20,21].

Differential diagnosis

The first entity to exclude in the differential diagnosis of SmCCx is metastatic SmCC from other sites, in particular the lung. Other