Gynecologic Oncology 126 (2012) 481–490

Contents lists available at SciVerse ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Review

Clear cell carcinoma of the ovary: A review of the literature

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ARTICLE INFO

Article history:
Received 6 March 2012
Accepted 16 April 2012
Available online 21 April 2012

Keywords:
Clear cell
Ovarian
Cancer
Surgery

ABSTRACT

Objective. Different histologic types of epithelial ovarian cancer may represent different diseases with unique clinical and molecular characteristics. Clear cell carcinoma (CCC) of the ovary has been reported as having a worse prognosis than high grade serous epithelial ovarian cancer (EOC). This article critically reviews the literature pertinent to the pathology, pathogenesis, diagnosis, management, and outcome of patients with ovarian CCC.

Methods. MEDLINE was searched for all research articles published in English between January 01, 1977 and January 30, 2012 which reported on patients diagnosed with ovarian CCC. Given the rarity of this tumor, studies were not limited by design or number of reported patients.

Results. Ovarian CCC tumors represent 5–25% of ovarian cancers. Its histologic diagnosis can be challenging, resulting often times in misclassification of these tumors. Ovarian CCC tends to present at earlier stages and has been associated with endometriosis, ARID1A and PIK3CA mutations. When compared to stage-matched controls, patients with early-stage ovarian CCCs may have a better prognosis than patients with high-grade serous tumors. For those with advanced stage disease, high-grade serous histology confers a better prognosis than ovarian CCC. Patients with Stage IC–IV have a relatively poor prognosis and efforts should center in discovery of more effective treatment strategies.

Conclusions. Ovarian CCC is a biologically distinct entity, different from high-grade serous EOC. Future studies should explore the role of targeted therapies in the management of ovarian CCC.

Contents

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doi:10.1016/j.ygyno.2012.04.021

Introduction

Epithelial ovarian cancer is the most lethal gynecologic malignancy. Effective screening strategies are lacking and most women are diagnosed with advanced stage disease. An estimated 22,280 new cases of ovarian cancer will be diagnosed in the United States in 2012, with close to 15,500 deaths [1]. Epithelial ovarian cancer (EOC) accounts for 90–95% of all cases, while sex-cord stromal tumors and malignant germ cell tumors remain rare. Various randomized, controlled clinical trials have been carried out and their results largely guide the management of most women with EOC. These trials are not discussed in the present review.

Methods

This article reviews the English language literature for studies on clear cell ovarian cancer. A 35-year period MEDLINE (PubMed) search of English literature published between January 01, 1977 and January 30, 2012 was performed. All publications with the keyword "ovary" were combined and then searched for the keyword "clear cell." Additional publications were identified via systematic review of all reference lists within publications retrieved from the MEDLINE search. Given the rarity of this tumor, and the concomitant lack of data in the form of large trials, all peer reviewed original report publications with an appropriate number of subjects were considered and included.

Epidemiology

Clear cell carcinoma (CCC) of the ovary accounts for 5–25% of all EOC, depending on the geographic location [2]. In North America and Europe, CCC is the second most common histologic sub-type of EOC, with an estimated prevalence of 1–12% [2–6]. In Japan, the prevalence of CCC is 15–25%, with a reported increase from 2002 to 2007, from 19% to 24.5%, respectively [7–10]. Among Asian women living in the United States, CCC was diagnosed twice as frequently (11.1%), when compared to white women (4.8%) [11].

Pathology

In 1973, the World Health Organization (WHO) defined ovarian CCCs as tumors with clear cells growing in solid, tubular or glandular patterns, and hobnail cells lining cysts and tubules [12]. In 2003, the WHO updated the definition of CCC to describe a neoplasm composed of clear cells, growing in a solid, tubular or papillary pattern, with hobnail cells lining tubules and cysts (Figs. 1 and 2) [13]. Given the rarity of these tumors, correct pathologic diagnosis can be challenging. Studies of CCCs reporting high rates of advanced stage disease at presentation, and high response rates to platinum-based chemotherapy, features more commonly associated with high-grade serous EOC, suggest that ovarian CCCs are often misclassified as serous EOC [14,15]. Han et al. reported on a series of tumors of mixed serous and clear cell histology, with similar stage, immunophenotypes and mitotic activity of those of pure serous histology, concluding that they likely represent pure serous EOC with clear cell changes [16]. In the study by Gilks et al., 23% of 575 cases of low-stage CCC cases were identified as such at review and were not reported as CCC at the time of original diagnosis [17]. In a different study, frozen section diagnosis was accurate for CCC only 41% of the time [18].

Given their distinctive biological and clinical features, the correct classification of ovarian CCCs is of critical importance. Several authors have described specific morphologic and immunohistochemical features that can be utilized to improve accuracy of pathologic classification. Immunohistochemical markers, including hepatocyte nuclear factor 1-beta (HNF1B), Wilms tumor 1 (WT1), estrogen receptor (ER), progesterone receptor (PR) and tumor protein 53 (p53) can be used. Ovarian CCCs stain positive for HNF1B and negative for WT1, ER, PR and p53. High-grade serous EOC have the opposite staining pattern [19–21]. Table 1 summarizes the different features characterizing ovarian CCC and high-grade serous EOC.

Mixed carcinomas with high-grade serous and clear cell features have been problematic in terms of diagnostic reproducibility. These mixed tumors are indistinguishable from high-grade serous EOC with respect to clinical, immunohistochemical and histopathologic features, such as mitotic index. Thus, some have suggested the term high-grade serous cancer with clear cell features, proposing that they represent a variant of high-grade serous EOC and are not related to CCCs. [16]. Mixed endometrioid-clear cell carcinomas are rare, accounting for approximately 1.3% of EOCs, but representing the most common mixed ovarian carcinoma [5]. This mixed histology is not surprising given that both endometrioid and clear cell EOC are associated with endometriosis and share reported mutations in the AT-rich interactive domain 1A [SWI-like] gene (ARID1A) and phosphatidylinositol 3-kinase (PI3K) pathway.

Pathogenesis

The molecular and genomic biology of CCC, although not entirely elusive, remains less well-understood than that of high-grade serous EOC. The most significant molecular features associated with CCC are summarized in Table 1. CCCs, unlike high-grade serous EOCs, are generally p53 wild-type, with a lower frequency of BRCA (breast cancer)

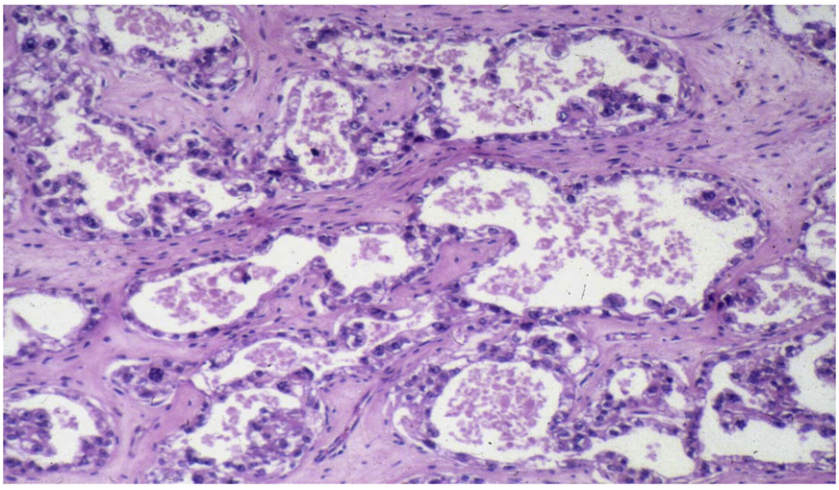

Fig. 1. Clear cell carcinoma of the ovary, depicting the characteristic tubulo-cystic histologic pattern.