Gynecologic Cancers
Molecular Updates 2018

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KEYWORDS

• Molecular pathogenesis • Ovarian carcinoma • Uterine carcinoma
• Endometrial carcinoma • Cell free nucleic acid

KEY POINTS

- Understanding the molecular basis of of uterine and ovarian carcinoma to explain prognosis in these tumors.
- Updates from The Cancer Genome Atlas (TCGA) in classifying endometrial carcinoma.
- New frontiers in early detection and monitoring of gynecologic disease.

MOLECULAR PATHOGENESIS OF EPITHELIAL OVARIAN CANCER

Globally, ovarian cancer is the sixth most common cancer in women and ranks seventh among the most lethal cancers. The estimated number of new cases yearly is about 204,000, and there are 125,000 deaths annually.[1] In the United States, there are 22,240 new cases and 14,030 deaths from ovarian cancer annually.[2]

The new molecular studies led to a division of ovarian cancer into 2 types based on clinical, pathologic, and genetic features. A dualistic model of ovarian carcinogenesis has been proposed. Type I tumors include low-grade endometrioid, low-grade serous, clear cell, mucinous, and Brenner tumors. The behavior of these tumors is not aggressive and they are usually confined to the ovaries (International Federation of Gynecology and Obstetrics [FIGO] stage I). The indolent progression of type I tumors reflects their relative genetic stability and they have multiple types of somatic mutations such as KRAS, phosphatase and tensin homolog (PTEN), BRAF, CTNNB, PIK3CA, PPP2R1A, ARID1A, and rarely TP53.[3,4] Type II tumors include high-grade serous

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carcinoma (HGSC), high-grade endometrioid, malignant mixed Müllerian tumor, and undifferentiated carcinoma. The behavior of these tumors is more aggressive in comparison with type I tumors and they invade rapidly (FIGO stages II–IV). The genetic characteristics are highly unstable and TP53 mutations are present in more than 95% of cases.[5] The mutations that exist in type I are rarely found in type II; P53 mutations are mostly restricted to type II.[6]

Type I Tumors

Low-grade serous carcinoma

Low-grade serous carcinoma (LGSC) represents a minority of ovarian serous carcinomas.[7] The morphologic and genetic evidence support the notion that cystadenomas/adenofibromas are precursors of LGSC. In this model, serous cystadenoma progresses to an atypical proliferative serous tumor, noninvasive micropapillary serous carcinoma, and finally to invasive LGSC.[8]

It is widely accepted that HGSC and LGSC are different type of tumors and have distinctive characteristics. LGSCs have a strong association with serous borderline tumors and express KRAS and BRAF mutations and do not express TP53 mutations, which have a strong expression in HGSCs.[9] Epidemiology studies have showed the differences in survival, age, annual incidence, and other parameters between LGSC and HGSC.[7] These data support the distinct identity of LGSC in comparison with HGSC.

Clear cell carcinoma

The presentation of clear cell carcinoma of the ovary (Fig. 1D) is characterized by a large adnexal mass, FIGO stage I, and highly malignant behavior. Some studies

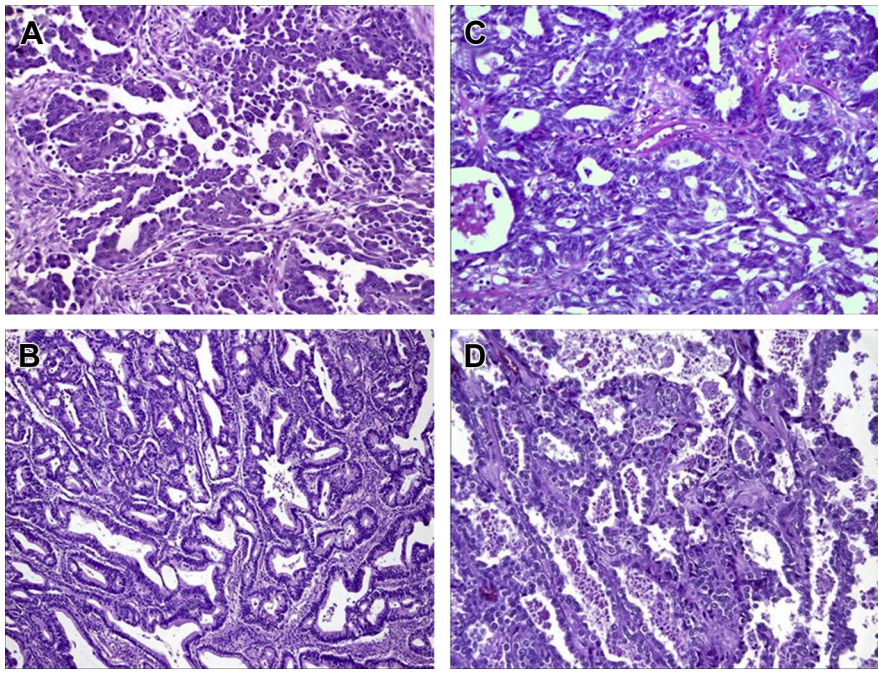

Fig. 1. (*A*) Ovarian serous carcinoma. (*B*) Ovarian mucinous carcinoma. (*C*) Ovarian endometrioid carcinoma. (*D*) Ovarian clear cell carcinoma (stain: hematoxylin and eosin; original magnification ×20). (*From* Ahmed Q, Alosh B, Bandyopadhyay S, et al. Gynecologic cancers: molecular updates. Clin Lab Med 2013;33(4):912; with permission.)