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Changing Paradigm in Diagnostic Pathology of Epithelial Ovarian Cancer

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Abbreviations: EOC: Epithelial Ovarian Cancer; HGSC: High-Grade Serous Carcinoma; CA-125: Cancer Antigen-125; HE4: Human Epididymis Protein 4

Short Communication

Epithelial ovarian cancer (EOC) is the leading cause of death among all gynecological malignancies. Due to late presentation and diagnosis at an advanced stage, the mortality rate from ovarian cancer continues to be high. A lot of research for development of specific newer biomarkers for diagnosis and prognosis in EOC is occurring at a rapid pace. EOC is a highly heterogeneous disease characterized by many diverse histological and molecular subtypes [1]. Morphologically, these tumours are typed into serous, mucinous, endometrioid, clear cell, brenner and seromucinous types. These are then further divided into benign, borderline and malignant depending on the degree of cell proliferation, nuclear atypia and presence or absence of stromal invasion [2]. Molecular characterization of EOC has led to a simplified dualistic model of classification into either type I or type II tumors, with implications for pathogenesis, clinical features and prognosis [3]. Over two-thirds of the ovarian epithelial tumours have serous histology and the other subtypes are much less common as compared with high-grade serous carcinoma (HGSC) [4].

The use of biomarkers not only helps to diagnose but also prognosticates patients and predicts better patient response [5]. The most commonly employed test in patients suspected to have EOC is serum Cancer antigen-125 (CA-125) levels. This test is used for the screening and diagnosis of ovarian cancer. But, raised serum levels may be seen in benign conditions including ovarian cysts and in pregnancy while some early stage EOC do not show increase in CA-125 levels. Hence, there is poor reproducibility and a trade-off between specificity and sensitivity. Human epididymis protein 4 (HE4), a product of the WFDC2 gene is used for early detection of EOC and it is also purported to have better potential than CA-125 in monitoring EOC patients [6]. In EOC, the differential expression of immunological markers related to the PD-1/PD-L1 pathway in blood can be used as potential diagnostic and prognostic marker and thus, have implication for therapeutic purposes [7]. Many studies have demonstrated use of multiplexed biomarkers to be more reliable than using a single protein biomarker [8].

Genetic biomarkers have been developed employing a host of methods, leading to an improvement in diagnosis, prognosis and therapeutics. Gene alterations in MAPK pathway, CDKN2A, PIK3CA, and PTEN etc. are seen particularly in type I lesions. High frequency of inactivating mutations in ARID1A in ovarian clear cell carcinomas and amplification of ERBB2 have been reported in mucinous tumors and clear cell carcinomas of the ovary.

TP53 mutations are rarely expressed in low grade serous tumours except for mucinous carcinomas while a high frequency of TP53 gene mutations are seen in HGSC. Most HGSCs show immune positivity for WT1, and p16 and exhibit a high Ki-67 proliferation index [9,10]. The most apparent genetic risk factors in EOC are the germline mutations in BRCA1 and BRCA2 genes. Efforts to develop and identify newer diagnostic tools to provide accurate and detailed information for early diagnosis of EOC are required. Meanwhile, routine serological testing for CA-125 levels, testing for circulating or cell free DNA, genetic and molecular biomarker assays and imaging are carried out to identify specific tumour characteristics and to potentially identify patients at a higher risk for developing EOC and hence, have implications for preventive strategies.

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