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Microsatellite Instability Testing In Endometrial Cancer - A Short Review

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Abstract:

Endometrial cancers are one of the most common cancers in women overall, and in the developed world form the most common malignancy in the gynecologic system. They have a heterogeneous in morphology, have varying genetic profiles, and differ in clinical outcomes. Microsatellite instability (MSI) testing is becoming increasing important in a number of tumors. The National Comprehensive Cancer Network recommended MSI testing in all endometrial carcinomas. MSI can be sporadic or associated with Lynch Syndrome to harbor risk for other malignancies, requiring screening. Recently four molecular subtypes of endometrial carcinoma were reported with implications for prognosis and therapy, the four subtypes including MSI hypermutated, POLE, copy number low and copy number high. This short review discusses testing for mismatch repair deficiency in endometrial carcinomas.

Keywords: Lynch syndrome; Microsatellite instability; Endometrial cancer; MLH1 hypermethylation; MLH1; PMS2; MSH2; MSH6; EPCAM

Endometrial carcinomas have been historically grouped into type 1 and type 2, based on multiple features. Type 1 endometrial carcinomas are of the endometrioid subtype, arise in a background of endometrial hyperplasia, expressed hormone receptors for estrogen and progesterone, do not express p53, usually low grade, and often carried a favorable prognosis. The type 2 endometrial carcinomas are of the serous subtype, arise in the background of endometrial atrophy, express p53, often high grade, and carried an unfavorable prognosis [1-4]. In context to studied. This study highlights the awareness of molecular signatures of carcinomas for better therapy. Hereditary Non Polyposis Colon Cancer also known as Lynch syndrome is characterized by microsatellite instability that hamper DNA mismatch repair, is autosomal dominant with high penetrance of about 80%. It is defined to be due to a germline deleterious mutation in mismatch repair (MMR) genes, the mutations could be large germline deletions as well as point mutations, involving one of the most common MLH1, MSH2, MSH6, PMS2 and EPCAM genes. The mismatch repair enzymes correct errors that spontaneously occur during the process of DNA replication, e.g. mismatched bases, short insertions or deletion. The germline mutation causes a heterologous status, which in case of a second hit causing mutational inactivation of the wild-type allele leads to mismatch repair defects. Lynch syndrome confers a high risk for colon, endometrial, gastric, intestinal, colonic, pancreatic, brain and bladder carcinomas [8-10]. Among endometrial cancers, 2 to 5% are likely to be associated with Lynch syndrome, in women either endometrial or colorectal carcinomas could be the presenting or sentinel cancer. Microsatellite instability can also be sporadic, by acquired mutations of mismatch repair genes. Lynch syndrome confers a 14 to 54% risk of developing endometrial cancer and 27 to 74% risk of developing colon cancer. Clinical criteria to predict the likelihood of Lynch Syndrome include Amsterdam, Bethesda, Society of Gynecologic Oncology, etc., are not accurate and molecular testing of tumors is required to confirm or exclude Lynch Syndrome. A Lynch Like syndrome or suspected Lynch syndrome has been

MSI group (MLH1 promoter methylation, KRAS and PTEN mutations), copy number low (microsatellite stable, frequent CTNNB1 mutations), and copy number high (TP53 mutations). While the groups POLE, MSI and molecular alterations, in type 1 common are PTEN, KRAS, PIK3A, ARID1a, MSI, and

CTNNB1, whereas in type 2 common are HER2/neu amplification, PIK3CA with less often PTEN, KRAS. The type 1 endometrioid carcinomas are responsive to radiotherapy and hormonal therapy, whereas the type 2 serous carcinomas warrant use of chemotherapy. The limitations of these two types are that about 10 to 19% of endometrial carcinomas do not fit in either of two types by histopathology or molecular features. There is some overlap between the two groups with heterogeneity within the two types. The current world health organization classification system is refined by morphological subtypes. Microsatellite instability has been reported to confer prognostic value and predict response to chemotherapy in colon cancer. However, the need for research into better diagnostic, prognostic and therapeutic biomarkers exits for better therapy.

The Cancer Genome Atlas (TCGA) research network reported four major molecular subtypes of endometrial carcinoma with potential diagnostic, prognostic and therapeutic uses. The four groups were: POLE group (high mutation rates and hot spot mutation in exonuclease domain of POLE a DNA polymerase involved in replication and repair),chromatin remodeling complexes was frequently mutated in the MSI group (in 23.1%) than in either copy number low microsatellite stable endometrioid (5.6%) or copy number high serous tumors (0%). The study found approximately 25% high grade endometrioid carcinomas have a molecular phenotype similar to uterine serous carcinomas, and their possible response to chemotherapy as opposed to radiation therapy needs to be further

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