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 morphology, having varying genetic profiles, and differ in clinical outcomes. Microsatellite instability (MSI) testing is becoming increasingly 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 [1-3]. 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 [1-4]. 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 contrast to 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 [1-3]. The type 1 endometrioid carcinomas are responsive to radiotherapy and hormonal therapy, whereas the type 2 serous carcinomas warrant use of chemotherapy [3]. 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 [1,3]. There is some overlap between the two groups with heterogeneity within the two types [1,3]. The current world health organization classification system is refined by morphological subtypes [5]. Microsatellite instability has been reported to confer prognostic value and predict response to chemotherapy in colon cancer [6,7]. 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 [3]. 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), 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 copy number low were mainly endometrioid carcinomas, the copy number high group was composed of serous carcinomas, along with mixed morphology an high grade endometrioid carcinomas [1,3]. In the four groups, the POLE group had better progression free survival, whereas the copy number high group had poor progression free survival [3]. The mutation frequency was extremely high in the POLE group, high in the MSI group compared to the microsatellite stable copy number low group [3]. ARID5B, same family as ARID1A 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%) [3]. 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 studied [3]. 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% [7]. 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 [7]. The mismatch repair enzymes correct errors that spontaneously occur during the process of DNA replication, e.g. mismatched bases, short insertions or deletions [8]. 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 [7]. 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 [11,12]. Microsatellite instability can also be sporadic, by acquired mutations of mismatch repair genes [7]. Lynch syndrome confers a 14 to 54% risk of developing endometrial cancer and 27 to 74% risk of developing colon cancer [8]. 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 [13-15]. A Lynch Like syndrome or suspected Lynch syndrome has been
described in which tumors carry mismatch repair defects without detectable germline mutations of common mismatch repair genes or without known sporadic mutations or hypermethylation that cause sporadic mismatch repair defects [14-16]. The risk of development of carcinomas in Lynch Like or suspected Lynch syndrome though lower than Lynch syndrome, is higher than families with sporadic colon cancer [14,16]. Morphologically the tumors with mismatch repair defects appear similar to microsatellite stable tumors [14,15]. These reports support greater awareness of universal screening of tumors for mismatch repair defects that has implications for prevention and screening for the patient and family members.

About 20% of endometrial carcinomas have microsatellite instability, though only 2 to 5% are associated with Lynch syndrome [12,17]. Most of the microsatellite unstable endometrial carcinomas are endometrioid type, with occasional other subtypes including mucinous, serous, clear cell and carcinosarcoma [18,19]. Some studies have reported a greater proportion of endometrial carcinomas in the lower uterine segment to be associated with Lynch syndrome to arise in the lower uterine segment [11,18,20]. Microsatellite unstable endometrial carcinomas have been reported to have higher tumor infiltrating lymphocytes [6]. However, these indicators are not very sensitive or specific and molecular testing is required to rule out Lynch syndrome in all cases of endometrial cancer.

Nation Comprehensive Cancer Network guidelines recommend universal testing of all endometrial carcinomas for MMR defects or MSI [21]. Testing is recommended to be performed on hysterectomy specimen, and if hysterectomy is not performed then on biopsies [21]. The MMR protein occur in two complexes MLH1/PMS2 and MSH2/MSH6, of these MLH1 and MSH2 stable without their counterpart, and PMS2 and MSH6 depend on the complex for stability [22]. PMS2 and MSH6 therefore, are not expressed if their counterparts are not expressed, causing loss of MLH1/PMS2 in case of MLH1 defect, and loss of MSH2/MSH6 in case of MSH2 defect. A combination approach for MMR testing of immunohistochemistry (IHC) and polymerase chain reaction (PCR) testing for MSI can be used for screening for Lynch syndrome [13,23]. Immunohistochemistry if performed first can give an idea of which of the common MMR proteins are lost from MLH1, PMS2, MSH2, and MSH6 [13,23]. In case of loss of MSH2/MSH6 loss, further germline testing for MSH2 is performed [13,23]. In case MSH2 testing is negative, further testing for germline abnormalities in EPCAM is indicated [8]. With loss of MSH6 only, germline testing for MSH6 is performed and with loss of PMS2 only germline testing for PMS2 is performed [13,23]. Loss of MLH1 protein on IHC could be due to MLH1 hypermethylation, likely sporadic and not require further testing for Lynch syndrome in most cases [13,23]. In these cases, MLH1 hypermethylation testing is performed and if hypermethylation is present, indicates a sporadic cause for the MMR defect [13]. As opposed to colon carcinomas, the MLH1 hypermethylation in endometrial carcinomas is not associated with BRAF (V600E) mutations [23]. BRAF (V600E) testing therefore cannot be used as an indicator of sporadic MMR defect, to rule out Lynch Syndrome [23]. If MLH1 hypermethylation is absent, further germline testing for MLH1 is indicated [23]. In cases with strong clinical suspicion of Lynch syndrome with MLH1 hypermethylation, germline methylation or germline epimutation is likely, though studies are lacking [23]. PCR testing for MSI can be performed first instead of IHC, however if MSI is detected, IHC is required to investigate which proteins are not expressed to direct further germline testing as mentioned above [13]. In patients with strong clinical suspicion of Lynch syndrome genetic counseling and screening is recommended despite lack of MMR deficiency [21]. The increased risk of malignancies in this set of patients highlights the importance of universal screening of endometrial carcinomas for mismatch repair deficiency and Lynch syndrome [21]. Similar to colon cancer, presence or absence of mismatch repair defects could be investigated further in relation to response to chemotherapy [3,7]. Mismatch repair deficiency and its association with increased tumor infiltrating lymphocytes, may indicate potential for investigating immune checkpoint based therapies in endometrial cancer [24].

References


