Microsatellite Instability (MSI) Testing in Extra-colonic Tumors

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Microsatellites are short tandem repeats that are present throughout the genome and are sensitive to errors during the cell cycle. Malfunctioning of the DNA repair mechanisms many occur as a result of germ line mutations in the MMR genes (MLH1, MSH2, PMS2 and MSH6) as in the autosomal dominant disorder hereditary non-polyposis syndrome (HNPCC), also known as Lynch syndrome (LS) or due to hypermethylation of the MLH1 gene. LS is associated with colorectal carcinoma (CRC) and extra-colonic malignancies including tumors of the endometrium, ovary, pancreas, urinary bladder, stomach, skin, biliary tract and the central nervous system. Early identification and management of such patients and their family members can significantly reduce morbidity and mortality associated with such tumors. Current literature suggests that MSI testing is important not only in the genetic context, but it also has prognostic and predictive value, as has been shown in treatment of CRC. Initial screening mechanisms such as the Amsterdam criteria and Bethesda guidelines were based on personal and family history. Since then various clinical prediction models have been developed that utilize clinical and pathologic features in the risk assessment of patients with MMR deficiency. However, due to the limitations in these screening methods, many institutions are moving towards universal screening of patients with CRC and endometrial carcinomas. In this review, we outline the rationale for and current methods of testing for MSI, along with their relative merits, and discuss the thorny question of screening criteria and who should be screened.

Keywords: Microsatellite instability testing; Lynch syndrome; DNA mismatch repair

Abstract

Faulty DNA repair due to defects in the mismatch repair genes results in microsatellite instability (MSI). Microsatellites are short tandem repeats that are present throughout the genome and are sensitive to errors during the cell cycle. Malfunctioning of the DNA repair mechanisms many occur as a result of germ line mutations in the MMR genes (MLH1, MSH2, PMS2 and MSH6) as in the autosomal dominant disorder hereditary non-polyposis syndrome (HNPCC), also known as Lynch syndrome (LS) or due to hypermethylation of the MLH1 gene. LS is associated with colorectal carcinoma (CRC) and extra-colonic malignancies including tumors of the endometrium, ovary, pancreas, urinary bladder, stomach, skin, biliary tract and the central nervous system [1]. Early identification and management of such patients and their family members can significantly reduce morbidity and mortality associated with such tumors [2]. Current literature suggests that MSI testing is important not only in the genetic context, but it also has prognostic and predictive value, as has been shown in treatment of CRC. Initial screening mechanisms such as the Amsterdam criteria and Bethesda guidelines were based on personal and family history. Since then various clinical prediction models have been developed that utilize clinical and pathologic features in the risk assessment of patients with MMR deficiency. However, due to the limitations in these screening methods, many institutions are moving towards universal screening of patients with CRC and endometrial carcinomas (EC) [3-6].

In this review, we outline the rationale for and current methods of testing for MSI, along with their relative merits, and discuss the thorny question of screening criteria and who should be screened.

Introduction

Faulty DNA repair due to defects in the mismatch repair genes results in microsatellite instability (MSI). Microsatellites are short tandem repeats that are present throughout the genome and are sensitive to errors during the cell cycle. Malfunctioning of the DNA repair mechanisms many occur as a result of germ line mutations in the MMR genes (MLH1, MSH2, PMS2 and MSH6) as in the autosomal dominant disorder hereditary non-polyposis syndrome (HNPCC), also known as Lynch syndrome (LS) or due to hypermethylation of the MLH1 gene. LS is associated with colorectal carcinoma (CRC) and extra-colonic malignancies including tumors of the endometrium, ovary, pancreas, urinary bladder, stomach, skin, biliary tract and the central nervous system. Early identification and management of such patients and their family members can significantly reduce morbidity and mortality associated with such tumors. Current literature suggests that MSI testing is important not only in the genetic context, but it also has prognostic and predictive value, as has been shown in treatment of CRC. Initial screening mechanisms such as the Amsterdam criteria and Bethesda guidelines were based on personal and family history. Since then various clinical prediction models have been developed that utilize clinical and pathologic features in the risk assessment of patients with MMR deficiency. However, due to the limitations in these screening methods, many institutions are moving towards universal screening of patients with CRC and endometrial carcinomas (EC) [3-6].

Importance of Identification of MSI Patients

Patients with LS have a significant lifetime risk of developing colonic and extra-colonic malignancies that may occur in a synchronous or metachronous fashion. Much of what we understand about the pathogenesis of MSI is based on research performed on CRC. Endometrial carcinoma has captured considerable attention lately; because of its higher prevalence in the group compared to other extra-colonic malignancies, and also due to the fact that it often is the sentinel cancer in women with MSI [7]. All other neoplasms are much less rigorously studied. Current literature states that MSI-associated tumors have an overall improved survival with lower risk of regional and systemic metastasis, indicating that the patients may be managed with a more conservative approach. For example, CRC tumors that are positive for MSI have been shown to be less sensitive to standard chemotherapy with 5-FU and more responsive to irinotecan. Whether extra-colonic MSI tumors have unique responses to conventional treatment is unknown at this point in time. Work to delineate the mechanism of these sorts of chemo-resistance in MSI tumors is also needed to better predict which alternative therapies may be preferred.

Deciding Whom to Screen

While the practice of reflex MSI testing in CRC and EC appears to be well accepted at NCI Comprehensive Cancer Centers (NCI-CCCs), and is being increasingly adopted by other sizeable medical centers in the United States, it appears that this strategy faces many barriers...
when it comes to other tumors included in the spectrum of LS. First of all, the cumulative risk of the extra-colonic malignancies varies by gender and individual MMR gene mutations [8-11]. Secondly, given the low incidence of the tumors, the use of IHC and molecular testing may not be cost-efficient in routine clinical practice. However, on an individual case basis, the evaluation of MSI status may be of considerable importance in the treatment of tumors and further testing of first-degree relatives. So the question arises when extra-colonic malignancies, other than EC, should be tested for MSI. The initial screening mechanisms such as the Amsterdam criteria, which were first developed in 1990 relied on physicians to obtain adequate family history and were met with significant challenges [12]. The Bethesda guidelines were proposed by the NCI in 1997 and revised in 2004 for the selection of patients and families that would benefit from genetic testing (Table 1).

<table>
<thead>
<tr>
<th>Initial Screening Models</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amsterdam Criteria I (1990)</td>
<td>47-91%</td>
<td>62-84%</td>
</tr>
<tr>
<td>Amsterdam Criteria II (1998)</td>
<td>77-81%</td>
<td>46-68%</td>
</tr>
</tbody>
</table>

Table 1: Sensitivity and specificity of initial screening models.

At this point in time, the application of clinical prediction models including MMRpredict, the PREMM [1,2,6] model and MMR Pro is directed towards the detection of MSI-related CRC. These approaches have been shown to be superior to the revised Bethesda recommendations [13,14]. However, these systems are not very sensitive and their efficacy is largely dependent on the clinician’s index of suspicion and the ability to obtain a complete family history. Based on their scoring of predicted probability, the sensitivity ranges from 62% with MMRpro to 100% for the PREMM model (Table 2).

<table>
<thead>
<tr>
<th>Model</th>
<th>Predicted Probability (%)</th>
<th>Number of Individuals</th>
<th>Number of carriers Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMRpredict</td>
<td>75-100</td>
<td>26</td>
<td>22 (84.62%)</td>
</tr>
<tr>
<td>PREMM</td>
<td>75-100</td>
<td>7</td>
<td>7 (100%)</td>
</tr>
<tr>
<td>MMRpro</td>
<td>75-100</td>
<td>50</td>
<td>31 (62%)</td>
</tr>
</tbody>
</table>

Table 2: Comparison of MMR predict, PREMM and MMRPro prediction models.

<table>
<thead>
<tr>
<th>Morphologic Characteristics of MSI-high tumors assessed in Clinical Prediction Models</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor infiltrating lymphocytes</td>
</tr>
<tr>
<td>Crohn’s like inflammatory pattern</td>
</tr>
<tr>
<td>High grade histology</td>
</tr>
<tr>
<td>Medullary, signet ring, or mucinous phenotype</td>
</tr>
</tbody>
</table>

Table 3: Morphologic characteristics of MSI-high tumors assessed in clinical prediction models.
defined threshold, or if their tumor has histologic features in Table 3 above (Figure 1).

References