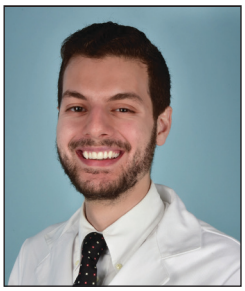
The DNA Mismatch Repair System in Sebaceous Tumors: An Update on the Genetics and Workup of Muir-Torre Syndrome



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RESIDENT **PEARLS**

- When patients present with a solitary sebaceous tumor, there is a high likelihood they have Muir-Torre syndrome (MTS) and thus are at a high risk to develop visceral malignancies.
- It is important to perform further testing using immunohistochemistry for DNA mismatch repair proteins and microsatellite instability gene analysis in some cases to confirm the diagnosis of MTS and to perform the appropriate cancer screening tests.

Mutations in the genes encoding the DNA mismatch repair (MMR) are identified in most sebaceous neoplasms. Sebaceous tumors are rare in the general population; however, they are common in patients with inherited or acquired mutations in the MMR system. This article describes the DNA MMR system and its implication in sebaceous tumors as well as discusses the recent recommendations for screening for Muir-Torre syndrome (MTS) in patients presenting with sebaceous tumors.

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It is well known by now that tumor formation is driven by accumulation of numerous genetic and epigenetic mutations. Human cells are equipped with an apparatus called the DNA mismatch repair (MMR) system that corrects errors during replication.[1] If these genes are themselves mutated, cells then start accumulating mutations in other genes, including oncogenes and tumor suppressor genes, which results in the development of sustained proliferative signaling pathways, evasion of growth suppression, resistance to cell death, and the potential for invasion and metastasis.[2]

Gene mutations in DNA MMR have been detected in several tumors, such as sebaceous tumors,[3] colorectal adenocarcinomas,[4] keratoacanthomas,[5] and other visceral malignancies.[6] Sebaceous tumors are rare in the general population; however, they are common in patients with inherited or acquired mutations in MMR genes.[5] These patients also have been found to have other visceral malignancies such as colorectal adenocarcinomas and breast, lung, and central nervous system (CNS) tumors.[7] This observation was made in the 1960s, and patients were referred to as having Muir-Torre syndrome (MTS).[8] This article serves to briefly describe the DNA MMR system and its implication in sebaceous tumors as well as discuss the recent recommendations for screening for MTS in patients presenting with sebaceous tumors.

The DNA MMR System

Mismatch repair proteins are responsible for detecting and repairing errors during cell division, especially in microsatellite regions.[9] Microsatellites are common and widely distributed DNA motifs consisting of repeated nucleotide sequences that normally account for 3% of the genome.[10] Mutations in MMR result in insertion or deletion of nucleotides in these DNA motifs, making them either abnormally long or short, referred to as microsatellite instability (MSI), which results in downstream cumulative accumulation of mutations in oncogenes and tumor suppressor genes, and thus carcinogenesis.[9]

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There are 7 human MMR proteins: MLH1, MLH3, MSH2, MSH3, MSH6, PMS1, and PMS2. These proteins are highly conserved across different living species.[11] Loss of MMR proteins can be due to a mutation in the coding sequence of the gene or due to epigenetic hypermethylation of the gene promoter.[12] These alterations can be inherited or acquired and in most cases result in MSI.

When assessing for MSI, tumor genomes can be divided into 3 subtypes: high-level and low-level MSI and stable microsatellites.[13] Tumors with high-level MSI respond better to treatment and show a better prognosis than those with low-level MSI or stable microsatellites,[14] which is thought to be due to tumor-induced immune activation. Microsatellite instability results in the generation of frameshift peptides that are immunogenic and induce tumor-specific immune responses.[15] Several research laboratories have artificially synthesized frameshift peptides as vaccines and have successfully used them as targets for immune therapy as a way for preventing and treating malignancies.[16]

Sebaceous Tumors in MTS

A typical example of tumors that arise from mutations in the DNA MMR system is seen in MTS, a rare inherited genetic syndrome that predisposes patients to sebaceous neoplasms, keratoacanthomas, and visceral malignancies.[17] It was first described as an autosomal-dominant condition in patients who have at least 1 sebaceous tumor and 1 visceral malignancy, with or without keratoacanthomas. It was then later characterized as a skin variant of Lynch syndrome, also known as hereditary nonpolyposis colorectal cancer syndrome.[18]

Sebaceous tumors are the hallmark of MTS. Although sebaceous hyperplasia is common in the general population, sebaceous tumors are rare outside the context of MTS. There are 3 types of sebaceous tumors with distinct pathologic features: adenoma, epithelioma, and carcinoma.[19] Sebaceous adenomas and epitheliomas are benign growths; however, sebaceous carcinomas can be aggressive and have metastatic potential.[20] Because it is difficult to clinically distinguish carcinomas from the benign sebaceous growths, biopsy of a large, changing, or ulcerated lesion is important in these patients to rule out a sebaceous carcinoma. Other aggressive skin tumors can develop in MTS, such as rapidly growing keratoacanthomas and basal cell carcinomas with sebaceous differentiation.[21]

Types of MTS

For most cases, MTS is characterized by germline mutations in DNA MMR genes. The most common mutation involves *MSH2* (MutS Homolog 2)—found in approximately 90% of patients—followed by *MLH1* (MutL Homolog 1)—found in approximately 10% of patients.[22] Other MMR genes such as *MSH6* (MutS Homolog 6), *PMS2* (PMS1 homolog 2, mismatch repair system component), and *MLH3* (MutL Homolog 3) less commonly are reported in MTS. There is a subset of patients who lose *MSH2* or *MLH1* expression due to promoter hypermethylation rather than a germline mutation. Methylation results in biallelic inactivation of the gene and loss of expression.[23]

A new subtype of MTS has been identified that demonstrates an autosomal-recessive pattern of inheritance and is referred to as MTS type 2 (autosomal-recessive colorectal adenomatous polyposis).[24] In contrast to the classic MTS type 1, MTS type 2 exhibits microsatellite stability. Recent molecular analyses revealed that type 2 is due to a mutation in a base excision repair gene called *MUTYH* (mutY DNA glycosylase).[25] These patients are likely to develop hundreds of polyps at an early age.

Muir-Torre syndrome also can occur sporadically without inheriting a germline mutation, which has been reported in a transplant patient from de novo somatic mutations or promoter hypermethylation.[26] A case report of a renal transplant patient showed that switching from tacrolimus to sirolimus halted the appearance of new sebaceous neoplasms, which suggests that patients with MTS who undergo organ transplantation should potentially avoid tacrolimus and be put on sirolimus instead.[27]

Visceral Malignancies in MTS

Apart from frequent skin examinations, MTS patients should have frequent and rigorous visceral malignancy screening. Patients most commonly develop colorectal adenocarcinoma, especially in the proximal parts of the colon.[28] In addition, they can develop numerous premalignant tumors, especially in MTS type 2. Other common tumors include endometrial, ovarian, genitourinary, hepatobiliary, breast, lung, hematopoietic, and CNS malignancies.[29]

Studies showed that specific loss of certain MMR proteins predispose patients to different types of visceral malignancies.[30-32] For example, loss of *MSH2* predisposes patients to development of extracolonic tumors, while loss of *MLH1* more strongly is associated with development of colorectal adenocarcinoma.[30] Patients with *MSH2* also are at risk for development of CNS tumors, while patients with *MLH1* mutations have never been reported to develop CNS tumors.[31] Patients with loss of *PMS2* have the lowest risk for development of any visceral malignancy.[32]

Diagnosing MTS

Let us consider a scenario whereby a dermatologist biopsied a solitary lesion and it came back as a sebaceous tumor. What would be the next step to establish a diagnosis of MTS?

Sebaceous tumors are rare outside the context of MTS. Therefore, patients presenting with a solitary sebaceous tumor should be worked up for MTS, as there are implications for further cancer screening. One helpful clue that can affect the pretest probability for MTS diagnosis is location of the tumor. A sebaceous tumor inferior to the neck most likely is associated with MTS. On the other hand, tumors on the head and neck can be spontaneous

or associated with MTS.[33] Another helpful tool is the Mayo score, a risk score for MTS in patients with sebaceous tumors.[34] The score is established by adding up points, with 1 point given to each of the following: age of onset of a sebaceous tumor less than 60 years, personal history of visceral malignancy, and family history of Lynch syndrome–related visceral malignancy. Two points are given if the patient has 2 or more sebaceous tumors. The score ranges from 0 to 5. A risk score of 2 or more has a sensitivity of 100% and specificity of 81% for predicting a germline mutation in MMR genes.[34]

These criteria are helpful to determine which patients likely have MTS; however, the ultimate diagnostic test is to look for loss of MMR genes and presence of MSI. It is important to keep in mind that if a patient has a high Mayo risk score, it is suggestive of MTS and molecular testing would be confirmatory rather than diagnostic. However, if the patient has a low Mayo risk score, then it is important to pursue further testing, as it will be crucial for diagnosis or ruling out of MTS.

Testing for loss of MMR proteins is performed using immunohistochemistry (IHC) as well as microsatellite gene analysis on the biopsied tumor. There is no need to perform another biopsy, as these tests can be performed on the paraffin-embedded formalin fixed tissue. Immunohistochemistry testing looks for loss of expression of one of the MMR proteins. Staining usually is performed for MSH2, MSH6, and MLH1, as the combination offers a sensitivity of 81% and a positive predictive value of 100%.[23,35,36]

If IHC shows loss of MMR proteins, then MSI gene analysis should be performed as a confirmatory test by using MSI gene locus assays, which utilize 5 markers of mononucleotide and dinucleotide repeats. If the genome is positive for 2 of 5 of these markers, then the patient most likely has MTS.[13]

One caveat for IHC analysis is that there is a subset of patients who develop a solitary sebaceous tumor due to a sporadic loss of MMR protein without having MTS. These tumors also exhibit *BRAF* (B-Raf proto-oncogene, serine/threonine kinase) mutations or loss of p16, features that distinguish these tumors from those developed in MTS.[37] As such, in a patient with a low Mayo score who developed a solitary sebaceous tumor that showed loss of MMR protein on IHC without evidence of MSI, it is reasonable to perform IHC for *BRAF* and p16 to avoid inaccurate diagnosis of MTS.

Another caveat is that standard MSI analysis will not detect MSI in tumors with loss of *MSH6* because the markers used in the MSI analysis do not detect MSI caused by MSH6 loss. For these patients, MSI analysis using a panel composed of mononucleotides alone (pentaplex assay) should be performed in lieu of the standard panel.[38]

It is important to note that these molecular tests are not helpful for patients with MTS type 2, as the sebaceous tumors maintain MMR proteins and have microsatellite stability. As such, if MTS is highly suspected based on the Mayo score (either personal history of malignancy or strong family history) but the IHC and MSI analysis are negative, then referral to a geneticist for identification for *MUTYH* gene mutation is a reasonable next step. These patients with high Mayo scores should still be managed as MTS patients and should be screened for visceral malignancies despite lack of confirmatory tests.

Final Thoughts

Dermatologists should be highly suspicious of MTS when they diagnose sebaceous tumors. Making a diagnosis of MTS notably affects patients' primary care. Patients with MTS should have annual skin examinations, neurologic examinations, colonoscopies starting at the age of 18 years, and surveillance for breast and pelvic cancers in women (by annual transvaginal ultrasound and endometrial aspirations) or for prostate and testicular cancers in men.[17,39,40] Other tests to be ordered annually include complete blood cell count with differential and urinalysis.[19]

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