Muir-Torre Syndrome: A Rare But Important Disorder

Holly H. Hare, MD; Neetu Mahendraker, MD; Sandhya Sarwate, MD; Krishnarao Tangella, MD

GOAL

To understand Muir-Torre syndrome (MTS) to better manage patients with the condition

LEARNING OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Identify diagnostic criteria for MTS.
2. Interpret the inheritance pattern of MTS.
3. Propose treatments for MTS.

CME Test on page 265.

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Muir-Torre syndrome (MTS) is a rare disorder characterized by the presence of at least one sebaceous gland neoplasm and at least one visceral malignancy. Sebaceous adenomas, sebaceous carcinomas, and sebaceomas (sebaceous epitheliomas) are all characteristic glandular tumors of MTS. The most common visceral malignancies associated with MTS are colorectal, followed by genitourinary. These visceral malignancies frequently have a more indolent course in patients with MTS than they would otherwise. Muir-Torre syndrome is an autosomal dominant disorder; however, sporadic cases are known to develop. It often is associated with germ-line mutations in the mutS homolog 2, colon cancer, nonpolyposis type 1 (Escherichia coli) *gene,* MSH2, *and the mutL homolog 1, colon cancer, nonpolyposis type 2* (E coli) *gene,* MLH1 *(similar to hereditary*

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Dr. Hare is a dermatology resident, Department of Dermatology, University of Missouri, Columbia. Dr. Mahendraker is Visiting Clinical Associate, Department of Internal Medicine, University of Illinois, Urbana. Dr. Sarwate is a pathologist, Christie Clinic Department of Pathology, Urbana, and Clinical Associate Professor, Department of Pathology, University of Illinois, Urbana. Dr. Tangella is a pathologist, Christie Clinic Department of Pathology, Urbana, and Clinical Assistant Professor, Department of Pathology, University of Illinois, Urbana.

Correspondence: Holly H. Hare, MD, Department of Dermatology at the University of Missouri, 1 Hospital Dr, MA111, Columbia, MO 65212 (hareh@health.missouri.edu).

nonpolyposis colon cancer [HNPCC]). The diagnosis of MTS currently is based on clinical criteria; however, immunohistochemical staining for MSH2 *and* MLH1 *can confirm the diagnosis. We report 2 patients with MTS who developed colon adenocarcinomas in conjunction with sebaceous carcinomas. Both patients demonstrated loss of* MSH2 *expression in tumor cells on immunohistochemical staining. One of these patients later developed gastric carcinoma, a very uncommon malignancy associated with MTS. We conclude that the diagnosis of rare sebaceous lesions associated with MTS may represent a marker of visceral disease and warrants further investigation for internal malignancies in the individual and at-risk family members.*

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Muir-Torre syndrome (MTS) was first described by Muir et al[1] in 1967 and Torre[2] in 1968 as a disorder characterized by the association of sebaceous gland neoplasms and visceral malignancies, most commonly colon cancer. Diagnostic criteria for MTS are the synchronous or metachronous occurrence of at least one sebaceous gland neoplasm and at least one visceral malignancy.[3,4] The sebaceous gland neoplasms include adenomas, carcinomas, and sebaceomas (sebaceous epitheliomas). The visceral malignancies are most commonly colorectal and genitourinary but can include a variety of other visceral cancers. Diagnosis of MTS also can be established if the patient has multiple keratoacanthomas with multiple visceral malignancies and a family history of MTS.[5] It is a rare autosomal dominant genodermatosis of variable expressivity that is thought to result from a mutation in mismatch repair genes and associated microsatellite instability.

Muir-Torre syndrome represents a genetic predisposition to visceral neoplasia and the diagnosis can be suggested based on a cutaneous finding. In some cases, the histopathologic findings of a sebaceous neoplasm may serve as the first clue to the diagnosis. Thus, the pathologist may play an important role in the initial diagnosis.

According to Curry et al,[6] more than 200 cases of MTS have been described since 1982. We report 2 patients with MTS; the pathologist first suggested the diagnosis in both patients.

Case Reports

Patient 1—A 52-year-old woman with a history of colon adenocarcinoma and multiple skin lesions presented to the dermatologist in 2006 for a lesion on the left lower eyelid. The lesion was excised and sent to pathology for evaluation. On microscopic examination, a well-differentiated sebaceous carcinoma was noted. Immunoperoxidase studies were performed. The stain for the mutS homolog 2, colon cancer, nonpolyposis type 1 *(Escherichia coli)* gene, *MSH2*, showed loss of expression in tumor cells. Expression of the mutL homolog 1, colon cancer, nonpolyposis type 2 *(E coli)* gene, *MLH1*, was intact.

The patient's medical history included sebaceous hyperplasia of the left naris in 1993, and the right naris and right temple in 1994. In December 1995, at 41 years of age, the patient was diagnosed with Dukes C node-positive colon adenocarcinoma and underwent subtotal colectomy and subsequent adjuvant chemotherapy. In 1999, she had a sebaceous adenoma removed from her right forehead and a sebaceous lesion, with differential including sebaceous hyperplasia and adenoma, removed from her mid forehead. The patient underwent total hysterectomy and bilateral salpingo-oophorectomy in 2000 for leiomyomas.

The patient's family history was equally complex. Her mother had a history of colon, gastric, uterine, and urethral cancer. Two brothers died from colon cancer, one at 16 and the other at 39 years of age. The patient's maternal grandfather, maternal uncle, and a maternal first cousin were all diagnosed with colon cancer. One maternal aunt was diagnosed with uterine cancer and another with ovarian cancer. One maternal cousin was diagnosed with both breast and colon cancer and another was diagnosed with renal cell carcinoma.

Patient 2—A 55-year-old man presented in 2005 with an indurated, elevated, smooth, dome-shaped papule approximately 4 mm on the right supraclavicular region. Results of shave excision showed poorly differentiated sebaceous carcinoma. Immunoperoxidase stains were performed using antibodies directed against DNA mismatch repair proteins MLH1, MSH2, mutS homolog 6 *(E coli)* MSH6, and postmeiotic segregation PMS2. Neoplastic cells showed aberrant loss of *MSH2* and *MSH6* gene expression with retention of *MLH1* and *PMS2* gene expression. The patient had a medical history of moderately differentiated adenocarcinoma of the cecum at 35 years of age. A diagnosis of MTS was made. Since 2005, several sites of actinic keratoses, a moderately differentiated squamous cell carcinoma on the left cheek and right aspect of the neck, and a malignant melanoma in situ (superficial spreading type) on the right side of the flank were found and removed.

In September 2006, the patient presented with concerns of worsening epigastric pain and belching. Endoscopic evaluation demonstrated a large ulcer in the fundus of stomach. A biopsy specimen of the ulcer showed poorly differentiated adenocarcinoma. The patient later died from complications of gastric surgery.

The patient's family history included uterine and fallopian tube tumors in his mother. Several other relatives died from unknown cancers.

Comment

Muir-Torre syndrome is the association of at least one sebaceous gland neoplasm and at least one visceral malignancy (Table).[3,5,7-10] Colonic polyps and keratoacanthomas also are frequent findings.[3,4] We diagnosed both our patients with MTS based on their histories of colon adenocarcinomas in conjunction with sebaceous carcinomas. Genetic testing supported this diagnosis.

The most common visceral malignancies associated with MTS are colorectal, followed by genitourinary.[3,4,7,11-15] Less frequently occurring cancers in MTS are breast carcinoma and hematologic disorders.[11] A variety of other visceral cancers also have been reported. Unlike colorectal carcinoma in the general population, colorectal carcinoma in patients with MTS usually is proximal to or at the splenic flexure.[4,16] In addition, on average, it occurs about a decade earlier in patients with MTS (median age, 50 years) than in the general population (age range, 55–65 years). Approximately 15% of women with MTS develop endometrial cancer.[4] Upper gastrointestinal tract cancers, as seen in patient 2, are uncommon. A review of the literature revealed only 2 other reported cases of gastric carcinoma.[17,18]

There are 3 types of cutaneous neoplasms characteristic of MTS, including (1) sebaceous adenomas, (2) sebaceous carcinomas, and (3) sebaceomas. Sebaceous adenomas are composed of dermal sebaceous lobules with a peripheral layer of smaller basaloid cells.[6] Cystic sebaceous adenoma and sebaceous adenoma with features of keratoacanthoma are considered highly specific markers of MTS.[3,6,8] In fact, cystic sebaceous neoplasms have only been observed in patients with MTS to date.[8,19] Sebaceous carcinomas are malignant neoplasms that demonstrate variable sebocytic differentiation, irregular architecture of the lobules, and cytologic features of malignancy (ie, pleomorphism, hyperchromatism, mitotic activity).[16,20] Sebaceomas, sebaceous epitheliomas, and basal cell carcinomas with sebaceous differentiation are characterized by nests of basaloid cells randomly admixed with sebocytes. The small basaloid cells outnumber the mature sebocytes. There are scattered mitoses but no atypia.[21]

Investigators have suggested that any sebaceous neoplasm that is difficult to classify should be considered a marker for MTS.[3,6,8,13] Sebaceous hyperplasia has not been associated with MTS; however, lesions of sebaceous gland hyperplasia with unusual features should lead to further investigation. Basal cell carcinomas and actinic keratoses rarely have been described in MTS.[3] Keratoacanthoma alone may be associated with MTS, but if there is sebaceous differentiation histologically or if keratoacanthomas are present in multiplicity in an individual with a family history of visceral malignancy, they are deemed to be highly specific markers for MTS.[6]

Diagnostic Criteria for Muir-Torre Syndrome

At least one visceral malignancy plus at least one of the following:

- Sebaceous adenoma
- Sebaceous carcinoma
- Sebaceoma
- Keratoacanthoma with sebaceous differentiation

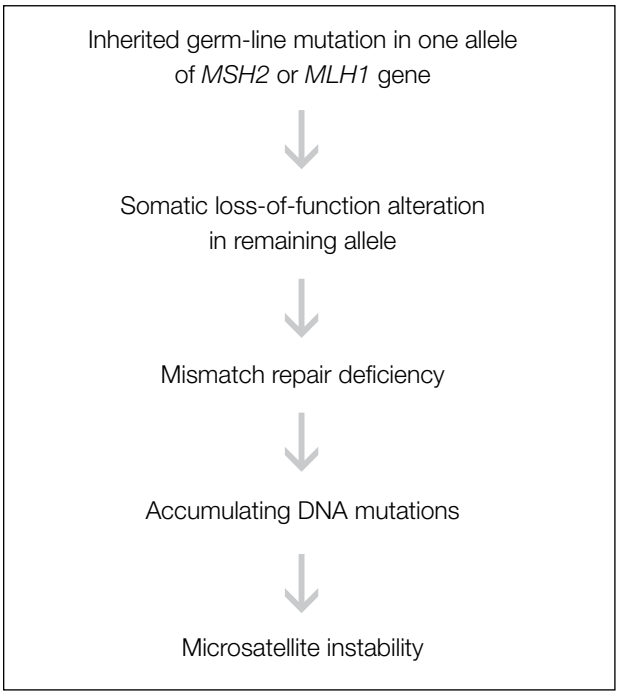
or

All of the following:

- Multiple keratoacanthomas
- Multiple visceral malignancies
- Family history of Muir-Torre syndrome

Most sebaceous lesions in MTS occur in the head and neck region and a small proportion involve the eyelid. Sebaceous neoplasms usually are of low malignancy, with the exception of sebaceous carcinomas of the eyelid, which have been reported to metastasize in at least a few cases.[7] Because they have almost no metastatic potential, sebaceous adenomas and epitheliomas can be treated with complete excision. However, sebaceous carcinomas, which constitute 30% of the sebaceous neoplasms in MTS,[22] have an aggressive growth pattern and metastatic potential and should be treated with wide surgical excision or Mohs micrographic surgery, which nearly eliminates the chance of recurrence in extraocular locations. Unfortunately, lesions of the eyelid may have metastatic recurrence, even with adequate initial excision.[4] Oral isotretinoin alone or in combination with interferon alfa may suppress the development of sebaceous neoplasms in MTS.[3,12]

Sebaceous gland neoplasms precede the visceral cancer diagnosis in 22% of patients, occur concurrently in 6% of patients, and appear after the visceral malignancy in 56% of patients.[13] In some cases, the cutaneous findings may precede the appearance of the internal disease by as many as 25 years or follow the diagnosis of an initial cancer by as many as 37 years.[4] The mean age for the appearance of skin tumors is 53 years and the detection of the initial



Development of microsatellite instability in Muir-Torre syndrome. *MSH2* indicates mutS homolog 2, colon cancer, nonpolyposis type 1 *(Escherichia coli)* gene; *MLH1,* mutL homolog 1, colon cancer, nonpolyposis type 2 *(E coli)* gene.

visceral neoplasm usually is approximately 50 years.[3,4] The disease is more common in men.[3,4,14,15,19,23] Approximately 40% of patients with sebaceous neoplasms have one or more visceral malignancies.[8,12,19] Therefore, all patients with a diagnosis of sebaceous neoplasm should undergo an evaluation for the presence of underlying visceral malignancies.

The inheritance pattern of MTS is autosomal dominant with a high degree of penetrance and variable expression. Sporadic cases also are known to develop. Germ-line mutations of the DNA mismatch repair genes *MSH2* and *MLH1* in patients with MTS suggest it often represents a phenotypic variant of hereditary nonpolyposis colon cancer (HNPCC). Hereditary nonpolyposis colon cancer is an autosomal dominant predisposition to colorectal cancer and other malignancies that also are frequently associated with mutations of *MSH2* and *MLH1* genes. Accordingly, affected family members of patients with MTS may manifest characteristic HNPCC tumors with or without cutaneous tumors typical of MTS.[24] In HNPCC, the proportion of *MSH2* mutations is almost equivalent to the proportion of *MLH1* mutations, but MTS is most frequently caused by germ-line mutations in *MSH2*.[23-25] Recently, Singh et al[26] noted that in the 94 cases of sebaceous neoplasms they examined, *MSH2* and *MSH6* status was the same. Thus, when one was intact, the other was intact, and when one was deficient, the other was deficient, which mirrors our findings in patient 2. No mutation is found in 25% of patients with HNPCC as well as in some cases of MTS.[13,27]

Once an inherited germ-line mutation in one allele of either DNA mismatch repair gene *MSH2* or *MLH1* occurs, a somatic loss-of-function alteration of the remaining wild-type allele results in a mismatch repair deficiency. The mismatch repair system normally repairs small errors in repeat sequences of the DNA (microsatellites), which occur during replication. Therefore, mismatch repair deficiency results in accumulating mutations of these microsatellites, which is termed *microsatellite instability* (Figure). Tumor tissue in both patients with HNPCC and MTS shows microsatellite instability.

Currently, the diagnosis of MTS is based on clinical criteria. Immunohistochemical staining for *MSH2* and *MLH1* is a practical initial approach to confirm the diagnosis of MTS. Once a sebaceous skin tumor is noted, the pathologist may perform immunohistochemical staining using antibodies against MSH2 and MLH1 proteins in skin tumor tissue as an initial screening for mismatch repair defects. This procedure is an efficient and cost-effective method of screening and has a high predictive value for the diagnosis of DNA mismatch repair–deficient MTS.[22,25] If immunohistochemical staining shows loss of MSH2 or MLH1 protein expression, molecular genetic analysis could then be performed. Moreover, cancer surveillance as well as genetic testing and counseling for the patient and family members can be initiated.

Cancers, including both sebaceous neoplasms and visceral malignancies, associated with MTS have a more indolent course than they would if unassociated with this syndrome, even after metastases develop.[3,4] Because these low-grade malignancies tend to permit prolonged survival, even metastatic disease may respond well to aggressive surgical treatment. One of our patients (patient 1) remains cancer free 13 years after treatment of her node-positive colon adenocarcinoma, which may reflect the indolent course of visceral malignancies associated with MTS.

Conclusion

We recommend consideration of MTS in any patient who has sebaceous neoplasms, particularly because sebaceous gland neoplasms are rare and cutaneous lesions may be the first sign of the disease. Immunohistochemical stains for MSH2 and MLH1 protein expression in skin tumor tissue should be performed, and patients should have a complete evaluation for gastrointestinal or genitourinary cancers. Because this syndrome has an autosomal dominant inheritance pattern, genetic counseling should be offered to all family members. All relatives who inherit the DNA mismatch repair defect have a substantially increased risk for visceral malignancies and therefore

should also undergo routine cancer surveillance. The identification of occult malignancies is especially important in these patients, as the tumors often are amenable to treatment, even in the presence of metastasis.

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