Muir-Torre Syndrome: A Case Report and Review of the Literature

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GOAL

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

OBJECTIVES

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

1. Discuss the clinical presentation of MTS in patients.
2. Explain the treatment options for MTS.
3. Describe the genetics of MTS.

CME Test on page 156.

This article has been peer reviewed and approved by Michael Fisher, MD, Professor of Medicine, Albert Einstein College of Medicine. Review date: February 2005.

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Drs. Pettey and Walsh report no conflict of interest. The authors report no discussion of off-label use. Dr. Fisher reports no conflict of interest.

The presence of sebaceous skin tumors with visceral neoplasms is known as Muir-Torre syndrome (MTS). It is a phenotypic subset of hereditary nonpolyposis colorectal cancer and is caused by mutations in genes encoding for mismatch repair (MMR) proteins. The presence of a sebaceous gland neoplasm should raise concern for a potential diagnosis of MTS. Immunohistochemical analysis of the sebaceous skin tumors can be helpful in screening for an MMR defect and preselecting patients who are at increased risk of a visceral malignancy. We report a case of MTS and show immunohistochemical analysis of the sebaceous neoplasm. We also review the literature on MTS and the effectiveness of immunohistochemical analysis in screening patients at risk for MTS.

Cutis. 2005;75:149-155.

Accepted for publication January 7, 2005.

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Muir-Torre syndrome (MTS) is an autosomal-dominant condition characterized by sebaceous skin tumors and visceral neoplasms.[1]

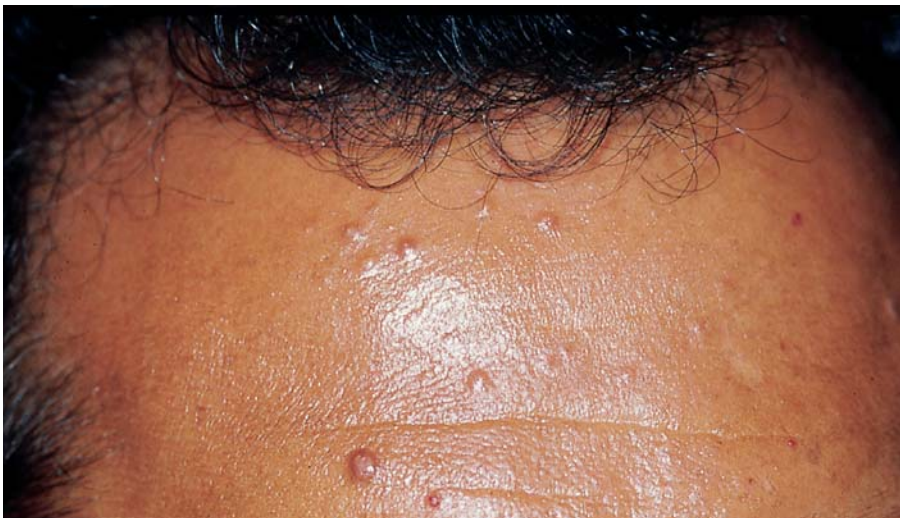

Figure 1. Pink papules and nodules representing sebaceous tumors on the forehead.

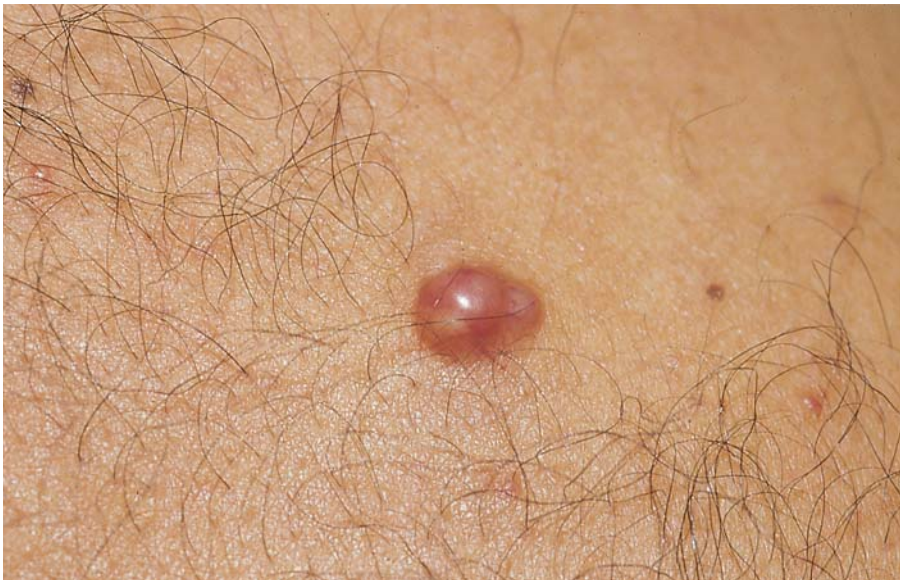

Figure 2. Nodule on the back representing a sebaceous epithelioma.

The first descriptions of this syndrome came independently from Muir et al[2] and Torre.[3] Advances in genetic research have demonstrated that MTS is a phenotypic subset of hereditary nonpolyposis colorectal cancer and, in most cases, arises from germline mutations in genes encoding for mismatch repair (MMR) proteins. We report a case of MTS and review the relevant literature.

Case Report

A 49-year-old white man presented to a dermatologist with the complaint of a cyst on the right side of his neck. The lesion was excised, and the histopathology results revealed a sebaceous epithelioma. One year later, the patient underwent a screening colonoscopy. Two polyps were removed, with the histopathology results demonstrating one juvenile polyp and one tubulovillous adenoma. Follow-up colonoscopy results one year later revealed a sessile lesion in the sigmoid colon for which the results of a biopsy demonstrated adenocarcinoma. Because of this malignancy and the patient's strong family history, a subtotal colectomy was performed. The patient subsequently developed new papules and nodules on his forehead and back (Figures 1 and 2). The histopathology of 3 of these lesions revealed sebaceous epitheliomas (Figure 3). The patient later developed a keratoacanthoma.

The patient's family history is remarkable for colon cancer in his maternal grandmother, mother, father, paternal aunt, paternal uncle, and sister. His mother was diagnosed with colon cancer at 52 years of age. His father was diagnosed at 63 years of age and died at age 67. His sister was diagnosed at

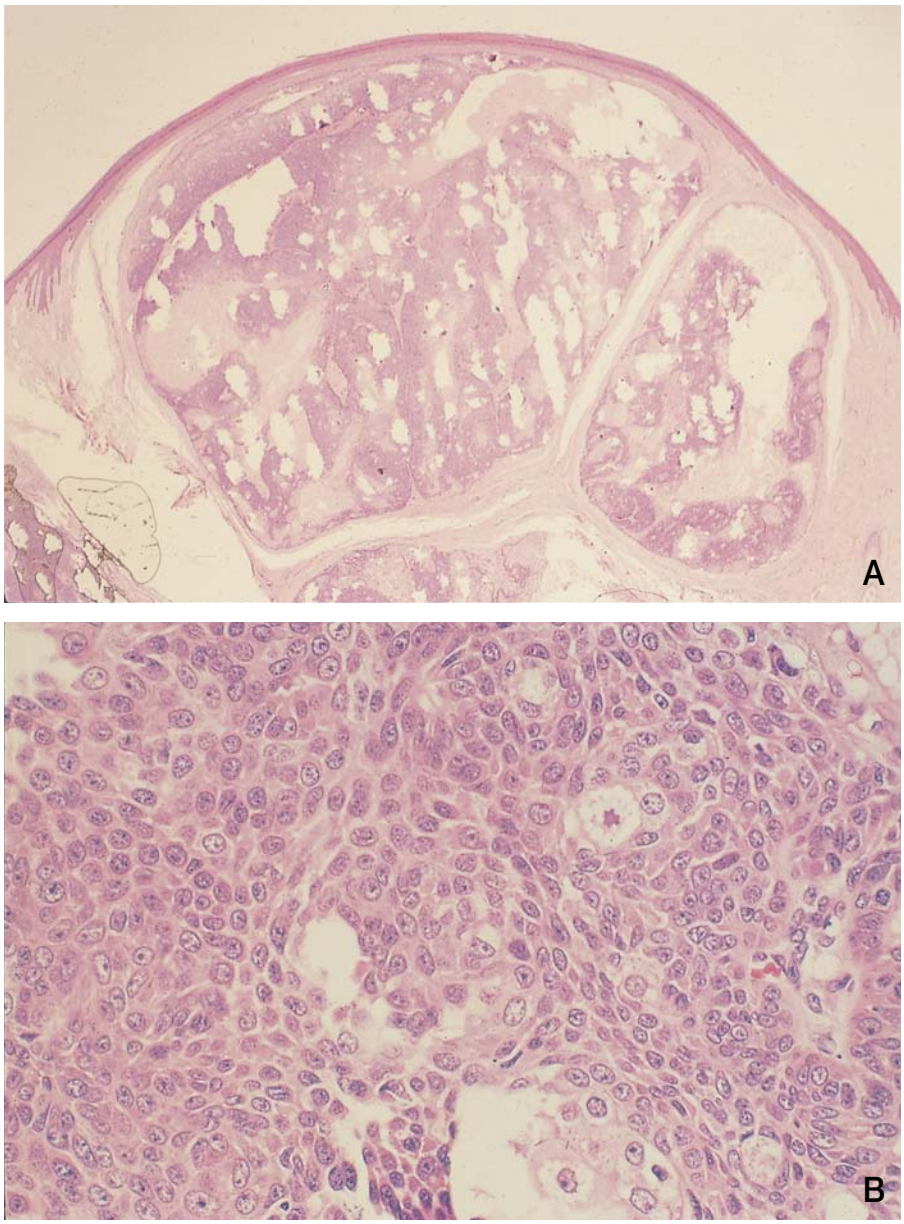

Figure 3. Sebaceous epithelioma (A and B)(H&E, original magnifications ×20 and ×200).

40 years of age and died at age 42. Two brothers are apparently unaffected. The patient has 5 children aged 21 to 32 years, none of whom have been screened for malignancy.

Results of immunohistochemical studies performed on the colonic tumor revealed a lack of normal expression of MMR proteins hMSH2 and hMSH6. Similarly, immunohistochemical studies performed on a sebaceous epithelioma demonstrated absent hMSH2 and hMSH6 expression (Figure 4). Molecular analysis was performed on the colonic tumor by protein truncation assay, and results revealed a mutation in the hMSH2 gene. Further testing of the tissue revealed high-grade microsatellite instability.

Based on these clinical, histopathologic, and molecular findings, the patient was diagnosed with MTS. Because both the patient's maternal and paternal families are affected, it is unclear from which parent this patient inherited the disorder.

Comment

Muir-Torre syndrome is inherited in an autosomal-dominant manner, demonstrating a high degree of penetrance with variable expression.[4] Since 1982, more than 200 cases of MTS have been described in the literature. The mean age at diagnosis is 53 years, with the male-to-female ratio being 2:1.[5,6] Clinically, the diagnosis usually is made by the

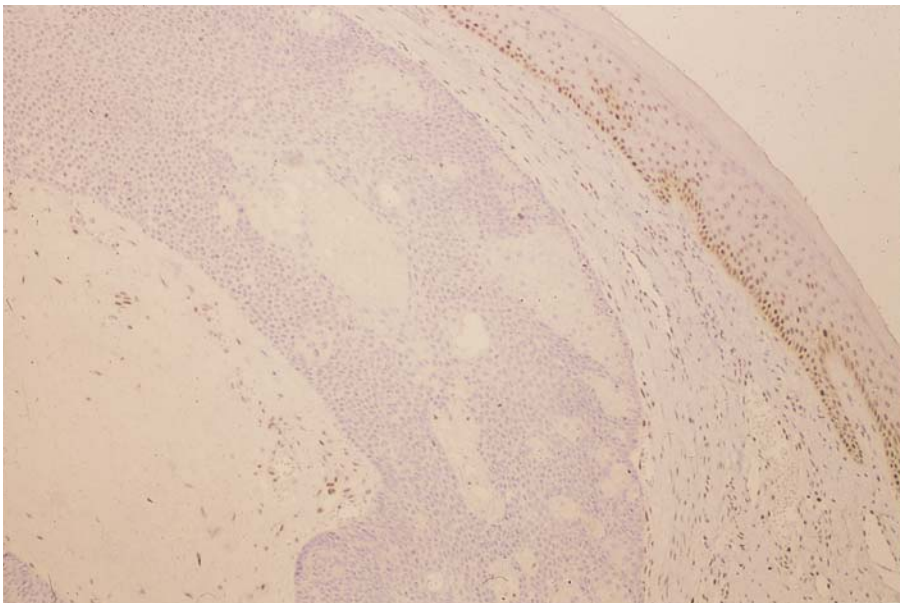

Figure 4. Absent hMSH2 staining in the sebaceous epithelioma. Note normal hMSH staining in the epidermis (immunohistochemistry, original magnification ×100).

presence of at least one sebaceous neoplasm associated with at least one primary visceral malignancy. Multiple keratoacanthomas and a visceral neoplasm occurring in the setting of a positive family history also fulfills diagnostic criteria.[7,8] In one review, sebaceous tumors were found to precede the visceral malignancy in 22% of patients, occur concurrently in 6% of patients, and appear after the internal malignancy in 56% of patients.[6]

The sebaceous tumors required to make a diagnosis of MTS include sebaceous adenomas, sebaceous epitheliomas, and sebaceous carcinomas. Sebaceous adenomas are the most common diagnostic skin lesion in MTS. Sebaceous hyperplasia, though seen in patients with MTS, does not fulfill diagnostic criteria.[8] Clinically, most sebaceous tumors have a nonspecific appearance, most often presenting as a pink to yellowish papule or nodule. Some lesions may be umbilicated, resembling molluscum contagiosum.

Histopathologically, sebaceous adenomas are characterized by sebaceous lobules with a peripheral germinative layer of small basaloid cells that transition to mature sebaceous cells centrally. In sebaceous epitheliomas, the peripherally located small basaloid cells outnumber the mature sebaceous component. Sebaceous carcinoma demonstrates an architecturally malignant basaloid neoplasm with cytologic atypia, scattered mitoses, and variable sebaceous differentiation.[9,10] Pagetoid spread may be seen, particularly in the periocular variant. Immunohistochemically, these tumors demonstrate positive staining for keratin, epithelial membrane antigen, and androgen receptors.[11,12] Although sebaceous neoplasms may occur sporadically, cystic sebaceous tumors are specifically reported for MTS.[9,13] Keratoacanthomas occurring in the setting of MTS may be of the ordinary type or demonstrate sebaceous differentiation.[6]

In general, sebaceous gland tumors are rare lesions. An archival review of the histopathologic specimens stored in the dermatology department at the Mayo Clinic over a 60-year period found only 59 patients with one or more of these lesions. Of these 59 patients, 25 (42%) had one or more visceral malignancies.[14] Visceral malignancies reported in patients with MTS include gastrointestinal, urogenital, breast, hematologic, head and neck, lung, mesothelioma, pancreas, melanoma, biliary, paraganglioma, and chondrosarcoma. Gastrointestinal malignancies, particularly colonic tumors, are the most common (61%), followed by urogenital cancers (22%). It is not uncommon for patients to have multiple primary visceral neoplasms.[6,7] Frequently, the visceral malignancies of MTS patients display a surprisingly indolent course with long survival despite metastatic disease.[1,8] Because MTS is now recognized as a phenotypic subset of hereditary nonpolyposis colorectal cancer, it is not surprising that the spectrum of internal malignancies in MTS is almost identical to that of hereditary nonpolyposis colorectal cancer syndrome.[15]

The management of MTS patients and their families requires a multidisciplinary approach, including the primary care physician, dermatologist, gastroenterologist, surgeon, and oncologist. From the dermatologist's perspective, sebaceous adenomas and sebaceous epitheliomas should be

completely excised. Given their aggressive growth pattern and metastatic potential, sebaceous carcinomas should undergo wide excision.[8,16] Mohs micrographic surgery has been successfully used to excise eyelid sebaceous carcinomas.[17] Chemoprophylaxis with oral isotretinoin alone or in combination with interferon alfa has been shown to suppress the development of sebaceous neoplasms in MTS.[18]

Over the past decade, advances in genetic research have established MTS as a fuller phenotypic expression of hereditary nonpolyposis colorectal cancer.[6,19] MTS and hereditary nonpolyposis colorectal cancer are caused by a germline mutation in one of the DNA MMR genes hMSH2, hMLH1, hPMS2, or hMSH6.[15,20] MMR proteins ensure genomic integrity by identifying and excising mismatches of single nucleotide bases, as well as mismatches that result from insertions and deletions that occur during DNA replication.[21] A person with an inherited MMR mutation develops a complete MMR defect when the corresponding MMR gene is inactivated by a "second hit."[22] This MMR defect results in an accumulation of replication errors resulting in tumorigenesis. Tumors associated with a DNA MMR defect exhibit microsatellite instability, which is characterized by size variations in microsatellite sequences in tumor DNA compared with matching normal DNA.[21] Microsatellite instability and germline mutations in MMR genes are frequently detected in families with MTS and hereditary nonpolyposis colorectal cancer. In one study, Kruse et al[19] found microsatellite instability in 23 of 24 skin tumors from 16 patients with MTS. Microsatellite instability was found in at least 1 skin tumor from all 16 patients. All 7 visceral tumors from these MTS patients demonstrated microsatellite instability.[19] Machin et al[23] also found microsatellite instability in all cutaneous and visceral tumors from 6 patients with MTS. Entius et al[24] identified microsatellite instability in 9 of 13 tumors of MTS patients and 0 of 8 sporadic sebaceous tumors.

The 2 most frequently affected MMR genes in hereditary nonpolyposis colorectal cancer and MTS are hMSH2 and hMLH1. In hereditary nonpolyposis colorectal cancer, hMSH2 accounts for 53% and hMLH1 accounts for 36% of germline mutations. In MTS, 92% of germline mutations occur in hMSH2 and 8% in hMLH1.[15] The pathogenicity of hMSH6 mutations is not clear. Mutations in this gene alone have not been linked to high-grade microsatellite instability and are not associated with the hereditary nonpolyposis colorectal cancer and MTS phenotype (Baudhuin LM, Burgart LJ, Leontovich O, et al, unpublished data, 2004).[25] As demonstrated in this case, loss of protein expression for hMSH2 and hMSH6 is highly correlated with germline mutations in hMSH2. It has not been clearly elucidated why a lack of hMSH6 expression occurs in association with germline mutations in hMSH2. Because these proteins bind as MMR complexes, it is possible that the loss of one binding partner of a complex affects the proper expression of the other partner (Baudhuin LM, Burgart LJ, Leontovich O, et al, unpublished data, 2004).

Sebaceous gland neoplasms are rare tumors; in patients with MTS, these tumors frequently precede or occur concurrently with the visceral malignancy. Recognition of these lesions and differentiating them from sporadic sebaceous gland tumors is therefore critical in patient management. In the previously mentioned archival study at the Mayo Clinic,[14] 42% of patients with sebaceous tumors had at least one visceral malignancy. Kruse et al[26] found microsatellite instability in 15 of 25 randomly selected sebaceous neoplasms. Subsequently, it was found that 9 of those 15 patients with microsatellite instability–positive sebaceous tumors were identified as having MTS.[26] Popnikolov et al[27] found loss of MMR (either hMSH2 or hMLH1) in 50% of consecutive sebaceous adenomas and 43% of consecutive sebaceous carcinomas. In those patients who were subsequently found to have an associated malignancy, 80% of sebaceous lesions demonstrated a loss of either hMSH2 or hMLH1. In comparison, 23% of sebaceous lesions not associated with a visceral malignancy showed a loss of hMSH2 or hMLH1.[27] Because sebaceous tumors precede the visceral malignancy in one fourth of patients, the identification of sebaceous tumors demonstrating microsatellite instability or MMR loss without an associated visceral malignancy may represent the initial expression of MTS, which would indicate an increased risk of visceral malignancy in these patients.

Identifying a germline mutation in one of the DNA MMR genes can be helpful in preselecting patients with sebaceous tumors or multiple keratoacanthomas with an increased risk for visceral malignancy. Screening for microsatellite instability or searching for mutations in either hMSH2 or hMLH1, however, can be arduous, expensive, and time consuming.[28,29] Instead, immunohistochemical analysis using antibodies against hMSH2 and hMLH1 proteins in MTS–associated skin tumors may be used as an initial screening for MMR defects. Mathiak et al[28] reported immunohistochemical

investigation of 28 skin tumors from 17 patients using antibodies against hMLH1 and hMSH2 proteins. Twenty of these tumors were from 10 patients with known germline mutations in hMSH2 or hMLH1; 8 tumors were sporadic. Seventeen of 19 (one sample was not immunoreactive and was not included) tumors from patients with known germline mutations showed a loss of either hMSH2 or hMSH1 expression (89% sensitivity). All 8 sporadic tumors showed normal expression of both hMSH2 and hMLH1 (100% specificity). Overall, in 93% (26/28) of skin tumors, the staining pattern matched the molecular results.[28] From these results, we can conclude that immunohistochemical analysis of MTS–related skin tumors is an efficient and cost-effective method of screening for MMR defects. It is important to realize that a negative immunohistochemical analysis result does not exclude an MMR defect because certain germline defects may give rise to MMR proteins that are antigenically recognizable but functionally deficient. In these cases, only molecular germline analysis would disclose the MMR gene defect.

Presentation of the MTS phenotype or the identification of a solitary sebaceous neoplasm should suggest a potential hereditary MMR mutation. In theory, all patients with a sebaceous neoplasm should be screened for an MMR defect and MTS. However, as previously mentioned, testing for microsatellite instability and performing mutational analysis on all patients would be impractical and cost prohibitive. Immunohistochemical analysis of neoplasms seems to be an extremely useful and practical initial step in screening for hereditary MMR mutations. If immunohistochemical analysis suggests an MMR mutation, molecular genetic analysis could then be performed. This would provide valuable information to the clinician and enable efficient cancer surveillance along with specific genetic testing and counseling for the patient and family members.

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