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

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Muir-Torre syndrome (MTS), a subtype of Lynch syndrome II, presents as at least one internal malignancy associated with at least one sebaceous skin tumor. This autosomal-dominant genetic disorder is thought to arise from microsatellite instability. Although not all patients with sebaceous tumors have MTS, even a single biopsy-proven sebaceous adenoma may warrant evaluation for MTS. We report the case of a 76-year-old man with a marked family history of colon cancer; a personal history of colon cancer status post–partial resection of the colon; and multiple cutaneous neoplasms including sebaceous adenomas, sebaceous gland hyperplasia, and basal and squamous cell carcinomas. We review the literature describing MTS and highlight the important role of dermatologists and dermatopathologists in the potential early detection and initial diagnosis of this familial or hereditary colon cancer in patients presenting with cutaneous sebaceous adenomas. Correct diagnosis may be lifesaving in patients with MTS and their at-risk relatives who would benefit from earlier colonoscopy, tumor surveillance, and potential early cancer detection. Muir-Torre syndrome represents yet another dermatologic symptom of an internal disease.

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Muir-Torre syndrome (MTS), a subtype of Lynch syndrome II, is a rare autosomal-dominant genodermatosis characterized by the association of internal malignancies and cutaneous tumors, either of the sebaceous glands or keratoacanthomas.[1-4] The temporal relationship between the appearance of internal and cutaneous lesions varies; the visceral malignancy may be diagnosed before or after the cutaneous lesion, and the most common visceral malignancy is colorectal cancer.[5] Patients with MTS can experience a relatively nonaggressive course with a good prognosis, especially with early detection, treatment, and continued surveillance.

Case Report

A 76-year-old man presented to our center with a medical history of colon cancer (status post–partial resection). A strong family history of colon cancer in 5 first-degree relatives had been contributory for the patient's diagnosis in 1987. A diagnosis of MTS was made in 2003 after results from a shave biopsy revealed a solitary sebaceous adenoma of the right nasolabial fold. In the 5 years following the diagnosis of MTS, the patient required multiple dermatologic procedures including more than 15 biopsies of sebaceous adenomas, sebaceous gland hyperplasia, basal cell carcinomas, squamous cell carcinomas, and keratoacanthomas on his face, neck, trunk, and arms. Figure 1 demonstrates a new sebaceous adenoma on the patient's cheek. Figure 2 shows the typical histopathology of a sebaceous adenoma with sharply demarcated, incompletely differentiated sebaceous lobules that were irregular in size and shape. The dermal lobules were composed of undifferentiated basaloid cells and mature sebaceous cells.[6]

The patient consistently declines chemoprophylaxis with oral acitretin or isotretinoin. He continues to have regular colonoscopy at 3-year intervals and regular skin surveillance with his dermatologists every 3 to 4 months. He currently remains free of colon cancer at more than 20 years of follow-up; however, he has extensive actinic keratosis and severe actinic damage for which he undergoes periodic cryotherapy and photodynamic therapy with aminolevulinic acid 20% and blue light (417 nm).

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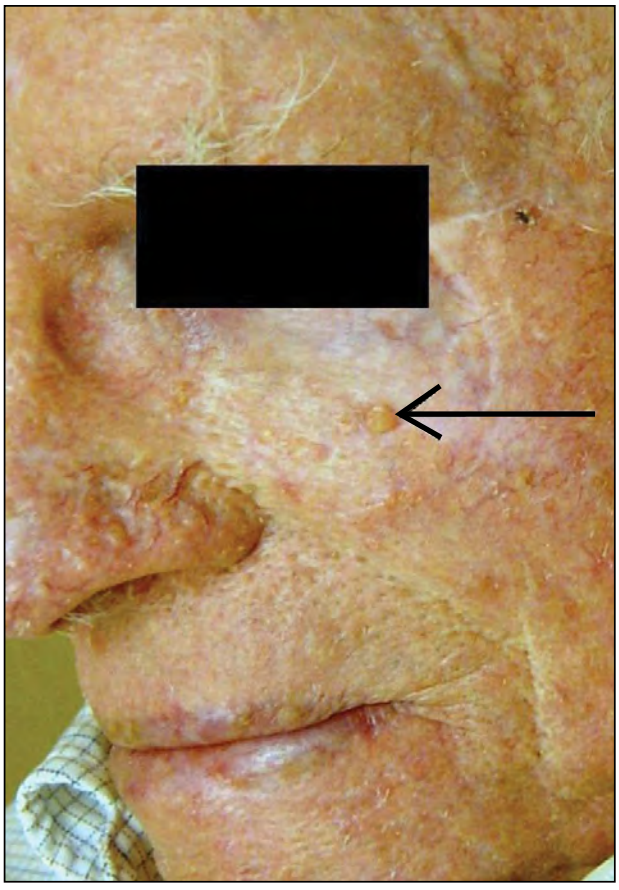

Figure 1. Sebaceous adenoma on the cheek (arrow) and extensive actinic neoplasms on the face.

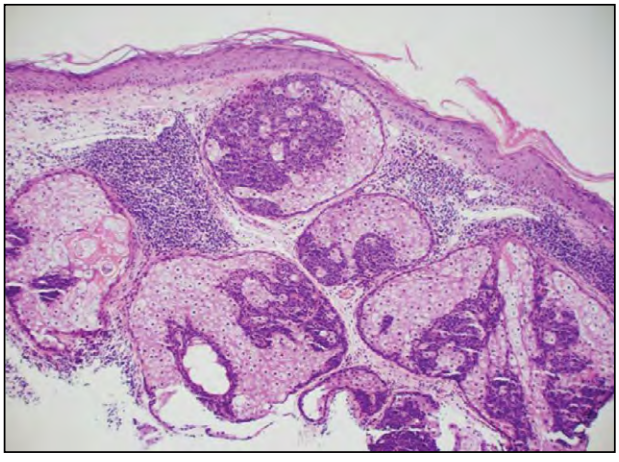

Figure 2. Histopathology of a sebaceous adenoma of the cheek showing sharply demarcated, incompletely differentiated sebaceous lobules that were irregular in size and shape. The dermal lobules were composed of undifferentiated basaloid cells and mature sebaceous cells (H&E, original magnification ×10).

Comment

First described by Muir et al[1] in 1967 and Torre[2] in 1968, MTS is a genodermatosis that is characterized by the association of internal malignancies and cutaneous sebaceous tumors, with or without keratoacanthomas. It may be inherited in an autosomal-dominant fashion with high penetrance and variable expression, though sporadic cases also are known to develop.[3] Occurrence and diagnosis of the cutaneous lesions may precede or follow the internal malignancy. In a 1999 world literature review by Akhtar et al[5] of 205 MTS patients with common presentation of sebaceous tumors with a low-grade visceral malignancy, the sebaceous tumors appeared before the internal malignancy in 22% of patients, concurrently in 6%, and after in 56% (a temporal relationship was not reported for the remaining 16%). Muir-Torre syndrome occurs with a slightly higher prevalence in males, and patients have ranged in age from 37 to 89 years at diagnosis.[3]

The clinical features of MTS include at least one sebaceous adenoma, sebaceous epithelioma, basal cell epithelioma with sebaceous differentiation, or sebaceous carcinoma, and at least one low-grade visceral cancer (with or without colonic polyps). Not all patients with sebaceous tumors have MTS, but cystic sebaceous tumors are almost pathognomonic for the condition. Sebaceous hyperplasia and nevus sebaceous of Jadassohn, with or without a sebaceous epithelioma within it, do not contribute to diagnostic criteria. Multiple keratoacanthomas associated with 2 or more internal malignancies in a patient with a family history of MTS or a keratoacanthoma with histologic sebaceous differentiation also are markers for the syndrome.[3] Multiple sebaceous neoplasms, whether they are adenomas, epitheliomas, or carcinomas, increase the possibility of future development of MTS, even if no internal malignancy is evident at the time of initial screening.[3,5]

Colorectal cancer is the most common primary internal malignancy associated with MTS (56% of the tumors), followed by cancers of the genitourinary system (22%).[5] Of patients with colorectal cancer, more than half had tumors proximal to or at the splenic flexure.[7] Other organs, such as the uterus and breast, also can be sites of malignancy. Keratoacanthomas were noted in 23% of patients and neoplasms in the meibomian gland comprised 23% of sebaceous carcinomas in the 1999 study.[5] Presence of a sebaceous carcinoma in the meibomian glands may therefore be grounds for screening for MTS.

Genetic research suggests that MTS is related to the cancer family syndrome or Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer).[4,8,9] Loss-of-function mutations in DNA mismatch repair genes *MSH2* (mutS homolog 2, colon cancer, nonpolyposis type 1 [*Escherichia coli*] gene) and *MLH1* (mutL homolog 1, colon cancer,

nonpolyposis type 2 [*E coli*] gene),[8] as well as DNA microsatellite instability[10] seen both in MTS and Lynch syndrome tumors, suggest that MTS is a variant of Lynch syndrome, a syndrome that predisposes individuals to develop colorectal and other visceral malignancies associated with germline mutations in DNA mismatch repair genes, including *MSH6* (mutS homolog 6 [*E coli*] gene) and *PMS2* (postmeiotic segregation increased 2 [*Saccharomyces cerevisiae*] gene).[8] One study of 50 families with Lynch syndrome revealed that MTS, as defined by genetic criteria, was found in as many as 14 families.[8] Immunohistochemical testing of MTS-related skin tumors for *MSH2* and *MLH1* is considered a reliable screening method with high predictive value for the diagnosis of the DNA mismatch repair–deficient MTS.[11] Although some sources suggest a greater predominance of *MSH2* gene mutations than *MLH1* mutations,[12] others have failed to find a statistically significant difference in the frequency of *MSH2* versus *MLH1* mutations in MTS.[8] There also may be evidence that the status of the *MSH2* and *MSH6* genes can be linked; for instance, data from a 2008 case report of a 52-year-old man with MTS showed tumor cells with loss of *MSH2* and *MSH6* gene expression.[13] According to this concept, when one gene is intact, the other is intact, and when one is mutated, the other is mutated. Clinical, biomolecular, and immunohistochemical characterization of sebaceous skin lesions and keratoacanthomas may be used to screen for families at risk for MTS. In one study, the following findings were detected in first-degree relatives of 7 patients with MTS: adenomatous polyps; colon, gastric, bladder, and renal carcinomas; non-Hodgkin lymphoma; breast tumors; and laryngeal tumors.[14] These findings demonstrate the importance of family testing, genetic counseling, and clinical vigilance.

Once detected, treatment options for the cutaneous lesions in MTS include cryosurgery, electrodesiccation and curettage, surgical excision, Mohs micrographic surgery, and radiotherapy. Routine surveillance examinations, such as annual colonoscopy, for gastrointestinal and genitourinary cancers are advised because of the high frequency of colorectal cancer.[3] Possible combination treatment with topical retinoids and/or oral retinoids such as isotretinoin or acitretin may be advisable. More data on retinoids are needed, though topical retinoids may have some effect in treating actinic keratoses[15] and oral retinoids including acitretin may prevent skin cancers in solid-organ transplant recipients, including cardiac and renal transplants, who tend to develop more aggressive skin cancers.[16-18] Oral retinoids appear promising for patients with MTS if the preventative benefit can be extended. Combination with interferon also may hold promise.[19] Efficacy of oral isotretinoin for MTS skin lesions may indeed suggest retinoids as a possible treatment of existing sebaceous tumors and a therapy to prevent development of new cutaneous lesions in patients with MTS.[19,20] Retinoids, however, would reduce the incidence of cutaneous malignancies (not visceral malignancies) but only while patients remain on therapy.

Findings of sebaceous tumors of the meibomian glands and eyelid[13] indicate the importance of physicians such as ophthalmologists in aiding the dermatologist in diagnosing and managing treatment of MTS.

Conclusion

A single biopsy-proven sebaceous neoplasm including sebaceous adenomas, sebaceous epitheliomas, and sebaceous carcinomas may warrant further evaluation for MTS. Patients with multiple cutaneous sebaceous adenomas should be questioned about relevant family history and be referred for potential screening with colonoscopy and gastrointestinal evaluation. Muir-Torre syndrome is another dermatologic sign of a serious internal disease. Dermatologists and dermatopathologists can aid in the potential early diagnosis, treatment, and possible lifesaving surgical cure of this hereditary internal cancer.

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