Muir-Torre syndrome (MTS): An update and approach to diagnosis and management

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Muir-Torre syndrome (MTS) is a rare genetic condition that predisposes individuals to skin tumors and visceral malignancies. Because of the potentially aggressive nature of internal malignancies and sebaceous carcinoma, and the tendency to have multiple low-grade visceral cancers, close cancer surveillance is required in individuals and their families with this usually autosomal dominant disorder. Although the majority of MTS is caused by mutations in DNA mismatch repair genes resulting in microsatellite instability, a newly described subtype of MTS does not demonstrate microsatellite instability and may be inherited in an autosomal recessive pattern. In addition, MTS may be unmasked in transplant recipients taking specific immunosuppressant drugs or other immunosuppressed patients. Neoplasms may be subject to immunohistochemistry or both immunohistochemistry and genetic testing to confirm the diagnosis of MTS. Here, we offer an update and an approach to the diagnosis and management of MTS with a particular emphasis on the role of immunohistochemistry and genetic testing. (J Am Acad Dermatol 2016;74:558-66.)

Key words: immunohistochemistry; keratoacanthoma; Lynch syndrome; microsatellite instability; mismatch repair; Muir-Torre; sebaceous adenoma; sebaceous carcinoma; sebaceous epithelioma; sebokeratoacanthoma.

Muir-Torre syndrome (MTS) (Online Mendelian Inheritance in Man [OMIM] #158320) is a rare condition characterized by a genetic predisposition to sebaceous neoplasms and visceral malignancies. First described by Muir et al in 1967[1] and Torre in 1968,[2,3] it represents a variant of the autosomal dominant hereditary nonpolyposis colorectal cancer (HNPCC) syndrome, also known as Lynch syndrome (OMIM #120435). HNPCC occurs in about 1 of 350 individuals in the general population[4]; MTS is evident in about 9.2% of individuals and 28% of families with HNPCC.[5] The most characteristic cutaneous markers are sebaceous neoplasms.[6]

Abbreviations used:

ERF:	eukaryotic release factor
HNPCC:	hereditary nonpolyposis colorectal cancer
IHC:	immunohistochemistry
MLH:	Mutator L Homologue
MMR:	mismatch repair
MSH:	Mutator S Homologue
MSI:	microsatellite instability
MTS:	Muir-Torre syndrome
OMIM:	Online Mendelian Inheritance in Man
PMS:	Postmeiotic Segregation Increased

PATHOGENESIS

The majority of cases of MTS (MTS I) demonstrate autosomal dominant inheritance with high penetrance and variable expression. It may also occur sporadically, most commonly documented in transplant recipients.[7]

In the majority of cases of MTS (MTS I), germline mutations have been detected in mismatch repair (MMR) genes: Mutator S Homologue (MSH)2 (OMIM #609309), Mutator L Homologue (MLH)1 (OMIM #120436), MSH6 (OMIM #600678), and Postmeiotic Segregation Increased (PMS)2 (OMIM #600259). The MMR proteins are responsible for detecting and repairing errors during DNA replication, particularly in microsatellite regions, which are characterized by

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repetitive mono- or di-nucleotide repeats. The most commonly disrupted gene is MSH2, found in over 90% of patients with MTS I.[8] To date, 70 mutations have been found in MSH2. A "second hit" of the corresponding MMR allele is necessary for accumulation of replication errors and increase in microsatellite instability (MSI) and tissue carcinogenesis. MSI causes malfunctioning of tumor suppressor genes.[9]

It has been estimated that around 35% of tumors in patients with MTS do not display MSI, comprising the second subtype of MTS (MTS II).[9] In contrast to MTS I, this subtype shows microsatellite stability (Table I). In MTS II, biallelic inactivation of MYH (OMIM #604933), a base excision repair gene, leads to an autosomal recessive inheritance pattern.[9-11]

Although there are no clear factors that predispose an individual to developing tumors earlier in life, ultraviolet radiation, radiotherapy, and immunosuppression have been implicated in MTS I. One study reported the development of sebaceous tumors in the pelvic region, to which radiotherapy had been applied 8 years earlier in the treatment of uterine cancer. The radiotherapy likely triggered loss of the corresponding MMR allele, allowing for the accumulation of DNA replication errors.[12] In addition, certain immunosuppressants have been associated with increased tumor development in MTS I, including tacrolimus and cyclosporine. These agents increase activity of transforming growth factor beta and interleukin 6, facilitating tumor invasiveness, progression, and metastases.[13-15] In contrast, sirolimus has antineoplastic effects and is recommended for patients with MTS I after transplantation.[15]

CAPSULE SUMMARY

- Muir-Torre syndrome is an inherited syndrome characterized by sebaceous neoplasms and visceral malignancies.
- A newly identified subtype of Muir-Torre syndrome displays microsatellite stability and autosomal recessive inheritance. Immunohistochemistry for mismatch repair gene products may be considered as part of the diagnostic criteria.
- An approach to diagnosis based on modified criteria and management is offered to guide dermatologists when evaluating patients with sebaceous neoplasms.

EPIDEMIOLOGY

Overall, MTS has a male predilection, with a male to female ratio of 3:2.[16] One study of 205 cases of MTS documented sebaceous tumors appearing before internal malignancy in 22% of cases, concurrently in 6% of cases, and after in 56% of cases; 16% of cases demonstrated no temporal relationship.[17] The average age that sebaceous neoplasms present is 53 years, ranging from 21 to 88 years.[17] In addition, cutaneous tumors occur as long as 25 years before or 37 years after visceral malignancy.[18]

CLINICAL PRESENTATION

Cutaneous tumors

Although sebaceous gland hyperplasia is frequently encountered in the general population, sebaceous neoplasms—adenoma, epithelioma, and carcinoma—are rarely seen, except in patients with MTS. Sebaceous adenoma is the most common subtype, with a frequency of 68%.[19] Approximately one quarter (27%) of sebaceous neoplasms are sebaceous epitheliomas, and 30% are sebaceous carcinomas.[18] Other cutaneous tumors include keratoacanthoma, basal cell carcinoma with sebaceous differentiation, and cystic sebaceous tumors[6,20,21] (Fig 1).

Sebaceous neoplasms with MMR deficiency may occur outside the head and neck region, in contrast to sporadic sebaceous tumors that tend to arise on the nose and eyelid.[22] However, sebaceous neoplasms in the head and neck area should still be subject to immunohistochemical analysis. These neoplasms are first evident as painless, slow-growing, pink or yellow papules, plaques, or nodules, often with central umbilication and ulceration. Although most of the sebaceous tumors are benign, sebaceous carcinoma can be aggressive, resulting in local invasion and metastases. It may be first evident as a cystic nodule, often with ulceration. Because of its benign appearance, biopsy is often delayed.[23] Cystic sebaceous tumors are well circumscribed with a thin cyst wall and tend to be larger and more deeply located than their noncystic counterparts.[24]

Keratoacanthomas in MTS usually demonstrate sebaceous differentiation. The presence of multiple keratoacanthomas should prompt immunohistochemical analysis. These keratoacanthomas are typical morphologically, evident as bud-, dome-, or berry-shaped nodules with central craters filled with keratinized matter. They often rapidly increase in size, going through 3 stages: proliferative, mature, and resolving. When subject to immunohistochemical analysis, keratoacanthomas associated with MTS I demonstrate a loss of MMR gene products.[20,25,26]