A possible association between mycosis fungoides and Muir-Torre syndrome: Two disorders with microsatellite instability

Daniel J. Lewis, BA,[a,b] and Madeleine Duvic, MD[b]
Houston, Texas

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INTRODUCTION

Muir-Torre syndrome (MTS) is a rare, hereditary, autosomal dominant cancer syndrome that is a variant of hereditary nonpolyposis colorectal carcinoma (HNPCC) or Lynch syndrome.[1] MTS is characterized by sebaceous neoplasms and HNPCC-associated malignancies such as colorectal, endometrial, and urothelial cancers.[1] The underlying genetic causes of MTS are mutations in or, more rarely, hypermethylation of DNA mismatch repair (MMR) genes, such as *MLH1*, *MSH2*, and *MSH6*.[1] Impaired MMR leads to errors in DNA repair during replication, which can cause microsatellite instability (MSI) and subsequent carcinogenesis.[2]

Loss of MMR function leading to MSI has also been identified in a number of leukemias and lymphomas,[2,3] including mycosis fungoides (MF), a subtype of cutaneous T-cell lymphoma. Little is known about the molecular pathogenesis of MF, and unlike nodal lymphomas, specific chromosomal translocations have not been detected for MF.[4,5] However, MSI might play a pivotal role in causing MF. In fact, there is evidence of *MLH1* promoter hypermethylation and loss of *MSH2* expression in MF.[2,6]

Although MSI has been identified in both MF and MTS, there is no known association between the 2 disorders to date. Herein, we describe a 65-year-old man with a 7-year history of MF who was later also diagnosed with MTS, and we suggest a possible association between MF and MTS.

Abbreviations used:

ECP:	extracorporeal photopheresis
HNPCC:	hereditary nonpolyposis colorectal carcinoma
ICL:	interstrand crosslink
MF:	mycosis fungoides
MMR:	mismatch repair
MSI:	microsatellite instability
MSI-H:	high levels of microsatellite instability
MTS:	Muir-Torre syndrome
PUVA:	psoralen plus ultraviolet A

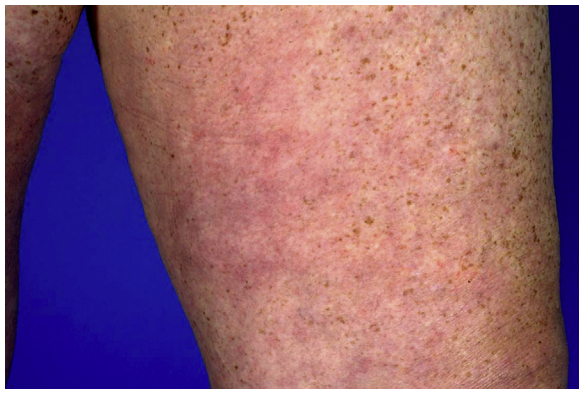

Fig 1. Erythematous mycosis fungoides patches on the left thigh.

CASE REPORT

In 2014, a 65-year-old white man sought treatment in a clinic at MD Anderson Cancer Center for MF. In 2009, he had presented to his local dermatologist with erythematous patches on his left thigh in a

From the School of Medicine, Baylor College of Medicine, Houston[a]; and Department of Dermatology, The University of Texas MD Anderson Cancer Center, Houston.[b]
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Correspondence to: Daniel J. Lewis, BA, The University of Texas MD Anderson Cancer Center, Department of Dermatology, 1515 Holcombe Blvd, unit 1452, Faculty Tower/Pickens 411, Houston, TX 77030-4008. E-mail: daniel.lewis@bcm.edu.

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Table I. Patient history of tumors and malignancies

Tumor or malignancy	Age	Description
Colon adenocarcinoma	59	Located in cecum and ascending colon Status post right hemicolectomy
Mycosis fungoides	60	Located on left arm and left thigh Treated with clobetasol and radiation
Squamous cell carcinoma (×5)	61 (×3)	Located on right cheek, right ear, left arm
	65	Located on right elbow
	67	Located on right foot
Basal cell carcinoma (×3)	Unknown	Located on left ear
	63	Located on right scalp
	65	Located on back
Small bowel adenocarcinoma	64	Located in jejunum
Sebaceous adenoma	65	Located on left back Status post excision
Esophageal adenocarcinoma	67	Preceded by Barrett esophagus Status post endoscopic resection of mass
Sebaceous adenocarcinoma	61	Located on the left upper eyelid

Table II. Patient family history of malignancies

Malignancy	Age	Relative
Endometrial adenocarcinoma (×2)	40	Sister
	65	Paternal grandmother
Brain cancer, unknown type	43	Paternal cousin
Melanoma	64	Sister
Esophageal cancer, unknown type	98	Paternal cousin
Renal cell carcinoma	Unknown	Father
Colon adenocarcinoma	Unknown	Paternal uncle
Gastric adenocarcinoma	Unknown	Paternal cousin

sun-shielded area (Fig 1). Microscopic examination demonstrated an atypical lymphoid infiltrate with focal epidermotropism, and immunohistochemistry showed a CD4:CD8 ratio of 4:1 and loss of CD7 expression. These findings were all consistent with MF. He reported resolution of most of his lesions with clobetasol 0.05% ointment and of a recalcitrant patch with 4 Gy of radiation. His skin has remained free of MF involvement as of February 2017.

The patient's medical and social history was remarkable for a 52-pack per year smoker with an extensive personal and family history of HNPCC-associated malignancies (Tables I and II), including small bowel and colon malignancies. Histopathologic examination of his cancerous small bowel following resection in 2014 showed high levels of MSI (MSI-H), defined as $\geq 40\%$ altered markers.[2] This finding, together with his personal history of malignancies in the setting of a family history of endometrial, colon, and brain cancers, was suggestive of HNPCC.

Given the suspicion for HNPCC, he was referred for a genetics consultation. His small bowel and colon tumors were tested for *MLH1*, *MSH2*, *MSH6*, *EPCAM*, and *PMS2* mutations via immunohistochemistry with both tumor sites exhibiting loss of staining of *MSH2* and *MSH6*. MSI testing by polymerase chain reaction was not performed. Analysis of *MSH2* revealed a duplication of exons 5-7, a mutation interpreted as a deleterious genetic variant, which lead to the diagnosis of HNPCC.

In 2016, the patient developed a papule on his left back that was biopsied and found to be a sebaceous adenoma, which was subsequently excised. Given his history of HNPCC and sebaceous neoplasms, as well as a Mayo MTS risk score of 4 (Table III),[1] he was given a diagnosis of MTS. In 2017, loss of staining of *MSH2* and *MSH6* was also observed via immunohistochemistry in the original MF patch on his left thigh, suggesting a possible association between MF and MTS.

Table III. Mayo MTS risk score algorithm[1]

Variable	Score	Patient's score
Age at diagnosis of first sebaceous neoplasm		
≥60 years	0	0
<60 years	1	
Number of sebaceous neoplasms		
<2	0	2
≥2	2	
Personal history of HNPCC-related cancer		
No	0	1
Yes	1	
Family history of any HNPCC-related cancer		
No	0	1
Yes	1	
Total MTS risk score*		4

HNPCC, Hereditary nonpolyposis colorectal carcinoma; *MTS*, Muir-Torre syndrome.
*A risk score >2 is highly predictive of MTS.

Table IV. Summary of microsatellite instability and MMR defects in MF[2,6-8]

Microsatellite instability	Frequency, %
MSI-L	20[2]
MSI-H	8[2]
Early-stage MF (T1-2)	20[2]
Tumor-stage MF (T3)	47[2]
Molecular defects	
Loss of *MLH1* expression	46[6]; promoter hypermethylation in 64[2]; possible resistance to PUVA or ECP[8]
Loss of *MSH2* expression	35[6]; predilection for T-cell lymphoma[7]; possible response to PUVA or ECP[8]

ECP, Extracorporeal photopheresis; *MF*, mycosis fungoides; *MMR*; mismatch repair; *MSI-H*, high levels of microsatellite instability; *MSI-L*, low levels of microsatellite instability; *PUVA*, psoralen plus ultraviolet A.

DISCUSSION

MSI is a hypermutable phenotype caused by defects in the DNA MMR system. Both HNPCC and MTS are characterized by MSI-H, but lower levels of MSI, defined as <40% altered markers, have been identified in MF (20%) (Table IV).[2,6-8] The highly unstable MSI-H phenotype has also been found in 8% of MF cases, across all stages of disease.[2] In fact, MSI might be associated with disease progression in MF, as it has been more frequently detected in tumor-stage MF (47%) than in early-stage MF (20%).[2] It is possible, though, that MSI in MF might occur during somatic cancer evolution in MF without being the disease driver.[9,10]

Loss of *MLH1* expression causing MSI has been observed in MF (46%),[6] as has epigenetic silencing via hypermethylation of MMR gene-specific promoters. Aberrant methylation of the *MLH1* promoter was detected in 64% of MF patients demonstrating MSI.[2] This hypermethylation has primarily been found in early-stage MF, suggesting that these epigenetic changes might arise early in the development of MF.[2] Thus, both loss of *MLH1* expression and a specific mechanism for it, *MLH1* transcriptional silencing, have been identified in MF.

Aside from *MLH1*, *MSH2* might also be an important gene in MF. *MSH2*-knockout mice have been shown to develop predominantly T-cell lymphomas,[7] and loss of *MSH2* expression was observed in 35% of MF cases.[6] Moreover, *MSH2* is important in the repair of psoralen DNA interstrand crosslinks (ICLs).[8] If *MSH2* defects are present in MF, then they might explain why some MF patients are particularly responsive to psoralen plus ultraviolet A (PUVA) or extracorporeal photopheresis (ECP). In contrast, *MLH1*-deficient cells have been found to be more resistant to psoralen ICLs,[8] which might explain why other MF patients fail to respond to PUVA or ECP. *MSH2* deficiency is also associated with increased spontaneous and ultraviolet-induced skin carcinogenesis,[11] which would explain our patient's numerous skin cancers.

Despite the extreme rarity of both MF and MTS, our patient represents the third reported case of MF in a patient with MTS.[12,13] Evidence of MSI-H and *MLH1* promoter hypermethylation in both MF and MTS suggests a subset of MF cases might share the same molecular pathogenesis as cases of sebaceous neoplasms or gastrointestinal malignancies in MTS. A disease association notwithstanding, *MLH1* and *MSH2* might have clinical relevance in MF. Demethylating agents, such as azacitidine or decitabine, could theoretically treat MF by reversing *MLH1* silencing. Furthermore, distinguishing MF lesions as *MLH1*- or *MSH2*-deficient might help predict response to psoralen ICL-inducing therapies such as PUVA or ECP.[8] More work on the molecular pathogenesis of MF is needed to establish an association between MF and MTS.

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