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

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Key words: cutaneous T-cell lymphoma; hereditary nonpolyposis colon cancer; Lynch syndrome; microsatellite instability; *MLH1*; Muir-Torre syndrome; *MSH2*; mycosis fungoides.

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

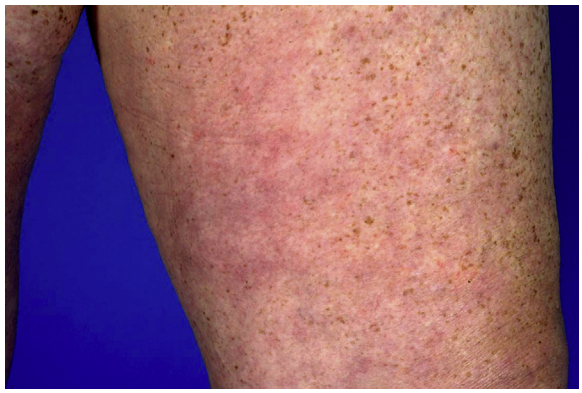

Fig 1. Erythematous mycosis fungoides patches on the left thigh.

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

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Funding sources: None.
Conflicts of interest: None declared.
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JAAD Case Reports 2017;3:358-61.
2352-5126

http://dx.doi.org/10.1016/j.jdcr.2017.04.007

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.