CASE REPORT

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

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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.

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

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

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

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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 ≥40% altered markers. 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), 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 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       |
observed in MF (46%), as has epigenetic silencing (ICLs). If the repair of psoralen DNA interstrand crosslinks is defective, then they might explain why some MF patients are particularly resistant to psoralen ICL-inducing therapies, which might mean why other MF patients fail to respond to PUVA or ECP. MSH2 deficiency is also associated with increased spontaneous and ultraviolet-induced skin carcinogenesis, 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. Evidence of MSH2 deficiency is also associated with increased spontaneous and ultraviolet-induced skin carcinogenesis, which would explain our patient’s numerous skin cancers.

Aside from MSH2-deficient cells having been identified in MF, MSH2-knockout mice have been shown to develop predominantly T-cell lymphomas, and loss of MSH2 expression was observed in 35% of MF cases. Moreover, MSH2 is important in the repair of psoralen DNA interstrand crosslinks (ICLs). 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, which might explain why other MF patients fail to respond to PUVA or ECP. MSH2-deficient might help predict response to psoralen ICL-inducing therapies such as PUVA or ECP. More work on the molecular pathogenesis of MF is needed to establish an association between MF and MTS.

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Table III. Mayo MTS risk score algorithm

| 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

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

ECM, 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.
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