Genetic heterogeneity in a patient with Muir-Torre syndrome

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Key words: genetic heterogeneity; MMR genes; Muir-Torre syndrome; sebaceous adenoma.

INTRODUCTION

Muir-Torre syndrome is an autosomal-dominant disorder caused by germline mutations in 1 of the 4 key DNA mismatch repair (MMR) genes, *MSH2, MSH6, PMS2,* and *MLH1*. Patients with Muir-Torre syndrome present with skin lesions, which play an important role in early detection of the disease and are considered cutaneous markers. The diagnostic criteria for Muir-Torre syndrome are at least 1 skin neoplasm with sebaceous differentiation, at least 1 visceral malignancy, and germline mutation of the MMR genes.[1,2] Sebaceous adenoma is rare and is considered the most significant cutaneous marker for Muir-Torre syndrome.[3] Abbas and Mahalingam[4] suggested that when a young patient presents with a sebaceous neoplasm outside the head and neck area, immunohistochemical analysis of the MMR genes should be conducted for Muir-Torre syndrome screening. If loss of any MMR proteins is identified, microsatellite instability study or germline analysis is warranted for further diagnosis. In addition, presence of multiple keratoacanthomas should also prompt immunostaining studies for screening.[3] In Muir-Torre syndrome, the keratoacanthoma usually presents with sebaceous differentiation.[3]

For a specific patient, loss of MMR proteins in the skin lesions and in the visceral tumors should be in concordance because of the presence of germline mutation. However, here we examined a visceral tumor and all 16 skin lesions from a patient with Muir-Torre syndrome and found genetic heterogeneity among several samples. All 13 sebaceous adenomas and the visceral tumor showed the same expression pattern of the MMR genes in line with the germline mutation, whereas other skin lesions such as keratoacanthoma and squamous cell carcinoma (SCC) showed aberrant expression patterns. To our knowledge, this is the first study reporting the phenomenon of genetic heterogeneity in a Muir-Torre syndrome patient.

Abbreviations used:

MMR: mismatch repair
SCC: squamous cell carcinoma

CASE REPORT

A 63-year-old man presented with sebaceous adenomas, keratoacanthomas, SCCs, and transverse colon adenocarcinoma he had had for years. Germline mutation analysis by using peripheral blood detected the familial *MSH2* variant *c.942 + 3A>T*, also known as *IVS5 + 3A>T*, in heterozygous state (LabCorp, Research Triangle, NC). This variant of *MSH2* has been associated with an increased risk for Lynch syndrome.[5] Together with the sebaceous neoplasm and colonic adenocarcinoma, this patient met the diagnostic criteria for Muir-Torre syndrome.

A review of the patient's pathology tallied a total of 17 specimens, including 1 colonic adenocarcinoma and 16 skin biopsies. Among the skin lesions, there were 13 sebaceous adenomas, 2 keratoacanthomas, and 1 SCC. Fig 1 shows 3 representative gross skin lesions, all of which presented as red papules, with 1 identified on the nose (Fig 1, *A*) and the other 2 on the back (Fig 1, *B* and *C*). All 3 lesions

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Funding sources: None.
Conflicts of interest: None disclosed.

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JAAD Case Reports 2020;6:886-91.
2352-5126

https://doi.org/10.1016/j.jdcr.2020.07.006

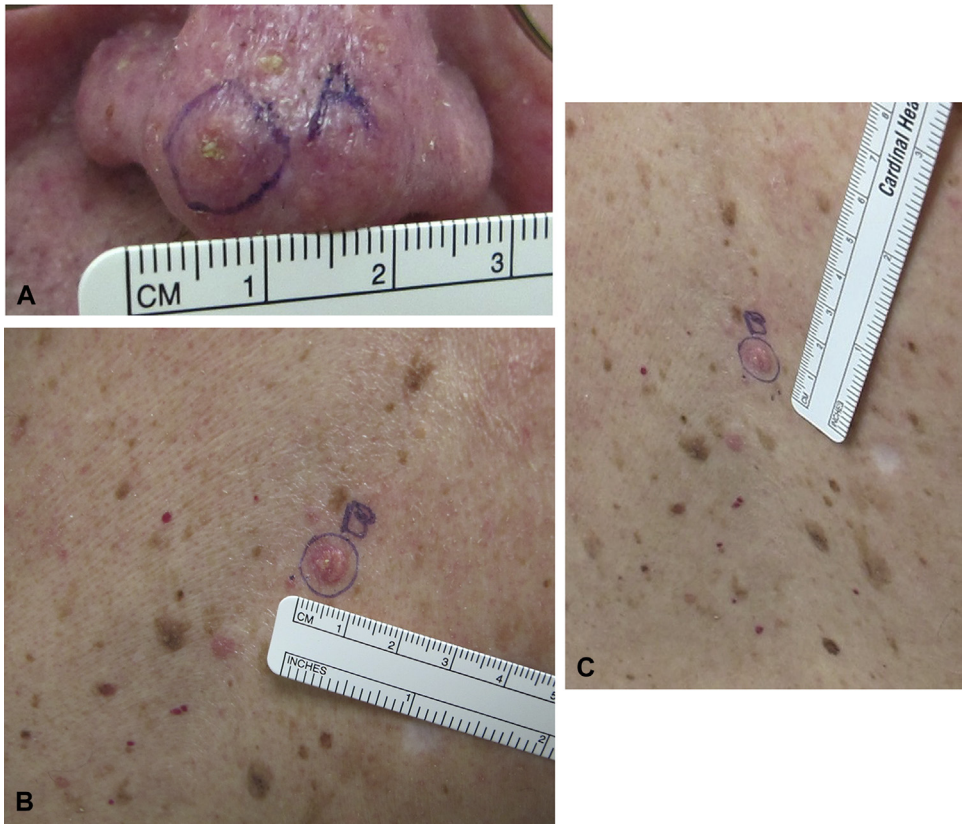

Fig 1. Representative gross skin lesions. A red papule identified on the nose (**A**) and 2 red papules on the back (**B**, **C**). All the lesions were proven to be sebaceous adenoma according to histopathology.

proved to be sebaceous adenoma according to histopathology. We performed immunostaining for *MSH2, MSH6, PMS2,* and *MLH1* on all 16 skin lesions and the colonic adenocarcinoma to examine their expression status. All 13 sebaceous adenomas, the colonic adenocarcinoma, and 1 of the 2 keratoacanthomas showed loss of *MSH2* and *MSH6* expression but retained *PMS2* and *MLH1* expression. This is consistent with the patient's germline mutation in *MSH2* (the absence of MSH2 leads to loss of MSH6 because these 2 proteins form heterodimers and play an important role in DNA damage repair as a function unit[6]). The immunostain for the MMR proteins on a representative sebaceous adenoma is shown in Fig 2. In contrast, the immunostain for the MMR proteins on the SCC showed loss of *PMS2* and retained *MSH2, MSH6,* and *MLH1* (Fig 3). In addition, the other keratoacanthoma shows retention of all 4 MMR genes. The SCC and the 2 keratoacanthomas had no sebaceous differentiation. The 2 keratoacanthomas and their different immunostaining pattern of *MSH2* and *MSH6* are shown in Fig 4. The immunostaining results on all the skin lesions are summarized in Table I.

DISCUSSION

Here we report a case of a 63-year-old man with Muir-Torre syndrome presenting with colonic adenocarcinoma and multiple skin lesions, including 13 sebaceous adenomas, 2 keratoacanthomas, and 1 SCC. All of the sebaceous adenomas and the colonic adenocarcinoma showed no deviation of MMR expression pattern from the germline mutation, but the other skin lesions, including the SCC and keratoacanthomas, showed heterogeneity with either no loss of MMR proteins or loss of a different MMR protein. Our study suggests that in Muir-Torre syndrome patients, the MMR genetic change is faithful in sebaceous adenomas but less so in squamous neoplasms.

Keratoacanthomas can occur in up to 20% of Muir-Torre syndrome patients with or without a concurrent sebaceous neoplasm.[4] Simultaneous multiple keratoacanthomas or keratoacanthoma with sebaceous differentiation can be highly suggestive of Muir-Torre syndrome.[3,4,7-9] We identified 2 keratoacanthomas on our patient and neither of them showed sebaceous differentiation. However, one keratoacanthoma lost *MSH2* and *MSH6* proteins (in

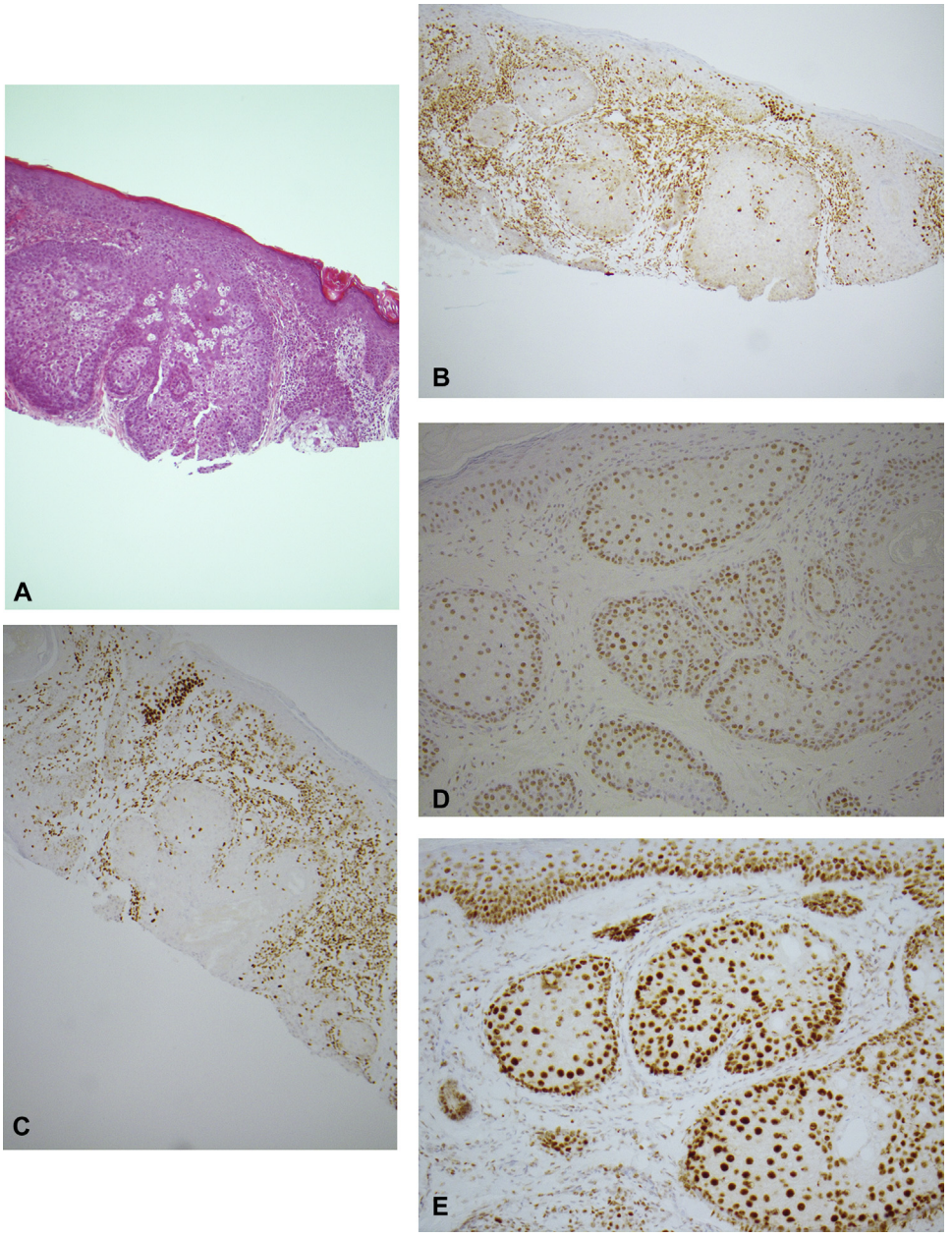

Fig 2. Hematoxylin-eosin stain of a representative sebaceous adenoma and immunostains of the MMR genes. **A**, Sebaceous adenoma. Immunostain with *MSH2* (**B**) and *MSH6* (**C**) showing that the proteins are lost in sebaceous adenoma. Immunostain with *MLH1* (**D**) and *PMS2* (**E**) showing that the proteins are retained in the sebaceous adenoma. (**A**, Hematoxylin-eosin stain; original magnification: ×100.)

alignment with the germline mutation), whereas the other had no loss of MMR expression. This finding suggests genetic heterogeneity behind keratoacanthoma development in Muir-Torre syndrome patients.

To date, the relationship between SCC and Muir-Torre syndrome has not been well clarified. A few studies reported an association of SCC and Muir-Torre syndrome,[7-9] in which the expression pattern of MMR genes in the SCC was the same as the germline mutation. However, the SCC in our case showed loss of *PMS2,* whereas germline mutation was on *MSH2*. It is uncertain whether the loss of *PMS2* in the SCC is related to germline mutation of *MSH2* or is just a sporadic event.

In conclusion, by studying the pathology of the specimens from a patient with Muir-Torre syndrome, we confirmed that sebaceous adenomas are faithful

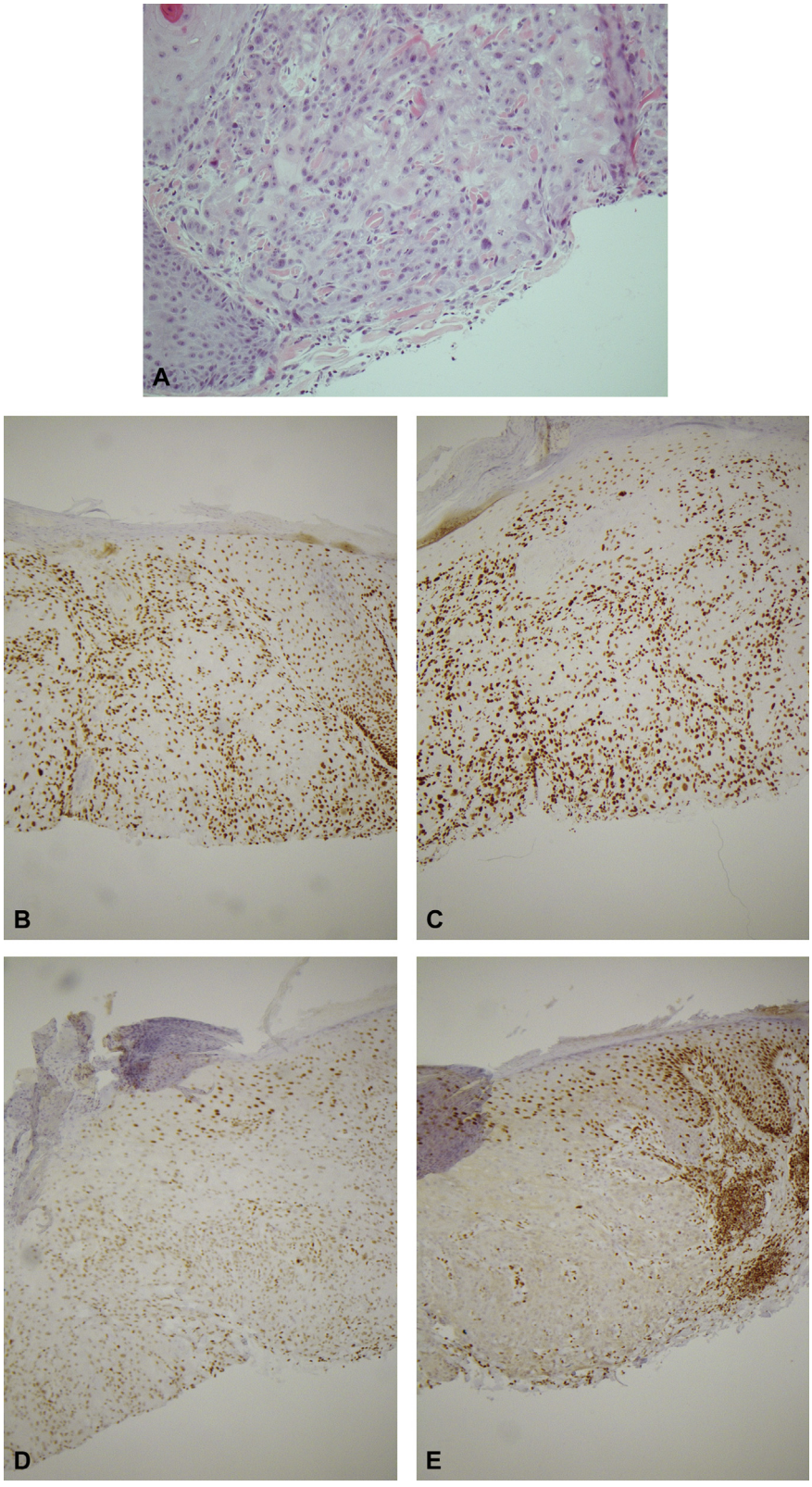

Fig 3. Hematoxylin-eosin stain of the squamous cell carcinoma and immunostains of the MMR genes. **A**, Squamous cell carcinoma, moderately differentiated. Immunostain with *MSH2* (**B**), *MSH6* (**C**), and *MLH1* (**D**) showing that the proteins are retained in squamous cell carcinoma. **E**, Immunostain with *PMS2* showing that the protein is lost in squamous cell carcinoma. (**A**, Hematoxylin-eosin stain; original magnification: ×200.)

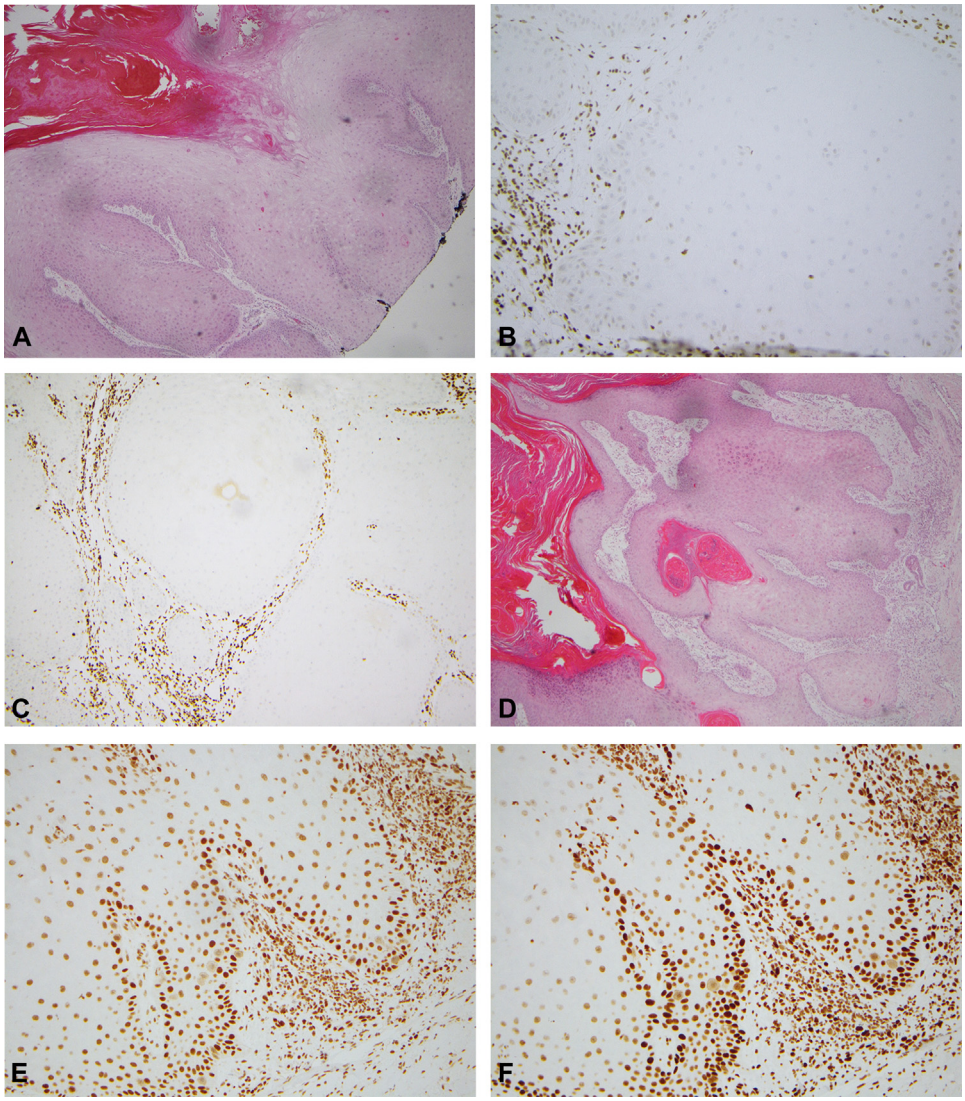

Fig 4. Hematoxylin-eosin stain of the 2 keratoacanthomas and immunostains of *MSH2* and *MSH6*. **A**, Keratoacanthoma 1, with no sebaceous differentiation. Immunostain with *MSH2* (**B**) and *MSH6* (**C**) showing that the proteins are lost in keratoacanthoma 1. **D**, Keratoacanthoma 2, with no sebaceous differentiation. Immunostain with *MSH2* (**E**) and *MSH6* (**F**) showing that the proteins are retained in keratoacanthoma 2. (**A** and **D**, Hematoxylin-eosin stain; original magnifications: ×100.)

Table I. Summary of the mismatch repair gene expression patterns in the colorectal adenocarcinoma and all the skin lesions in the Muir-Torre syndrome patient

	MMR genes			
Tumors	***MSH2***	***MSH6***	***MLH1***	***PMS2***
Colorectal adenocarcinoma	−	−	+	+
All 13 sebaceous adenomas	−	−	+	+
Squamous cell carcinoma	+	+	+	−
Keratoacanthoma 1	−	−	+	+
Keratoacanthoma 2	+	+	+	+

MMR, Mismatch repair.

with germline MMR mutation and therefore are valuable material for early screening of Muir-Torre syndrome. In contrast, keratoacanthomas and SCCs show different expression pattern of the MMR genes and exhibit a phenomenon of genetic heterogeneity.

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