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New facial papules in a sixty-six year-old woman with bladder cancer

Radhika N. Nakrani, B.S.^a, Arunima Ghosh, M.B.B.S., Ph.D.^b, Chyi-Chia Richard Lee, M.D., Ph.D.^b, Piyush K. Agarwal, M.D.^c, Andrea B. Apolo, M.D.^d, and Edward W. Cowen, M.D., M.H.Sc.^a

^aDermatology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland ^bLaboratory of Pathology, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland ^cUrologic Oncology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland ^dGenitourinary Malignancies Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland

Key Teaching Points

Muir-Torre Syndrome (MTS) is an autosomal dominant cancer syndrome that results from a mutation in mismatch repair genes. It is characterized by sebaceous neoplasms, keratoacanthomas, and visceral neoplasm(s) affecting the colon, uterus, ovaries, bladder, or other organs.

Mismatch repair immunohistochemistry and microsatellite instability testing of sebaceous neoplasms is available to confirm a diagnosis of MTS.

Early recognition of cutaneous features of MTS could lead to early diagnosis and prevention of advanced neoplasms in patients and family members.

CASE SUMMARY

History

A 66-year-old woman from India was referred to the Dermatology Consultation Service at the National Institutes of Health for evaluation of multiple small, skin-colored papules on her forehead. She was undergoing follow-up after achieving a near pathologic complete response to neoadjuvant chemotherapy with dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) chemotherapy followed by a radical cystectomy and

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Correspondence: Edward W. Cowen, MD, MHSc, Dermatology Branch, Center for Cancer Research, National Cancer Institute, Bldg 10/Room 12N238, 10 Center Dr. MSC 1908, Bethesda, MD 20892-1908. cowene@mail.nih.gov Phone: 301-496-4299, Fax: 301-402-2943.

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ileal conduit formation for muscle-invasive urothelial bladder carcinoma. The first facial papule was identified by the patient around the time of her bladder cancer diagnosis 2 years prior. The lesion had increased in size and multiple similar appearing smaller papules had subsequently developed. The papules had remained asymptomatic.

The patient's past medical history was significant for endometrial cancer at age 41 and colon polyps at age 53. At age 63 she was diagnosed with low-grade papillary urothelial cancer, which progressed to high-grade disease with muscle invasion. Her family history was significant for early-onset colon cancer in three of eleven siblings, and renal cell carcinoma in one sibling. Her mother died of esophageal cancer at age 55. By report, multiple siblings were affected with similar skin lesions, but histologic confirmation of sibling skin lesions was not available.

Physical Examination

On examination, the patient had approximately six pinpoint to 2-mm scattered, raised round skin-colored papules on her forehead, midface, and lateral aspect of the neck. Several papules had a milia-like round appearance. Others were more sessile, slightly yellow multilobulated lesions. The largest lesion, a 4-mm skin-colored raised round papule approximately 1-cm superior to her right eyebrow, was chosen for biopsy (Fig 1A–B). The rest of her skin exam was unremarkable.

Histopathology

Histopathologic examination of a skin biopsy from the forehead papule demonstrated a well-demarcated, non-encapsulated tumor nodule with a predominance of basaloid cells with few small clusters of sebocytes and ducts and no nuclear atypia (Fig 2A–C).

Immunohistochemical stains indicated that tumor cells were positive for p63 (**2D**) and focally positive for EMA (**2E**). Ber-EP4, CK7, CK20, and TTF1 were negative. Overall, the histologic features and immunohistochemical staining profiles were consistent with sebaceous epithelioma. Additional staining for mismatch repair (MMR) proteins revealed absence of MSH2 and MSH6 expression (Fig 3A–B) and preservation of MSH1 and PMS2 expression (Fig 3C–D).

Other Significant Diagnostic Studies

PCR based assay for microsatellite instability (MSI) of the sebaceous tumor was performed. The tumor specimen was compared to skin from an unaffected area. Five informative mononucleotide repeat markers were tested: BAT-25, BAT-26, MONO-27, NR-24, and NR-21 (Fig 4A–E). Tumor microsatellite instability was detected in markers BAT-25, BAT-26, MONO-27, and NR-21, demonstrating a high-frequency MSI phenotype, MSI-H.

Diagnosis

Muir-Torre syndrome with sebaceous epithelioma and associated bladder and endometrial carcinoma.

Follow-up

The patient was referred for genetic counseling, germ line testing for MSH2 mutations, and malignancy screening, including upper endoscopy, colonoscopy, and mammography. She will continue routine post-surgery follow-up for muscle-invasive urothelial carcinoma of the bladder. Urine cytology and CT scan of chest/abdomen/pelvis performed during this visit showed no evidence of disease recurrence.

DISCUSSION

Muir-Torre syndrome (MTS) is a variant of Lynch Syndrome, or hereditary nonpolyposis colorectal cancer (HNPCC), a hereditary cancer syndrome with increased risk of colorectal and extracolonic malignancies. MTS is distinguished by the development of at least one cutaneous sebaceous neoplasm (sebaceous adenoma, sebaceous epithelioma, sebaceous carcinoma) or multiple keratoacanthomas, in addition to at least one visceral neoplasm.^{1–4} MTS-associated skin lesions are seen in approximately 9% of individuals with Lynch Syndrome.⁵ MTS is inherited in an autosomal dominant pattern with high penetrance, but variable expressivity, and is associated with mutations in DNA mismatch repair (MMR) genes, including MSH2, MLH1, and MSH6. MSH2 mutations appear to predominate in the MTS phenotype and are common in patients who develop urothelial carcinoma.⁶

Patients with MTS are at highest risk of colorectal cancer (56%), followed by genitourinary (22%), breast, and other neoplasms.⁷ The majority of colorectal neoplasms are at or proximal to the splenic flexure, in contrast to the general population.⁴ Accordingly, complete colonoscopy rather than sigmoidoscopy is recommended in patients with suspected MTS.⁸ Urothelial carcinoma of the bladder is also associated with MTS, but is less common than urothelial carcinoma of the upper urinary tract including the ureter and renal pelvis.^{7, 9} Exposure to environmental mutagens in the gastrointestinal and genitourinary tract may contribute to the increased risk of mismatch repair-related neoplasms.^{10, 11} Interestingly, malignancies associated with MTS tend to have a more indolent course than sporadic malignancies.^{4, 12} Anecdotally, bladder cancer associated with HNPCC appears to respond favorably to chemotherapy as in this patient who had a near complete pathologic response to the neoadjuvant chemotherapy with no invasive residual disease. Therefore, patients with high grade upper tract urothelial carcinoma or muscle-invasive urothelial carcinoma of the bladder suspected to have HNPCC or MTS should be offered cisplatin-based neoadjuvant chemotherapy prior to cystectomy.

Sebaceous neoplasms and keratoacanthomas precede the diagnosis of visceral malignancy in 22–60% of patients with MTS.^{4, 5, 7, 13–15} Sebaceous adenoma is most common, occurring in 68% of patients.⁴ Sebaceous carcinoma and sebaceous epithelioma are seen in 30% and 27% of patients, respectively.⁴ Patients presenting with two or more sebaceous neoplasms have a high likelihood of MTS.¹⁶ A single sebaceous neoplasm in a person under 60 years with a personal or family history of Lynch-related cancer (colorectal, endometrial, ovarian, small bowel, urothelial, biliary tract) also confers a high likelihood of MTS.¹⁶ Sebaceous hyperplasia is a frequent finding in MTS but is of less diagnostic value due to its high frequency in the general population. Keratoacanthomas occur in approximately 20% of MTS patients.⁷ A clinical scoring system for patients with sebaceous neoplasms has recently been

proposed and includes: the number of sebaceous tumors, age at diagnosis, and personal and family history of Lynch-related cancers.¹⁶ Diagnostic screening guidelines generally include colonoscopy every 1–2 years beginning at age 25, annual hemeoccult, and annual pelvic exam with Pap test and vaginal ultrasound or endometrial biopsy.^{17–20}

Loss of normal DNA MMR function is associated with microsatellite instability (MSI), a type of genetic instability characterized by length changes in short repeated DNA sequences normally of fixed length scattered throughout the genome. Several different mutation patterns in MMR have been reported in MTS. Our patient's tumor tissue exhibited loss of MSH2 and MSH6 immunostaining. This pattern is more likely with germline mutations in MSH2 rather than MSH6.²¹ MSH2 and MSH6 mutations portend a higher risk of multiple cancers, particularly endometrial cancer.^{22–24}

A germline mutation in MSH2 or MSH6 is likely in our patient, given her personal and family history of Lynch-related cancers; however MMR and MSI studies do not distinguish between somatic and germline mutations. Mutations in tumor specimens may differ from mutations found by germline testing.¹⁶ Germline testing provides the opportunity for genetic counseling of family members and avoids unnecessary screening procedures in those unaffected. Given the cost of genetic testing and similar screening guidelines for individuals with a known mutation and those at risk without a confirmed mutation, directly proceeding to malignancy screening in family members is also reasonable.

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ABBREVIATIONS

MTS	Muir-Torre Syndrome
HNPCC	Hereditary Nonpolyposis Colorectal Cancer

MMR	Mismatch repair
MSI	Microsatellite instability
MLH1	MutL homolog 1
MSH2	MutS homolog 2
MSH6	MutS homolog 6
PMS2	Postmeiotic segregation increased 2

Fig 1. Muir-Torre syndrome. **A**, Multiple skin-colored papules on the forehead. **B**, Sebaceous epithelioma prior to biopsy.

Fig 2. Histopathology of sebaceous epithelioma in Muir-Torre syndrome. **A–C**, Histology demonstrates nodular proliferation of basaloid tumor cells with small clusters of sebocytes and ducts (Hematoxylin-eosin stain; original magnifications: **A**, $\times 4$; **B**, $\times 40$; **C**, $\times 60$). **D**, p63 stain demonstrates diffuse positivity in the tumor cells (Original magnification: $\times 60$). **E**, EMA stain demonstrates positivity in the ducts (Original magnification: $\times 60$).

Fig 3. Mismatch repair immunohistochemistry of sebaceous epithelioma demonstrating loss of MSH2 and MSH6 staining. **A**, MSH2. **B**, MSH6. **C**, MLH1. **D**, PMS2.

Fig 4.

Microsatellite instability analysis comparing the patient's sebaceous epithelioma (upper panel) to the patient's normal skin (lower panel) using microcapillary array electrophoresis. Arrows indicate alleles with different lengths detected in the tumor specimen, signifying microsatellite instability. **A–D**, Microsatellite instability detected in patient's tumor in four of five informative markers (**A**, BAT-25, **B**, BAT-26, **C**, MONO-27, **D**, NR-21). **E**, Microsatellite instability not detected in patient's tumor in the fifth informative marker, NR-24.