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## Case Report

# Muir-Torre Syndrome: The Importance of a Detailed Family History

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## Keywords

Muir-Torre syndrome · Lynch syndrome · Sebaceous carcinoma

## Abstract

Muir-Torre syndrome, a variant of Lynch syndrome or hereditary nonpolyposis colorectal cancer, is an autosomal dominant disease characterized by skin neoplasms (sebaceous or keratoacanthomas) and visceral malignancies. Due to the rarity of the syndrome there are no firm guidelines on how and when to test patients with its typical skin lesions. We describe a case that highlights the importance of a detailed family history.

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## Introduction

Muir-Torre syndrome (MTS), a variant of Lynch syndrome or hereditary nonpolyposis colorectal cancer, is an autosomal dominant disease characterized by skin neoplasms (sebaceous or keratoacanthomas) and visceral malignancies [1]. Described separately by Muir and Torre in the same year (1967), it was Henry Lynch, in 1981, who realized that these conditions were variants of what would become known as Lynch syndrome [2–4]. Caused by a germline mutation in a DNA mismatch repair gene, the characteristic tumors are associated with microsatellite instability (MSI). Due to the rarity of the syndrome (approximately 200 cases reported before the turn of the century) [5–7] there are no firm guidelines on how and when to test patients with its typical skin lesions.

## Case Report

A 44-year-old man complained of a recurrent bleeding, erythematous, scaly, papillomatous left lower eyelid lesion for 2 years (Fig. 1a). Two prior biopsies of this lesion were diagnosed as skin tags. Past medical history included three fatty tumors removed as a child (left forehead, lower abdomen, and back). Histopathology of the most recent shave biopsy showed skin with an intradermal proliferation of basaloid cells surrounding foamy cells, which formed lobules (Fig. 1b). Many mitotic figures were seen. The epithelium contained hyperkeratosis, parakeratosis, and pagetoid spread of atypical foamy cells, consistent with a well-differentiated sebaceous carcinoma. The remainder of the tumor was removed with Mohs micrographic surgery, and negative margins were confirmed by Oil Red O staining. The defect was closed directly. Though his lesion was stage IA (T1N0M0) based on its size, superficial nature, and his clinical examination, due to the patient's young age and family history of colon cancer (2 maternal aunts), there was suspicion for an associated MTS, and immunohistochemistry (IHC) was ordered for the mismatch repair proteins: MLH1, MSH2, MSH6, and PMS2 (Ventana Medical Systems, Tucson, AZ, USA), along with MSI testing (Life Technologies; Carlsbad, CA, USA).

IHC showed a loss of the mismatch repair proteins MSH2 and MSH6 (Fig. 1c). Formalin-fixed paraffin-embedded tissue sections were reviewed by a surgical pathologist, who macrodissected tumor and nontumor tissues separately using an automated procedure (Promega, Madison, WI, USA). Multiplex PCR amplification of five mononucleotide microsatellite (BAT25, BAT26, NR21, NR24, and NR27) and two pentanucleotide microsatellite loci (PentaC and PentaD) was performed on the DNA extracted from tumor and nontumor samples. The mononucleotide markers were used for MSI assessment, while the pentanucleotide markers were used to detect potential laboratory errors and/or contamination. Fluorescently labeled amplification products were separated by denaturing electrophoresis and detected using a fluorescent capillary analyzer (Life Technologies). The size profiles of the mononucleotide products were compared directly to those of nontumor tissue. MSI, defined as a change in any length due to insertion or deletion of repeating units within a microsatellite of a tumor compared to nontumor (normal) tissue, was not detected (tumor was MSI-stable). Due to these discordant results, a more detailed patient history was obtained, revealing a family history meeting the Revised Amsterdam II criteria for the diagnosis of Lynch syndrome (Table 1; Fig. 1d) [8]. The patient was referred to a genetic counselor to coordinate testing for a germline

mutation. A heterozygous germline MSH2 mutation (c.1226\_1227del) known to result in the premature truncation of the MSH2 protein at amino acid position 415 was identified, confirming Lynch syndrome (COLARIS®, Myriad Genetics, Inc., Salt Lake City, UT, USA).

## Discussion

Due to their rarity, some suggest screening all sebaceous lesions with IHC for loss of mismatch repair proteins [9]. Most of the IHC and MSI research thus far has been on colon tumors and presents a conundrum for the pathologist and clinician trying to apply this to cutaneous sebaceous lesions [10, 11]. Roberts et al. [11] found IHC in sebaceous neoplasms to have an 85% sensitivity but only a 48% specificity and 22% positive predictive value for MTS. Interestingly, they found a family history of colorectal cancer in two or more family members to have a 92% sensitivity, 99% specificity, and 92% positive predictive value. IHC in our case was effective as a screening tool, showing a loss of staining for the MSH2 and MSH6 proteins. This was confirmed by germline testing, which demonstrated an MSH2 gene abnormality and a normal MSH6 gene. MSH2 and MSH6 proteins form a heterodimer, explaining how loss or abnormality of one could cause a loss of IHC staining for both [12, 13]. Positive IHC staining confirms the presence of but not the functionality of the mismatch repair proteins, which further complicates interpretation of the results. MSI testing is better at demonstrating a functional loss but has not been approved by the US Food and Drug Administration for this purpose and must be performed with caution. Abbas and Mahalingam [14] have developed a useful diagnostic algorithm for diagnosing MTS in cutaneous sebaceous neoplasms, but their approach does not apply to head and neck tumors. We recommend that all patients with sebaceous neoplasms be screened for MTS. Family history is the most cost-effective screening tool with the highest positive and negative predictive values, and should be utilized first, in order to guide the administration and interpretation of the more expensive confirmatory tests.

## Statement of Ethics

The collection and evaluation of protected patient health information was HIPAA-compliant, and the ethical principles outlined in the Declaration of Helsinki as amended in 2013 were adhered to. The patient gave informed consent to participate in this study, which was approved by our institution's committee on human research.

## Disclosure Statement

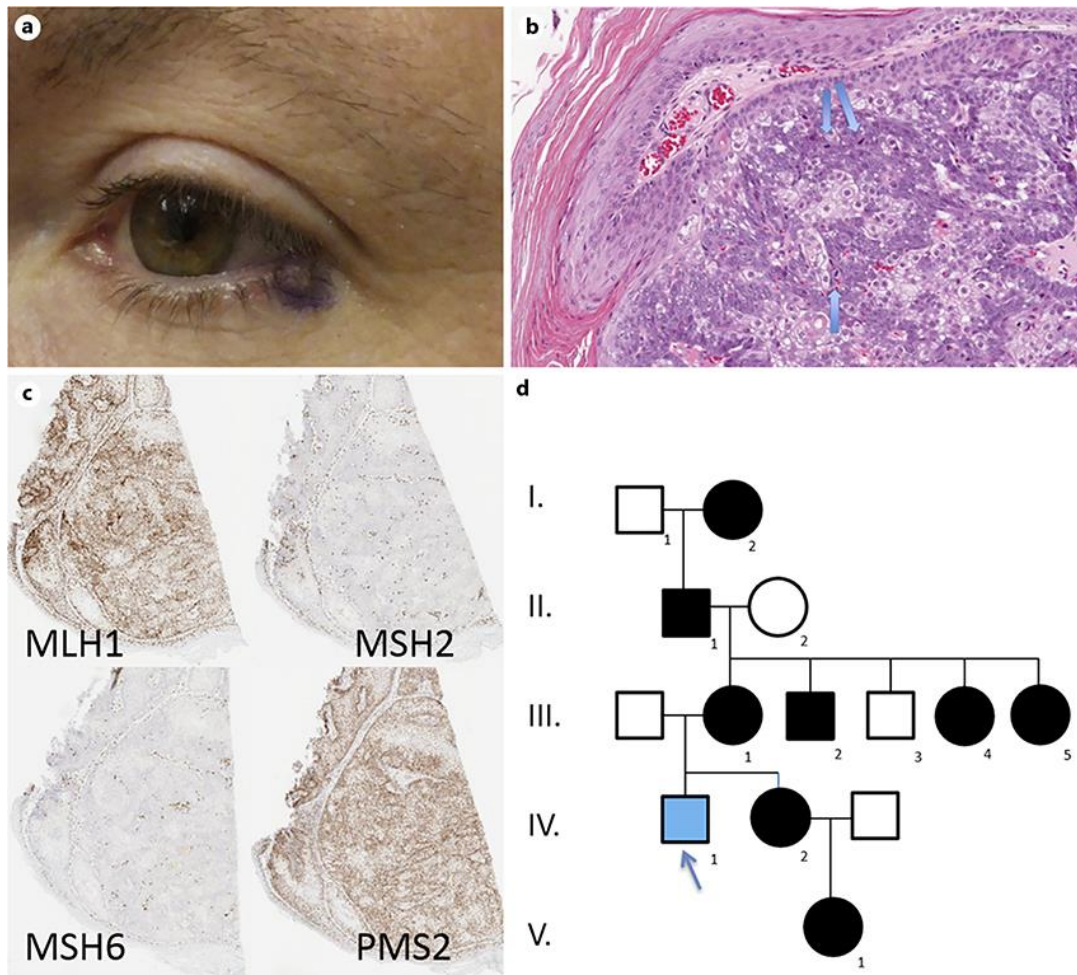
The authors have no conflicts of interest to declare.

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**Fig. 1.** **a** Left eye with lower lid lesion marked with a blue surgical marking pen. **b** Biopsy with intradermal lobules composed of proliferating basaloid cells and foamy cells. Many mitotic figures are seen (arrows), consistent with a well-differentiated sebaceous carcinoma. Hematoxylin and eosin.  $\times 20$ . **c** Immunohistochemistry shows the presence of MLH1 and PMS2 and the absence of functional MLH2 and MSH6 (MLH1, MSH2, MSH6, and PMS2.  $\times 6$ ). **d** Family history (proband designated by arrow). I.2 Uterine cancer, colon cancer (33 years old). II.1 Skin cancer (19 years old), colon cancer (45 years old), prostate cancer (60 years old). III.1 Endometrial cancer (50 years old), squamous cell carcinoma (64 years old). III.2 Skin cancer. III.4 Endometrial cancer (42 years old), ureter cancer (65 years old), colon cancer (66 years old), squamous cell carcinoma (68 years old). III.5 Endometrial cancer (64 years old), colon cancer (61 years old). IV.1 Sebaceous carcinoma (45 years old), 3 fatty tumors removed as a child. IV.2 Pre-endometrial cancer (40 years old), pre-skin cancer (41 years old). V.1 Cervical cancer (19 years old).

**Table 1.** Revised Amsterdam Criteria (Amsterdam Criteria II) [8]

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There should be at least three relatives with an HNPCC-associated cancer (cancer of the colorectum, endometrium, small bowel, ureter, or renal pelvis) and:

- One should be a first-degree relative of the other two
  - At least two successive generations should be affected
  - At least one should be diagnosed before the age of 50
  - Familial adenomatous polyposis should be excluded
  - Tumors should be verified by pathological examination
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