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*Case Report*

# Muir–Torre syndrome – An Indian case report

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## ABSTRACT

We report a case of Muir–Torre syndrome in an Indian male patient with strong family history of colon cancer. Next generation sequencing (NGS) based exome analysis revealed a heterozygous NM_000249.4:c.793C>T (p.Arg265Cys) pathogenic variant in MutL Homolog 1 gene. Familial cancers need to be genetically evaluated to identify "at-risk" family members, aid pre-symptomatic testing, and institute appropriate surveillance and preventive measures.

**Keywords:** Familial cancer, Muir–Torre syndrome, Lynch syndrome Type 2, Exome sequencing

## INTRODUCTION

Familial cancer syndromes account for 5–10% of total cancer cases. Widespread genetic testing has unveiled molecular pathologies in more than 200 cancer syndromes. We report a case of Muir–Torre syndrome (MTS) in a male patient with strong family history of colon cancer, where next-generation sequencing (NGS)-based whole exome analysis revealed a pathogenic variant in MutL Homolog 1 (*MLH1*) gene.

## CASE

A 42-year-old male was referred in view of recently detected colon cancer. He was initiated on regular surveillance through colonoscopy since 2015, when his elder sister was diagnosed with colorectal cancer. Before that, his father was diagnosed with colon cancer and succumbed at the age of 56 years. There was no history of any skin lesions/tumors in the family. Our patient was found to have a pedunculated polyp on his first colonoscopy and underwent polypectomy and biopsy. There was no histopathological evidence for malignancy and a conservative management followed. His annual colonoscopy findings were normal over the next 5 years.

The following year, colonoscopy could not be performed in the scheduled time due to the viral pandemic. The patient developed bleeding per rectum, progressive abdominal pain and on evaluation, was found to have an ulceroproliferative lesion measuring 4 cm × 4 cm along the transverse colon. Carcinoembryonic antigen levels were elevated to 20 ng/mL (normal range: 0–4.7). Positron emission tomography showed FDG avid heterogeneously enhancing, asymmetric, circumferential mural thickening involving mid-transverse colon with few perilesional lymph nodes. The patient underwent extended right hemicolectomy in view of the above findings.

The resected specimen showed features consistent with moderately differentiated adenocarcinoma. Immunohistochemistry for the study of mismatch repair (MMR) proteins showed loss of expression for *MLH1* and post-meiotic segregation 2 (PMS2), suggesting microsatellite instability (MSI). Exome sequencing was performed on patient's blood sample to look for pathogenic variants associated with Lynch syndrome or related familial cancer syndromes. A heterozygous NM_000249.4:c.793C>T (p.Arg265Cys) variant was identified in exon 10 of *MLH1* and *PMS2* gene. This variant is absent from population databases and has been previously reported "pathogenic" across multiple mutation databases – ClinVar, Online Mendelian Inheritance in Man, and human genome mutation database. Thus, he was diagnosed with *MLH1*-associated autosomal dominant hereditary non-polyposis colon cancer (HNPCC) syndrome Type 2 or MTS. Familial segregation studies could not be performed since blood samples of other affected family members were unavailable.

## DISCUSSION

MTS is a distinct germ line disorder with susceptibility to cancers and cutaneous lesions and was described independently by Muir *et al*. and Torre.[1,2] It is a rare Lynch syndrome/HNPCC variant, with a reported incidence of 1:350[3,4] and is caused due to pathogenic mutations in MMR proteins. The defective proteins render the cell susceptible to genetic insults and hasten oncogenesis. Most commonly implicated genes include *MLH1*, MutS homolog (MSH)2, MSH6, and PMS2.[5] MutL-alpha is a heterodimer of *MLH1* and PMS2, which explains why loss of *MLH1* results in loss of PMS2 expression as well, as witnessed in our patient's IHC.[6] Muir–Torre accounts for <10% of HNPCC, with slight male preponderance and a variable penetrance.[4,5,7] The hallmark cutaneous tumors include sebaceous adenoma, keratoacanthoma, and epithelium. The cutaneous lesions may themselves be undifferentiated in few cases, with histological features of malignancy and evidence of MSI. The most common systemic malignancy reported in this syndrome is colorectal cancer followed by urothelial cancer and they usually predate cutaneous lesions by several years in more than 50% of cases.[8,9] Cancers of endometrium, ovary, breast, etc., are relatively less common.[10]

MTS has an autosomal dominant inheritance, can affect both males and females, with a recurrence risk of 50% among siblings/offspring. Autosomal recessively inherited MTS is associated with mutations of MYH, where the typical MSI is absent.[5] Screening may be offered for other family members through targeted variant analysis by Sanger sequencing. Mutations identified in the family have important implications in recognizing asymptomatic at-risk relatives, offering accurate genetic counseling, initiating regular surveillance, and instituting specific measures for potential prevention or early cure of cancers. Surveillance must include annual endoscopy/colonoscopy, ultrasonography, breast examination, urinalysis with cytology, and dermatological consult starting at the age of 20–25 years. Prenatal diagnosis in familial cancers is controversial in view of variable expressivity, variable penetrance, availability of appropriate surveillance measures, and treatment modalities.

Most case reports on MTS can be found in dermatological publications, with diagnosis mainly based on identification of typical cutaneous lesions and retrospective elucidation of family history of various cancers. Very few reports have genetic diagnosis, probably due to the relative scarcity of genetic testing services and geneticists, until recently. Lack of specific therapeutic options has also discouraged most other specialists from actively evaluating such cases, despite its implications on the entire family. The clinicopathologic features and patient demographics from few recent case reports are compared in Table 1.[7,11-16]

Published literature on MTS is hardly rare, but our case report attempts to illustrate by example, the crucial role of genetic diagnosis, in providing psychological closure and improved awareness in dealing with the disease. This is the only scenario, where finding diagnosis in a single patient can save several others. Genetic testing also reveals common mutations in the population, allows accurate genotype-phenotype correlation, and may guide discovery of novel targeted therapies.

This case report also reiterates the significance of detailed history and clinical information in evaluating patients with familial cancers, in general. Young age onset, positive family history, and associated systemic signs should hint any clinician regarding the possibility of an underlying genetic disorder and should be promptly evaluated in consult with a geneticist. Genetic counseling addresses specific family concerns, to enable well-informed decisions and patient cooperation on further management of disease. In the current era, when genetic services are readily available, this opportunity should never be missed.

## CONCLUSION

Familial cancers must be actively evaluated using NGS-based focused/exome analysis, especially when there is clinical and histopathological evidence of genetic etiology. Definitive molecular diagnosis enables accurate prognostication, screening of at-risk relatives, and institution of appropriate surveillance and treatment. It also provides a deeper insight into the genetic etiopathogenesis of these cancer syndromes, to facilitate appropriate modification of clinical guidelines and enable discovery of novel targeted therapies.

**Table 1:** Comparison of demographic and clinical features of recently reported patients with Muir Torre syndrome.

| Study | Age of the index patient | Affected family members | Type of cancers in the family | Type of skin lesion | Site of skin lesions | Immunohistochemistry | Molecular diagnosis |
|---|---|---|---|---|---|---|---|
| Arch Dermatol. 2006, Marazza *et al.* | 54 Y/M | 3 | Colorectal cancer | Large sebaceous adenomas, epitheliomas | Nose and hack | Loss of MSH-2 and MSH-6 | NA |
| Cutis 2008, Hare HIT, Mahendraker *et al.* | 52 Y/F<br>55/M | >5<br>>5 | Colorectal, colon, gastric, uterine, and urethral cancer, and gastric cancer | Face | Sebaceous carcinoma<br>Actinic keratosis, sq cell carcinoma, malignant melanoma | Loss of MSH2<br>Loss of MSH2 and MSH6 | NA. |
| J Clin Aesthet Dermatol. 2009, Higgins *et al.* | 81 Y/M | 0 | Colorectal cancer | Basal cell carcinoma, actinic keratosis, and sebaceous adenoma | Face, trunk, and back | NA | NA |
| Indian Journal of Dermatoloy, Venerology, 2014, Kansal and Awns | 65 Y/M | 5 | Gastric cancer, colorectal cancer, breast cancer, endometrial cancer, and cutaneous malignancy | Squamous cell carcinoma | Right ale of nose, back, and forehead | NA | NA |
| Case reports in dermatological medicine, 2016, Kaitlin vanderback *et al.* | 57 Y/F | 7 | Endometrial adenocarcinoma, colorectal carcinoma, glioblastoma multiforme, osteosarcoma | Sebaceoma | Back | Loss of MS112 | NA |
| BMC Nephrology, 2019, Tomonari *et al.* | 43 Y/F | 0 | Colorectal cancer | Sebaceous carcinoma | Head | Loss of MSH2 and M5H6 | 1226_1227delAG in the MSH2 exon 7 |
| Case Reports in Ophthalmology, 2019, Burris, Rodriguez *et al.* | 44 Y/M | 2 | Colorectal, uterine, endometrial, skin cancers | Sebaceous adenoma | Left lower eyelid | Loss of MSH-2 and MSH-6 | Heterozygous germ line MSH2 mutation (c. 1226_1227del) |
| Our patient, 2020 | 42 Y/M | 2 | Colorectal cancer | Nil | NA | Loss of MLII 1 and PMS2 | Heterozygous c. 793C>T in exon 10 of *MLH1* |

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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### Conflicts of interest

There are no conflicts of interest.

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