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Perspectives in Dermatopathology

Cutaneous sebaceous neoplasms as markers of Muir-Torre syndrome: a diagnostic algorithm

Sebaceous gland neoplasms such as adenoma, epithelioma, and carcinoma are uncommon cutaneous tumors. Although sporadic, their occurrence is clinically significant because of their association with Muir-Torre syndrome (MTS). MTS is a rare autosomal dominant genodermatosis characterized by the occurrence of sebaceous gland neoplasms and/or keratoacanthomas associated with visceral malignancies that include gastrointestinal and genitourinary cancers. MTS is usually the result of germline mutation in one or more of the DNA mismatch repair (MMR) genes. MMR genes commonly implicated include *MSH*-2 and *MLH*-1 and, more recently, *MSH*-6. Recent evidence suggests that immunohistochemistry is very sensitive and effective in detecting these defects in cutaneous tumors in MTS. In addition, the genetic instability of cutaneous and visceral tumors in MTS caused by the defects in MMR genes can also be detected, using polymerase chain reaction (PCR)-based techniques, for microsatellite instability (MSI). Given that some sebaceous neoplasms represent cutaneous markers of MTS, what should we as dermatopathologists be advocating? Should we be looking for absence/loss of MMRs in all sebaceous neoplasms? When should we recommend assaying for MSI? This review attempts to address all of these issues with a view to streamlining the work-up of a patient presenting for the first time with a sebaceous neoplasm and no prior personal or family history of internal malignancies.

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Ossama Abbas[1] and Meera Mahalingam[2]

[1]Department of Dermatology, American University of Beirut Medical Center, Beirut, Lebanon, and [2]Dermatopathology Section, Department of Dermatology, Boston University School of Medicine, Boston, MA, USA

Meera Mahalingam, MD, PhD, F.R.C.Path, Dermatopathology Section, Department of Dermatology, Boston University School of Medicine, 609 Albany Street, J-301, Boston, MA 02118, USA
Tel: 617 638 5574
Fax: 617 638 5575
e-mail: mmahalin@bu.edu

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Introduction

Independently reported by Muir in 1967 and Torre in 1968, Muir-Torre syndrome (MTS) is a rare autosomal dominant genodermatosis with a high degree of penetrance and variable expressivity.[1–3] It is characterized by the association of cutaneous lesions (sebaceous neoplasms or keratoacanthomas) and internal malignancies. Diagnosis is based on the presence of at least one sebaceous neoplasm and a visceral malignancy, or alternatively multiple keratoacanthomas associated with visceral malignancies and a family history of MTS.[1] Visceral malignancies most commonly observed in association with MTS include colorectal and genitourinary carcinomas, although other types of cancers, such as breast and upper gastrointestinal cancers, have also been uncommonly reported.[1] Nearly half of patients with MTS develop two or more visceral malignancies.[1] Of interest, both cutaneous and visceral neoplasms in patients with MTS have been shown to behave less aggressively compared to their sporadic counterparts.[1]

Sebaceous tumors include hyperplasia, adenoma, epithelioma, and carcinoma. Of these, the frequent occurrence of sebaceous hyperplasia in the general population, contrasting sharply with the purported rare incidence of MTS, softens the possibility of this representing a cutaneous marker of MTS.[1,4,5] Further in support of this, several studies have shown that the association of sebaceous hyperplasia with MTS varies from 0 to 10%, reiterating that it does not point to MTS with clinically expedient specificity.[1,4–8] Evidence of an increased incidence of the other three sebaceous neoplasms in patients with MTS comes from several studies (Table 1). Of the three, sebaceous adenoma is considered to be the most specific marker of MTS with a reported association ranging from 25 to 60%.[4,6,7,9] The association of sebaceous epithelioma and/or carcinoma with MTS is lower, although recent studies indicate that the association may not be as low as previously believed.[4,7,9] The incidence of sebaceous epithelioma in patients with MTS varies anywhere from 31 to 86%, whereas that of sebaceous carcinoma varies from 66 to 100%.[4,7,9] Other sebaceous neoplasms associated with MTS, and believed to be fairly specific, include cystic sebaceous tumors,[10] although a recent study has questioned this association based on the low frequency of mismatch repair (MMR) protein deficiencies in sebaceous neoplasms exhibiting cystic changes.[11] In addition to the histologic subtype, one study shows that sebaceous neoplasms occurring in extrafacial sites are more commonly associated with MTS.[8] The spatial relationship of sebaceous neoplasms and MTS varies with studies showing sebaceous neoplasms occurring before (22%), concurrent with (6%), or even after the diagnosis of a visceral malignancy (56%).[12,13] The range is also wide with one study indicating that sebaceous neoplasms may precede the visceral malignancy by 25 years and another indicating that they may occur after 37 years.[1,5]

Cutaneous manifestations of MTS other than sebaceous neoplasms include keratoacanthomas which occur in up to 20% of MTS patients either with, or without, a concurrent sebaceous neoplasm.[5] Hybrid lesions "sebokeratomas" or architecturally keratoacanthoma-like lesions, with histologic features of keratoacanthoma and sebaceous adenoma, are rare, but when present considered to be highly suggestive of MTS.[1,4,11]

A mismatch repair protein (MMR) is essential for the maintenance of genomic integrity by eliminating mismatches of single nucleotide bases caused by small insertions or deletions that occur during deoxyribonucleic acid (DNA) replication.[1,14] A somatic "second hit" mutation, complementing a germline mutation in one of the alleles of a MMR gene, causes a MMR defect, which in turn results in the accumulation of replication errors.[15] These MMR abnormalities lead to genetically unstable visceral and cutaneous tumors in patients with MTS.[1] Germline mutations in patients with MTS most commonly affect *MSH*−2 (>90%), followed by *MLH*−1 (<10%).[1] More recently, lack of expression of *MSH*-6 in sebaceous tumors of patients with MTS has been shown suggesting that a mutation in *MSH*-6 gene is not so uncommon.[16] Perhaps this is not unexpected given that studies on eukaryotes indicate that *MSH*-2 forms a heterodimer with *MSH*−6.[11,17,18] Thus, a mutation in one would understandably lead to the absence of the other. While this implies that "absence" of *MSH*-6 is a consequence of loss of *MSH*-2 and not inherently reflective of a germline mutation in *MSH*−6, Chhibber et al. have recently shown loss of *MSH*-6 alone in three patients with other clinical stigmata of MTS.[9]

Several studies have shown that the spectrum of internal malignancies observed in patients with MTS is similar to that observed in hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome, raising the possibility that MTS, or one of its subtypes, represents a phenotypic variant of HNPCC.[1,19,20] Further in support of this is the occurrence of MTS in individuals with a family history of HNPCC.[21] There is evidence to indicate that the germline mutations in both entities involve the same DNA MMR genes.[21–23] While these studies show that the overall incidence of an underlying MMR defect is similar in patients with MTS and HNPCC (69 versus 64%), the frequencies differ in terms of the specific MMR involved (Table 2).[20,22] For example, in one study, a germline mutation, identified in 9 of 13 patients with MTS (69%), involved *MSH*-2 in 89% and *MLH*-1 in 11%.[20] On the other hand, a study on 48 patients with HNPCC identified germline mutations in MMR genes in 64% of patients, of which 31% involved *MSH*-2 while 33% involved *MLH*−1.[22]

Table 1. Percentage of MTS among patients presenting with sebaceous neoplasms

	SA as marker of MTS	SE as marker of MTS	SC as marker of MTS
Popnikolov et al.[6]	(3 of 12) 25%	—	—
Kruse et al.[7]	(2 of 6) 33%	(5 of 16) 31%	(2 of 3) 66%
Chhibber et al.[9]	(9 of 15) 60%	(6 of 7) 86%	(5 of 5) 100%

MTS, Muir-Torre syndrome; SA, sebaceous adenoma; SE, sebaceous epithelioma; SC, sebaceous carcinoma.

Table 2. Comparison of the frequency of MMR gene mutations between MTS and HNPCC patients

MMR gene	MTS[20,24]	HNPCC16[22]
MLH-1	7[24] (2 of 27) to 11%[20] (1 of 9)	33%[22] (16 of 48)
MSH-2	89[20] (25 of 27) to 93%[24] (8 of 9)	31%[22] (15 of 48)
MSH-6	Few reports[24]	7.6%[25]
MLH-3	None yet	2.5%[25]
PMS-2	None yet	1.2%[25]

MMR, mismatch repair; MTS, Muir-Torre syndrome; HNPCC, hereditary nonpolyposis colorectal cancer.

In this review, we discuss the currently available methodologies available for MMR and/or microsatellite instability (MSI) assessment and the utility of each as an adjunct for a definitive diagnosis of MTS.

Immunohistochemical analyses

Immunohistochemistry (IHC) is based on the principle that antibodies bind to a specific antigen in biological tissues. The advent of monoclonal antibodies for use on formalin-fixed paraffin-embedded tissue to MMR proteins commonly implicated in MTS has greatly facilitated the use of this methodology as a histologic adjunct.[26–28] This technique, which is easy to perform and interpret, is considered to be highly sensitive and specific because the antibodies used are directed against the MMR enzymes.[1,25,29] Staining is nuclear and interpreted in light of staining of the internal control, i.e., normal "non-lesional" sebaceous glands in the tissue. Using this criterion, absence of MMR refers to complete absence of nuclear staining in the lesional tissue (Figs. 1–3).[1,25,29]

Using IHC, several studies document loss of one or more MMR proteins in sporadic sebaceous neoplasms including those associated with MTS.[1,11,15,21–23] Using this methodology in patients with MTS, absence of *MSH*-2 varies from 55 to 86% in sebaceous adenomas, is around 17% in sebaceous epithelioma, and varies from 31 to 100% in sebaceous carcinoma; absence of *MLH*-1 varies from 14 to 33% in sebaceous adenomas, is around 83% in sebaceous epitheliomas, and approximately 31% in sebaceous carcinomas; while absence of *MSH*-6 varies from 50 to 78% in sebaceous adenomas, is

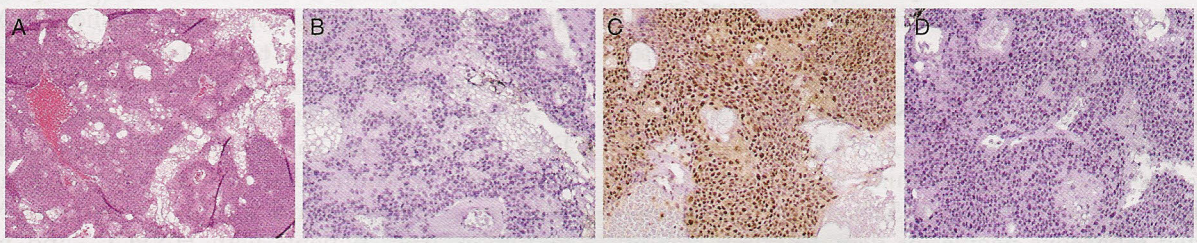

Fig. 1. Representative example of immunohistochemical staining demonstrating lack of expression of *MLH*-1 in a sebaceous neoplasm.

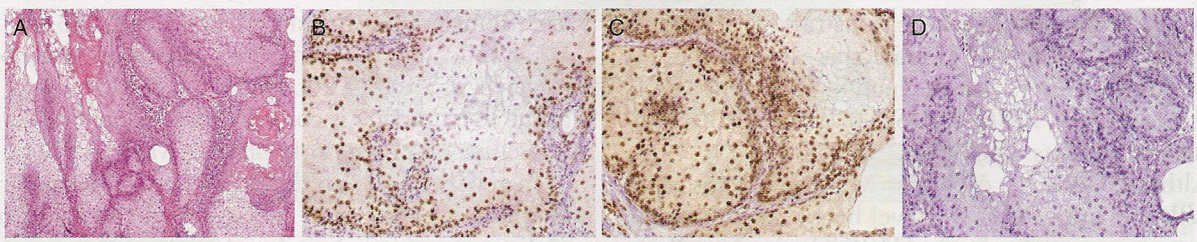

Fig. 2. Representative example of immunohistochemical staining demonstrating lack of expression of *MSH*-6 in a sebaceous neoplasm.

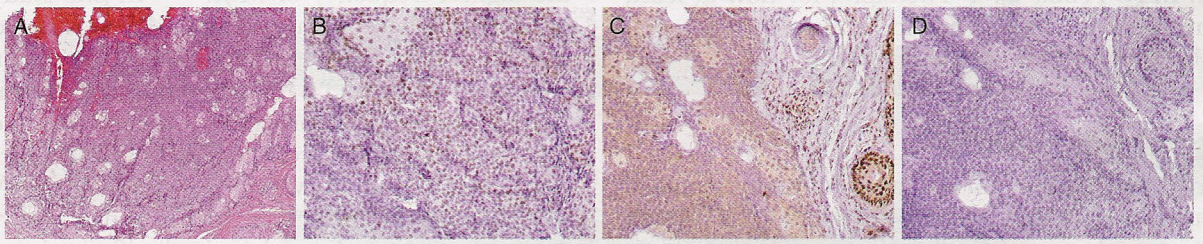

Fig. 3. Representative example of immunohistochemical staining demonstrating lack of expression of *MSH*-2 and *MSH*-6 in a sebaceous neoplasm.

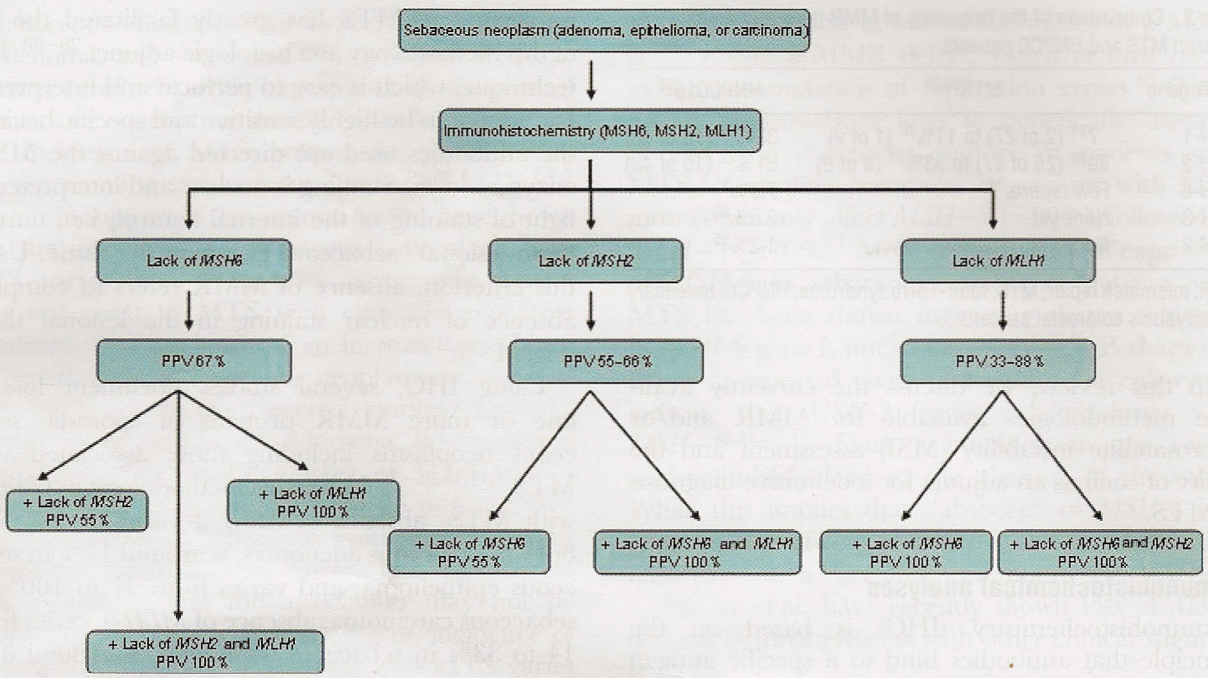

Fig. 4. Positive predictive values (PPVs) of MMR proteins (*MLH*-1, *MSH*-2, *MSH*-6) in MTS.

around 33% in sebaceous epitheliomas, and approximately 100% in sebaceous carcinoma.[6,8,9,26–28] In studies on unselected sebaceous neoplasms, the positive predicative value of lack of expression of each of the MMR proteins with MTS varies from 33 to 88% for *MLH*-1, 55 to 66% for *MSH*-2, and is around 67% for *MSH*-6.[6,9] Combining these markers, the positive predictive value is 55% for MTS in unselected sebaceous neoplasms demonstrating lack of both *MSH*-2 and *MSH*-6, is 100% for neoplasms demonstrating lack of both *MLH*-1 and *MSH*-6, and also 100% for neoplasms demonstrating lack of all three MMRs (Fig. 4).[6] Despite these varied results, these studies underscore the high incidence of MMR defects (*MLH*-1, *MSH*-2, *MSH*-6) in sebaceous neoplasms of patients with MTS.

Although defects of other MMR proteins such as *PMS*-2 and *MLH*-3 have been, albeit rarely, detected in patients with HNPCC, to date there are no reports of *PMS*-2 or *MLH*-3 defects in patients with MTS (Table 2).[25] Therefore, for now at least, there appears to be no evidence to make them integral to the initial MMR screening panel.

Microsatellite instability

Microsatellites are normal and common repeated sequences of DNA of 1–6 base pairs in length that are characteristically of constant length in the same individual but can vary from person to person.[1,25,30] Mutations in DNA repair genes result in the accumulation of errors in microsatellite sequences so that they become either longer or shorter. MSI refers to the appearance of abnormally long or short microsatellites in an individual's DNA due to defects in the normal DNA repair process.[1,25,30] Five markers, also called the Bethesda markers, have been recommended by the National Cancer Institute as the standard screen for assessing MSI in tumors from patients with HNPCC, and most studies looking for MSI in tumors from patients with MTS use these markers too. Of the five, three are dinucleotide repeats (D2S123, D5S346, and D17S250) and the other two are mononucleotide tracts (BAT25, BAT26). Detection of MSI in any two of the five markers is considered a positive result and indicative of a high probability of MSI.[1,26,25,31]

In general, compared to other benign or malignant neoplasms of the skin including melanocytic nevi, malignant melanoma, basal cell carcinoma, and squamous cell carcinoma, sebaceous neoplasms show the highest frequency of MSI.[32,33] In one study of unselected sebaceous neoplasms, MSI was detected in 60% of adenomas, epitheliomas, and carcinomas compared to only 3% of sebaceous hyperplasias.[7] Several studies have provided evidence to indicate that lesional tissue from cutaneous and visceral neoplasms in patients with MTS often exhibit MSI secondary to the defects in MMR genes.[8,10,20,26,28] An awareness of these data is significant because it dictates the necessity of additional workup in a patient with the diagnosis of a sebaceous neoplasm,

but no relevant clinical or family history. Overall, the prevalence of MSI in patients with MTS is similar in sebaceous (60–100%) and visceral (50–100%) neoplasms.[8,10,12,20,26,28,34]

It is important to bear in mind that both sebaceous and/or visceral neoplasms associated with MTS have been known to be microsatellite stable (MSS) and also that sporadic sebaceous neoplasms have been shown to be MSI.[8,9,28] This may be a reflection of the battery of probes used in MSI analyses (dinulceotide versus a mononucleotide panel) or a consequence of the MMR protein that is mutated. For example, there is some evidence to indicate that germline mutations associated with *MSH*-6 are of a weaker phenotype.[1,9,16,18,35]

Diagnostic approach

Increasing evidence supports the use of IHC as the initial screening test. These include data reinforcing the sensitivity and ability of IHC to detect the involved MMR protein, reproducibility of results using this methodology, and a good correlation between results from IHC and MSI analyses. Additional minor, yet practically relevant, factors relate to ease of the methodology which translates to a rapid turn-round-time (TRT).[10,11,27] Studies in MTS patients indicate that lack of expression of either *MLH*-1 or *MSH*-2 is associated with MSI in 100% of cases while maintenance of expression of both is predictive of microsatellite stability in 93% of the cases.[10,11,27] On a cautionary note, however, maintenance of expression of the MMR proteins does not exclude the possibility of an underlying DNA repair defect. In such cases, and if clinical suspicion of MTS persists, it may be prudent to do MSI analyses as a "second line of action".

In contrast to IHC, MSI analysis is complex, expensive, and cumbersome to perform. As a consequence, the TRT for results using this technique is typically anywhere from 7 to 10 days. Furthermore, the presence of MSI is not reflective of the specific gene defect present.

When immunohistochemical staining and MSI analyses are indicative of a MMR mutation, germline mutation analyses of *MLH*-1, *MSH*-2, and *MSH*-6 may be done to confirm the mutation.[33] A germline mutation in *MSH*-2 was detected in around 61% in one study on patients with MTS while, in another, a germline mutation in *MLH*-1 was detected in less than 10% of the cases.[21,24] The absence of a detectable germline mutation suggests an involvement of other MMR proteins, perhaps by pathways that include somatic mutations or hypermethylation of the promoter region.[1,24] Confirmation of a hereditary MMR defect uncovers patients with an inherited cancer predisposition which will then require the institution of preventive cancer screening programs based on guidelines issued by the international collaborative group on hereditary nonpolyposis colorectal cancer (ICG-HNPCC).[36]

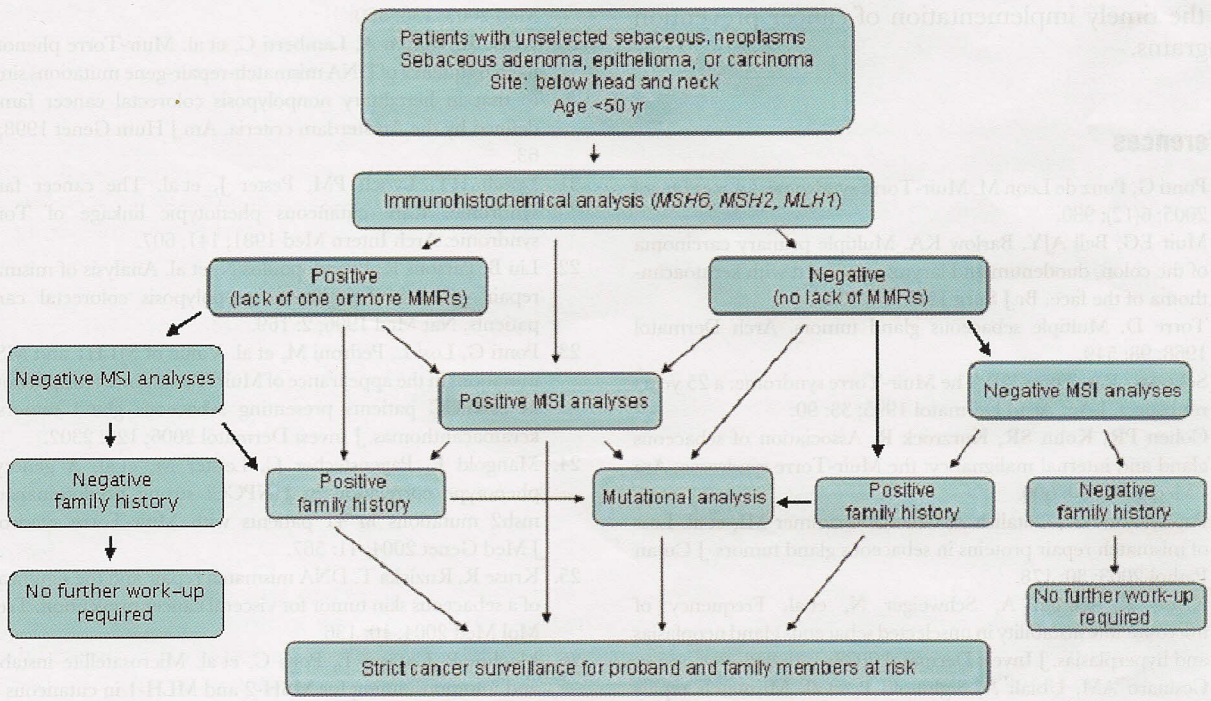

Fig. 5. Diagnostic algorithm for a patient presenting with an unselected sebaceous neoplasm.

Based on our recent experience, a judicious diagnostic approach is illustrated (Fig. 5). Briefly, the diagnosis of a sebaceous neoplasm located outside the head and neck area in a young patient (<50 years of age) mandates additional work-up. As a first line, this refers to immunohistochemical analyses to ascertain expression of *MSH*-2, *MLH*-1, and *MSH*-6. Lack of expression of any one of these proteins warrants MSI analyses. If MSI is detected, this indicates that the proband and his family members will require strict cancer surveillance. If MSI is not detected, a positive family history warrants germline mutation analysis. If this is positive, the proband and his family members will require cancer surveillance. If MSI is not detected and there is a negative family history, nothing further needs to be done. If MMR proteins are intact, and the index of suspicion for MTS is still high, then MSI analysis can be done as a second-line screening tool. If MSI is detected, then this can be followed by germline mutation analysis. However, if MSI analysis is negative despite a high index of suspicion of MTS, then we can do germline mutation analysis or try to identify those patients with MTS based on family history of visceral cancers.

Conclusion

The early identification of patients with MTS is of paramount significance for the dermatologist and the dermatopathologist because of the increased risk of visceral malignancies. Recognition of "high-risk" patients or those with a propensity for will allow for the timely implementation of cancer prevention programs.

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