Sebaceous lesions and their associated syndromes: Part II

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Sebaceous lesions are associated with two syndromes with widespread multisystem disorders and tumors. Linear sebaceous nevus syndrome has been traditionally known as the triad of sebaceus nevus of Jadassohn, seizures, and mental retardation. This syndrome encompasses a much broader spectrum of multisystem disorders, which is explored below. Muir—Torre syndrome is described as the presence of sebaceous tumors or keratoacanthomas with an underlying visceral malignancy. It is caused by mutations in DNA mismatch repair genes. We discuss its relationship with Lynch syndrome and suggest a comprehensive algorithm on how to screen patients with sebaceous neoplasms for Muire—Torre syndrome. We also provide suggested intensive cancer screening guidelines based on recommendations for patients with Lynch syndrome that may also be of value for patients with Muir—Torre syndrome. (J Am Acad Dermatol 2009;61:563-78.)

Learning objectives: After completing this learning activity, participants should be able to discuss the characteristics of Lynch and Muir—Torre syndromes, both of which are associated with sebaceous lesions, evaluate a patient who might have epidermal nevus syndrome, formulate an approach to identify patients at risk for Muir—Torre syndrome who have a newly diagnosed sebaceous neoplasm, and discuss screening recommendations for patients who are identified as having Muir—Torre syndrome.

Key words: DNA mismatch repair; epidermal nevus syndrome; linear nevus sebaceus syndrome; Lynch syndrome; microsatellite instability; MLH-1; MSH-2; MSH-6; Muir—Torre syndrome; nevus sebaceus of Jadassohn; PMS-2.

Sebaceous lesions are associated with two systemic disorders: linear nevus sebaceus syndrome (LNSS) and Muir—Torre syndrome (MTS). LNSS has been traditionally defined as the triad of linear nevus sebaceus, seizures, and mental retardation. Many reports have shown that this syndrome actually encompasses a broad spectrum of multisystem disorders. MTS is an autosomal dominant tumor syndrome resulting from defects in DNA mismatch repair (MMR) genes. Affected patients may develop multiple tumors of the digestive and urogenital tracts. Testing for this syndrome has become more sophisticated as our understanding of the underlying pathophysiology has expanded.

Abbreviations used:

ENS:	epidermal nevus syndrome
HNCCS:	hereditary nonpolyposis coli cancer syndrome
HPV:	human papillomavirus
IHC:	immunohistochemistry
KA:	keratoacanthoma
LNSS:	linear nevus sebaceus syndrome
MMR:	mismatch repair
MSI:	microsatellite instability
MTS:	Muir—Torre syndrome
NSJ:	nevus sebaceus of Jadassohn

The management of both these syndromes can be a complex and daunting task. There is a large amount of literature available on these two topics, though much of it—with regard to MTS—has been published outside of the field of dermatology. Approaches to both of these syndromes are explored in detail below.

LINEAR NEVUS SEBACEUS SYNDROME

Key points

- **A subset of the epidermal nevus syndrome**
- **Associated with a broad spectrum of neurologic, ophthalmic, skeletal, cardiovascular, and urologic defects**

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- **Workup for patients who may have this syndrome should include: electroencephalogram, cerebral computed tomographic scan or magnetic resonance imaging, radiologic analysis of the entire skeleton, analysis of liver and renal function, and calcium and phosphate levels in serum and urine**

CAPSULE SUMMARY

- Sebaceous lesions are associated with two syndromes: linear nevus sebaceus syndrome and Muir—Torre syndrome.
- Linear nevus sebaceus syndrome is associated with a wide constellation of abnormalities beyond the initial triad of linear sebaceous nevus, mental retardation, and seizures.
- Muir—Torre syndrome is thought to be a phenotypic subset of Lynch syndrome. It is caused by mutations in DNA mismatch repair genes.
- Testing is available for patients at risk for Muir-Torre syndrome.

As discussed by Warnke et al,[1] Schimmelpenning[2] reported two cases of a linear nevus associated with epilepsy and mental retardation in 1957. Since that time, the number of reports and findings has expanded to include a broad spectrum of nevi, including linear nevus sebaceus of Jadassohn (NSJ), that are associated with neurologic, ophthalmic, skeletal, cardiovascular, and urologic defects.[1,3-5] These syndromes have been reported under a variety of names, including LNSS, Schimmelpenning- Feufstein-Mims syndrome, and Solomon syndrome.[1,3,4]

Solomon and Esterly[4] reviewed an extensive series of different types of nevi associated with other internal anomalies and grouped them under the heading of epidermal nevus syndrome (ENS). LNSS, nevus comedonicus syndrome, Becker nevus syndrome, phakomatosis pigmentokeratotica, Proteus syndrome, and congenital hemidysplasia with ichthyosiform nevus and limb defects syndrome are all considered subsets of ENS.[3] Presumably, each syndrome has a different underlying genetic defect.

The estimated incidence of epidermal nevi is about 1 to 3 per 1000 live births, with no sexual predilection.[4,6,7] The incidence of extracutaneous abnormalities associated with epidermal nevi is unknown.[8]

LNSS appears to be largely sporadic.[3] However, a report detailing a possible inherited syndrome was published by Bianchine.[9] It is unclear whether this report represents a case of true inherited LNSS.

LNSS is thought to result from genetic mosaicism from a defect in a lethal autosomal dominant gene.[10] Some suggest that the neurologic defects are the result of defective neuronal migration and organization.[11] A recent study has found evidence of the genomic integration of human papillomavirus (HPV) in lesional skin taken from NSJ patients.[12] Whether the integration of viral DNA into fetal embryonic cells also play a role in LNSS is currently unknown.

Epidermal nevi are not the only cutaneous finding in patients with ENS. Other findings are present in up to 30% of patients.[3,13,14] These include large hypopigmented patches, hemangiomas, lesions resembling acanthosis nigricans, café au lait spots, and multiple early onset nevi.[13]

Skeletal abnormalities are present in the majority of affected patients with ENS.[15] These include the following abnormalities: dental irregularities, clefting of the secondary palate, congenital dislocation of the hip, rib notching, malformed clavicle, benign cortical defect of the humerus, medial bowing of the distal ulna, ameloblastoma of the mandible, megacranium, deformed temporal bone, sella turcica abnormalities, hyperostosis of frontal skull, fibrous dysplasia of the cranium, spreading of the sutures, kyphoscoliosis, asymmetry of the sphenoid wings, slanting of auricles, highly arched palate, hypoplastic dentition, lytic defects of ribs, clavicular malformation, scoliosis, hypoplastic iliac wings, pes valgus deformity, osteomalacia, unilateral hypoplasia of any bony structure, and different forms of vitamin D—resistant rickets and hypophosphatemia.[2,5-25]

Ocular abnormalities have been reported in 59% of patients with ENS.[15] Lesions are often bilateral. Reported eye findings include: strabismus, ipsilateral hypoplasia of the optic radiation with hemimegalencephaly, colobomata, cataracts (usually unilateral), corneal vascularization, ocular hemangiomas, downward slanting of the palpebral fissures, ptosis, ectropion, hamartomas on the eyelid, epibulbar tumors, corneal vascularization, choristomas, scleral fibromas, nonspecific cortical cataracts, peripapillary choroidal atrophy, exudative retinal detachment, generalized retinal degeneration, unilateral proptosis, microphthalmos, and cortical blindness.[3,9,20,22,25-44]

LNSS is one of the most common subtypes of ENS.[3] However, very few nevi are exclusively of one type.[4] Different parts of the same lesion may contain a variety of different tissue components.[4]

Van de Warrenburg et al[15] reviewed the literature on LNSS and found that 66% of affected patients had neurologic findings.[15] Reported findings have

included brain dysgenesis, cortical dysplasia, glial hamartomas, low-grade gliomas, hemimegalencephaly (usually ipsilateral to the nevus), and enlargement of the lateral ventricles.[15,43,45] Epilepsy was present in up to 67% of patients.[15] In their review of 12 LNSS patients, Lovejoy and Boyle[24] found that seizures usually began within the first year of life. Patients with epidermal nevi on the head and face have a higher incidence of central nervous system abnormalities than those with nevi elsewhere.[4] Normal intelligence is rare in this syndrome and is strongly associated with a normal computed tomographic (CT) scan.[11] Levin et al[11] performed CT scans on 11 LNSS patients and found that the only two patients with normal CT scans of the head were also the only children with normal neurologic examinations and normal levels of intelligence.[11]

Other organ system disorders have also been described. These include patent ductus arteriosus, patent foramen ovale, ventricular septal defect, coarctation of the aorta, hypoplasia of the aorta, atrial flutter/fibrillation, atrial premature systoles, horseshoe kidney, duplicated urinary collection system, undescended testes, enlarged clitoris, hepatosplenomegaly, and failure to thrive.[17,20,26,32,36-38,42,43]

Because of the high incidence of findings other than the classic triad of linear NSJ, seizures, and mental retardation, the criteria to define this syndrome has been expanded.[15] In cases where LNSS is suspected, it is wise to search for other disorders aside from neurologic disorders.[15] There does not appear to be a minimum size described that should alert the clinician to the possibility of the syndrome. However, in the series of 12 patients with epidermal nevi reviewed by Solomon et al,[42] the only two that were free of other associated defects had nevi that were <10 cm in length. A review of several articles where photographs or details of the nevus location have been available indicates that most nevi associated with other systemic disorders encompass more than one dermatome (unpublished observation). Rogers et al[13] conducted a study of 119 unselected patients with epidermal nevi and found that 33% had one or more abnormalities in other organ systems. Neurologic symptoms may not manifest for several months after birth.[5] In cases where the syndrome is being considered, the following preliminary laboratory studies have been recommended: electroencephalogram, cerebral CT scan or magnetic resonance imaging, radiologic analysis of the entire skeleton, analysis of liver and renal function, and calcium and phosphate levels in serum and urine.[15,18] These should supplement a thorough physical examination that includes an ophthalmology evaluation, neurologic examination, limb length measurement, and cutaneous examination.[4]

Lovejoy et al,[24] in their analysis of 13 cases, concluded that seizures, when present, occur by the end of the first year of life.[24] Mental impairment may range from none to severe. Lumbar punctures are usually normal. The cutaneous lesions were all present at birth, and were often midline and linear. They found no racial predilection.[24]

Also of concern are reports of systemic malignancies associated with ENS.[4,17,24,42,46-49] These may arise at an early age, and it is suggested that as patients reach puberty a systemic search should be undertaken.[4] Reported tumors have included: Wilm's tumor, nephroblastoma, bilateral salivary gland adenocarcinoma, carcinoma of the stomach and esophagus, astrocytoma, ameloblastoma of the mandible, mammary adenocarcinoma, ameloblastic fibroodontoma, and metastatic squamous cell carcinoma.[4,17,24,42,46-49] Some authors also advocate evaluation for the presence of Wilm's tumor while the child is still an infant.[4]

MUIR–TORRE SYNDROME AND LYNCH SYNDROME

Key points

- **Muir–Torre syndrome (MTS) is defined as the concurrent or sequential development of a sebaceous neoplasm and an internal malignancy or multiple keratoacanthomas, an internal malignancy, and a family history of MTS**
- **MTS is most likely a subset of the hereditary nonpolyposis coli cancer syndrome (Lynch syndrome)**
- **Cause is a mutation in one of the mismatch repair genes: MLH1, MSH2, or MSH6**

MTS was identified independently by both Muir and Torre in 1967.[50-52] These physicians described a syndrome of multiple sebaceous neoplasms and keratoacanthomas (KAs) associated with internal malignancy.[50,51] Criteria to define the syndrome have been proposed as concurrent or sequential diagnosis of a sebaceous neoplasm (adenoma, epithelioma, seboacanthoma, or carcinoma), and a minimum of one internal malignancy or a family history of MTS with a personal history of multiple KAs and visceral malignancies (Table I).[50-59] Sebaceous neoplasms may occur without internal malignancy, but are rare, and MTS should be considered when they are found.[52] MTS is thought to be a phenotypic variant of Lynch syndrome.[60-63] Supporting this supposition, a recent study found that 9.2% of patients who have Lynch syndrome also have MTS-related skin lesions.[63]

Table I. Suggested diagnostic criteria for Muir–Torre syndrome*

Group A
Sebaceous adenoma
Sebaceous epithelioma
Sebaceous carcinoma
Keratoacanthoma with sebaceous differentiation
Group B
Visceral malignancy
Group C
Multiple keratoacanthomas
Multiple visceral malignancies
Family history of Muir–Torre syndrome

In order to achieve a diagnosis of Muir–Torre syndrome, the patient must fulfill one criterion each from groups A and B or fulfill all three criteria from group C.
*Proposed by Schwartz and Torre.[52]

Lynch syndrome is also known by the names of hereditary nonpolyposis coli cancer syndrome (HNCCS) and cancer family syndrome.[64] This entity is characterized by an increased incidence of cancer in the proximal colon without extensive polyposis.[53,65-69] It is the most common heritable colorectal cancer syndrome.[70] Other tumors are known to be a part of this syndrome,[53,65-69] including cancers of the endometrium, ovaries, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, and skin.[53,65-69] The syndrome is inherited in an autosomal dominant manner with an estimated penetrance of 85% by 80 years of age.[71,72]

Some authors have stratified HNCCS into three subgroups: Lynch I, Lynch II, and Lynch III.[64,73] The Lynch I group is comprised of patients with familial colorectal tumors, while Lynch II consists of patients with familial extracolonic tumors.[64] Lynch III has been proposed for patients with familial gliomas, hematologic malignancies, and gastrointestinal cancers.[73]

Regardless of whether one groups these disorders all under the single term of Lynch syndrome or prefers further subclassification, they are caused by mutations in DNA MMR genes.[53,65-69] Thus far, four genes (MSH2, MLH1, PMS2, and MSH6) have been identified as causes of Lynch syndrome.[74-77] The role of other MMR genes, such as PMS1, MSH3, MLH3, and EX01, is questionable.[77-81] MMR genes are responsible for maintaining accurate DNA replication.[65] Defects in these genes allow cells to accumulate errors at 30 to 1000 times that of normal.[65] Tumors with these mutations typically show changes in the lengths of chromosomal microsatellites as they replicate.[65,67,74] These changes in microsatellite length are called microsatellite instability (MSI) and are present in 90% of patients with Lynch syndrome.[65,67,74]

The Muir–Torre variant of Lynch syndrome is associated with sebaceous neoplasms or KAs and a high rate of MSI.[82] The sebaceous neoplasms associated with MTS were discussed in part I of this review ("Sebaceous Lesions," Table I). Before 2007, MTS had only been known to be caused by MutL homolog (MLH)-1 (8% of cases) and MutS homolog (MSH)-2 (92% of cases).[83] Recently, cases of MTS caused by a mutation in MutS homolog (MSH)-6 have also been reported.[84-88] As with Lynch syndrome, defects in the function of these proteins result in MSI.

MUIR–TORRE SYNDROME–ASSOCIATED MALIGNANCIES

Key points

- **Underlying visceral malignancies are present in a high number of patients with sebaceous neoplasms**
- **The most common Muir–Torre syndrome–associated malignancies are colorectal carcinoma (47%), genitourinary tumors (21%), breast carcinomas (12%), and hematologic disorders (9%)**

While a majority of sebaceous neoplasms are unassociated with internal malignancy, the proportion of those who are affected with MTS remains significant (42% in one study).[89] At least two studies have looked at the temporal relationship between the development of cutaneous sebaceous neoplasms and internal malignancies.[56,89] Twenty-two percent to 32% of patients with MTS present with a sebaceous neoplasm before the advent of an internal one.[56,89] The mean age for presentation with a sebaceous neoplasm in one study was 63 years (range, 37-85 years).[89] Nine percent to 12% percent are diagnosed simultaneously with a cutaneous and internal malignancy, and 56% to 59% of affected patients with MTS are diagnosed with an internal malignancy before a cutaneous sebaceous one.[56,89] Therefore, the diagnosis of a cutaneous sebaceous neoplasm presents the opportunity for early diagnosis of a tumor of the urogenital or digestive tracts.

The most common visceral malignancies in MTS in one study were colorectal carcinoma (47%), genitourinary tumors (21%), breast carcinomas (12%), and hematologic disorders (9%; Table II).[56] This is in contrast to patients with Lynch syndrome, for whom the most common malignancies after colorectal carcinoma are cancer of the endometrium, ureter, renal pelvis, and small bowel.[74,90-92] Other types of internal malignancies that have been found include those of the parotid gland, larynx, biliary, paraganglioma, and chondrosarcoma.[93,94] In one study,

Table II. Visceral malignancies associated with Muir–Torre syndrome*

Biliary
Bladder
Breast
Cervix
Chondrosarcoma
Chronic lymphocytic leukemia
Colorectal
Duodenum
Gastric
Hodgkin lymphoma
Hypernephroma
Ileum jejunum
Laryngeal inner ear
Lip
Lung
Melanoma
Non-Hodgkin lymphoma
Ovary
Pancreas
Parotid
Polycythemia vera
Prostate
Renal pelvis
Testicle
Tongue
Ureter
Uterus
Vulva

*As outlined by Cohen et al.[56]

gastrointestinal cancers developed in 61% of those with MTS and tended to be proximal to the splenic flexure.[56] Ominously, a review of 147 patients with MTS revealed that 47% had two or more visceral malignancies.[95]

Although the internal malignancies associated with MTS generally metastasize more often, median survival appears to be significantly longer than for those not associated with MTS.[52,56,96,97]

Much is being discovered about the causes of and risks associated with MTS, but the health risks associated with the presentation of sebaceous neoplasms are only just beginning to be understood. Several reviews have looked at the risk of internal malignancies associated with sebaceous neoplasms.[88,98] Jakobiec[98] and Rulon and Helwig[99] each found a 5% risk of visceral malignancy with the presentation of a single sebaceous neoplasm. In another review of patients with sebaceous skin lesions and KAs, 36 patients were found with sebaceous neoplasms, five (14%) of whom had visceral malignancies.[88] Eighty-four had KAs, of which two (2.4%) also had visceral malignancies.[88] While the majority of visceral tumors were adenocarcinomas of the colon, there were individuals who developed adenocarcinomas of the kidney, renal pelvis, stomach, and thyroid.[88]

MICROSATELLITE INSTABILITY AND IMMUNOHISTOCHEMISTRY TESTING

Key points

- **Microsatellite instability and immunohistochemistry testing are both useful for screening patients for Muir–Torre syndrome**
- **Preliminary evidence suggests that using more antibodies may increase the sensitivity of immunohistochemistry**

Testing of sebaceous lesions for MSI is one method of evaluating a patient for MTS. Microsatellites are repeated sequences of DNA found in everyone's genome, and they are normal.[100] They vary in length from person to person, but are typically the same length within individuals.[100] These repeated sequences of DNA are susceptible to mutations. When mutations are not repaired, this can cause their lengths to become abnormally short or long.[100] This variation in length is termed MSI and is a marker for defects in DNA MMR.[100] MSI testing can generally be performed on formalin-fixed tissue.[100] The lengths of certain segments of DNA in tumor tissue are compared to the same segments in normal adjacent tissue or peripheral blood.[100] There are two accepted MSI phenotypes: MSI-H and MSI-L.[101] MSI-H shows a high degree of MSI, and MSI-L shows a low degree of MSI. The amount of MSI depends on the genes affected. Defects in hMSH2 or hMLH1 result in a MSI-H phenotype, whereas defects in hMSH-6 result in the MSI-L phenotype.[102-106] The National Cancer Institute defines MSI-H as when two or more of five standard satellite markers display instability, and MSI-L as when one of five standard satellite markers displays instability.[104] If no MSI is detected, it is termed microsatellite stable.[104] MSI testing is only available in specialized laboratories.

MSI is relatively common in sebaceous neoplasms.[104] One study of unselected sebaceous neoplasms (adenomas, epitheliomas, and carcinomas) showed that 15 of 25 (60%) had MSI compared to only one of 32 (3%) of sebaceous hyperplasias. Nine of the 15 (60%) were subsequently found to have MTS.[107] Studies have reported MSI prevalence in patients with MTS that range from 25% to 100%.[62,108,109] It should also be noted that up to 15% of sporadic colorectal carcinomas show MSI as a result of MLH1 promoter hypermethylation. Hypermethylation results in the loss of expression and subsequently function of the affected gene.[106]

The incidence of hypermethylation of MLH1 in sebaceous neoplasms has not been studied.

Recently, immunohistochemical staining for MLH1, MSH2, and MSH6 has become more widely performed. The loss of expression of these proteins is an indicator of a potential defect in germline DNA MMR. In one recent study, 86% (32/37) of patients with a clinical diagnosis of MTS had MSH2 defects, as shown by the lack of staining with the MSH2 antibody during immunohistochemistry (IHC).[84] Four patients (11%) were found to have MLH1 defects, and a single patient had an MSH6 defect.[84] Another study of colorectal carcinomas and visceral tumors associated with Lynch syndrome (a total of 201 cancers) found that staining for MLH1 or MSH2 had a sensitivity of 92.7% and a specificity of 99.3% for identifying defects in the MMR system.[110] Still, some authors believe that the interpretation of IHC for MMR proteins may be subjective.[111] A study performed by Overbeek et al[111] to address this concern concluded that when performed by experienced pathologists, IHC is a valid tool to identify patients who are at risk for Lynch syndrome.[111]

Given the high percentage of patients with sebaceous neoplasms who have underlying visceral malignancies, testing of all MTS-related cutaneous tumors is advocated by many authors, even if the patient has no personal or family history of MTS.[112,113] Although the risk of MTS in patients with KAs is low, testing of patients with multiple KAs who have a concerning family history also appears reasonable.

The number of MMR proteins to test for is not yet agreed upon. Certainly, both MLH1 and MSH2 should be performed at a minimum, because most patients with the syndrome will have loss of expression of one of these genes.[114] MSH6 mutation was, until recently, thought to be a rare event in MTS.[84] However, Chhibber et al[85] studied the loss of expression of MLH1, MSH2, and MSH6 in 41 unselected sebaceous neoplasms.[85] Of the 10 patients who had a clinical history suggestive of MTS, three had defects in only MSH6, and five had defects in both MSH2 and MSH6.[85]

Other studies have found high agreement between the expression of MSH2 and MSH6. When MSH2 is deficient, MSH6 often is, too.[115] This is not surprising because the protein products of MSH2 and MSH6 form a heterodimer MMR recognition factor. Previous studies have shown that MSH6 is unstable without MSH2 and is quickly degraded.[116-118] The opposite is not true. MSH2 expression may appear normal in the face of MSH6 mutations.[119] It should also be noted that MLH1 forms a heterodimer with PMS2.[120] Similar to MSH2 and MSH6, PMS2 is unstable without MLH1.[120] It is thought that mutations in MSH6 and PMS2 can be partially compensated by other MMR proteins, such as MSH3, MLH3, and PMS1, which would allow stable but dysfunctional complexes of MLH1 or MSH2 to escape degradation.[119]

In patients with Lynch syndrome, defects in MSH6 have been found to lead to late-onset colorectal carcinomas that do not meet the classic clinical criteria for the syndrome.[102] It is not known whether a similar relationship exists in patients with MTS. Because the cost of performing IHC is relatively low, we agree with the recommendation by Chhibber et al[85] that MSH6 should be part of the IHC panel used to evaluate all sebaceous neoplasms for the possibility of MTS.[85] Even though no PMS2 mutations have been found in MTS yet, staining with this antibody as a way to help detect missense MLH1 mutations can also be considered. As mentioned previously, PMS2 is unstable without a functional MLH1 protein. Therefore, if there is a mutation in MLH1, then PMS2 may not be detectable using IHC. IHC for PMS2 is helpful to detect MLH1 missense mutations that would allow expression of an antigenic but nonfunctional protein.[120]

Performance of either MSI or IHC as an initial way to evaluate sebaceous neoplasms is reasonable, because there is a very high agreement between the two in detecting DNA MMR defects.[121,122] Both MSI and IHC have advantages and tradeoffs. IHC is widely available, fast, inexpensive, and may help direct mutation analysis in those suggested to benefit from germline testing.[123] However, IHC cannot differentiate between loss of MLH1 expression caused by a germline mutation versus somatic hypermethylation.[78] Also, some germline missense mutations may be erroneously interpreted as normal by IHC, because they may result in an antigenically intact but nonfunctional protein.[78,124,125]

The advantage of MSI is that some studies have shown it to be somewhat more sensitive at detecting patients with germline MMR defects than IHC.[121,122,126-132] Vasen et al[123] found in their review of prospective studies looking at the sensitivity of MSI versus IHC that MSI was indeed more sensitive than IHC (98% vs 94%, respectively). However, most studies only used two antibodies (MLH1 and MSH2).[123] Two studies that used four antibodies (MLH1, MSH2, MSH6, and PMS2) showed equal or greater sensitivity to MSI, but these included a relatively small number of patients.[121,125,127] Studies concerning MSH6 mutations have revealed that between 5% and 7% of all patients with Lynch syndrome have germline mutations in this gene;

additional staining with more antibodies is likely to increase sensitivity.[124,133]

If a MSI-H or MSI-L phenotype is detected, many authors suggest that it should be followed by IHC, because IHC may help guide germline analysis.[121,122,126-132] Still other authors advocate using both MSI and IHC to screen tumors in patients with a concerning family history.[78] Spanish investigators studied 1222 patients with colorectal cancers and found that strategies using either MSI or IHC resulted in similar specificity, sensitivity, and positive predictive values at identifying patients with germline MMR mutations.[122]

SIGNIFICANCE OF HYPERMETHYLATION OF MLH1 AND BRAF-600E MUTATIONS

Key points

- **Hypermethylation of the MLH1 promoter or mutations in BRAF-600E suggest somatic rather than germline mutations**
- **Testing for MLH1 promoter methylation and BRAF-600E should be considered in all patients with MLH1 expression defects detected by immunohistochemistry**

For patients with defects in MLH1 as detected by IHC, analysis of methylation of the promoter region of MLH1 should be considered before germline testing. Hypermethylation of this region can lead to a loss of MLH1 function. This is an indication that the lack of MLH1 expression maybe the result of somatic rather than germline mutation.[121,134] No studies have been performed with regard to MTS and hypermethylation, but it is reasonable to expect similar results given that Lynch syndrome and MTS share the same genetic cause.

Some tumors, such as MSI-positive endometrial carcinomas, have very high rates of somatic inactivation as a result of hypermethylation (77% in one study).[135] Also, BRAF-600E mutation analysis may be helpful in excluding patients from germline analysis. Mutations in this gene are highly associated with somatic mutations of MLH1.[78,136-139] BRAF is a gene from the Raf family of Ras-regulated kinases. BRAF mutations have been reported in a variety of sporadic tumors, such as melanomas, colorectal cancers, ovarian tumors, and Barrett adenocarcinoma.[78,136,140] Some authors suggest that larger studies need to be performed on the use of BRAF clinically despite the fact that it is already commercially available.[78] Both tests are performed on tissue extracted from the patient's tumor.

Previous studies have shown that MSH2 and MSH6 promoters are for the most part not prone to hypermethylation.[141,142] Therefore, no analysis of these genes for hypermethylation is thought to be necessary.

CLINICAL CRITERIA FOR LYNCH SYNDROME AND GERMLINE TESTING

Key points

- **The Amsterdam II and revised Bethesda guidelines have been suggested as a basis for the clinical diagnosis of hereditary nonpolyposis coli cancer (Lynch) syndrome and for identifying tumors for microsatellite analysis, respectively**
- **The revised Bethesda criteria are more sensitive than the Amsterdam II criteria at detecting germline mismatch repair mutations, but have a lower positive predictive value**
- **Patients who have uninformative germline testing are not excluded from having Muir—Torre syndrome because the test is not 100% sensitive**

Germline testing, which is usually performed on peripheral blood, is very expensive, and only 5% to 10% of patients with colorectal carcinomas are thought to be affected by Lynch syndrome. The Amsterdam II and revised Bethesda guidelines have been suggested as a basis for the clinical diagnosis of Lynch syndrome and for identifying tumors for microsatellite analysis, respectively (Tables III and IV).[123,143] Several studies have been performed looking at the sensitivity of the Bethesda and Amsterdam criteria at identifying patients with MMR defects. The Amsterdam criteria have been reported to achieve a sensitivity of about 40% in identifying these patients, and the Bethesda guidelines about 90%.[121-123,131,132,144,145] The increase in sensitivity of the revised Bethesda guidelines over that of the Amsterdam II criteria are related to the less restrictive nature of the Bethesda guidelines. However, the tradeoff for the increased sensitivity is a lower positive predictive value of finding a germline defect (10%-20% for the revised Bethesda guidelines vs 50% for the Amsterdam II criteria).[146,147]

A careful family history is required for both the Amsterdam II and revised Bethesda guidelines. Given the similar underlying genetic defects of both MTS and Lynch syndrome, we think using the criteria for either of these systems, in addition to the MTS inclusion criteria to identify individuals and family members for germline testing and genetic counseling, is reasonable. Any patients meeting these inclusion criteria should consider IHC testing followed by germline testing. As mentioned earlier, IHC may help guide germline analysis. When no

Table III. Amsterdam II criteria for the diagnosis of Lynch syndrome*

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

For patients with at least three relatives with colorectal carcinoma or another Lynch syndrome–associated tumor, all of the above should apply.
*As outlined by Wolf et al.[143]

defect is detected via germline testing, this does not mean that the patient has been excluded from having MTS or Lynch syndrome, because not all mutations are known for this syndrome. Instead of a negative test, it is considered an "uninformative test." The sensitivity of germline mutation analysis ranges from 50% to 95% depending on the methodology.[78] For patients in whom a mutation is identified, the sensitivity for the proband's family is nearly 100%, and significantly less expensive than the initial analysis.[78]

APPROACH TO EVALUATION OF A PATIENT WITH AN MTS-RELATED NEOPLASM

Key points

- **A careful family history in all patients with sebaceous neoplasms looking for Muir–Torre syndrome–related tumors is recommended**
- **Patients with concerning family histories or mismatch repair defects shown with microsatellite insufficiency testing or immunohistochemistry should be considered for genetic counseling and germline analysis**

Developing an approach to screening patients with an MTS-related neoplasm can be a daunting undertaking, especially because most clinicians rarely encounter these tumors. Also, it is unclear how well one can extrapolate the results of studies on Lynch syndrome to MTS. There have been no cost analysis or cost benefit studies performed for the evaluation of patients at risk for MTS or for intensive screening of those who have MTS.

We have devised an algorithm that favors testing for all patients with a MTS-related neoplasm (Fig 1). Studies for Lynch syndrome have shown that a testing-based approach identifies more patients with underlying germline mutations than clinical criteria–based approaches.[121] Given the high underlying probability of visceral malignancies associated with sebaceous tumors (5%-42%), and their rare nature, testing seems reasonable.[88,89,98,99,123] Our algorithm is similar to what has been proposed by some for screening patients with colorectal cancers for Lynch syndrome.[121,146] Clearly, without studies we cannot say whether this approach is better than others or cost effective. It should at least provide a framework for approaching these lesions for those that have not already formulated one.

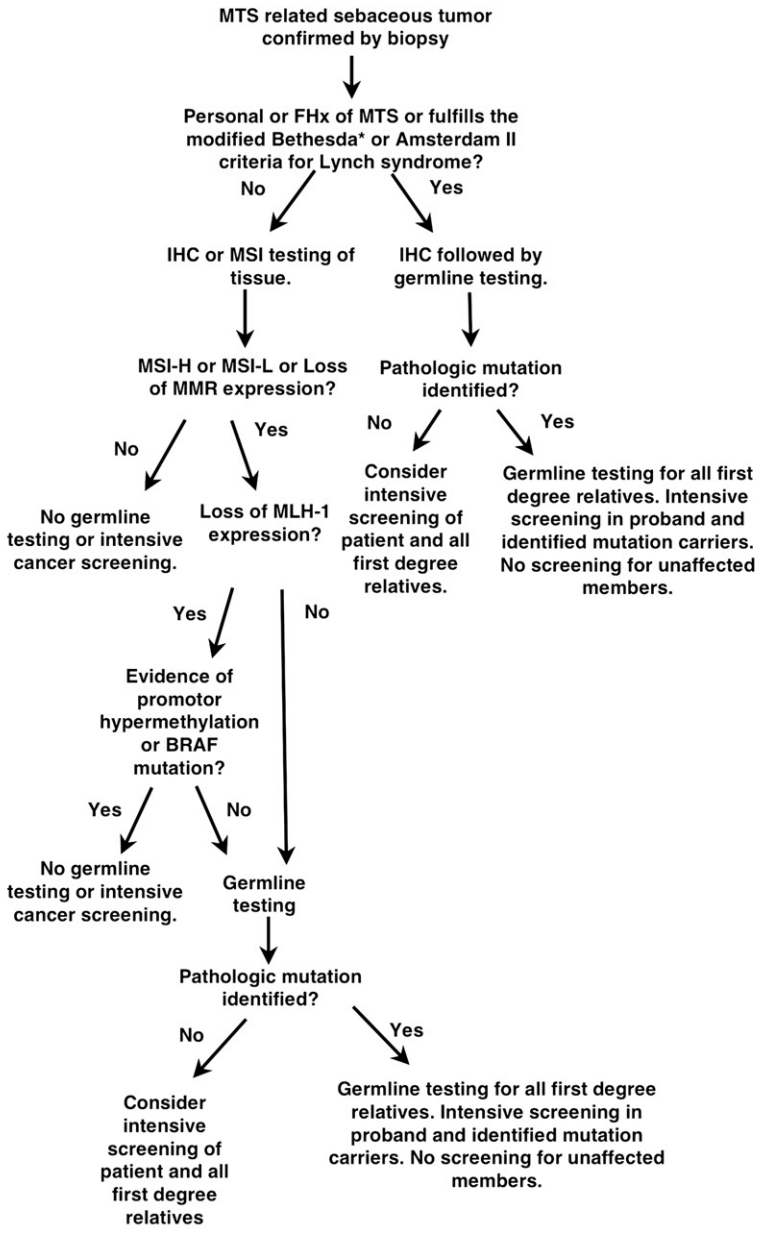
Regardless of how one feels about testing, a careful family history should be obtained with respect to fulfilling the revised Bethesda guidelines, the Amsterdam II criteria, or the criteria for MTS in all patients with newly diagnosed sebaceous tumors (Tables I, III, and IV). Patients without a concerning family history and with no indication of MMR deficits with either IHC or MSI analysis are unlikely to have MTS. Therefore, they will probably not benefit from germline analysis or intensive cancer screening.

For patients who do not have a family history that is significant for MTS or Lynch syndrome, but who have been shown to have a loss of expression of their MMR genes by either IHC or MSI analysis, genetic counseling and germline testing should be considered. If MSI was performed initially, IHC may help direct germline mutation analysis, and so it should be considered after positive MSI testing.[123] If IHC reveals a loss of expression of MLH1, promoter methylation and BRAF-600E studies should be considered first to exclude the high chance of somatic mutations.[137,138] If MLH1 promoter hypermethylation or BRAF-600E mutations are found, no germline testing or intensive cancer screening is probably necessary.

Patients with demonstrable MMR germline defects should be considered for intensive screening of internal malignancies similarly to those with Lynch syndrome. First-degree relatives of those with an identifiable mutation should also be offered genetic counseling and germline testing, because they may benefit from intensive cancer screening.[123] Family members that are found not to possess a pathogenic mutation can then be removed from screening.

Those without a concerning family history who have an abnormal IHC or MSI result but an uninformative germline analysis should still be considered for intensive screening along with their first-degree relatives. As mentioned earlier, an uninformative germline analysis does not mean the patient is excluded from having MTS or Lynch syndrome.

Patients who have met the criteria for MTS by either the revised Bethesda guidelines or Amsterdam II criteria should also be considered for IHC followed by germline testing. This will facilitate the identification of family members who may benefit from intensive cancer screening. With



*Suggest Bethesda criteria include one other element besides sebaceous adenoma. Most of these testing suggestions have good quality patient-oriented evidence to support them, but the algorithm itself has not been scientifically validated. Information regarding which laboratories offer germline testing, genetic counseling, methylation and BRAF mutation analysis, and MSI testing can be found at http://www.genetests.org/. Abbreviations: Muir-Torre syndrome (MTS), immunohistochemistry (IHC), family history (FHx), mismatch repair (MMR), microsatellite insufficiency (MSI).

Fig 1. Algorithm for assessing a patient with a newly diagnosed Muir—Torre syndrome—related neoplasm.

regard to the revised Bethesda guidelines, it should be noted that it is meant for patients with a newly diagnosed colorectal carcinoma, not sebaceous neoplasms (Table IV). We suggest that criteria 2, 4, and 5 be modified to include patients with newly diagnosed sebaceous neoplasms. Because all patients with a newly diagnosed MTS-related malignancy meet criteria 2, we think an additional criterion should be necessary other than sebaceous adenoma or keratoacanthoma. For criteria 4, we recommend removing the requirement for a personal history of colorectal carcinoma and keeping the requirement for first-degree relatives with Lynch syndrome—related neoplasms. Similarly, for criteria 5, we recommend dropping the requirement of personal history of colorectal cancer, but keeping the requirement for family history of two or more relatives with Lynch syndrome—related

Table IV. Revised Bethesda guidelines for the identification of patients who should undergo microsatellite insufficiency testing*

Just one of the following criteria needs to be met:
1. Individual diagnosed with colorectal cancer before 50 years of age
2. Synchronous or metachronous colorectal or other HNPCC-related tumors,† regardless of age
3. Colorectal cancer with a MSI-H histology‡ that was diagnosed before 60 years of age
4. Colorectal cancer diagnosed in one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed before 50 years of age
5. Colorectal cancer with two or more first- or second-degree relatives with colorectal cancer or other HNPCC-related tumors, regardless of age

HNPCC, Hereditary nonpolyposis colorectal cancer; *MSI-H*, microsatellite insufficiency high.
*According to Umar et al.[162]
†HNPCC-related tumors: stomach, bladder, endometrium, ureter, renal pelvis, biliary tract, brain (usually glioblastoma), sebaceous gland adenomas, keratoacanthomas, pancreas, and carcinoma of the small bowel.
‡MSI-H histology shows the presence of tumor infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullar growth pattern.

tumors. The modification of these criteria has not been scientifically validated for MTS. However, patients meeting them would likely raise a high clinical concern for possible germline mismatch repair mutations.

Again, if germline mutation analysis is to be performed, IHC should be considered before testing because it may help germline mutation analysis. Clearly, all patients who are considered for germline analysis should also have genetic counseling. Patients with an identifiable germline mutation can then have their first-degree relatives offered germline analysis. Those without the mutation can avoid intensive cancer screening. If the mutation is detected, intensive cancer screening for all first-degree relatives may be considered.

Information regarding which laboratories offer germline testing, genetic counseling, methylation and BRAF mutation analysis, and MSI testing can be found at http://www.genetests.org/.

INTENSIVE CANCER SCREENING STRATEGIES FOR THOSE AT HIGH RISK FOR OR WHO HAVE MTS

Key points

- **Intensive cancer screening for colorectal cancers has been shown to detect tumors at an earlier stage in patients with Lynch syndrome**
- **The efficacy of surveillance for extracolonic tumors is lacking**
- **Prophylactic surgery has been advocated in select patients**

For patients with Lynch syndrome, intensive cancer screening has been shown to lead to the detection of colorectal cancers at an earlier stage than historical controls.[123,148-156] It is likely that patients with MTS would also benefit from the same intensive screening as Lynch syndrome patients.

The collaborative group of the European experts in hereditary gastrointestinal cancer has recommended a comprehensive set of surveillance guidelines for patients with Lynch syndrome, or familial clustering of Lynch syndrome–related cancers without evidence of MMR defects (Table V).[123] Applying this regimen to patients with MTS or with a concerning family history of tumors of the urogenital and digestive tracts seems reasonable. The group recommends colonoscopy every 1 to 2 years starting between 20 and 25 years of age.[123] For women, a gynecologic examination, including transvaginal ultrasound and aspiration biopsy, is recommended because of the high incidence of endometrial carcinoma. This is recommended for patients beginning between 30 and 35 years of age.[123] If gastric cancer runs in the patient's family or if the patient lives in a location with a high incidence of gastric cancer, then esophagogastroduodenoscopy is advised every 1 to 2 years.[123] A recommendation for abdominal ultrasound, urinalysis, and urine cytology is advocated for patients with a family history of urinary cancer, beginning at 30 to 35 years of age and occurring at an interval of every 1 to 2 years.[123] Patients who have a familial clustering of colorectal carcinoma and evidence of MSI but do not meet the criteria for Lynch syndrome are recommended to have a colonoscopy starting between the ages of 45 and 50, or 5 to 10 years before the earliest family member diagnosis of colorectal carcinoma.[123] The proposed surveillance interval is every 3 to 5 years.[123]

Evidence to support the above recommended screening of extracolonic cancers is not as good as that for colorectal cancers. A study performed by Dove-Edwin et al[157] that included 269 women, 171 from Lynch syndrome families and 98 from Lynch syndrome–like families, found no benefit to performing annual or biennial pelvic ultrasound examinations. Trials on screening for the other cancers are lacking.

Some authors have advocated prophylactic surgery.[158,159] Selected patients with recurrent adenomas may benefit from prophylactic subtotal colectomy.[123,160] There is only anecdotal evidence to

Table V. Intensive cancer screening regimen recommended by the collaborative group of the European experts in hereditary gastrointestinal cancer*

Disorder	Age to start screening, y	Examination(s) (evidence level)	Interval, y
Lynch syndrome	20-25	Colonoscopy (I)	1-2
	30-35	Gynecologic examination, transvaginal ultrasound, and aspiration biopsy (III)	1-2
	30-35	Gastroduodenoscopy† (III)	1-2
	30-35	Abdominal ultrasound, urinalysis, and urine cytology‡ (III)	1-2
Amsterdam-positive families without MSI	45-50, or 5-10 years before age at diagnosis of first colorectal carcinoma in family	Colonoscopy (III)	3-5

MSI, Microsatellite instability.
Levels of evidence: I—good quality, patient-oriented evidence; I—limited quality, patient-oriented evidence; and III—other evidence, including consensus guidelines, extrapolations from bench research, opinion, or case studies.
*According to Vasen et al.[146]
†If gastric cancer runs in the family or if the patient lives in a country with a high incidence of gastric cancer.
‡For patients with a family history of urinary tract cancer.

support this conclusion.[159] Because of the high risk of endometrial cancer and moderate risk of ovarian cancer in women, hysterectomy and bilateral salpingo-oophorectomy has also been suggested.[159] Schmeler et al[161] reported results from a retrospective study of 315 women with known MMR gene defects in which 61 patients had prophylactic surgery and were followed-up for 10 years.[161] No endometrial or ovarian cancers were detected in the prophylactic surgery group.[161] Thirty-three percent who did not have surgery developed endometrial cancer, and 5.5% developed ovarian cancer.[161] This is espoused as an option for women 35 years of age or older who do not want any more children.[160,161]

CONCLUSION

LNSS and MTS are two complex syndromes associated with sebaceous lesions. LNSS typically presents with multisystem disorders that extend beyond the initially described triad of linear nevus sebaceus, mental retardation, and seizures. A comprehensive examination and ancillary studies should be considered in neonates with an extensive nevus sebaceous. One should also be cognizant of the suggested relationship of malignancies associated with this syndrome and consider screening for them. The algorithm presented within this paper relating to MTS is similar to what has been proposed for Lynch syndrome. Although we acknowledge that it has limitations and has not yet been validated in a clinical study, it draws on our current understanding of the syndrome to provide a framework for physicians to use when encountering patients with these lesions. Based upon our current knowledge of Lynch syndrome, intensive cancer screening for patients with MTS is likely to be beneficial.

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