Muir-Torre Syndrome

Feriyl Bhaijee, MD; Alexandra S. Brown, MD

• Muir-Torre syndrome (MTS) is a rare autosomal-dominant genodermatosis characterized by sebaceous neoplasms and one or more visceral malignancies. Sebaceous tumors include sebaceous adenoma and carcinomas, which may be solitary or multiple. Visceral malignancies most often arise in the colorectum and endometrium. Because a subset of patients with phenotypic MTS will have germline mutations in the DNA mismatch repair genes hMSH2 and hMLH1, MTS is considered a phenotypic subtype of Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer syndrome), in which inherited defects in DNA mismatch repair genes result in microsatellite instability. Pathologists have an important role in the early detection and initial diagnosis of MTS: identification of at-risk individuals allows appropriate screening and surveillance for visceral malignancies, thereby reducing morbidity and mortality. Herein, we describe the clinical-pathologic features of MTS.


First described by Muir et al1 in 1967 and Torre2 in 1968, Muir-Torre syndrome (MTS) is a rare autosomal-dominant genodermatosis characterized by at least one sebaceous gland neoplasm and at least one visceral malignancy.3,4 Muir-Torre syndrome follows an autosomal-dominant pattern of inheritance in most cases with high penetrance and variable expression, but sporadic cases have also been reported. Because MTS is associated with germline mutations in the DNA mismatch repair (MMR) genes hMSH2 and hMLH1, it is considered a phenotypic subtype of Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer syndrome), in which inherited defects in DNA MMR genes result in microsatellite instability.5 Although germline disruption of hMLH1 and hMSH2 is evenly distributed in Lynch syndrome, more than 90% of MTS patients show hMSH2 disruption.6

CLINICAL FEATURES

Muir-Torre syndrome is rare, with approximately 200 cases reported.4 A family history can be elicited in about 50% of affected patients. Individuals with MTS may present with one or more sebaceous gland neoplasms or visceral malignancies. Males are more commonly affected, with a male to female ratio of 3:2, and individuals can present at any age.7 Sebaceous neoplasms present at a mean age of 53 years and visceral malignancies are diagnosed at a mean age of 50 years.7 Muir-Torre syndrome precedes visceral malignancy diagnosis in 22%, occur simultaneously in 6%, and develop subsequently in 56% of reported MTS cases.8–10

Muir-Torre syndrome–associated sebaceous gland neoplasms include sebaceous adenoma, sebaceoma/sebaceous epithelioma, sebaceous carcinoma, keratoacanthoma with sebaceous differentiation, and basal cell carcinoma (BCC) with sebaceous differentiation.4 These neoplasms can arise in any body site containing sebaceous glands and, in sporadic cases, show a predilection for areas with abundant sebaceous glands, such as the nose and eyelid. In MTS, sebaceous tumors below the neck are more common than facial or eye lesions.11 Sebaceous adenomas and sebaceomas typically present as painless, yellow, round papules or subcutaneous nodules, some of which may show central umbilication (similar to molluscum contagiosum). Sebaceous carcinomas usually arise in the meibomian glands but may also occur anywhere else, including the face, ears, and external genitalia. On the eyelids, these carcinomas manifest as firm, yellow nodules with varying degrees of ulceration and may be mistaken for chalazia, chronic blepharoconjunctivitis, or carbuncles. Because sebaceous neoplasms are rare in the general population, patients presenting with sebaceous tumors should be screened for visceral malignancies (including review of systems and appropriate clinical investigations). Some authors advocate genitourinary surveillance in addition to upper and lower gastrointestinal endoscopy for all patients with sebaceous tumors.12 A rigorous screening approach may include interval chest radiographs, serum carcinoembryonic antigen levels, cervical and urine cytology, endometrial biopsies, and abdominal computerized tomography.13 Basal cell carcinoma may also occur in the head and neck region of individuals with MTS. Although BCC is the commonest human cancer, presentation with multiple or early-onset lesions should prompt consideration of an underlying Mendelian disorder (such as basal cell nevus syndrome or xeroderma pigmentosum) or other genodermatoses characterized by defective DNA replication/repair, such as MTS.14

The most common MTS-associated visceral malignancies are colorectal adenocarcinoma, followed by genitourinary carcinoma; less common malignancies include breast carcinoma, hematologic cancers, endometrial carcinoma, and gastric adenocarcinoma. Muir-Torre syndrome–associ-
ated colonic adenocarcinomas tend to occur proximal to the splenic flexure.3

PATHOLOGIC FEATURES

Muir-Torre syndrome–related sebaceous tumors include sebaceous adenoma, sebaceoma/sebaceous epithelioma, sebaceous carcinoma, keratoacanthoma with sebaceous differentiation, BCC with sebaceous differentiation, and cystic sebaceous neoplasms. In cutaneous tumors, sebaceous differentiation manifests as cells with coarsely vacuolated cytoplasm and starry nuclei (so-called mulberry cells).15 Sebaceous cells are immunoreactive for epithelial membrane antigen.

Sebaceous adenoma is a well-circumscribed dermal nodule composed of sebaceous lobules with a peripheral germinative layer of small basaloid cells that transition to mature sebocytes centrally (Figure 1).15 Sebaceous adenomas lack a central draining duct (in contrast to the more commonly encountered sebaceous hyperplasia). Muir-Torre syndrome–associated tumors are often nodulocystic and commonly occur on the trunk and extremities.

Sebaceoma (formerly known as sebaceous epithelioma) is a variant of sebaceous adenoma in which the basaloid epithelial cells comprise 50% or more of the tumor. Sebaceoma consists of variably sized lobules of predominantly basaloid cells admixed with single or clustered mature sebocytes (Figure 2). These tumors also contain sebaceous ductal elements and, rarely, focal squamous metaplasia. The verrucous variant of sebaceoma shows a connection between the sebaceous lobules and a hyperplastic infundibulum, a prominent granular layer, and basosquamous differentiation, features reminiscent of a seborrheic keratosis.16

Unlike benign sebaceous neoplasms, sebaceous carcinoma shows features of malignancy: it is asymmetrical with poor circumscription, and has an infiltrative growth pattern, a preponderance of pleomorphic basaloid cells arranged in solid sheets, marked cytologic atypia, high mitotic activity, and variable tumor necrosis (Figure 3).15 The basaloid tumor mass may contain scattered sebocytes. Unlike in BCC, peripheral palisading and artefactual clefting are notably absent. Superficial (pagetoid) spreading in the overlying epidermis may be seen occasionally.17 Histologic variants of sebaceous carcinoma include the basaloid, spindle cell, squamoid, and dedifferentiated (pleomorphic) variants.15 Basaloid sebaceous carcinoma consists of small basaloid cells in lobules with peripheral palisading and inconspicuous sebocytes. The spindle cell variant is composed predominantly of spindle cells with foci of squamous metaplasia. Sebaceous carcinoma is immunoreactive for cytokeratins AE1/AE3, low molecular weight cytokeratin, epithelial membrane antigen, anti-breast carcinoma-associated antigen-225 antibody (CU18), anti-CA 15.3 antibody, and androgen receptor protein; it is not immunoreactive for carcinoembryonic antigen, S100 protein, or gross cystic disease fluid protein 15.18,19

Keratoacanthoma and BCC with sebaceous differentiation show the typical features of the respective tumor type as well as an accompanying sebaceous proliferation. Anti–epithelial membrane antigen reactivity will highlight areas of sebaceous differentiation.

Cystic sebaceous neoplasms comprise a spectrum from benign cystic adenomas to proliferative cystic sebaceous tumors.20,21 These rare neoplasms have only been reported
in patients with MTS. Histologically, cystic sebaceous tumors are well circumscribed, deep dermal or subcutaneous sebaceous proliferations with cystic growth patterns. Cystic sebaceous adenomas have thin cyst walls lined by basoid cells, which show regular maturation into sebocytes toward the lumen; mitotic figures are rare. Proliferative cystic sebaceous tumors have cystic, lobulated growth patterns with basoid cells, cytologic atypia, and prominent mitotic activity. As in cutaneous MTS-related tumors, epithelial membrane antigen expression confirms sebaceous differentiation.

Muir-Torre syndrome–related sebaceous and visceral malignancies are more likely to show increased tumor infiltrating lymphocytes and peritumoral lymphocytic infiltrates compared with their non–MTS-related counterparts. Although colorectal carcinomas in MTS patients often show higher tumor infiltrating lymphocyte counts and histologic heterogeneity (ie, some tumors have mucinous morphology whereas others show medullary morphology), histologic features are not sufficiently specific to predict microsatellite instability.

**ANCILLARY STUDIES**

Because a subset of patients with phenotypic MTS will have germline mutations in the DNA MMR genes hMSH2 and hMLH1, MTS is considered a phenotypic subtype of Lynch syndrome in which inherited defects in DNA MMR genes result in microsatellite instability. Approximately 70% of MTS-associated tumors have microsatellite instability, which can alter tumor suppressor gene expression, leading to the development of visceral malignancies. Thus, although the diagnosis of MTS is based on clinical criteria, germline testing for microsatellite instability is required to confirm the diagnosis.

Given the relative infrequency of sebaceous neoplasms in the general population and the association with MTS in almost 50% of affected individuals, it is advisable to test all sebaceous tumors immunohistochemically, regardless of tumor burden, tumor location, or patient age. In a study of 41 sebaceous gland neoplasms, Chhibber et al reported positive predictive values of MLH1, MSH2, and MSH6 of 88%, 55%, and 67%, respectively. Only two combinations achieved a positive predictive value of 100%: MLH1 þ MSH2 and MLH1 þ MSH2 þ MSH6. Therefore, immunohistochemical panels should include at least MLH1, MSH6, and PMS2, with or without MSH2.

Although loss of MMR protein expression by immunohistochemistry (IHC) is highly suggestive of germline mutations, it may also represent sporadic mutations in MMR genes, which occurs with higher frequency in transplant patients. Thus, germline microsatellite instability testing is required to confirm the diagnosis of MTS. Given the vagaries of MMR protein IHC results, Roberts et al suggest that the following statement be appended to reports for sebaceous neoplasms:

This neoplasm may be sporadic or associated with MTS, a variant of Lynch syndrome (HNPCC) [hereditary nonpolyposis colorectal cancer]. If this patient has a personal or family history of colon cancer, MMR IHC could be considered to further evaluate for the presence of a defective MMR gene. However, abnormal MMR IHC alone is not sufficient for making the diagnosis of MTS.

When a sebaceous tumor shows abnormal MMR IHC, the patient should be referred to a genetic counselor for microsatellite instability testing. If a sebaceous tumor shows intact MMR proteins by IHC, genetic counseling may still be indicated for patients with a personal or family history of colorectal cancer.

Because IHC is relatively inexpensive and widely available, it frequently precedes microsatellite instability testing, which is expensive and requires sophisticated molecular techniques. Paraffin-embedded tissue can be used for microsatellite instability testing.

**DIFFERENTIAL DIAGNOSIS**

The differential diagnosis of sebaceous neoplasms includes hyperplastic and hamartomatous lesions (sebaceous hyperplasia and nevus sebaceous, respectively), benign neoplasms (sebaceous adenoma and sebaceoma/sebaceous epithelioma), and malignancies (sebaceous carcinoma and BCC with sebaceous differentiation). Sebaceous hyperplasia may be seen in MTS, but does not fulfill diagnostic criteria.

Sebaceous hyperplasia consists of a single enlarged sebaceous gland with 5 or more lobules of bland, immature sebocytes that open into a single dilated follicular infundibulum. One or 2 cell layers of basoid germinative cells are usually present at the periphery of the lobules but, in contrast to sebaceous adenoma, the sebocytes and surrounding basoid cells are not intimately admixed. Sebaceous hyperplasia resembles rhinophyma, in which the sebaceous gland hyperplasia is associated with perifollicular inflammation and dermal fibrosis.

Nevus sebaceus is a congenital epithelial hamartoma composed of large sebaceous glands, heterotopic apocrine glands, malformed hair follicles, acanthosis, and epithelial papillomatosis. It occurs on the scalp and face and may rarely transform to BCC, trichoblastoma, or squamous cell carcinoma.

Sebaceous adenomas are usually smaller and more superficial than sebaceomas. Sebaceous adenomas should also be differentiated from angiofibroma with sebaceous hyperplasia (as seen in tuberous sclerosis). Both lesions may present as solitary, dome-shaped, firm nodules, but the latter contains increased blood vessels with dilated lumina, fibroblastic stroma with stellate or multinucleated atypical cells, numerous hair follicles surrounded by collagen fibers, and vacuolated clear cells in the epidermis, which often shows slight acanthosis.

Although sebaceoma and BCC with squamous differentiation both represent aggregates of basoid germinative cells, there are well-defined histologic differences between the 2 neoplasms. Sebaceoma contains monomorphic cells with benign architectural features, whereas BCC with sebaceous differentiation shows pleomorphic cells with infiltrative, malignant architecture. Sebaceomas rarely can show other common features of BCC, such as peripheral palisading, artefactual clefting, or basaloid tumor necrosis.

The differential diagnosis for sebaceous carcinoma includes BCC with sebaceous differentiation and clear cell squamous cell carcinoma. As above, sebaceous carcinoma is unlikely to show the common features of BCC. Clear cell squamous cell carcinoma may be mistaken for a sebaceous neoplasm because the hydropic degeneration of tumor cells leads to accumulation of intracellular fluid (not lipid); evidence of squamous differentiation, however, and a negative fat stain (oil red O) support a diagnosis of squamous cell carcinoma rather than sebaceous carcinoma.
can therefore be treated by complete surgical excision. 3,4 Associated cutaneous neoplasms have low malignant potential, angi invasion, or distant metastases. 3,15,36 The high periocular region) may be aggressive with potential recurrence in extraocular locations. 4,36

MTS-associated sebaceous carcinomas (especially in the head, neck, upper trunk region) may be aggressive with potential recurrence in extraocular locations. 4,36 These neoplasms have low malignant potential, angi invasion, or distant metastases. 3,15,36

The high periocular region) may be aggressive with potential recurrence in extraocular locations. 4,36

Multiple trichoepitheliomas (possibly a phenotypic variant of Brooke-Spiegler syndrome) may be aggressive with potential recurrence in extraocular locations. 4,36

Multiple keratoacanthomas; trichoepitheliomas, 32 basal cell nevus syndrome, 33 multiple skin-colored nodules on the face. 30

Multiple keratoacanthomas: Ferguson-Smith syndrome

Multiple trichoepitheliomas (possible phenotypic variant of Brooke-Spiegler syndrome) may be aggressive with potential recurrence in extraocular locations. 4,36

Basal cell nevus syndrome (Goltz syndrome) may be aggressive with potential recurrence in extraocular locations. 4,36

Multiple keratoacanthomas: Ferguson-Smith syndrome

Multiple skin-colored nodules on the head, neck, upper trunk

Tuberous sclerosis

Adolescent-onset ulcerative keratoacanthomas with spontaneous resolution and recurrence

Cortical hamartomas (tubers) and tumors (subependymal giant cell astrocytoma), angioblastomas, lymphangioliomyomatosis, angiomyolipoma, cardiac rhabdomyoma, mental retardation, seizures

Cutaneous nodules are found in many other disorders, including Gardner syndrome, Cowden syndrome, multiple trichoepitheliomas, 32 basal cell nevus syndrome, 33 multiple keratoacanthomas, 34 and tuberous sclerosis 35 (Table).

CURRENT TREATMENT AND PROGNOSIS

With the exception of sebaceous carcinoma, most MTS-associated cutaneous neoplasms have low malignant potential with almost no propensity for metastasis, and can therefore be treated by complete surgical excision. 3,4 Despite a better prognosis compared with sporadic cases, MTS-associated sebaceous carcinomas (especially in the periocular region) may be aggressive with potential recurrence, angioinvasion, or distant metastases. 3,15,36 The high frequency of metastasis and death (up to 25% in some studies) necessitates wide surgical excision or Mohs micrographic surgery in order to reduce the risk of recurrence in extraocular locations. 3,36

Although MTS is rare, pathologists have an important role in the early detection and initial diagnosis of MTS: identification of at-risk individuals (affected patients and family members) allows appropriate screening and surveillance for visceral malignancies, thereby reducing morbidity and mortality.

The authors would like to thank Jennifer Schulmeier, MD, of Dermatopathology Associates, Jackson, Mississippi, for her invaluable assistance with this manuscript.

References


Hereditary Tumor Syndromes Associated With Cutaneous Nodules

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Mode of Inheritance</th>
<th>Genetic Defect</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muir-Torre syndrome</td>
<td>Autosomal dominant</td>
<td>Defective mismatch repair genes hMLH1 and hMSH2 in 70%</td>
<td>Sebaceous neoplasms, keratoacanthomas, visceral malignancies (colorectal, endometrial, endometrial)</td>
</tr>
<tr>
<td>Gardner syndrome (phenotypic variant of FAP)</td>
<td>Autosomal dominant</td>
<td>APC gene mutations (5q21)</td>
<td>Multiple gastrointestinal polyps, osteomas, epithemid cysts, desmoid tumors</td>
</tr>
<tr>
<td>Cowden syndrome (multiple hamartoma syndrome)</td>
<td>Autosomal dominant</td>
<td>PTEN gene mutations (10q23)</td>
<td>Mucocutaneous hamartomas (trichilemmomas, oral mucosal papillomatosis, keratosis) and visceral malignancies (breast, thyroid, colon, kidney)</td>
</tr>
<tr>
<td>Multiple trichoepitheliomas (possible phenotypic variant of Brooke-Spiegler syndrome)</td>
<td>Autosomal dominant</td>
<td>CYLD gene mutations (16q12–13)</td>
<td>Multiple skin-colored nodules on head, neck, upper trunk</td>
</tr>
<tr>
<td>Basal cell nevus syndrome (Goltz syndrome)</td>
<td>Autosomal dominant</td>
<td>PITCH gene mutations (9q22.3)</td>
<td>Early-onset basal cell carcinomas, palmar/plantar pits, odontogenic keratocysts, medulloblastoma, dural calcifications</td>
</tr>
<tr>
<td>Multiple keratoacanthomas: Ferguson-Smith syndrome</td>
<td>Autosomal dominant</td>
<td>MSSE gene mutations (9q22–31)</td>
<td>Adolescent-onset ulcerative keratoacanthomas with spontaneous resolution and recurrence</td>
</tr>
<tr>
<td>Tuberous sclerosis</td>
<td>Autosomal dominant</td>
<td>TSC1 gene (hamartin protein) mutation on 9q34; TSC2 gene (tuberin protein) mutation on 16p13</td>
<td>Cortical hamartomas (tubers) and tumors (subependymal giant cell astrocytoma), angioblastomas, lymphangioliomyomatosis, angiomyolipoma, cardiac rhabdomyoma, mental retardation, seizures</td>
</tr>
</tbody>
</table>

Abbreviations: APC, adenomatous polyposis coli; CYLD, cylindromatosis (turban tumor syndrome); FAP, familial adenomatous polyposis; hMLH1, human mutL homolog 1; hMSH2, human mutS homolog 2; MSSE, multiple self-healing squamous epithelioma; PITCH, patched homolog; PTEN, phosphatase and tensin homolog; TSC1, tuberous sclerosis 1; TSC2, tuberous sclerosis 2.


