Muir-Torre Syndrome: the implications of sebaceous neoplasms

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Summary

Muir-Torre Syndrome (MTS) is a rare familial cancer syndrome defined as the association of an internal malignancy with sebaceous neoplasm. It is considered to be a phenotypic variant of Lynch syndrome. We present a case of MTS to highlight the importance of its early recognition and proper work-up.

KEY WORDS: Muir-Torre Syndrome; sebaceous neoplasm; Lynch syndrome.

The case

A 38-year-old Caucasian female with a history of chronic lower back pain and endometrial hyperplasia status post hysterectomy presented for evaluation of a skin growth on the left medial cheek that had been present for 8 months (Figure 1). A biopsy revealed a sebaceous epithelioma with keratoacanthoma features. Stains for mismatch repair (MMR) genes MSH-2 and MSH-6 were negative, suggesting the possibility of MTS.

While discussing the appropriate next steps for MTS work-up, the patient reported new onset abdominal pain and worsening lower back pain. An expedited CT scan of the abdomen and pelvis revealed a large left-sided renal mass with areas of local and distant metastasis. Pathology of the mass revealed a collecting duct carcinoma.

The diagnosis

The patient was sent to a genetic counselor. Her hereditary cancer panel results showed a pathogenic mutation in MSH-2. The patient met the Amsterdam Criteria for Lynch Syndrome (1) (Table 1). Germline genetic testing confirmed the diagnosis. Her family history was significant for various cancers, including skin, uterine, breast, colon, and brain cancers on her maternal side; and lung, bladder, and thyroid cancers on her paternal side (Figure 2).

The patient’s disease progressed despite aggressive treatment with multiple chemotherapy regimens and extensive surgical de-bulking. The patient was subsequently placed in hospice care due to the refractory nature of her internal malignancy. She expired a year after her initial diagnosis.

Discussion

MTS is a rare autosomal dominant syndrome with high degree of penetrance and variable expressivity involving sebaceous neoplasms with one or more visceral malignancies. Nearly half of patients with MTS develops two or more visceral malignancies (2). MTS-related sebaceous tumors include sebaceous adenoma, sebaceous epithelioma, sebaceous carcinoma, and keratoacanthoma (KA) with sebaceous differentiation (3). When sebaceous adenomas with KA features arise, they are considered to be highly suggestive of Muir-Torre (4). A genomic replication error known as microsatellite instability (MSI) caused by alterations in at least 1 of 4 DNA mismatch repair genes underlies the pathogenesis. Germline mutations in patients with MTS most commonly affect MSH-2 (>90%), followed by MLH-1 (<10%) (2). As a result, MTS is considered a phenotypic variant of Lynch syndrome, which also exhibits defects in MMR genes (3). In this case, the patient had a positive family history of cancers; while the cancers are not all Lynch-associated cancers, it is important to obtain a family history given the high degree of penetrance of this autosomal dominant condition.

In the absence of a personal or family history of MTS, sebaceous neoplasms could represent sporadic lesions unrelated to this genetic condition. Therefore, a clinical practice algorithm was proposed for MTS following identification of sebaceous neoplasms (5). Immunohistochemical (IHC) screening of sebaceous neoplasms should be obtained followed by a thorough family history searching for malignancies commonly associated with Lynch syndrome in first- and second-
degree relatives. Genetic referral is subsequently recommended for patients with sebaceous neoplasms and any of the following: absent MMR protein expression on IHC, normal MMR protein expression but a family history of Lynch syndrome-associated malignancies, or more than one sebaceous neoplasm. Lack of expression of MMR proteins on IHC warrants MSI analyses (4). Germline mutation analyses of MLH-1, MSH-2, and MSH-6 may be done to confirm the mutation (6). In studies on unselected sebaceous neoplasms, the lack of expression of individual MMR proteins in MTS had a positive predicative value (PPV) that ranged from 33 to 88%. Combined deficits of both MSH-2 and
MSH-6, as in our patient, resulted in 55% PPV. Deficits of both MLH-1 and MSH-6 resulted in 100% PPV (7). A subsequent retrospective study concluded that MMR IHC is less reliable when completed on sebaceous neoplasms than on colon or endometrial tumors. Personal and family history was deemed to be the most important factor identifying MTS cases (8). Most MTS-related cutaneous neoplasms have no susceptibility for metastasis and can be treated with surgical removal (3). However, MTS-associated sebaceous carcinomas can be aggressive in periorcular regions. A combination of oral isotretinoin and interferon alpha-2a has been reported to reduce the growth of cutaneous tumors (9). Both early detection and curative treatment of the internal malignancies are challenging however.

Conclusion

Sebaceous tumors have been detected prior to visceral malignancy in MTS 22% of the time and in 6% of cases, the visceral and cutaneous neoplasms are simultaneously discovered (3). It is thus essential for the medical provider to have a high suspicion upon biopsy of sebaceous tumors so that patients are appropriately screened for visceral malignancies. Immunohistochemistry, family history-taking for internal malignancy, and genetic referral are critical aspects of early recognition and proper work-up. Early detection and diagnosis of MTS will reduce mortality and morbidity.

Acknowledgement

All Authors, Mindy X. Wang, Rajiv Nathoo, Puja Kathrotiya, and Alissa K. O’Brien, contributed to the scientific content and provided technical support. The study had no external funding.

Funding/Support

No funds were involved in the design and conduct of the manuscript or in the decision to submit the manuscript for publication.

Conflict of interest disclosures

No conflict of interest.

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