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Muir-Torre Syndrome

Muir-Torre syndrome (MTS) is a rare, inherited disorder characterized by the presence of sebaceous tumors and keratoacanthomas, in addition to one or more visceral malignancies. This syndrome is considered a subtype of Lynch syndrome, which predisposes individuals to various types of cancers, primarily those of the gastrointestinal tract, but also including genitourinary, breast, and other malignancies.

Clinical Manifestations

The hallmark features of MTS are the presence of sebaceous tumors (such as sebaceous adenomas, sebaceous epitheliomas, and sebaceous carcinomas) and keratoacanthomas. Sebaceous tumors are the most common cutaneous manifestations of MTS.

- ***Sebaceous Tumors*:** Sebaceous adenomas are typically multiple, yellowish papules or bumps found on the trunk, face, and scalp. In some cases, a solitary sebaceous tumor may be present. Sebaceous epitheliomas and sebaceous carcinomas, more advanced forms of sebaceous adenomas, can also occur. Sebaceous carcinomas are particularly concerning when they involve the eyelids, as they can invade the orbit and metastasize to surrounding tissues. Sebaceous carcinomas are aggressive and require early detection and intervention to prevent metastatic spread.
- ***Keratoacanthomas (KAs)*:** KAs are dome-shaped nodules that typically present with a central keratin plug. These lesions are less commonly associated with MTS but can occur as single or multiple nodules on the face, neck, or other areas of the body. KAs are typically well-defined and may have a rapidly growing course, but in the context of MTS, their occurrence should raise suspicion for an underlying visceral malignancy.

Visceral Malignancies in MTS

MTS is strongly associated with a variety of visceral malignancies, with colorectal cancer accounting for the majority of cases (around 50%). Other common cancers include genitourinary cancers (25%), such as renal cell carcinoma, and breast, lung, gastric, and small intestine cancers. In some cases, hematological malignancies may also be observed. These cancers often develop later than the cutaneous tumors but can present concurrently or even precede the appearance of sebaceous tumors. Despite the association with multiple cancers, the malignancies in MTS tend to be low-grade and typically progress in a non-aggressive manner.

Pathogenesis and Genetic Basis

Muir-Torre syndrome is caused by mutations in the hMSH2 and hMLH1 genes, which are involved in DNA mismatch repair. These mutations impair the ability of cells to correct errors that occur during DNA replication, leading to microsatellite instability, a hallmark of Lynch syndrome and its subtypes, including MTS. While MTS follows an autosomal dominant inheritance pattern, the severity of clinical manifestations can vary significantly among affected individuals, even within the same family. Genetic testing is critical for confirming the diagnosis of MTS, particularly in individuals with a strong family history of colorectal cancer or other related malignancies.

Diagnosis

The diagnosis of Muir-Torre syndrome is primarily based on the clinical identification of sebaceous tumors (adenomas, carcinomas) and KAs in the context of a family history of colorectal cancer or other associated malignancies.

- ***Immunohistochemical Testing*:** The presence of microsatellite instability in tumor tissue can be identified via immunohistochemical staining for mismatch repair proteins. Loss of expression of these proteins strongly suggests the presence of MTS. This method is often used when cutaneous lesions are suspicious, and further genetic testing is warranted.
- ***Genetic Testing*:** If immunohistochemistry indicates the possibility of MTS, genetic testing is employed to identify mutations in the hMSH2 or hMLH1 genes. This confirmation not only helps establish the diagnosis but also aids in identifying at-risk family members who may benefit from early screening for internal malignancies.

Management and Treatment

The management of MTS involves a multidisciplinary approach, including dermatologic, oncologic, and genetic counseling interventions. Treatment is aimed at controlling the cutaneous manifestations and screening for visceral malignancies.

- ***Excisional Removal of Tumors*:** Surgical excision of sebaceous tumors and KAs is the mainstay of treatment for cutaneous lesions. Excisional removal is indicated for lesions that are symptomatic, cosmetically concerning, or at risk of malignant transformation. Due to the high risk of recurrence and the potential for malignancy, regular follow-up is essential for monitoring the skin.
- ***Oral Isotretinoin*:** Oral isotretinoin has been shown to be effective in reducing the number and size of sebaceous tumors in MTS. It can help prevent the development of additional cutaneous lesions, especially in patients with multiple or recurrent tumors. Isotretinoin therapy should be considered in individuals with multiple sebaceous adenomas or those who have persistent lesions despite surgical treatment.
- ***Cancer Screening*:** Early detection of visceral malignancies is critical in MTS. Routine screening for colorectal cancer with colonoscopy should begin at an early age, typically around 20-25 years, and be performed at regular intervals (every 1-2 years). Additionally,

urinary tract and pelvic examinations, along with breast and other relevant cancer screenings, are recommended. Genetic counseling is essential for affected individuals and their families to discuss the implications of the diagnosis and the need for ongoing cancer surveillance.

- ***Genetic Counseling*:** Since MTS is inherited in an autosomal dominant pattern, genetic counseling is recommended for affected individuals and their families. Counseling provides information on inheritance patterns, risks to offspring, and the importance of genetic testing for at-risk family members.

Prognosis

The prognosis for Muir-Torre syndrome is generally favorable, especially when internal malignancies are diagnosed early and managed appropriately. Most cases of MTS involve low-grade malignancies, which tend to follow a non-aggressive course. However, the presence of multiple sebaceous tumors or sebaceous carcinoma requires careful monitoring due to the risk of local recurrence and potential for metastasis. Ongoing multidisciplinary management, including dermatologic surveillance and cancer screening, is key to optimizing outcomes.

Conclusion

Muir-Torre syndrome is a rare genetic disorder characterized by sebaceous tumors and keratoacanthomas, often associated with internal malignancies, particularly colorectal cancer. Early recognition and genetic testing are essential for confirming the diagnosis and initiating appropriate surveillance and treatment. The treatment of MTS involves excisional removal of tumors, management with oral isotretinoin to prevent new lesions, and comprehensive cancer screening. With proper care and monitoring, the prognosis for individuals with MTS can be favorable, though long-term follow-up is crucial due to the risk of both cutaneous and visceral malignancies.

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