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Lynch syndrome – Muir-Torre variant: implication in gynecologic oncology

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First described by Muir et al. in 1967 [1] and Torre in 1968 [2], Muir-Torre syndrome (MTS) is a rare hereditary condition which is considered as an uncommon variant of Lynch syndrome [3]. In current literature, less than 300 cases of patients affected by MTS have been described [2]. It has been reported that MTS is associated with an increased risk of several types of cancer, particularly colonic, genitourinary and skin tumors.

The concomitant presence of the following criteria is mandatory to diagnose MTS: 1) single or multiple sebaceous gland tumor(s) (either adenoma, epithelioma, carcinoma) or multiple keratoacanthomas and 2) at least a single visceral cancer. An association with non-Hodgkin lymphoma is reported [3].

Women's lifetime risk of developing gynecological malignancies is increased if they are diagnosed with MTS (risk estimated for endometrial cancer from 20% to 60%; risk estimated for ovarian cancer from 9% to 12%). In particular, the increased risk is related to both low malignant potential (i.e., borderline) and invasive ovarian tumor. However, knowledge and awareness of MTS is still limited. Here, we reviewed the current evidence regarding MTS in order to evaluate the implication of MTS in the gynecologic oncology field.

MTS is caused by inherited mutations that impair the DNA mismatch repair (MMR) such as MutL homolog 1 (*MLH1*), MutS protein homolog 2 (*MSH2*), and rarely mutS homolog 6 (*MSH6*). MTS has an autosomal dominant pattern of inheritance in about 60% of cases and it is characterized by a high degree of penetrance and variable expression [3].

Searching the literature, we were able to detect only a small amount of data regarding the implication of MTS for gynecologic disease. To date, only few reports reported an association of MTS with cervical adenocarcinoma, carcinoma of the uterine corpus and of the ovary [4]. Cases of sebaceous tumor growing within ovarian teratoma are reported as well [5]. MTS represents a variant of Lynch syndrome, characterized by pathognomonic features (i.e., cutaneous tumors) that can help for an easier and more intriguing diagnosis. Interestingly, sebaceous and visceral tumors occurring along with MTS have been described to be lower aggressive than their sporadic counterparts [3].

Although MTS is considered to be an uncommon condition compared with Lynch syndrome, the prevalence of MTS is likely to be underreported. South et al. [6], evaluated the frequency of MTS in Lynch syndrome families. Among 50 Lynch syndrome families (ascertained from

a population-based series of cancer patients who were newly diagnosed with colorectal or endometrial carcinoma), they observed MTS in 28% (14/50) of the families evaluated and in 9.2% (14/152) of the individuals with Lynch syndrome [3]. However, literature reports also a subgroup of sporadic cases, not related to deficiency in MMR genes [3]. The pathogenesis of sporadic MTS (approximately 35% of all MTS) remains unclear and challenging [3]. Biological, molecular, and immuno-histochemical characterizations should be used for identifying patients at risk for MTS [3].

MST is defined as the occurrence of at least 1 sebaceous-gland tumor, or keratoacanthoma, in conjunction with visceral tumor(s).

Diagnosis of gynecological malignancies, along with simultaneous or sequential cutaneous tumors and keratoacanthomas, might indicate the presence of MTS. Patients and their relatives should be counseled about this risk of future occurrence of gynecologic malignancies. Reconstruction of detailed family history could allow the identification or the suspicion of MTS, and the selection of patients in whom to proceed with clinical, molecular, and immuno-histochemical examinations. Knowledge and awareness on MTS should be improved within gynecologic oncology community.

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