

Muir-Torre syndrome: A case report and review of the literature

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Muir-Torre syndrome is a rare autosomal dominant genodermatosis characterized by the occurrence of sebaceous gland neoplasm associated with visceral malignancies. Most patients present with sebaceous adenomas, but cystic sebaceous neoplasms have been reported as specific markers of the syndrome. Gastrointestinal and genitourinary cancers are the most common internal malignancies. Colorectal cancer is the commonest visceral neoplasm in Muir-Torre syndrome patients. In this case report, we describe a rare case of Muir-Torre syndrome associated with colon cancer, and we demonstrate the important role of the dermatopathologist in alerting the clinician to the possibility of Muir-Torre syndrome when the diagnosis of sebaceous neoplasm is made.

Key words: Muir-Torre syndrome, sebaceous adenoma, colon cancer, colonoscopy

Muir-Torre sendromu: olgu sunumu ve literatürün gözden geçirilmesi

Muir-Torre sendromu nadir görülen otosomal dominant geçişli bir genodermatoz olup sebace bez tümörüyle, iç organ malignitesinin birlikteliğiyle karakterizedir. Çoğu hastada sebace adenom saptanmaktadır, fakat kistik sebace tümörler hastalığın spesifik bulgusu olarak rapor edilmiştir. Gastrointestinal ve genitoüriner tümörler en sık görülen tümörlerdir. Kolorektal kanser Muir-Torre sendromu olan hastalarda en sık görülen kanser türüdür. Bu vakada kolon kanseri ile ilişkili olan Muir-Torre sendromu vakası sunulmaktadır ve sebace tümör tespit edildiğinde Muir-Torre sendromu açısından dermatopatoloğun klinisyeni uyarmasının önemi vurgulanmaktadır.

Anahtar kelimeler: Muir-Torre sendromu, sebace adenom, kolon kanseri, kolonoskopi

INTRODUCTION

Muir-Torre syndrome (MTS) is an autosomal dominant subtype of nonpolyposis colorectal carcinoma characterized by development of sebaceous gland tumors and visceral malignancies. The cutaneous characteristics of the syndrome are sebaceous adenoma, carcinoma, basal cell carcinoma, and keratoacanthoma with sebaceous differentiation, whereas visceral malignant diseases include colorectal, endometrial, urological, and upper gastrointestinal tumors. Early recognition of the syndrome

in patients with sebaceous gland tumors facilitates early detection of malignancies. Colorectal cancer is the commonest visceral neoplasm to occur in MTS patients (1).

In this case report, we describe a rare case of MTS associated with colon cancer, and we demonstrate the important role of the dermatopathologist in alerting the clinician to the possibility of MTS when the diagnosis of sebaceous neoplasm is made.

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CASE REPORT

A 57-year-old man presented with hyperkeratotic plaque on his upper lip. The lesion had slowly increased in size. The patient had suffered from pain and bleeding. The lesion was a well-demarcated, 2x1.5 cm, irregularly shaped hyperkeratotic plaque. No palpable lymph node enlargement was perceived. The patient's family history was positive for cancer diagnosis. His sister was diagnosed with colon, his mother with pancreas and his father with stomach cancer. The patient had a history of tobacco use (one pack/day), and was in an employment with a daily sun exposure of 5-6 hours/day. The lesion was removed. The histopathological diagnosis was moderately differentiated squamous cell carcinoma (SCC), which showed nests of atypical squamous cells imposing on the dermis (Figure 1). The margins were tumor-free.

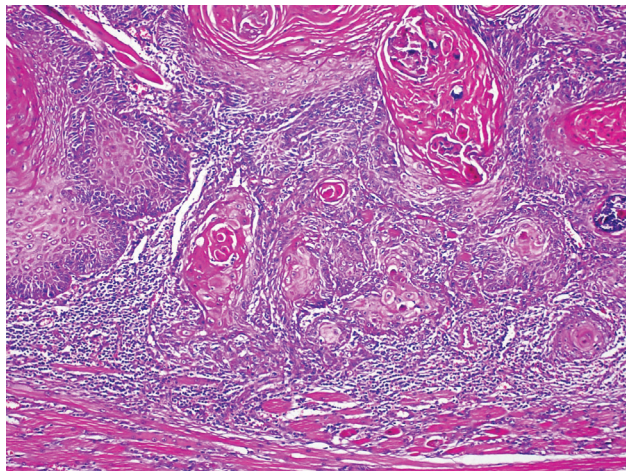


Figure 1. Moderately differentiated squamous cell carcinoma of the upper lip (H&E, x100).

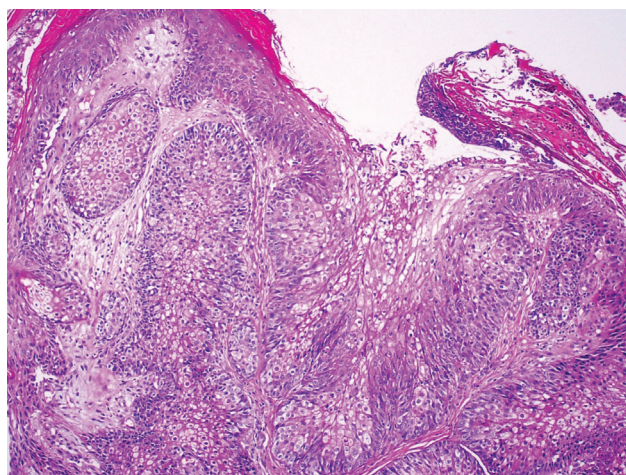


Figure 2. Sebaceous adenoma on the forehead (H&E, x100).

The lesion was clinically staged as T1N0M0. On physical examination, there were also numerous yellow-white, slightly raised lesions on the face. Histopathological examination of the forehead lesion revealed lobules of sebaceous cells in the dermis with a minority of surrounding basaloid cells, which was consistent with a diagnosis of sebaceous adenoma (Figure 2). Due to various sebaceous lesions and the family history of cancer, the diagnosis of MTS was suggested. Colonoscopy evidenced a mass lesion at the hepatic flexura of the ascending colon. Biopsy specimen showed poorly differentiated invasive adenocarcinoma at the colon, staged as T3N0M0 (Figure 3). Right hemicolectomy was performed. No visceral metastases or lymph node involvement was noted. The patient was referred to the Oncology Department for further management.

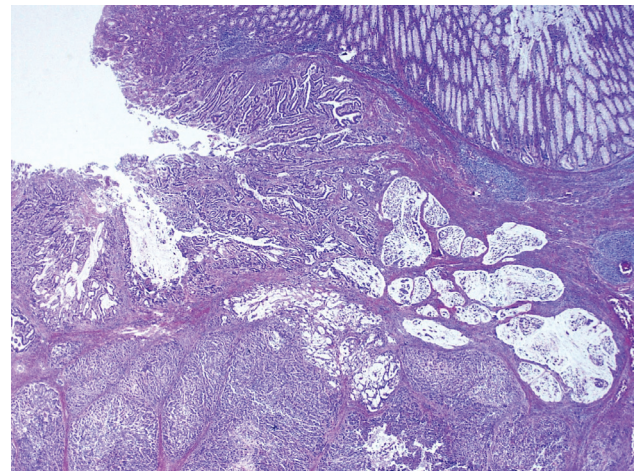


Figure 3. Adenocarcinoma of the colon (H&E, x20).

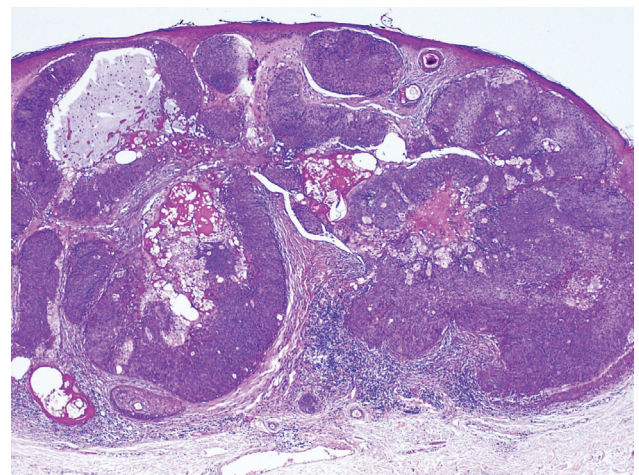


Figure 4. Basal cell carcinoma with adnexal differentiation type of the chest (H&E, x40).

Two years later, the patient presented with a nodular lesion on the chest. The lesion was treated with wider excision and follow-up. Histopathological examination showed basal cell carcinoma, differentiated type. The tumor showed adnexal differentiation. Surgical margins were negative (Figure 4).

The patient and his family receive regular follow-up including gastroenterology, dermatology and oncology departments. Follow-up examination at 12 months revealed no evidence of relapse for the SCC or colon carcinoma.

DISCUSSION

Muir-Torre syndrome (MTS) is rare genodermatosis defined by sebaceous neoplasms, keratoacanthomas and high incidence of internal malignancies, commonly colon cancer (2). Accepted criteria for the diagnosis of the syndrome include the presence of at least one sebaceous neoplasm (sebaceous adenoma, sebaceous carcinoma) and visceral malignancy. Multiple primary carcinomas at different sites are characteristics of this syndrome.

Sebaceous tumors are unusual neoplasms, reported as specific markers of MTS. Sebaceous adenoma generally appears on the face, scalp and eyelids as yellow papules or nodules. It shows irregularly shaped, closely packed sebaceous glands that communicated with one or more dilated infundibula or directly to the surface. These tumors are deeply located in the dermis and exceptionally show pleomorphism (3). Sebaceous carcinoma is a rare aggressive malignant tumour most commonly occurring in the periocular region. Since the tumor often presents with an appearance similar to more common benign lesions, it is frequently misdiagnosed. Thus, the benign lesions should be considered in the differential diagnosis of any eyelid lesion. The tumor appears as a firm yellow nodule with tendency to ulcerate and invade the adipose tissue of the orbit. The tumor cells are pleomorphic (4). Although it is thought to be resistant to radiation therapy, some case reports have shown remission with treatment (5). The sebaceous cancers in MTS are less aggressive than sporadic types. The studies have shown sebaceous neoplasms occurring before (22%), concurrent with (6%) or even after the diagnosis of visceral malignancy (56%) in MTS patients (6). In our patient, SCC and sebaceous adenomas were diagnosed before the colorectal cancer.

Squamous cell carcinoma (SCC) is the most frequent second cancer of the skin. Solar radiation, occupation, tobacco and/or alcohol abuse, as well as infectious agents such as human papilloma virus and herpes simplex virus, are among the etiological factors. The most commonly accepted exogenous cause of skin SCC is exposure to UV light with subsequent DNA damage, hyperkeratinization, keratinocyte transformation, and associated mutagenicity (7). UV-mediated hyperkeratinization results in an increase in the production of proinflammatory cytokines, which are potent synergistic inducers of endothelin-1 synthesis (8). Elevated plasma endothelin-1 levels in actinic keratosis (regarded as a precancerous lesion of SCC) have been reported (9). Increased endothelin-1, resulting indirectly in hypersecretion of certain growth factors [e.g., basic fibroblast growth factor, stem cell factor, and granulocyte-macrophage colony-stimulating factor (10)], or directly functioning as potential growth factor and mitogen, leads to further hyperkeratinization, keratinocyte transformation and DNA damage. Repair of DNA damage is essential for genomic integrity. The failure of DNA repair mechanisms together with familial and other genetic predispositions (including defects in DNA mismatch repair genes and microsatellite instability seen in MTS) results in multiple tumorigenesis. It is well known that tobacco abuse may also cause the DNA damage. More than 95% of diagnosed cases of lip SCCs arise from the lower lip because the upper lip is far less exposed to the sun than the lower (11). No conclusive results have been reported regarding the association of lip cancer with tobacco smoke. Smoking can affect both lips equally. SCC in our case was at the upper lip. Because the SCC is a multifactorial disease, we suggest that smoking, sun exposure, and insufficient DNA repair mechanisms together contribute to malignant transformation.

Colorectal cancer is the most common cancer in patients with MTS. The lesions are located more in the proximal colon. The discovery of colorectal tumors in MTS patients occurs about one decade earlier than in the general population. The findings of proximal colon cancers are similar to those seen in cancer family syndromes (12). Fifty-one percent of MTS patients develop at least one colorectal cancer. Colonic polyps and adenomas are common in MTS patients. They are especially prevalent in patients with colorectal carcinoma (13). Colorectal cancer in MTS patients tends to be of

low grade and has a relatively low incidence of metastasis. The patient in our case presented aggressive adenocarcinoma of the colon; fortunately, no lymph node or visceral metastases were found. Early colonoscopy may be considered for the diagnosis of clinically non-evident lesions.

The second most common site of tumor development is the urogenital apparatus (endometrium, ovary, bladder, kidney, and ureter), diagnosed in 22% of these subjects. In addition, malignancies in many other sites including the breast, blood, inner ear, parotid, tongue, larynx, lung, and cartilage have also been reported (14).

There are two types of MTS. The most common type is a phenotypic variant of hereditary non-polyposis colorectal cancer. It is characterized by defects in DNA mismatch repair genes. This type of MTS develops at an early age and has a strong family history of cancer. Mutations may arise in either the *MSH2* or *MLH1* gene. Studies have shown that mutations in *MSH2* are the most common, comprising about 90% of MTS cases. In addition, about 10% of MTS patients have mutations in *MLH1* (15). Recently, patients with mutations in *MSH6* have also been identified. Interestingly, in 31% of the MTS patients constituting the second type of the syndrome, there are no known defects in mismatch repair genes. That type of MTS has been associated with mutations in MuY homolog (*MYH*), a base excision repair gene, involved in the repair of the mutations related to accentuated oxidative stress. This type shows cancers with late onset and a less pronounced family history. The pathogenesis for this subtype is undefined (16). Mismatch repair is an important form of DNA repair. The products of mismatch repair genes play important roles in distinguishing and repairing mispairing and slippage errors in DNA synthesis. Mutations in mismatch repair genes cause defects in associated proteins, which in turn result in the accumulation of replication errors and genetic instability in visceral and skin tumors in patients

with MTS (17). In addition, mutations in DNA repair genes result in accumulation of errors in microsatellite sequences (common repeated sequences of DNA consisting of 1-6 base pairs), so they become either shorter or longer. Thus, microsatellite instability appears. Many skin neoplasms including melanocytic nevi, malignant melanoma, basal cell carcinoma, and SCC show the highest frequency of microsatellite instability (18).

Immunohistochemistry assessment for *MSH2*, *MLH1* and *MSH6* and microsatellite instability analysis are two screening tests for MTS patients. According to the American Society of Clinical Oncology, genetic testing should only be offered when there is a strong family history of cancer, an early age of cancer onset, interpretable test results, and direct consequences for patient management. Unfortunately, in view of their costs, we could not perform immunohistochemistry staining and microsatellite instability analyses in our patient.

MTS patients need a multidisciplinary approach including oncologist, internist, dermatologist, and gastroenterologist and genetic counseling. Annual history, physical examination, and urinalysis, periodic endometrial sampling, and transvaginal ultrasound (US) are important in those patients. A detailed personal and family history of malignancy is necessary. Cohen et al. (2) suggested a surveillance program for patients with MTS including annual clinical examination, carcinoembryonic antigen assessment, cervical smear, chest radiography, and urine cytology, and colonoscopy or barium enema every three to five years. Other authors suggested colonoscopy should be more frequent, starting at 25-30 years of age and repeated every two to three years (19). There is disagreement about whether to continue lifelong screening or to stop between 65-75 years of age. It seems reasonable to consider the patient's overall state of health, comorbidities and personal preference when deciding when to terminate the surveillance regimen.

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