Acta Dermatovenerol Croat 2023;31(3):144-147 CASE REPORT

Muir-Torre Syndrome with Novel Mutation in the MSH2 Gene

Eda Ustaoglu[1], Senay Agirgol[2], Huri Sema Aymelek[3], Ezgi Isil Turhan[4]

[1]Department of Dermatology, Bursa City Hospital, Bursa, Turkey; [2]Department of Dermatology, Cam and Sakura Hospital, Istanbul; [3]Department of Medical Genetic, Bursa City Hospital, Bursa, Turkey; [4]Department of Pathology, Bursa City Hospital, Bursa, Turkey

Corresponding author:
Eda Ustaoglu, MD
University of Health Sciences,
Bursa City Hospital
Dogankoy District, 16110 Nilufer
Bursa, Turkey
dredatemel@yahoo.com

Received: February 28, 2023
Accepted: May 22, 2023

ABSTRACT Muir-Torre syndrome (MST) is a rare autosomal dominant subtype of hereditary non-polyposis colorectal carcinoma. The diagnosis is established based on the coexistence of sebaceous gland tumors and visceral organ malignancies. Mutations in the mismatch repair genes are responsible for Muir-Torre syndrome. Internal malignancies seen in MTS are most commonly colorectal, gastrointestinal system, endometrial, genitourinary system, breast, lung, brain, and hepatobiliary system malignancies. Detection of sebaceous neoplasia is essential in investigating Muir-Torre syndrome, allowing early detection of internal malignancies. Herein, we present the case of a patient with sebaceous adenomas, internal malignancies, and a new mutation detected during the genetic examination.

KEY WORDS: hereditary carcinoma, sebaceous adenoma, MSH2 gene

INTRODUCTION

Muir-Torre syndrome (MTS) is a rare autosomal dominant subtype of hereditary non-polyposis colorectal carcinoma (HNPCC), also known as Lynch syndrome (1). Mutator S Homologue (MSH) 2, Mutator L Homologue (MLH) 1, Postmeiotic Segregation (PMS) 2 and, less frequently, MSH6 mismatch repair (MMR) genes are responsible for this syndrome (2). Germline mutations in these MMR genes lead to DNA microsatellite instability, increasing the likelihood of tumor formation. The diagnosis is established by at least one sebaceous gland tumor (sebaceous adenoma, sebaceous carcinoma, basal cell carcinoma with sebaceous differentiation) or the association of keratoacanthoma with sebaceous differentiation and visceral organ malignancy (3). Detection of sebaceous tumors is essential in investigating Muir-Torre syndrome, allowing early detection of internal malignancies and screening for possible malignancies.

Herein, we present the case of a patient with multiple sebaceous adenomas on the face diagnosed with Muir-Torre, with loss of MSH2 and MSH6 expression on immunohistochemical (IHC) examination and a new mutation in the MSH2 gene on genetic examination that has not been previously described in the literature.

CASE REPORT

A fifty-seven-year-old female patient was admitted to our clinic with a 5 mm diameter, erythematous, eroded and scaled papular lesion in the left zygomatic region lasting ten months (Figure 1). Two more yellow papular lesions with the diameter of a pin were found on the forehead and lateral side of the mouth in the dermatological examination of the patient. A punch biopsy specimen was taken from the most prominent lesion for histopathological examination (Figure 2). The patient had been operated on for

Acta Dermatovenerol Croat
2023;31(3):144-147

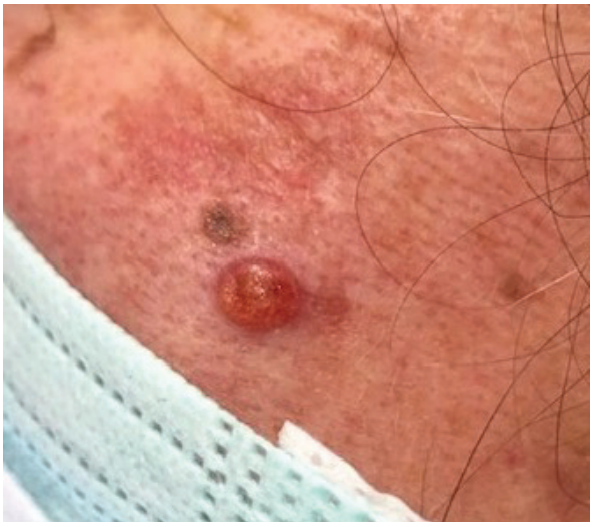

Figure 1. Erythematous, eroded, and scaled papular lesion in the left zygomatic region.

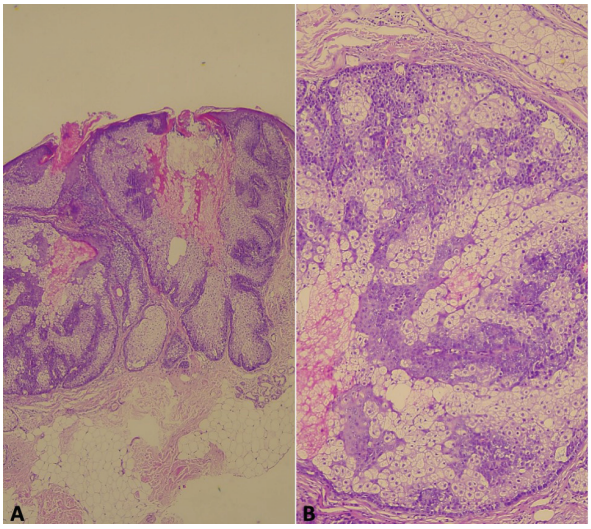

Figure 2. The tumor had a well-circumscribed appearance and a lobular growth pattern with adjacent epidermal junctions (hematoxylin and eosin, ×4). (A) The tumor had a light-dark appearance due to basaloid polygonal germinative cells (dark) in the periphery and sebaceous cells (light) containing a cytoplasmic lipid vacuole in the central area (hematoxylin and eosin, ×20) (B).

cecum cancer ten years ago and for rectal cancer eight years ago. In the patient's family history, her father had prostate cancer, her sister had cervical cancer, her brother had colon cancer and her nephew had brain cancer. Punch biopsy was also performed in terms of IHC examination with the suspicion of MTS, and MLH1 and PMS2 expression were observed, while MSH2 and MSH6 expression were absent (Figure 3). In genetic analysis, heterozygous c.1056_1057delTA, p.Asp352GlufsTer36 change was observed in exon 6 of the MSH2 gene. Although this change has not been reported in the literature before, it has been reported that it may have a damaging effect as it leads to early termination, according to the ACMG (American College of Medical Genetics) guidelines (4).

The patient was diagnosed with MTS and was screened for genitourinary system, gynecological, breast, lymphoma, and respiratory tract malignancies and was followed up annually.

DISCUSSION

MTS is a subtype of HNPCC diagnosed by associating sebaceous neoplasia or keratoacanthoma with visceral malignancies. Approximately 200 cases of this rare syndrome have been reported (5). Although

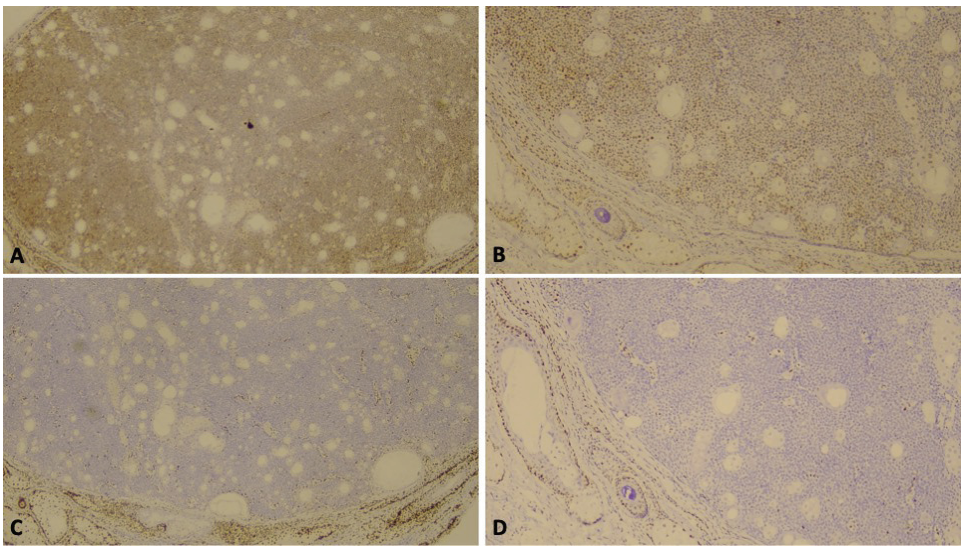

Figure 3. Sebaceous adenoma showed immunohistochemical expression for MLH1 (immunohistochemistry (IHC), ×10) (A) and PMS2 (IHC, ×10) (B). There was loss of expression of MSH2 (IHC, ×10) (C) and MSH6 (IHC, ×10) (D).

MTS can be observed sporadically, albeit rarely as a result of acquired somatic mutations, its autosomal dominant inheritance has been accepted (5). While mutations are primarily seen in the MSH2 and MLH1 genes, MTS was diagnosed with the coexistence of sebaceous adenoma and visceral malignancy as a result of the germline mutation in the MSH6 gene, with the first case reported in 2007 (6).

Muir-Torre syndrome mainly occurs as a result of germline mutations in DNA repair genes such as MLH1, MSH2, MSH6, and PMS2. In addition, mutations in some genes such as EPCAM can lead to the disease by causing suppression in these genes. Among these, MSH2 is one of the most common disease-causing genes (7-9). MSH2 and MSH6 gene analyses were performed in our patient because of the loss of expression in MSH2 and MSH6 in IHC analysis. A new mutation was detected in MSH2 that was predicted to be pathogenic and the was not previously described in the literature. Heterozygous pathogenic variants in the MSH2 gene are associated with an increased risk for extracolonic cancers (7-9). In addition to having a family history of extracolonic cancers such as brain tumors, cervical, and prostate cancers, the patient in our case had cecum cancer, while the patient's brother had colon cancer.

The absence of staining in MSH6 gene products was positive, predictive for the diagnosis of MTS alone at 67%, while MLH1 and MSH6 have 100% predictive value; MLH1, MSH2, and MSH6 have 100% positive predictive value in IHC analysis of sebaceous neoplasms (10). In our case, MHS2 and MSH6 expressions were absent in the immunohistochemical examination. In the study conducted by Chibber *et al.* (10), 31 sebaceous adenomas and ten sebaceous epitheliomas were examined in the IHC analysis. Mutations in at least one mismatch repair gene were found in 24 of these lesions, and MSH2 + MSH6 mutations were found in 11. MTS was diagnosed by clinical history in 6 of 11 cases (positive predictive value 55%).

The most common cutaneous tumors seen in MTS are sebaceous adenomas (68%). The others are sebaceous epithelioma, sebaceous carcinoma, keratoacanthoma, basal cell carcinoma with sebaceous differentiation, and cystic sebaceous tumors (3). Sebaceous neoplasms with MMR gene mutations can be located in other body areas besides the head and neck region. The probability of MTS is considered higher for neoplasms in these regions (1). Sporadic sebaceous neoplasms are frequently located in the face and neck; IHC is highly recommended for lesions in this area (3). Slow-growing, pink-yellow papules or nodular lesions with umbilication and ulceration establish the clinical picture. In our case, the 2 mm diameter papular lesion with the appearance of sebaceous hyperplasia on the lateral side of the mouth at the patient's first visit showed a rapid growth pattern and transformed into a papular lesion with telangiectasias, reaching a diameter of 7 mm at the follow-up three months later. This lesion was also histopathologically compatible with sebaceous adenoma.

Internal malignancies seen in MTS are most commonly colorectal, gastrointestinal system, endometrial, genitourinary system, breast, lung, brain, and hepatobiliary system malignancies (11). Almost half of the patients have two or more involved organs, and 10% have involvement of more than four visceral organs (12). Therefore, annual screening for visceral malignancies should be performed after the diagnosis of MTS. Annual upper and lower gastrointestinal endoscopy, breast and pelvic system examinations for women, and testicular and prostate examinations for men are recommended (1). In MTS, colorectal carcinoma tends to settle in the splenic flexure and proximal colon, unlike in the general population (11). Our patient had also undergone surgery for cecal cancer ten years ago, which is consistent with the literature.

Diagnosing MTS in patients presenting with sebaceous neoplasia is essential in detecting coexisting visceral malignancy and screening patients for possible malignancies.

References:

1. Gay JT, Troxell T, Gross GP. Muir-Torre Syndrome. StatPearls. StatPearls Publishing Copyright © 2022, StatPearls Publishing LLC.; 2022.
2. Ponti G, Manfredini M, Tomasi A, Pellacani G. Muir-Torre Syndrome and founder mismatch repair gene mutations: A long gone historical genetic challenge. Gene. 2016;589:127-32.
3. John AM, Schwartz RA. Muir-Torre syndrome (MTS): An update and approach to diagnosis and management. J Am Acad Dermatol. Mar 2016;74:558-66.
4. Richards S, Aziz N, Bale S, Bick D, Das S, Gastier-Foster J, *et al.* Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17:405-24.
5. Le S, Ansari U, Mumtaz A, Malek K, Patel P, Doyle A, *et al.* Lynch Syndrome and Muir-Torre Syndrome: An update and review on the genetics, epidemiology, and management of two related disorders. Dermatol Online J. 2017;23(11):13030/qt8sg5w98j.
6. Mahalingam M. MSH6, Past and Present and Muir-Torre Syndrome-Connecting the Dots. Am J Dermatopathol. Apr 2017;39:239-49.

7. Everett JN, Raymond VM, Dandapani M, Marvin M, Kohlmann W, Chittenden A, *et al.* Screening for germline mismatch repair mutations following diagnosis of sebaceous neoplasm. JAMA Dermatol. Dec 2014;150:1315-21.
8. Lamba AR, Moore AY, Moore T, Rhees J, Arnold MA, Boland CR. Defective DNA mismatch repair activity is common in sebaceous neoplasms, and may be an ineffective approach to screen for Lynch syndrome. Fam Cancer. 2015;14:259-64.
9. Jessup CJ, Redston M, Tilton E, Reimann JD. Importance of universal mismatch repair protein immunohistochemistry in patients with sebaceous neoplasia as an initial screening tool for Muir-Torre syndrome. Hum Pathol. 2016;49:1-9.
10. Chhibber V, Dresser K, Mahalingam M. MSH-6: extending the reliability of immunohistochemistry as a screening tool in Muir-Torre syndrome. Mod Pathol. 2008;21:159-64.
11. Hare HH, Mahendraker N, Sarwate S, Tangella K. Muir-Torre syndrome: a rare but important disorder. Cutis. 2008;82:252-6.
12. Coldron J, Reid I. Muir-Torre syndrome. J R Coll Surg Edinb. 2001;46:178-9.