An Illustrative Case of Muir-Torre Syndrome

Contribution of Immunohistochemical Analysis in Identifying Indicator Sebaceous Lesions

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Background: Muir-Torre syndrome (MTS) is an autosomal dominant genodermatosis characterized by the association of at least 1 cutaneous sebaceous tumor and 1 internal malignancy, often arising in the gastrointestinal tract. It is secondary to germline mutations in DNA mismatch repair genes, mainly MLH-1 and MSH-2.

Observations: We report the case of a 54-year-old man with a 2-year history of skin-colored papules clinically reminiscent of large sebaceous hyperplasias on the nose and back, but histologically diagnosed as sebaceous adenomas and epitheliomas. His family history was positive for colon cancer in the mother and 2 brothers. A colonoscopy done during the hospitalization revealed 2 sessile polyps in the left colon, both showing a low-grade dysplasia on the biopsy specimen. Immunohistochemical staining performed on the cutaneous and colic biopsy specimens revealed a lack of expression of MSH-2 and MSH-6. Genetic testing revealed microsatellite instability in the colon and cutaneous tumors.

Conclusion: The immunohistochemical testing for MSH-2, MSH-6, and MLH-1 is useful for rapid identification of an underlying mismatch repair defect and early diagnosis of MTS.

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MUIR-TORRE SYNDROME (MTS) is a phenotypic variant of the hereditary nonpolyposis colorectal cancer (HNPCC) characterized by the association of sebaceous skin tumors and internal malignancies, most frequently colon cancer. It was first described by Muir et al in 1967 and then by Torre in 1968.

The early identification of patients with MTS is important because affected patients are at increased risk of multiple primary malignancies. The dermatologist plays an important role because skin lesions often precede internal neoplasms. To this end, immunohistochemical analysis for the mismatch repair gene products MSH-2 and MLH-1 have been suggested to aid in the diagnosis of sebaceous neoplasms indicative of MTS.

REPORT OF A CASE

We report the case of a 54-year-old man without notable medical history but a 2-year history of multiple asymptomatic skin-colored papules on the nose and back. The lesions on the nose were excised and histologically identified as sebaceous adenomas. One year later he developed new identical lesions on the back (Figure 1). Histologic analysis revealed 2 sebaceous adenomas and 1 sebaceous epithelioma (Figure 2) on the nose and a sebaceous epithelioma on the back. The family history was positive for colon cancer in the mother and 2 brothers (the Amsterdam criteria for HNPCC was fulfilled).

Findings from further investigations, including a complete laboratory workup and chest radiography, were normal. A colonoscopy revealed 2 sessile polyps in the left colon, at 15 cm and 35 cm from the anus, histologically corresponding to low-grade dysplasia. Sigmoidectomy was subsequently performed because an endoscopic resection of the lesions was not possible. The pathologic findings revealed 2 adenomas with low- to high-grade zones of dysplasia.

To determine if loss of expression of DNA mismatch repair genes MSH-2, MSH-6, MLH-1, and PMS-2 was present in the patient’s neoplasm, tumor samples fixed in 4% buffered formalin and embedded in paraffin were evaluated by immunohistochemical analysis. Briefly, sections were submitted to microwave oven heating prior to staining, labeled with an-
tibodies against MSH-2 (clone FE11; Oncogene Research Products, Cambridge, Mass), MSH-6, MLH-1, and PMS-2 (all BD Biosciences, Franklin Lakes, NJ), and revealed using the avidin biotin complex (ABC) method. The sebaceous epithelioma of the back (Figure 3) and the adenoma of the colon (Figure 4) both showed a significant lack of expression of MSH-2 and MSH-6 and a normal expression of MLH-1 and PMS-2. Genetic testing demonstrated high-grade microsatellite instability with additional alleles of the microsatellite markers BAT25, BAT26, and D2S123 in the colon adenoma and BAT26 and D17S250 in the cutaneous adenoma on the back.

The diagnosis of MTS was therefore determined in our patient based on the presence of skin sebaceous tumors associated with colon polyps and a positive family history of colon cancer.

**COMMENT**

Muir-Torre syndrome is an autosomal dominant genodermatosis characterized by the association of at least 1 cutaneous sebaceous tumor and at least 1 internal malignancy, most frequently of the colon but also the endometrium, ovaries, breast, and urinary tract. More recently, keratoacanthomas without sebaceous lesions associated with MTS have also been reported. Sebaceous neoplasms have the potential to arise from any sebaceous gland in the body. They have the greatest predilection for the nose, the eyelids, and areas with abundant sebaceous glands. In MTS, sebaceous neoplasms generally occur after the visceral cancer, but they can also be the presenting sign of this syndrome.

A wide spectrum of benign and malignant sebaceous tumors is encountered in MTS, including sebaceous hy-
perplasias, sebaceous adenomas, sebaceous epithelio-
mas, and carcinomas. These tumors, showing highly
variable growth patterns, are sometimes difficult to classify.
Moreover, the terminology is still being debated. Troy and Ackerman10 coined the term sebaceaoma for lobular
tumors admixing small basaloid cells and a mature sebaceous component. Rutten et al11 recently described a series of large sebaceous tumors with a cystic growth pattern
mainly located on the trunk. They outlined that occurrence of these peculiar cystic sebaceous tumors is highly suggestive for MTS and represents an interesting cutaneous marker. In contrast, the frequent sebaceous gland hyperplasia is not indicative of this syndrome, but given the clinical similarity between the sebaceous neoplasms described herein—at least in their early stages of development—and sebaceous hyperplasia, identification of patients with sebaceous lesions indicative of MTS remains a challenge.

Muir-Torre syndrome is regarded as a variant of
HNPPC and is secondary to germline mutations in DNA mismatch repair genes, mainly MSH-2 and MLH-1. In MTS and HNPPC, germline mutation in 1 of the mismatch repair genes is complemented by a second somatic mutation localized in the contralateral allele, often a deletion. The usual consequence of this second somatic mutation is the lack of expression of the gene.3 The MSH-2 and MSH-6 proteins normally form a stable heterodimer. Consequently, mutation in the MSH-2 gene can produce an instability of this heterodimer, with secondary lack of expression of MSH-6 protein.3 Isolated MSH-6 and PMS-2 mutations have not been reported in the literature, and their analysis does not increase the sensitivity of the diagnosis of MTS. Nevertheless, MSH-6 and PMS-2 testing were performed as part of a standard battery of tests to screen for HNPPC.

Tumoral tissues in MTS generally exhibit high-grade microsatellite instability as a consequence of accumulated mutations in short repetitive DNA sequences (microsatellites) secondary to the mismatch repair deficiency. Sebaceous gland neoplasms show the greatest frequency of high-grade microsatellite instability compared with other benign or malignant neoplasms of the skin (benign melanocytic nevi, dysplastic melanocytic nevi, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, and Bowen disease).11 Furthermore, in a study of unselected sebaceous neoplasms, microsatellite instability has been shown in 60% of malignant sebaceous skin tumors (adenomas, epithelomas, and carcinomas) as opposed to only 3% of sebaceous hyperplasias.12 This is very important to know because a skin lesion clinically and histologically compatible with a sebaceous neoplasm may be suggestive of an underlying DNA mismatch repair defect.

The lack of expression of the mismatch repair genes can be typically identified in tumoral tissues by immunohistochemical analysis.3,5,12 In such cases, absence of immunohistochemically stained cells within a section that also contains normally stained cells is indicative of cells harboring a mutation in a mismatch repair gene. These immunohistochemical assays are highly sensitive and specific because the antibodies used are directed at the DNA mismatch repair enzymes, which are present in the nucleus of all but a very few terminally differentiated cells (eg, some germline cells). Thus, immunohistochemically identifiable expression of DNA mismatch repair enzymes indicates the absence MTS.

The presence of skin sebaceous tumors associated with a personal or a familial history of internal neoplasms is very suggestive of MTS, and the biopsy specimen should always be immunohistochemically stained. This is a fast and a simple analysis, useful for identifying the mutated gene and obtaining an early diagnosis. In the event of a negative staining result, indicative of a mismatch repair gene mutation, the latter can thereafter be confirmed by sequencing of DNA from the lesion biopsy specimens, as was done in our case.

The tumors in MTS must be treated by standard methods, usually surgical ones. There is no established prophylactic regimen, but successful management with isotretinoin and interferon alfa-2a has been described.10 In conclusion, this case illustrates the importance of the dermatologist and the use of new immunohistochemical techniques to evaluate MSH-2 and MLH-1 expression levels for the early diagnosis in patients with MTS presenting with skin lesions. Screening for internal malignancies must always be performed in patients presenting with sebaceous skin tumors because this can be life saving.3,17

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