OBSERVATION

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 colonic 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 and the nose (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.3 More recently, keratoacanthomas without sebaceous lesions associated with MTS have also been reported.4 5 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.6 7

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 sebocoma for lobular
tumors admixing small basaloid cells and a mature se-
baceous component. Rutten et al11 recently described a
series of large sebaceous tumors with a cystic growth pat-
ttern mainly located on the trunk. They outlined that oc-
currence 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 neo-
plasms 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
HNPPCC and is secondary to germline mutations in DNA
mismatch repair genes, mainly MSH-2 and MLH-1.3,2 In
MTS and HNPPCC, germline mutation in 1 of the mis-
catch repair genes is complemented by a second so-
matic mutation localized in the contralateral allele, of-
ten a deletion. The usual consequence of this second
somatic mutation is the lack of expression of the gene.5
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 sec-
ondary 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 sen-
sitivity of the diagnosis of MTS. Nevertheless, MSH-6 and
PMS-2 testing were performed as part of a standard bat-
tery of tests to screen for HNPPCC.

Tumoral tissues in MTS generally exhibit high-grade
microsatellite instability as a consequence of accumu-
lated mutations in short repetitive DNA sequences (mi-
crosatellites) secondary to the mismatch repair defi-
ciency. Sebaceous gland neoplasms show the greatest
frequency of high-grade microsatellite instability com-
pared with other benign or malignant neoplasms of the
skin (benign melanocytic nevi, dysplastic melanocytic
nevi, malignant melanoma, basal cell carcinoma, squa-
rous cell carcinoma, and Bowen disease).3,13 Furthermore,
in a study of unselected sebaceous neoplasms, mi-
crosatellite instability has been shown in 60% of malignant
sebaceous skin tumors (adenomas, epithelomas, and car-
cinomas) as opposed to only 3% of sebaceous hyperpla-
sias.14 This is very important to know because a skin le-
son 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 immu-
nohistochemical analysis.3,5 In such cases, absence of im-
nunohistochemically 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 spe-
cific 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
(e.g., some germline cells). Thus, immunohistochemi-
cally identifiable expression of DNA mismatch repair en-
zymes indicates the absence MTS.

The presence of skin sebaceous tumors associated with
a personal or a familial history of internal neoplasm 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 meth-
ods, usually surgical ones. There is no established pro-
phylactic regimen, but successful management with isotre-
tinoin and interferon alfa-2a has been described.16

In conclusion, this case illustrates the importance of the
dermatologist and the use of new immunohistochemi-
tical techniques to evaluate MSH-2 and MLH-1 expres-
sion levels for the early diagnosis in patients with MTS
presenting with skin lesions. Screening for internal mal-
gnancies must always be performed in patients present-
ing with sebaceous skin tumors because this can be life
saving.3,17

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