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Sebaceous Gland Tumors of the Eyelids and Conjunctiva in the Muir-Torre Syndrome

A Clinicopathologic Study of Five Cases and Literature Review

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Purpose: To study the sebaceous tumors of eyelid/conjunctiva associated with Muir-Torre syndrome (MTS) and to determine the role of immunohistochemical markers (MSH2, mismatch repair gene) in the diagnosis of patients with MTS.

Methods: A retrospective, noncomparative case series of 5 patients diagnosed with MTS from our laboratory. We also reviewed all previously reported cases of sebaceous eyelid tumors with a visceral malignancy.

Results: Four of the 5 patients were men, with a mean age of 55 years (range, 41 to 76 years). Four of the 5 patients had gastrointestinal carcinoma. On histopathological examination, 4 of the 5 tumors were classified as sebaceous adenomas that exhibited a distinct lobular pattern with prominent basaloid cells at the periphery of the lobules. One tumor was classified as a well-differentiated sebaceous gland adenocarcinoma. The diagnosis of MTS in all 5 patients was made after the diagnosis of the eyelid lesions. Immunohistochemical stains showed a lack of MSH2 expression in two tumors, which is highly consistent with MTS.

Conclusions: Muir-Torre syndrome should be considered in patients who develop sebaceous tumors of the ocular adnexa. Immunohistochemistry for MSH2 is a practical initial approach for screening MTS in patients with sebaceous tumors.

Muir-Torre syndrome (MTS) is a rare autosomal dominant genodermatosis, first described in 1967, characterized by the presence of sebaceous tumors and internal malignancies in the absence of other predisposing factors.[1] The sebaceous neoplasms characteristic of MTS comprise sebaceous adenomas, sebaceous epitheliomas, basal cell epitheliomas with sebaceous differentiation, cystic sebaceous tumors, and sebaceous carcinoma. The most common internal malignancies associated are gastrointestinal (47%), followed by genitourinary (21%) and breast (12%).[2]

Muir-Torre syndrome is now considered a subtype of the more common hereditary nonpolyposis colorectal cancer syndrome (HNPCC), which has been ascribed to mutations in the DNA mismatch repair (MMR) genes MSH2 or MLH1and is in close linkage to a locus on chromosome 2p.[3] Although MTS is rare, it is important to consider this entity in patients in whom solitary or multiple sebaceous tumors have been diagnosed, particularly since cutaneous lesions may be the first sign of the disease in 41% of these patients.[1] Most cutaneous lesions occur in the head and neck region; only a small proportion involve the eyelid.

We reviewed the literature focusing on the clinical characteristics and histopathologic features of the sebaceous tumors of eyelid/conjunctiva associated with visceral ma-

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lignancies. We summarized our experience with sebaceous gland tumors of eyelid/conjunctiva in patients with MTS and compare it with published cases. Furthermore, we tried to determine whether an immunohistochemical approach targeting expression of MSH2 in MTS-related skin tumors could be used as initial screening test. For this reason, we examined retrospectively the expression of MMR gene (MSH2) by immunohistochemistry on paraffin-embedded sections from two tumors.

METHODS

We performed a complete Medline (NCBI, NLM, 1967–2002) search for original articles on sebaceous gland tumors and associated internal malignancy.

All of the cases of sebaceous tumors of eyelids diagnosed in our laboratory were assessed for additional family and personal history.

A mouse antihuman monoclonal antibody was used for detection of the MMR protein MSH2 (MSH2 clone, FE11, Oncogene Research Products, Boston, Mass., U.S.A.). Five micra paraffin sections were deparaffinized in xylene, rehydrated in graded alcohols, and washed in deionized water. Heat-induced epitope retrieval (600-W microwave treatment twice for 15 minutes in prewarmed 10 mol/L sodium citrate buffer, pH 6) was used for MSH2 staining. Primary antibody was added (dilution: MSH2 1:80) and slides were incubated overnight at 4°C. Slides were then processed on an immunostainer (Dakoautostainer, Dako, Hamburg, Germany). The antigen-antibody binding was visualized by the dextran polymer conjugated to horseshoe rapid peroxidaxe. Replacement of the first antibody by phosphate-buffered saline was used as a negative control to assess the specificity of the antibodies. Normal meibomian glands of the eyelid and normal colonic mucosa were used as positive controls that disclose striking nuclear immunostaining.

RESULTS

Case 1

A 41-year-old Chinese man presented with a painless recurrent left upper eyelid nodule clinically resembling a chalazion. The lesion was completely excised and submitted for histopathologic examination. The patient had a history of nasopharyngeal carcinoma. Microscopically the tumor exhibited a lobular pattern with basaloid cells at the periphery of the lobules with central areas of sebaceous differentiation. Minimal mitotic activity was observed. The tumor had lobules and strands connected in multiple areas that formed a peculiar branching pattern

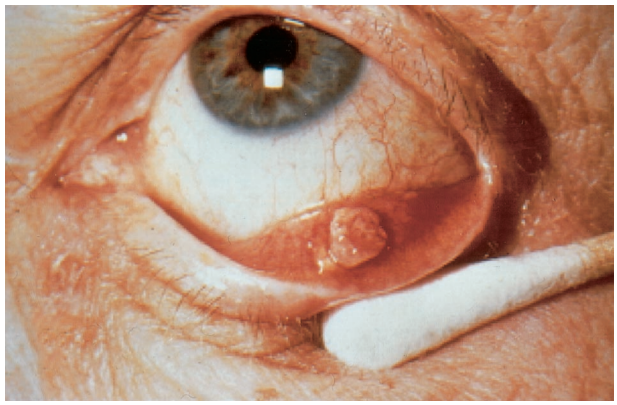

FIGURE 1. Case 2. A 63-year-old woman with a recurrent mass of the tarsal conjunctiva from the left lower eyelid.

to the conjunctival epithelium, which gave the lesion a hamartomatous appearance. At the base of the lesion, there were multinucleated giant cells surrounding lipid vacuoles, indicative of previous lipogranuloma (chalazion). The patient had a remarkable family history. His father had pancreatic carcinoma and one brother had gastrointestinal carcinoma.

Case 2

A 63-year-old woman had a recurrent lesion on the tarsal conjunctiva of the left lower eyelid (Fig. 1), which was diagnosed histologically as sebaceous adenoma. One month later she developed a similar lesion in her right eye, also diagnosed as sebaceous adenoma. Fourteen years before the appearance of the eyelid lesions, she was diagnosed with colon carcinoma. Two years later, she underwent hysterectomy for endometrial carcinoma.

Case 3

A 50-year-old man had a recurrent, pedunculated, lobulated, yellowish-tan mass of the left upper eyelid that was attached to the upper tarsus by a stalk (Fig. 2). On histopathologic examination, the tumor showed a papillary surface composed of tumor lobules with areas of central sebaceous differentiation. A diagnosis of sebaceous adenoma was made (Figs. 3 and 4). The patient had a poorly differentiated adenocarcinoma of the stomach 6 months prior to the eyelid lesion.

Case 4

A 78-year-old white man had a right upper eyelid lesion clinically resembling a viral papilloma (Fig. 5). On histopathologic examination, the tumor exhibited organoid features with basaloid proliferation toward the

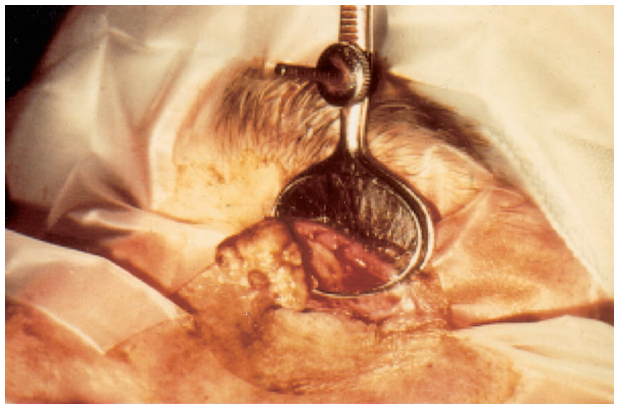

FIG. 2. Case 3. A 50-year-old man with a recurrent and pedunculated mass involving the left upper eyelid.

periphery of the lobules and central sebaceous differentiation. A diagnosis of sebaceous adenoma was made (Fig. 6). The patient had adenocarcinoma of the descending colon 9 years before the eyelid lesion.

Case 5

A 46-year-old black man had an ulcerated and hemorrhagic mass involving the left lower eyelid, clinically interpreted as a pyogenic granuloma (Fig. 7). Histologically, the tumor was diagnosed as a well-differentiated sebaceous adenocarcinoma. The tumor displayed prominent mitotic activity in some areas (Fig. 8). The patient had an adenocarcinoma of the colon diagnosed several years previously.

Results of Immunohistochemical Stains

Immunohistochemical stains for DNA mismatch repair gene (MSH2) lacked expression in the tumor lobules. In contrast, the normal meibomian gland showed striking nuclear staining (Fig. 9).

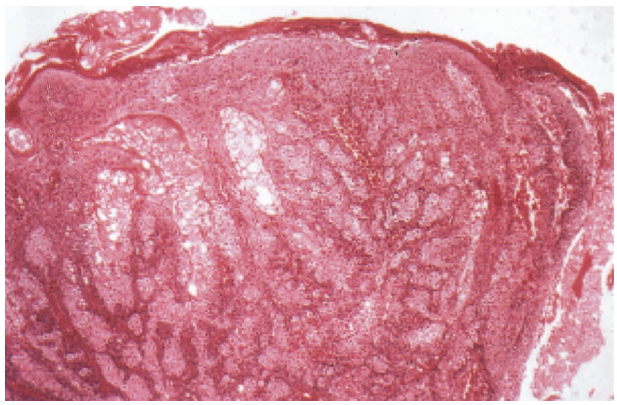

FIG. 3. Case 3. Sebaceous gland adenoma: The tumor-forming lobules and strands are connected in multiple areas to the overlying conjunctival epithelium, giving it a hamartomatous appearance (hematoxylin and eosin, original magnification ×60).

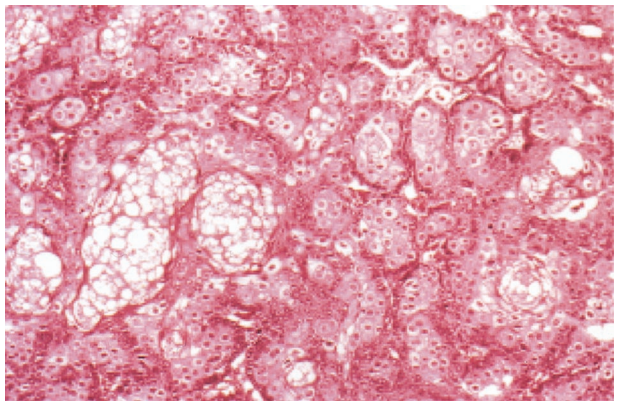

FIG. 4. Case 3. Higher magnification of Figure 3 shows mature lobules of sebaceous glands without cytologic atypia (hematoxylin and eosin, original magnification ×160).

Review of Literature

To date, a total of 24 cases of Muir-Torre syndrome involving the eyelid/conjunctiva have been reported[1,2,6,7–15,18] (see the Table). We report an additional 5 cases. Of the 24 cases we reviewed, the mean age of the diagnosis of the sebaceous tumor of eyelid was 53 years (range, 31 to 77 years), with a male/female ratio of 3:1. The location of the eyelid tumor was almost equal on the upper and lower eyelid, with one case arising in the medial canthal region. From the literature, the most common internal malignancies in the patients were of colorectal (43%) followed by genitourinary (21%), breast (14%), endometrial hyperplasia (1patient) and Hodgkins lymphoma (1 patient). The eyelid tumors observed in these patients were sebaceous carci-

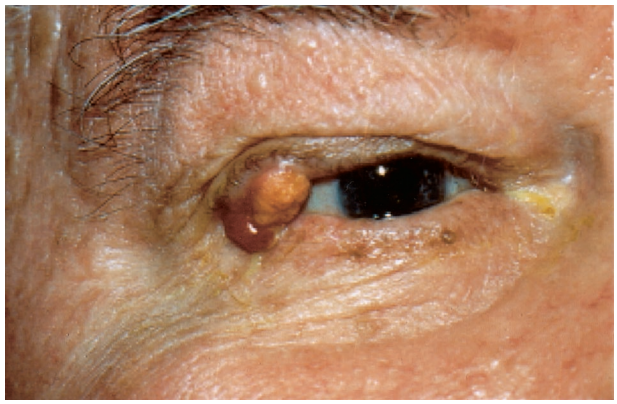

FIG. 5. Case 4. A 78-year-old man with a yellowish lobulated mass of the left upper eyelid and lateral canthus.

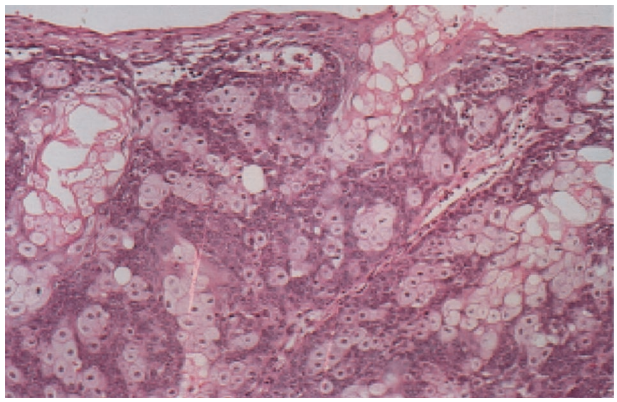

FIG. 6. Case 4. Sebaceous gland adenoma. The lesion from the patient shown in Figure 5 was diagnosed as sebaceous adenoma (hematoxylin and eosin, original magnification ×40).

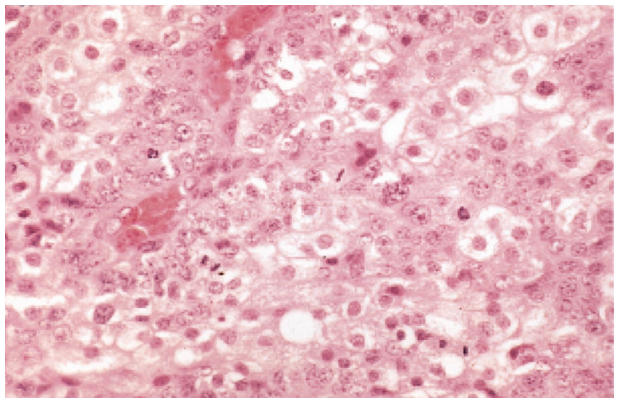

FIG. 8. Case 5. Well-differentiated sebaceous gland adenocarcinoma. The tumor is forming epithelial lobules with sebaceous differentiation. Prominent mitotic activity is present (hematoxylin and eosin, original magnification ×100).

noma 14 (58%) patients, sebaceous adenoma in 5 (21%) patients, sebaceous hyperplasia in 3 (13%) patients, and sebaceous epithelioma in 2 (8%) patients. There was a significant family history of visceral malignancies present in most of the patients. The diagnosis of MTS before the presentation of the eyelid tumor was made in only one patient.

DISCUSSION

Muir-Torre syndrome, described independently by Muir et al. in 1967 and Torre in 1968, is a disorder characterized by skin tumors showing sebaceous differentiation and visceral malignancies.[4,5] A subgroup of MTS cases represents an allelic variant of hereditary nonpolyposis colorectal cancer (HNPCC), an autosomal dominant predisposition to colorectal cancer and other internal malignancies. Whereas in HNPCC the proportion of MSH2 mutations almost equals the proportion of MLH1 mutations, MTS is most frequently caused by germ line mutations in MSH2.[3]

The occurrence of any sebaceous tumor mandates consideration of MTS and should suggest clinical evaluation of the patient to rule out visceral malignancies. Benign and malignant sebaceous gland tumors are relatively uncommon and a detailed clinical history might not be available initially, therefore the diagnosis of a sebaceous gland tumor should give rise to the suspicion of an inherited MMR gene defect to an ophthalmologist and pathologist.

MTS is more common in men. Four of 5 patients in

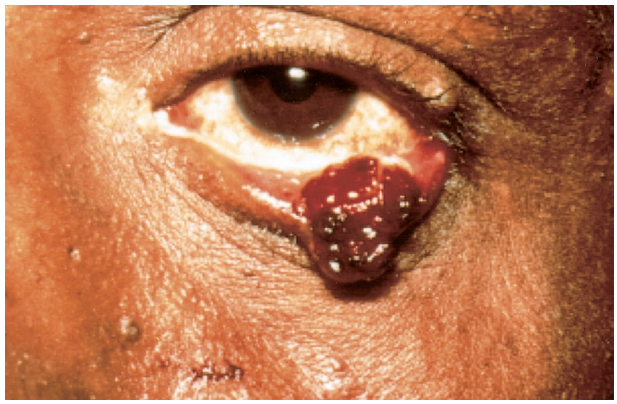

FIG. 7. Case 5. A 46-year-old man with an ulcerated, lobulated, and hemorrhagic mass involving the left lower eyelid.

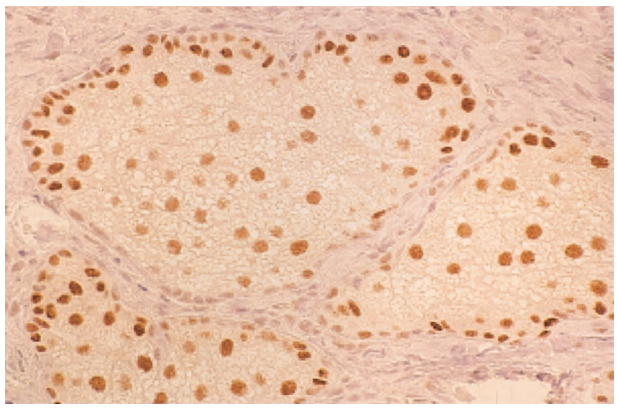

FIG. 9. Case 5. Immunohistochemistry for MSH2 on case shown in Figure 8 shows obvious nuclear staining in the normal sebaceous glands. In contrast, the tumor lobules lacked expression of MSH2 (MSH2 immunostain counterstained with hematoxylin, original magnification ×100).

TABLE 1. *Summary of clinical and histopathologic findings of cases of Muir-Torre Syndrome from the literature and the present study*

Case series/reports	No. of patients with eyelid tumors	Age/mean age of patients	Sex of patients	Location of eyelid tumor	Histologic findings of sebaceous lesions	Associated internal malignancies	Family history	Diagnosis of Muir-Torre before presentation of eyelid tumor
Mencia-Gutierrez et al.[7]	1	62	Male	Upper eyelid	Sebaceous carcinoma	Colon carcinoma, transitional cell carcinoma of ureter, rectal carcinoma	NS	Present
Spraul et al.[8]	1	61	Male	Lid margin of lower eyelid	Sebaceous hyperplasia	Colon polyp	Present	Absent
Stockl et al.[2]	1	56	Male	Upper eyelid	Sebaceous carcinoma	Cecum carcinoma	Present	Absent
Meier-Gibbons et al.[9]	1	42	Female	Lower eyelid	Sebaceous adenoma	Endometrial hyperplasia	Present	Absent
Cohen et al.[1]	1	31	Male	Upper eyelid	Sebaceous carcinoma In situ	Hodgkins lymphoma	Present	Absent
Jakobiec et al.[11]	2	70	Both male	1. Medial canthus 2. Lower eyelid	Sebaceous adenoma (n = 1) Squamous Cell carcinoma with Sebaceous differentiation (n = 1)	Testicular, caecum, rectosigmoid, colon carcinoma	Present	Present
Tillawi et al.[14]	6	51	4 Male 2 Female	NS	Sebaceous epithelioma (n = 1), adenoma (n = 2), hyperplasia (n = 2), carcinoma (n = 1)	Colon, prostate, breast carcinoma, lymphoma	Present in 5 patients	Absent
Page et al.[13]	1	77	Male	Lower eyelid	Sebaceous carcinoma	Prostate carcinoma	NS	NS
Charpentier et al.[6]	1	51	Female	Upper eyelid	Sebaceous carcinoma	Cecum carcinoma	NS	NS
Finan et al.[10]	2	NS	NS	NS	Sebaceous epithelioma (n = 1), Sebaceous carcinoma (n = 1)	Breast carcinoma, colon polyp	Present in both patients	Absent
Wolfe et al.[15]	6	NS	NS	NS	Sebaceous carcinoma (n = 6)	Breast, skin (most common)	NS	Absent
Jakobiec et al.[12]	1	48	Male	Upper eyelid	Sebaceous adenoma	Rectosigmoid carcinoma	Present	Absent
Rishi and Font (present study)	5	55	4 Male 1 Female	Upper or lower eyelid (5); outer canthus (1)	Sebaceous adenoma (4); well-differentiated sebaceous adenocarcinoma	Nasopharyngeal, colon, endometrial, stomach carcinoma	Present in 1; not available in 4	Absent

NS, Not specified.

our series were men, which is consistent with previous reports. The mean age in our series was 55 years, which is also comparable to that of the published literature (53 years). The most common internal malignancy in our case series was gastrointestinal tract, which is also consistent with that of the reported cases to date.

Although sebaceous carcinoma was present in 58% of patients in the reported cases, many of the sebaceous carcinoma cases were from large series for sebaceous carcinomas. In a study by Tillawi et al.,[14] benign sebaceous tumors were more commonly observed as part of the MTS than were sebaceous carcinomas. Similarly, 4 of the 5 lesions from our 5 patients with MTS were sebaceous adenomas; 1 had a well-differentiated sebaceous adenocarcinoma.

Because of the peculiar hamartomatous nature of the sebaceous adenoma in our cases, which we believe is similar to that observed in other cases of MTS, we investigated the personal and family histories of our patients. The diagnosis of MTS was made in all cases after the diagnosis of the sebaceous tumors of the eyelids was established.

It is important that patients with MTS be identified, because they are at risk of multiple primary internal malignancies. Whether the sebaceous neoplasm(s) or the visceral tumor(s) occur first, there may be a gap of many years before both elements are present at the same time to allow a diagnosis of MTS. Therefore, it is important to obtain complete clinical information, including the personal and family history of visceral malignancies and previous cutaneous tumors, when treating patients with sebaceous tumors of ocular adnexa.

Patients with MTS portend a more favorable prognosis than might be anticipated, as the visceral malignancies are usually of low malignant potential.[16] Because these indolent visceral malignancies tend to permit prolonged survival, even metastatic disease may respond well to aggressive surgical treatment.[16] The autosomal dominant inheritance of this syndrome may help in delineating the entire family, which should be carefully investigated.

The clinical diagnosis of MTS can be confirmed by identifying a germ line mutation in one of the MMR genes by using gene linkage and molecular studies. Immunohistochemistry for MSH2 and MLH1 has been recently found to be a practical initial approach to diagnose MTS.[3] The mutation in MMR genes may lead to micro- satellite instability (MSI), which combined with loss of MMR gene expression, can be used as markers for MTS in patients with sebaceous gland tumors.[17,18] We herein report the lack of expression of the MSH2 gene in the two tumors studied by immunohistochemistry, which may be a useful initial approach to screen patients for MTS. In cases with loss of MMR protein, further diagnostic procedures are warranted to rule out associated visceral malignancies. Furthermore, genetic counseling with a systematic evaluation of an extended pedigree and molecular genetic diagnostics should be offered to the patient.

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