Sebaceous Gland Adenoma of the Tarsal Conjunctiva in a Patient with Muir–Torre Syndrome

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Purpose: To highlight the recognition and diagnosis of Muir–Torre syndrome (MTS) in patients with sebaceous tumors of the eyelid/conjunctiva and to determine the role of immunohistochemical markers as a screening test in patients with Muir–Torre syndrome.

Design: Single interventional case report.

Methods: The clinical and family history was reviewed from the records of a 41-year-old man who had a sebaceous gland adenoma of the tarsal conjunctiva of the left upper eyelid. The lesion was completely excised and submitted for histopathologic examination. Immunohistochemical stains using an antibody to MSH2 were performed on the paraffin-embedded sections of the tumor.

Results: Histopathologic examination of the tumor showed a lobular pattern with basaloid cells at the periphery of the lobules with central areas of sebaceous differentiation. Immunohistochemical stains showed a lack of MSH2 expression in the tumor, which is highly consistent with MTS.


Muir–Torre syndrome (MTS) is a rare autosomal dominant genodermatosis first described in 1967 and 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 associated internal malignancies are gastrointestinal (47%) followed by genitourinary (21%) and breast (12%). 1

Muir–Torre syndrome is now considered a subtype of the more common hereditary nonpolyposis colorectal cancer syndrome, which has been ascribed to mutations in the DNA mismatch repair (MMR) genes MSH2 or MLH1 and is in close linkage to a locus on chromosome 2p. 2 Although MTS is rare, it is important to consider this entity in patients in whom sebaceous tumors have been diagnosed, particularly because cutaneous lesions might 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.

The purpose of this case report is to highlight the recognition and diagnosis of MTS in patients with sebaceous tumors of the eyelid. Furthermore, we wanted to determine whether an immunohistochemical approach targeting the expression of MSH2 in MTS-related skin tumors could be used as an initial screening test. For this reason, we examined retrospectively the expression of the MMR gene (MSH2) by immunohistochemistry on paraffin-embedded sections of the recurrent conjunctival tumor in this report.

Methods: Case Report

A 41-year-old Chinese man was seen with a painless recurrent left upper lid mass clinically resembling a chalazion (Fig 1). The lesion was completely excised and submitted for histopathologic and immunohistochemical analysis. The patient had been treated for nasopharyngeal carcinoma. The patient had a remarkable family history. His father had pancreatic carcinoma, and one brother had gastrointestinal carcinoma.

A diagnosis of MTS was established after the excision of the original and recurrent sebaceous adenoma involving the tarsal conjunctiva of the left upper eyelid.
Results

Histopathologic and Immunohistochemical Findings

Microscopically the tumor exhibited a lobular pattern with basaloid cells at the periphery of the lobules with central areas of sebaceous differentiation and with minimal mitotic activity. The tumor was forming interconnecting lobules and strands, forming a peculiar branching pattern to the overlying conjunctival epithelium, giving the lesion a peculiar hamartomatous appearance (Figs 2, 3). At the base of lesion, there were multinucleated giant cells surrounding lipid vacuoles, indicative of previous lipogranuloma (chalazion). In addition, there was exuberant granulation tissue with numerous branching capillaries and acute and chronic inflammatory cells.

A mouse antihuman monoclonal antibody was used for detection of the MMR protein MSH2 (MSH2 clone, FE11, Oncogene Research Products, Boston, MA). Fifty-micrometer 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 mM sodium citrate buffer, pH 6) was used for MSH2 staining. The 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 horseradish peroxidase. Replacement of the first antibody by phosphate-buffered saline was used as a negative control to assess the specificity of the antibodies. Meibomian glands of the eyelid and normal colonic mucosa were used as positive controls, disclosing striking nuclear immunostaining.

The immunohistochemical staining of the sebaceous adenoma in this case report showed a lack of expression of the MSH2 gene compared with the positive controls, which showed obvious nuclear staining (Fig 4). Immunohistochemical staining was absent in the tumor lobules of the sebaceous adenoma.

Discussion

Muir–Torre syndrome, described independently by Muir et al in 1967 and Torre in 1968, is a disorder characterized by skin tumors of sebaceous differentiation and visceral malignancies.4,5 A subgroup of MTS cases represents an allelic
variant of hereditary nonpolyposis colorectal cancer, an autosomal-dominant predisposition to colorectal cancer and other internal malignancies. Whereas in hereditary nonpolyposis colorectal cancer the proportion of MSH2 mutations almost equals the proportion of MLH1 mutations, MTS is most frequently caused by germline mutations in MSH2.12

The occurrence of any of the sebaceous tumors mandates consideration of MTS, even if solitary, and an evaluation of the patient to rule out visceral and other malignancies. Benign and malignant sebaceous gland tumors are relatively uncommon, and a detailed 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.

To date, a total of 24 cases of MTS involving the eyelid conjunctiva have been reported.2,6–13 Of the 24 cases we reviewed, the mean age at the time of the diagnosis of the sebaceous tumor of eyelid was 53 years (range, 31–77 years). The location of the eyelid tumor was almost equal on the upper and lower eyelid; in one case, the tumor was located in the medial canthal region.11 The most common internal malignancies in these patients were colorectal (43%) followed by genitourinary (21%), breast (14%), and Hodgkin’s lymphoma (one patient). The eyelid tumors present in these patients were sebaceous carcinoma in 14 patients (58%), sebaceous adenoma in 5 patients (21%), sebaceous hyperplasia in 3 patients (13%), and sebaceous epithelioma in 2 patients (8%). However, many of the sebaceous carcinoma cases were included from large series on sebaceous carcinomas.14,15 Tillawi et al.14 in a study found that benign sebaceous tumors were more commonly encountered in patients with MTS than were sebaceous carcinomas. Most of the patients had a strong family history of internal malignancies, and the diagnosis of MTS was not made until the recognition of the sebaceous tumors.

Similar to other cases from the published literature, our patient is a male with an upper eyelid mass, which clinically resembled a chalazion. Because of the peculiar hamartomatous nature of the sebaceous adenaoma, similar to that observed in other cases of MTS (personal observation by RL Font), we suggested investigating the personal and family history of the patient. The patient had a history of nasopharyngeal carcinoma and a strong family history of visceral malignancies, which confirmed the diagnosis of MTS.

Muir–Torre syndrome requires recognition, because affected patients are at risk of multiple primary malignancies. Whether the sebaceous neoplasm(s) or the visceral tumor(s) occur first, there might 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 investigating patients with sebaceous eyelid tumors. Patients with MTS portend the greater possibility of a favorable prognosis than might be anticipated, because the visceral malignancies are usually of low malignant potential.16 Because these indolent visceral malignancies tend to permit prolonged survival, even metastatic disease might respond well to aggressive surgical treatment.16 The autosomal-dominant inheritance of this syndrome might help in delineating the entire family, which should be carefully investigated.

The clinical diagnosis of MTS can be confirmed by identifying a germline mutation in one of the MMR genes by using gene linkage and molecular studies. More recently, immunohistochemistry for MSH2 and MLH1 has been found to be a practical initial approach to diagnose MTS.5 The mutation in MMR genes might lead to microsatellite instability, which, combined with loss of MMR gene expression, can be used as a marker for MTS in patients with sebaceous gland tumors.17 Similarly, the sebaceous tumor in our patient showed a lack of expression of the MSH2 gene showed by immunohistochemistry.

In conclusion, we report herein a case of sebaceous gland adenoma of the tarsal conjunctiva of the left upper eyelid in a patient who had a diagnosis of MTS. We recommend immunohistochemistry for MSH2 as an appropriate initial approach to screen for MTS caused by an inherited gene defect. 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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References


