Sebaceous Adenoma of the Eyelid in Muir-Torre Syndrome

Muir-Torre syndrome is a rare cancer predisposition syndrome characterized by unusual cutaneous tumors and internal malignancy. The cutaneous tumors associated with Muir-Torre syndrome include mainly sebaceous gland neoplasms (sebaceous adenoma and sebaceous carcinoma), keratoacanthoma, and basal cell carcinoma. Colorectal and genitourinary carcinoma are the common types of internal malignancies that occur in Muir-Torre syndrome. Although Muir-Torre syndrome is characterized by autosomal dominant inheritance, sporadic cases are known to occur. Significant variation can occur in the phenotypic manifestations of Muir-Torre syndrome, and in some cases Muir-Torre syndrome may resemble hereditary non-polyposis colorectal carcinoma.

Recent investigations into the molecular genetics of Muir-Torre syndrome have revealed genomic replication errors, known as microsatellite instabilities, due to mutations in the mismatch repair genes, hMSH2 and hMLH1. In this report, we present the clinical and histologic features of a patient with Muir-Torre syndrome who had multiple facial lesions, some of which involved the eyelid, in association with an internal malignancy.

Report of a Case. A 59-year-old man sought care in July 2003 for a progressively enlarging exophytic lesion that involved the left upper eyelid for the last 6 months. He had a history of biopsy-proven basal cell carcinoma of the right temple region, which had been treated with external beam radiotherapy in 1996. He had been treated for biopsy-proven advanced rectal adenocarcinoma with preoperative combined chemoradiotherapy followed by an abdominoperineal resection and sigmoid colostomy in 1996. He was free of local tumor recurrence or metastasis. There was no family history of any ocular disease or malignancy.

On examination, the patient’s corrected visual acuity was 20/20 OU. External examination revealed an 8 × 5 × 4-mm, yellowish-pink, warty growth of the left upper eyelid close to the margin (Figure 1A). The surface of the lesion had fine papillary projections without vascularity, crusting, or ulceration, and no surrounding induration was present. Numerous yellow-white, slightly raised lesions that ranged in size from 3 to 10 mm were distributed on the face in the central forehead region, nose, and adjacent cheek area (Figure 1B). Each lesion appeared to be a conglomeration of many smaller nodular lesions. The results of anterior segment examination and fundus evaluation of both eyes were unremarkable. The eyelid lesion and one of the facial lesions were excised and submitted for histopathologic evaluation.

Macroscopically, the eyelid lesion was composed of a 10 × 8 × 5-mm...
pentagonal piece of skin, with a 5 × 4-mm, firm, yellow exophytic nodule. The facial lesion was composed of a 10 × 6 × 3-mm elliptical-shaped piece of skin with a 6 × 4 × 3-mm, central yellow nodule.

Microscopy of the eyelid lesion demonstrated an exophytic neoplasm situated principally within the cutaneous compartment that was composed of multiple, irregularly shaped, closely packed, circumscribed sebaceous lobules, separated by compressed, dermal connective tissue septa (Figure 2A). The lobules communicated with the epidermal surface via several openings. Each lobule was composed of a peripheral, mitotically active basaloid germinative layer, which exhibited moderate cytologic atypia maturing to vacuolated sebocytes centrally, with transitional forms seen (Figure 2B). The mature, central sebocytes comprised most of the lesional tissue. Variable eosinophilic holocrine degeneration was seen. No convincing cystic change was identified. There was no evidence of an infiltrative growth pattern, pagetoid lesions, mitotic figures, or lymphovascular space invasion. The eyelid tissue adjacent to the lesion exhibited patchy, focal lipogranulomatous inflammation, constituting secondary chalazion formation. The cheek lesion demonstrated histologic features identical to those described herein (Figure 2A and 2B). The circumscript, mature sebaceous phenotype, lack of infiltrative borders, absence of aberrant mitotic figures, and necrosis of both lesions supported the diagnosis of benign sebaceous adenomas.

The rectal biopsy results from 1996 were reviewed, and a diagnosis of primary adenocarcinoma was confirmed (Figure 2C). The sebaceous adenoma and rectal adenocarcinoma underwent immunohistochemical analysis with antibodies directed at MLH1 (PharMingen, Oxford, England) and MSH2 (Cambridge Bioscience Ltd, Cambridge, England) proteins, using a conventional dianobenzidine detection method, with a brown chromogen. The sebaceous adenoma (Figure 2D) exhibited consistent nuclear positivity for MLH1 but was negative for MSH2.
Sebaceous hyperplasia consists of mature sebaceous lobules grouped around a single central dilated duct, which is often filled with debris. Sebaceous adenoma shows irregularly shaped, closely packed sebaceous glands that communicate with 1 or more dilated infundibula or directly to the surface. There are more basoid germinative cells than normal sebaceous glands, together with transitional forms, but there still tends to be a majority of mature vacuolated sebocytes, as described in the lesions in this case report. Sebaceous carcinoma is usually asymmetrical, infiltrative, and composed of lobules, nests, and sheets of principally basoid cells with variable sebaceous differentiation. The cells are often highly pleomorphic, and necrosis is usually present. The ocular variant commonly shows an in situ component.

Sebaceous adenoma associated with Muir-Torre syndrome can undergo cystic change, whereas those of sporadic type do not exhibit this feature. Meibomian glands and Zeis glands of the eyelids are modified sebaceous glands and can undergo similar histopathologic changes.

Sebaceous gland tumors, especially adenomas, occur rarely. Solitary or multiple sebaceous adenomas appear as yellow nodules, typically on the face, and are considered one of the diagnostic criteria of Muir-Torre syndrome. Sebaceous hyperplasia seen in elderly individuals is not associated with Muir-Torre syndrome. Although sebaceous gland carcinoma of the eyelid and extraocular sites has been reported in patients with Muir-Torre syndrome, such patients also had sebaceous adenomas. Sebaceous gland carcinoma of the eyelid by itself is not suggestive of Muir-Torre syndrome. Similarly, keratoacanthoma and basal cell carcinoma without sebaceous adenoma are not diagnostic of Muir-Torre syndrome.

In a review of 120 patients with Muir-Torre syndrome, sebaceous tumors were diagnosed before the internal malignancy in almost 40% of the patients. Almost half of patients with Muir-Torre syndrome develop colorectal adenocarcinoma, and one fourth develop genitourinary tumors. Adenocarcinoma of the colon in the setting of Muir-Torre syndrome and other genetic predispositions such as Gardner syndrome tends to occur almost a decade earlier than the sporadic cases. The adenocarcinoma tends to be multifocal and arises from the proximal colon in genetically predisposed cases compared with unifocal involvement of the distal aspect of the colon in sporadic cases. Diagnosis of solitary or multiple sebaceous adenomas should raise a strong suspicion of Muir-Torre syndrome. Such patients and their first-degree relatives should be screened for internal malignancy.

Table. Various Eyelid and Adnexal Tumors That Are Markers of Benign and Malignant Visceral Tumors

<table>
<thead>
<tr>
<th>Entity</th>
<th>Eyelid or Adnexal Tumors</th>
<th>Visceral Tumors</th>
<th>Associated Abnormalities</th>
<th>Locus and Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurofibromatosis type 1</td>
<td>Neurofibroma</td>
<td>Pheochromocytoma</td>
<td>Café au lait spots, Lisch nodules</td>
<td>17q, (\text{NF1 gene})</td>
</tr>
<tr>
<td>Gardner syndrome</td>
<td>Epidermoid cyst, fibroma, orbital osteoma</td>
<td>Colorectal polyps or carcinoma</td>
<td>Congenital hypertrophy of retinal pigment epithelium</td>
<td>5q21, (\text{APC gene})</td>
</tr>
<tr>
<td>Gorlin syndrome</td>
<td>Basal cell carcinoma</td>
<td>Ovarian fibroma or fibrosarcoma</td>
<td>Odontogenic cysts, bifid ribs, palmar pits</td>
<td>9q22, (\text{PTC gene})</td>
</tr>
<tr>
<td>Cowden syndrome</td>
<td>Trichoepithelioma</td>
<td>Breast fibroadenoma, adenocarcinoma</td>
<td>Thyroid adenoma or adenocarcinoma, oral papilloma</td>
<td>10q23, (\text{PTEN gene})</td>
</tr>
<tr>
<td>Carney complex</td>
<td>Myxoma</td>
<td>Testicular tumor</td>
<td>Spotty mucocutaneous pigmentation, schwannoma, endocrine overactivity</td>
<td>17q, (\text{PRKAR1A gene, chromosome 2})</td>
</tr>
<tr>
<td>MEN 2B</td>
<td>Conjunctival neuroma</td>
<td>Mucocutaneous neuroma, thickened corneal nerves</td>
<td>Thyroid carcinoma, pheochromocytoma</td>
<td>10q11.2, (\text{RET protooncogene})</td>
</tr>
<tr>
<td>Muir-Torre syndrome</td>
<td>Sebaceous adenoma, sebaceous adenocarcinoma, keratoacanthoma, basal cell carcinoma</td>
<td>Colorrectal adenocarcinoma, genitourinary, malignancy</td>
<td></td>
<td>2p, (\text{hMLH1, hMSH2})</td>
</tr>
</tbody>
</table>

Abbreviation: MEN, multiple endocrine neoplasia.
degree relatives should be encouraged to undergo detailed systemic evaluation to exclude gastrointestinal and genitourinary malignancy according to published protocols. Because systemic malignancy may occur many years after the onset of sebaceous adenoma, continued long-term surveillance is necessary.

The principal genetic aberrations in Muir-Torre syndrome are mutations in the mismatch repair genes, hMLH1 and hMSH2, leading to microsatellite instability. Microsatellite testing requires the services of a molecular diagnostic laboratory, but tumors that exhibit microsatellite instability can be detected with immunohistochemical staining. The absence of hMLH1 and hMSH2 nuclear expression identifies tumors with mismatch repair deficiencies. Application of this technique to cutaneous sebaceous neoplasms has proved to be a reliable screening method, with high predictive value for the diagnosis of DNA mismatch repair–deficient Muir-Torre syndrome. In this study, the sebaceous adenoma did not express hMSH2 protein but expressed MLH1 protein; the same pattern was seen in the rectal adenocarcinoma. The overall findings indicate mutations in the hMSH2 gene and, coupled with the clinical findings, are highly suggestive of Muir-Torre syndrome.

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Desmoplastic Small Round Tumor: A Potentially Lethal Neoplasm Manifesting in the Orbit With Associated Visual Symptoms

Desmoplastic small round cell tumor (DSRCT) is an uncommon yet potentially lethal tumor typically affecting young male adults. This extremely aggressive tumor was first described by Gerald and Rosai in 1989, and since then, more than 250 cases have been reported, with recent cytogenetic work revealing a unique translocation involving the Ewing sarcoma breakpoint region (EWSR1) at t(11;22)(p13;q12). In the largest case report to date, 94% of 109 cases were located in the abdominal cavity. Other serosal surfaces may be involved, including the testis, ovary, pleura, and parotid gland. Manifestations in the head are extremely uncommon. Desmoplastic small round cell tumor has been reported once in the ethmoidal sinuses and once in the posterior cranial fossa. The current report describes the first patient, to our knowledge, with DSRCT producing visual disturbances as an initial symptom.

Report of a Case. A 32-year-old man was in his usual state of health when he saw his physician and complained of blurry vision. The patient initially attributed his blurry vision to the recent administration of fluoxetine hydrochloride. Fluoxetine administration was discontinued, but the patient continued to experience blurry vision. In addition, the patient developed pain in his left eye and reduced vision with right gaze. He was evaluated by a general ophthalmologist who diagnosed an orbital abnormally in his left eye. Computed tomographic scans and magnetic resonance images of the patient’s orbits revealed a lobular heterogeneous soft tissue mass within the left orbit measuring 2.5 × 2.5 × 1.8 cm (Figure 1), producing proptosis of the left globe, and flattening and decrease-