Immunohistochemical Distinction of Ocular Sebaceous Carcinoma From Basal Cell and Squamous Cell Carcinoma

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Background: Diagnosis of sebaceous carcinoma of the periorbital region is often delayed. Clinically, this lesion can mimic several inflammatory disorders. Histopathologically, it can mimic either squamous cell or basal cell carcinoma.

Objective: To identify an immunohistochemical approach to assist in the diagnosis of periorbital sebaceous carcinoma.

Method: The immunohistochemical profiles of several cases of periorbital sebaceous, basal cell, and squamous cell carcinoma were examined.

Results: Although at least focal epithelial membrane antigen (EMA) staining can effectively distinguish sebaceous carcinoma (10 of 11 were positive) from basal cell carcinoma (1 of 16 were positive), most squamous cell carcinomas examined were also focally EMA positive (11 of 14). However, Cam 5.2 reactivity was seen in most sebaceous carcinomas (8 of 11) but no squamous cell carcinomas (0 of 14). In addition, at least focal BRST-1 reactivity was also seen in most sebaceous carcinomas (7 of 11) but no basal cell carcinomas (0 of 16).

Conclusions: Periorbital sebaceous, basal cell, and squamous cell carcinomas have different immunohistochemical staining profiles; a panel of commonly available antibodies, including anti-EMA, BRST-1, and Cam 5.2, may help distinguish these diseases from each other when that distinction cannot be clearly made by light microscopy alone.


SEBACEOUS CARCINOMA can be a diagnostic challenge for the clinician and the pathologist. It occurs more frequently in the periorbital region than elsewhere in the body, arising either from the meibomian glands or from the sebaceous glands associated with hair follicles at the lid margin—the glands of Zeis. When sebaceous carcinoma occurs in the periorbital region, it is likely to have a more aggressive clinical course.1,2 This is at least partly because sebaceous carcinoma can mimic a recurrent chalazion or unilateral blepharoconjunctivitis, causing the correct diagnosis to be delayed clinically. In a retrospective study4 at the Mayo Clinic, Rochester, Minn, of patients ultimately diagnosed as having sebaceous carcinoma of the eyelid, these patients had multiple clinical diagnoses (mean, 2.2) before the correct diagnosis was established. Histopathologically, the diagnosis can also be difficult because sebaceous carcinoma can exhibit several histological patterns, can spread within the epidermis in a single-cell fashion (pagetoid spread), and can mimic squamous cell carcinoma in situ or basal cell carcinoma. In one study,5 a correct diagnosis was made on initial histopathologic evaluation in only 23% of the cases.

Oil-Red-O staining of fresh-frozen tissue has traditionally been considered the best technique to confirm the diagnosis of sebaceous carcinoma.7 However, for several reasons, this is often not practical. Oil-Red-O staining is usually performed on frozen sections because the process of paraffin embedding extracts most of the lipid from the material. In many cases, a diagnosis of sebaceous carcinoma may not be suspected until the tissue is already paraffin embedded, precluding this approach. Some pathology laboratories have adopted the practice of bisecting all eyelid biopsy samples and processing only half of the material, reserving the remainder in case the question of sebaceous carcinoma arises. This approach is risky because the diagnostic tissue might be present only in the unprocessed portion. Most pathologists would feel uncomfortable calling a small biopsy sample “negative” until they had seen...
**MATERIALS AND METHODS**

After obtaining approval from the Human Investigation Committee of the Yale University School of Medicine, New Haven, Conn, archival paraffin-embedded biopsy and resection specimens were selected, by diagnosis, from the surgical pathology files of Yale–New Haven Hospital. All identified cases of sebaceous and squamous cell carcinoma from the periorbital region for which residual tissue samples were available were used in the study. In addition, a comparable number of cases of basal cell carcinoma in this region were also arbitrarily selected by case number, without regard to specific histological pattern. Slides from the selected cases were pooled, randomized, and independently diagnosed by the author. In all but one case, the original diagnosis was confirmed. One case (Table 1, patient 10) originally diagnosed as squamous cell carcinoma was actually a poorly differentiated sebaceous carcinoma mimicking squamous cell carcinoma in situ. A representative section from each case was selected and immunohistochemical stains were ordered from the original tissue block. Several antibodies were investigated, many of which are not reported here because they did not prove useful. This study reports the results with anti-keratin (AE1/AE3; Boehringer Mannheim, Indianapolis, Ind) (1:1200 dilution), anti-epithelial membrane antigen (EMA; Ventana Medical Systems, Tucson, Ariz) (prediluted), anti–BCA-225 (BRST-1; Signet Laboratories, Dedham, Mass) (1:40 dilution), and anti–low molecular weight keratin (Cam 5.2; Becton-Dickinson, San Jose, Calif) (1:20 dilution).

Anti-keratin (AE1/AE3), anti-EMA, and anti–low molecular weight keratin (Cam 5.2) staining were performed on an automated staining system (Ventana ES; Ventana Medical Systems). Per manufacturer recommendations, a protease-1 predigestion was used before AE1/AE3 staining (8 minutes of digestion and 30–32 minutes of primary antibody incubation) and Cam 5.2 staining (4 minutes of digestion and 30–32 minutes of primary antibody incubation). No antigen retrieval was used before EMA staining (16 minutes of primary antibody incubation). Anti–BCA-225 (BRST-1) staining was done manually using standard techniques. Sections were pretreated with 0.1% trypsin for 15 minutes and incubated overnight at 4°C with a 1:40 dilution of primary antibody.

Immunostains were scored as negative when no definite staining was found in any tumor cells or when only weak staining was found in fewer than 20% of cells. If definite staining was obtained, but in fewer than 20% of cells, staining was classified as "focal." When more than 20% of tumor cells stained just slightly above background but the staining pattern was nonetheless specific for the lesion, the staining was scored as "weak."

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**RESULTS**

**CLINICAL INFORMATION**

Patients ranged in age from 28 to 95 years (Table 1). Mean ages of patients with diagnoses of sebaceous, basal cell, and squamous cell carcinomas were 66, 72, and 72 years, respectively. Seventy-three percent of patients with sebaceous carcinoma were women vs only 44% with basal cell carcinoma and 36% with squamous cell carcinoma. Most lesions were on the eyelid but some were on the conjunctiva or the periorbital skin.

**HISTOPATHOLOGIC INFORMATION**

Most of the material examined was from excisional biopsy samples. For 2 patients (Table 1, patients 7 and 11), separate biopsy and resection specimens were available and showed identical staining patterns. Cases of sebaceous carcinoma ranged from well to poorly differentiated, with most being moderately differentiated. Intraepithelial spread was identified in 7 (64%) of 11 cases. Basal cell carcinomas included nodular, trabecular, metatypical, and morpheaform patterns. Four cases (Table 1, patients 24–27) showed a predominantly basal cell carcinoma growth pattern but focally exhibited sebaceous features. Squamous cell carcinoma cases included in situ and invasive tumors.

**AE1/AE3 IMMUNOREACTIVITY**

The AE1/AE3 cocktail is generally used as a "pankeratin" marker and routinely stains nearly all epithelial cells. In this study, it was used to verify the immunogenicity of the cases examined. AE1/AE3 stained normal surface epithelium, sebaceous glands, and eccrine glands and ducts. It also stained all cases of sebaceous, basal cell, and squamous cell carcinoma (Table 1, Table 2, and Figure 1). In most cases, the staining was strong and diffuse. In 2 cases (Table 1, patients 9 and 11)—both relatively poorly differentiated sebaceous carcinomas—staining with AE1/AE3 was only focal.

**EMA IMMUNOREACTIVITY**

In normal tissue, anti-EMA stained the apical surfaces of eccrine glands and ducts, the "apical" surfaces of normal sebaceous glands (for nests of cells, "apical" refers to the center of the nests), and the midportion of the surface epithelium (predominantly the stratum spinosum). All cases of sebaceous carcinoma except 1 were at least weakly or focally positive for EMA (Tables 1 and 2). In cases in which "well-differentiated" nests of sebaceous cells were identified, EMA staining was restricted to accurately identify intraepithelial spread—an important prognostic indicator for sebaceous cell carcinoma.

For all these reasons, I investigated the immunohistochemical staining characteristics of periorbital sebaceous carcinoma and contrasted them to the staining characteristics of basal cell and squamous cell carcinomas in this location.
to cells in the center of the nests, morphologically equivalent to apical cells (Figure 2, case 1). Less well-differentiated tumors showed patchy staining (Figure 1; Figure 2, cases 2 and 3), diffuse weak staining (Figure 2, case 4), or no staining (Table 1, patient 11). Sebaceous carcinoma cells spreading within the epithelium showed focal reactivity, but numerous nests of tumor cells and single tumor cells often did not stain with this antibody (Figure 3). Only 1 of 16 basal cell carcinomas showed any staining for EMA (patient 24). This case was high grade, with many mitoses, and contained some areas of sebaceous differentiation; EMA staining was restricted to the sebaceous areas. However, other areas showed clear peripheral palisading and separation artifact. In retrospect, this tumor may represent a basal cell carcinoma, in which the “sebaceous” areas are actually poorly differentiated, approaching sebaceous carcinoma. 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showed at least focal EMA staining, without any evidence of sebaceous differentiation.

BRST-1 IMMUNOREACTIVITY

In the eyelid and periorbital tissues, BRST-1 antibody will stain normal sebaceous glands, predominantly the more apically oriented cells. Weaker immunoreactivity is also often detected in the apical surfaces of eccrine ducts and glands and occasionally within suprabasal layers of the epidermis. At least focal staining was seen in nearly two thirds (7/11; 64%) of sebaceous carcinomas (Tables 1 and 2). Staining patterns ranged from diffuse (Figure 2, case 1) to patchy (Figure 2, case 2) to focal (Figure 2, case 3) to absent (Figure 2, case 4). No staining was seen for any basal cell carcinoma (0/16; 0%). Focal weak staining was seen in approximately one third (5/14; 36%) of squamous cell carcinomas (Figure 1 and Table 2). BRST-1 staining of squamous cell carcinomas was more commonly seen with well-differentiated tumors and always occurred in areas that were also EMA positive (although not all EMA-positive areas were also BRST-1 positive).

CAM 5.2 IMMUNOREACTIVITY

Anti–low molecular weight keratin antibody Cam 5.2 intensely stains normal eccrine glands and weakly stains normal sebaceous glands. It also stains intraepithelial goblet cells in the conjunctiva. Nearly three quarters (8/11; 73%) of the sebaceous carcinomas showed positive staining with this antibody (Tables 1 and 2), which was often diffuse (Figures 1-3). In well-differentiated nests of tumor cells, the less well-differentiated basal portions (ie, peripherally located) tended to stain more intensely than apical (ie, central) cells. This antibody also dramatically highlighted the intraepithelial spread of tumor cells, both in nests and as single cells (Figure 3). Seven of the 16 cases of basal cell carcinoma showed either diffuse or focal Cam 5.2 immunoreactivity. No cases of squamous cell carcinoma showed positive staining.

COMMENT

Sebaceous carcinoma of the eyelid is either the second (after basal cell carcinoma) or third (after basal cell and squamous cell carcinomas) most common malignancy of the eyelid, depending on the study,9 at Yale University School of Medicine, New Haven, Conn, sebaceous and squamous cell carcinomas occur with essentially the same frequency, each being far less common than basal cell carcinoma.

All but 1 of the sebaceous carcinomas examined showed at least focal staining for epithelial membrane antigen. This staining was often patchy and limited to areas at or near “apical” differentiation. Other investigators9 showed similar reactivity of extraocular sebaceous carcinoma to EMA, with 5 of 5 tumors staining.

Although sensitive, EMA staining is not specific for sebaceous carcinoma. Healthy squamous epithelium and most squamous cell carcinomas also showed patchy staining for EMA.

BRST-1 stained a subset of the cases that were immunoreactive for EMA and, although less sensitive than EMA, was more specific for sebaceous carcinoma. Positive staining was seen in two thirds of the sebaceous carcinomas examined, and these tended to be the better-differentiated tumors. No cases of basal cell carcinoma showed any staining for BRST-1, and only a third of the squamous cell carcinomas stained with this antibody (Table 2). As with sebaceous carcinoma, the better-differentiated squamous cell carcinomas were more likely to stain with BRST-1 than more poorly differentiated tumors. Of the antibodies used in this study, this antibody was, technically, the most difficult for our laboratory. Because the most common site for sebaceous carcinoma is the eyelid, however, most histological sections had normal sebaceous glands somewhere on the slide, and this served as an excellent internal positive control.

Other investigators noted BRST-1 immunoreactivity in sebaceous lesions at other sites. In one study,10 all 6 cases of extraocular sebaceous carcinoma and all 3 cases of basal cell carcinoma with sebaceous differentiation showed positive staining with BRST-1. This is contrary to the results of this study, in which no case of basal cell carcinoma, even those with sebaceous areas, showed positive staining with this antibody. BRST-1 immunoreactivity has also been seen previously in ocular sebaceous carcinoma.11

Cam 5.2, although only weakly immunoreactive against nonneoplastic sebaceous glands, was often strongly positive in sebaceous carcinoma (nearly three quarters of the cases show at least focal reactivity). This difference in staining is unlikely to be useful in distinguishing malignant sebaceous lesions from benign ones, however, because 1 case of sebaceous adenoma also showed diffuse, moderately strong staining (J.H.S., unpublished observations, January 1998). Cam 5.2 reactivity seems to be strongest in less-differentiated areas of the tumor, including the intraepithelial spread. Nonetheless, tumors that were entirely poorly differentiated tended to be less likely to stain with Cam 5.2 than better-differentiated tumors. Although no squamous cell carcinoma was immunoreactive for Cam 5.2, 44% of basal cell carcinomas were. Many of these immunoreactive cases were those lesions that exhibited focal sebaceous features. However, Cam 5.2 reactivity was not consistently restricted to the “sebaceous” regions.

Table 2. Immunohistochemical Staining by Tumor Type

<table>
<thead>
<tr>
<th>Tumor Antibody</th>
<th>Sebaceous Carcinoma (n = 11)</th>
<th>Basal Cell Carcinoma (n = 16)</th>
<th>Squamous Cell Carcinoma (n = 14)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ker AE1/AE3</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>EMA</td>
<td>91</td>
<td>6</td>
<td>79</td>
</tr>
<tr>
<td>BRST-1</td>
<td>64</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>Cam 5.2</td>
<td>73</td>
<td>44</td>
<td>0</td>
</tr>
<tr>
<td>EMA and BRST-1</td>
<td>64</td>
<td>0</td>
<td>36</td>
</tr>
<tr>
<td>EMA and Cam 5.2</td>
<td>73</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>BRST-1 and Cam 5.2</td>
<td>55</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*Antibodies are described in the “Materials and Methods” section. For purposes of this table, “weak” and “focal” cases were included with positive cases.
Figure 1. Immunohistochemical staining of normal eyelid tissue and various periorbital epithelial neoplasms. Normal eyelid tissue and 1 case each of sebaceous carcinoma (patient 5), basal cell carcinoma (patient 12), and squamous cell carcinoma (patient 37) were stained with anti-keratin (AE1/AE3), anti-epithelial membrane antigen (EMA), anti–BCA-225 (BRST-1), and anti–low molecular weight keratin (Cam 5.2). Identical fields were used for each antibody to allow direct comparison (except for BRST-1 staining of normal tissue; the serial section corresponding to the other sections no longer contained sebaceous glands) (original magnification ×25 for normal tissue and ×50 for each tumor).
Several cutaneous cancers have been investigated for reactivity with a variety of monoclonal antibodies specific for individual keratins. Although results vary, sebaceous carcinoma has routinely shown a greater degree of immunoreactivity for the low molecular weight, "simple" keratins. In particular, Cam 5.2 reactivity was seen in 73% of sebaceous carcinomas of the eyelid, identical to the 73% seen in this study.

The diagnostic use of these antibodies can be enhanced by looking at antibody combinations. Because all cases that were immunoreactive for BRST-1 were also immunoreactive for EMA (Table 1), stratifying cases based on reactivity with both of these antibodies does not improve the discrimination among these lesions beyond that of the BRST-1 antibody alone. However, three quarters of the sebaceous carcinomas examined stained with the anti-EMA and Cam 5.2 antibodies, compared with only 1 basal cell carcinoma (6%) and no squamous cell carcinoma (Table 1). In this study, 100% "specificity" could be achieved by assessing reactivity with BRST-1 and Cam 5.2. However, only 55% of sebaceous carcinomas met this criteria.

Just how useful these immunohistochemical markers are in actual practice is remarkably difficult to address. Precise calculations of their sensitivity and specificity as a stand-alone diagnostic test cannot be made because these performance characteristics are significantly affected by the prevalence of the diseases within the population; this variable was not included in this study design. Also, immunohistochemical staining is not used as a stand-alone test. It would not be appropriate to blindly

Figure 2. Variability of immunohistochemical staining in sebaceous carcinoma. Four separate cases were stained with anti–epithelial membrane antigen (EMA), anti–BCA-225 (BRST-1), and anti–low molecular weight keratin (Cam 5.2). Cases 1, 2, 3, and 4 correspond to patients 1, 4, 5, and 8, respectively, in Table 1. Fields were selected that best demonstrated the degree of staining, which in many cases was focal (original magnification ×50).
order these special studies on every periorbital biopsy specimen because most of these lesions can be accurately diagnosed on histological appearance alone. In fact, histological appearance must always be considered because the less common tumors of adnexal structures such as eccrine duct adenomas are also Cam 5.2 positive and may be BRST-1 immunoreactive but can be clearly distinguished from sebaceous carcinoma on cytologic criteria in standard hematoxylin-eosin–stained preparations (J.H.S. unpublished observations, July 1998). Nonetheless, for cases with borderline histological findings, small biopsy specimens, and specimens with artifacts compromising the tissue architecture, I have found the results of these marker studies helpful in supporting or suggesting the correct diagnosis.

Intraepithelial spread of sebaceous carcinoma is a most problematic feature and is present in 40% to 80% of cases—64% of those in this study. Clinically, intraepithelial spread can result in underassessment of the extent of a lesion; for the pathologist, it is often responsible for misdiagnosis of tumor involvement of the resection margins and can lead to confusion of the tumor with squamous cell carcinoma. BRST-1 reactivity was generally not seen in the intraepithelial component of the tumor, probably because it tends to be poorly differentiated. Staining with EMA can be used to help identify intraepithelial spread (Figure 3), but it is not reliable because normal squamous epithelium and most cases of squamous cell carcinoma were positive for EMA (Figure 2). This is particularly problematic because the region of squamous epithelium that stains—the suprabasal area—is the region most commonly involved in the intraepithelial spread of sebaceous carcinoma. Cam 5.2 reactivity, however, was extremely helpful in this respect (Figure 3). This antibody routinely highlighted each tumor cell (peripheral staining) in the main tumor and the intraepithelial tumor spread but did not stain the uninvolved squamous epithelium (original magnification ×50).

Figure 3. Epithelial membrane antigen (EMA) and anti–low molecular weight keratin (Cam 5.2) staining of intraepithelial spread of sebaceous carcinoma. Images are from patient 7. Epithelial membrane antigen focally stained the main tumor mass (lower left-hand corner of upper field) and weakly identified the intraepithelial spread of tumor cells in the overlying epithelium (upper field) and around a hair follicle (lower field). Epithelial membrane antigen staining was also observed in the uninvolved epidermis (right-hand side of upper field). In contrast, Cam 5.2 intensely stained the main tumor mass and intraepithelial tumor spread but did not stain the uninvolved squamous epithelium (original magnification ×50).
Recent advances in other diagnostic modalities suggest that, in the future, molecular techniques may be used to allow earlier diagnosis of sebaceous carcinoma. Mutations in the p53 gene have been seen in invasive but not in situ sebaceous carcinoma, and p53 and immunohistochemical staining for proliferating cell nuclear antigen seem to have some prognostic value. Aneuploidy, as assessed by DNA flow cytometry, seems to be predictive of intraepithelial spread. Certain strains of human papilloma virus have also been implicated in the pathogenesis of sebaceous carcinoma. An increased number of helper T cells were seen in basal cell carcinoma (vs sebaceous carcinoma), but this is not likely to be diagnostically useful. Immunoreactivity with the monoclonal antibody OKM5 has been reported to be relatively specific for sebaceous carcinoma compared with other neoplasms in this location, but that antibody is not routinely available in most clinical laboratories.

In conclusion, the immunohistochemical profiles of periorbital sebaceous, basal, and squamous cell carcinomas, using the antibodies EMA, BRST-1, and Cam 5.2, are different and can be useful in assisting the pathologist in distinguishing them. These antibodies are commonly used for other lesions and are readily available in most immunohistochemistry laboratories. Cam 5.2 was particularly useful—more so than EMA or BRST-1—in identifying the intraepithelial spread of sebaceous carcinoma cells.

**REFERENCES**


Be sure to visit the Archives of Ophthalmology’s World Wide Web site (http://www.ama-assn.org/ophth) and try your hand at our new Clinical Challenge interactive quiz. We invite visitors to make a diagnosis based on selected information from a case report or other feature scheduled to be published in the following month’s print edition of the ARCHIVES. The first visitor to e-mail our Web editors with the first correct answer wins an Archives of Ophthalmology CD-ROM and will be recognized in the print journal and on our Web site. A full discussion of the case featured in the quiz can be found in the following month’s print edition of the journal.