Distinction of Benign Sebaceous Proliferations From Sebaceous Carcinomas by Immunohistochemistry

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Abstract: Sebaceous lesions, including sebaceous hyperplasia, sebaceomas, and sebaceous adenomas and carcinomas, are histologically distinctive adnexal proliferations with a spectrum of biological behavior ranging from benign to frankly malignant. The histologic distinction between sebaceous adenomas and carcinomas may be challenging, especially in cases showing atypical features and in small or partial biopsies. We studied multiple oncogenic and therapeutic related proteins by immunohistochemistry to identify differences in expression between benign and malignant sebaceous proliferations. A total of 27 cases, including 9 sebaceous adenomas, 4 sebaceomas, 8 sebaceous carcinomas, and 6 cases of sebaceous hyperplasia, were examined by immunohistochemistry, with antibodies directed against Ki-67 (MIB-1), bcl-2, p53, p21WAF1, p27Kip1, c-erbB-2 (Her-2/neu), CD117 (c-kit), cyclin D1, MDM2, CD99, MLH-1, and MSH-2. We found that sebaceous adenomas and sebaceomas stained like sebaceous hyperplasia did, whereas carcinomas had statistically significantly increased levels of p53 (50% versus 11%, respectively) and Ki-67 (30% versus 10%). The carcinomas also had significantly reduced levels of bcl-2 (7% versus 56%, respectively) and p21 (16% versus 34%) compared to the adenomas. Thus, a combination of several of these markers may be diagnostically useful in challenging cases. In addition, we found little or no Her-2/neu and CD117 staining, indicating that immunotherapy with Herceptin or Gleevac would likely not be useful for sebaceous carcinomas. Moreover, these results show that sebaceous adenomas and carcinomas are distinct neoplasms and provide no support for the theory that all sebaceous adenomas are truly malignant.

Key Words: sebaceous adenoma, sebaceoma, sebaceous carcinoma, sebaceous hyperplasia

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INTRODUCTION

After basal cell carcinoma (BBC), squamous cell carcinoma (SCC) and sebaceous carcinoma are the most common eyelid malignancies.[1–3] By most accounts, sebaceous carcinoma is the most lethal of ocular adnexal tumors, with 5-year mortality rates up to 30%.[2] Sebaceous carcinoma typically presents as a nodular lesion that appears most commonly on the upper eyelid,[3] but has a predilection for the lacrimal drainage system and nasopharynx by spreading through the conjunctival epithelium and epidermis. Treatment options include Mohs micrographic surgery and wide surgical excision, with frozen section margins, but outcomes with Mohs and radiation therapy have been mixed, and no prospective clinical studies have been performed to date.[4]

These clinical characteristics make it of utmost diagnostic concern to distinguish sebaceous carcinoma from the various entities it may be confused with, including benign sebaceous proliferations and malignancies such as BCC, Paget disease, and SCC.[2,3,5–10] Histologic and immunohistochemical characteristics of sebaceous carcinoma have been relatively well established and can be used to distinguish sebaceous carcinoma from other malignancies.[2,3,5,6,9–18] However, histologic features alone may be insufficient to distinguish benign sebaceous lesions such as sebaceous adenoma and sebaceoma from carcinoma, especially in small, incompletely sampled biopsies from sensitive locations such as the eyelid. In addition, there are few published studies of immunohistochemical differences between benign and malignant sebaceous tumors.[5,6,10] In addition, to our knowledge, no studies have examined the expression of the potential treatment target protein CD117 (c-kit), and only a few have studied Her-2/neu in sebaceous carcinoma.[8,11]

Since Troy and Ackerman[19] first described sebaceomas, the term has become more accepted and further defined as a distinct benign adnexal neoplasm with sebaceous differentiation.[20] However, there is much histologic overlap between sebaceomas and sebaceous adenomas, as well as between sebaceomas and sebaceous carcinomas.[20] Therefore, immunohistochemical markers that could help to distinguish between benign and malignant sebaceous tumors would be of significant diagnostic utility. In addition, we also address the hypothesis that sebaceous adenoma and sebaceous carcinoma are indistinguishable. If this is true, as some have claimed,[13] then it would follow that their immunophenotypes should be identical.

In this study, we evaluate the immunohistochemical expression patterns of multiple oncogenic or proliferative markers in benign versus malignant sebaceous lesions, including

p53, Ki-67 (MIB-1), cyclin D1, p21, p27, bcl-2, MDM2, myc2 (CD99), MLH1, and MSH2, as well as the expression of markers that might be of potential clinicotherapeutic utility for sebaceous carcinoma, including Her-2/neu (c-erbB-2) and CD117 (c-kit).

MATERIALS AND METHODS

Immunohistochemical Analysis

The sebaceous tumors reviewed in this series included 9 sebaceous adenomas, 4 sebaceomas, 8 sebaceous carcinomas, and 6 cases of sebaceous hyperplasia, for a total of 27 cases. These cases were identified from the files of collaborators' institutions (Johns Hopkins University, National Cancer Institute, and Stanford University Medical Center).

All specimens were processed in a similar fashion: after fixation in 10% buffered formalin, they were processed and embedded in paraffin, cut at 5 μm, and stained with hematoxylin and eosin or processed for immunohistochemistry.

Immunohistochemical studies were performed on deparaffinized slides subjected to microwave-based antigen retrieval with the standard DAKO (Carpinteria, CA, USA) solution. Antibodies used and dilutions are listed in Table 1. Stains were performed on an automated immunohistochemistry machine (DAKO).

Only nuclear staining was recorded as positive for p53, MDM2, p21, p27, Ki-67, cyclin D1, MLH1, and MSH2, whereas cytoplasmic staining was scored for bcl-2, c-kit, and CD99. Most antibodies were scored for both intensity of staining (0-4+, negative to strongly positive) and percentage of positive cells. Ki-67 (MIB-1) antibody staining was scored as 0 or 1+ (<25% cell staining), 2+ (25–50%), or 3+ (50–75%). No samples were more than 3+. Her-2/neu was scored according to the DAKO Herceptest protocol as 0 (no staining or membrane staining in <10% of cells), 1+ (faint and partial membrane staining in >10% of cells), 2+ (weak to moderate complete membrane staining in >10% of cells), or 3+ (strong, complete membrane staining in >10% of cells).

Statistics

Cases were reviewed and scored by 2 pathologists, and the results were averaged. The paired Student's *t* test was used to determine the statistical significance (*P* value) of the mean in comparing the percentage of staining in the sebaceous tumors examined. For these statistical tests, a probability of error < 0.05 was required.

We also assessed the degree of difference between sebaceous hyperplasia, adenomas, carcinomas, and sebaceomas by principal components analysis (PCA) with Partek Genomics Solution Version 6.1 (St. Louis, MO, USA). The software clusters closely related data by plotting the first versus the second principal component, the second versus the third principal component, etc, giving a manageable, low-dimensional representation of high-dimensional expression data. Samples with similar expression plot closer in this 3-dimensional space versus those that are dissimilar.

TABLE 1. Antibodies Used to Immunostain Sebaceous Tumors

Antigen/Antibody	Clone	Source	Working Dilution
p53	D0-7	DAKO	1:200
MDM2	SMP14	DAKO	NIH standard
p21	SX118	DAKO	NIH standard
p27	SX53G8	DAKO	NIH standard
c-erbB-2	Her2-neu	DAKO	Herceptest kit
Cyclin D1	Sp4	Labvision	1:100
CD99	O13	Signet	1:50
bcl-2	124	DAKO	1:50
Ki-67	MIB-1	DAKO	1:200
CD117	c-kit	DAKO	1:200
MLH-1	G168-728	BD Biosciences	1:40
MSH-2	Fe11	CalBiochem	1:20

RESULTS

Immunohistochemical Analysis of Sebaceous Tumors

We studied 9 cases of sebaceous adenomas (Fig. 1A) and 8 sebaceous carcinomas (Fig. 1B), as well as 6 cases of sebaceous hyperplasia and 4 cases diagnosed as sebaceomas. The patient demographics and immunohistochemical results are presented in Table 2.

Although there was some overlap in immunohistochemical staining results, there were statistically significant differences in several markers between the benign sebaceous proliferations and carcinomas. Sebaceous carcinomas showed higher percentages of cells staining for p53 versus adenomas

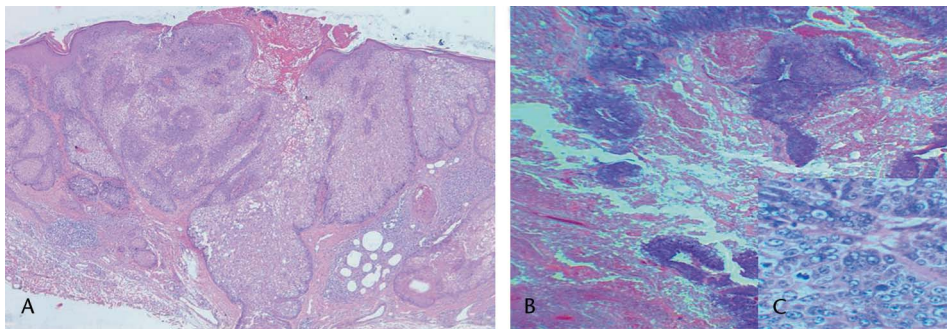

FIGURE 1. Histologic features of sebaceous adenoma and carcinoma. A, Representative histological features of a sebaceous adenoma (hematoxylin and eosin (H&E), 20×) and (B) a sebaceous carcinoma (H&E, 20×), also examined with (C, inset) a higher-power view of a sebaceous carcinoma showing prominent cytologic atypia and mitotic activity (H&E, 400×).

TABLE 2. Clinicopathological Characteristics and Immunohistochemistry for 27 Sebaceous Tumors

Age/Sex	Site	p53 Int	p53 % +	Her-2/neu Score	mib-1 Score	cycD1 Int	cycD1 % +	CD99 Int	CD99 % +	bcl-2 Int
Sebaceous carcinoma										
79M	Scalp	2+	90	0	1+	2+	5	0	0	0
72F	Nose	1+	2	0	2+	2+	<5	1+	20	0
71F	Nose	2–3+	60	1+	3+	1+	10	2–3+	90	1+
69F	Buttock	3+	80	1+	2+	2+	20	1+	30	0
38M	Forehead	2+	10	1+	2+	2+	5	1+	30	0
77F	Forehead	3+	80	2+	1+	1–2+	5	1–2+	70	1+
86M	Forehead	2+	70	0	1+	3+	5	0	0	0
71F	Eyelid	1+	70	0	3+	2+	3	2+	10	1+
Sebaceous adenoma										
84M	Cheek	2+	3	1+	1+	2+	20	2+	60	1+
69M	Cheek	2+	3	0	1+	2+	5	2+	50	1+
72F	Eyelid	2+	10	ND	1+	2+	5	2+	70	2+
66M	Back	2+	2	1+	0–1+	2–3+	40	1+	50	1+
64M	Nose	0	0	0	0	2+	10	2+	70	1+
67M	Neck	2+	5	0	0–1+	2+	10	1+	50	ND
84M	Cheek	2+	2	0	0	2+	5	0	0	1+
79M	Buttock	1+	30	1+	1+	2+	10	0	0	1+
62F	Nose	2+	20	Focal 2+	1+	2+	10	0	0	0
Sebaceoma										
71F	Scalp	1+	1	0	0–1+	2+	5	0	0	1+
90F	Nose	1+	2	0	1+	2+	10	0	0	1+
63M	Eyelid	2+	<5	0	2+	1–2+	5	2–3+	80	2+
76F	Nose	2+	10	Focal 1+	1+	2+	10	0	0	0
Sebaceous hyperplasia										
68M	Nose	0	0	0	1+	1+	<5	2+	50	2+
73F	Eyelid	2+	1	0	1+	2+	2	1+	80	1+
55M	Eyelid	0	0	0	0	1+	<2	1+	20	1+
55M	Eyelid	2+	<5	1+	1+	1+	<5	0	0	1+
47M	Cheek	1+	30	0	0	2+	5	0	0	0
43M	Cheek	2+	10	1+	0	2+	20	0	0	0

Age/Sex	bcl-2 % +	p21 Int	p21 % +	p27 Int	p27 % +	c-kit Int	c-kit % +	MDM2 % +	MLH1 Int	MLH1 % +	MSH2 Int	MSH2 % +
Sebaceous carcinoma												
79M	0	2+	1	2–3+	80	0	0	1	3+	50	1–2+	30
72F	0	2+	<5	3+	80	0	0	<10	2–3+	70	2+	50
71F	10	2–3+	60	3+	60	0	0	0	3+	80	2–3+	60
69F	0	3+	5	2+	30	0	0	0	1+	30	0	0
38F	0	2+	5	2+	90	0	0	0	ND	ND	ND	ND
77F	20	0	0	2+	30	0	0	0	ND	ND	2+	50
86F	0	1+	2	ND	ND	0	0	ND	ND	ND	2+	30
71F	10	ND	ND	ND	ND	1+	50	ND	2+	70	3+	70
Sebaceous adenoma												
84M	20	3+	60	0	0	0	0	0	ND	ND	2+	50
69M	80	2+	90	3+	90	1+	50	0	ND	ND	ND	ND
72F	30	ND	ND	2–3+	80	0	0	0	ND	ND	ND	ND
66M	10	2+	5	3+	70	0	0	0	ND	ND	ND	ND
64M	50	2+	5	3+	90	ND	ND	0	ND	ND	2+	60
67M	ND	ND	ND	ND	ND	0	0	ND	ND	ND	2+	20
84M	10	2+	25	ND	ND	ND	ND	ND	2+	50	2+	10
79M	5	ND	ND	ND	ND	0	0	ND	2+	70	0	0
62F	0	ND	ND	ND	ND	0	0	ND	2+	80	ND	ND

(*Continued*)

TABLE 2. (*continued*) Clinicopathological Characteristics and Immunohistochemistry for 27 Sebaceous Tumors

Age/Sex	bcl-2 % +	p21 Int	p21 % +	p27 Int	p27 % +	c-kit Int	c-kit % +	MDM2 % +	MLH1 Int	MLH1 % +	MSH2 Int	MSH2 % +
Sebaceoma												
71F	20	1+	1	ND	ND	0	0	ND	ND	ND	2+	40
90F	30	ND	ND	ND	ND	0	0	ND	ND	ND	3+	50
63M	25	2+	10	3+	50	0	0	0	3+	80	3+	90
76F	0	ND	ND	ND	ND	0	0	ND	3+	50	ND	ND
Sebaceous hyperplasia												
68M	50	2+	25	3+	70	0	0	0	ND	ND	ND	ND
73F	60	2+	30	2+	90	0	0	0	ND	ND	ND	ND
55M	20	2+	30	3+	90	0	0	ND	ND	ND	ND	ND
55M	10	2+	30	3+	90	0	0	ND	ND	ND	ND	ND
47M	0	ND	ND	ND	ND	0	0	ND	2+	50	ND	ND
43M	0	2+	40	ND	ND	0	0	ND	ND	ND	3+	60

Int, intensity; ND, not done.

(mean, 50% versus 11%, respectively, $P < 0.05$) (Fig. 2A, B) and Ki-67 (MIB-1) (average, 1.8+ versus 1.0+, $P < 0.05$) (Fig. 2C, D). In addition, the carcinomas had significantly reduced levels of bcl-2 (7% versus 56%, respectively, $P < 0.05$) (Fig. 2E, F) and p21 (16% versus 34%, $P < 0.05$) (Fig. 2G, H) compared to the adenomas.

The sebaceomas and sebaceous hyperplasia cases stained like the adenomas did (no significant differences), and the sebaceomas also had statistically significant lower expression levels of p53 ($P < 0.05$) and higher expression of bcl-2 ($P < 0.05$) compared to the sebaceous carcinomas (Table 2).

There were no statistically significant differences between the types of sebaceous proliferations in immunostaining for cyclin D1, p27, CD99, MDM2, or the DNA repair proteins MLH1 and MSH2 (Table 2). There was essentially negative Her-2/neu staining (0-1+) in almost all cases of both sebaceous carcinoma and adenoma, and only 1 carcinoma stained weakly positive throughout (2+) (Fig. 3). CD117 was only weakly positive in 1 case each of a carcinoma and adenoma (Table 2). Although none of the patients in this study carried a diagnosis of Muir-Torre syndrome, many of the lesions showed a partial reduction in MLH and MSH2 staining, but only 1 case each of a sebaceous carcinoma and adenoma had complete loss of MSH2 staining (Table 2). This sebaceous adenoma occurred in a patient with multiple benign sebaceous lesions and likely represents a case of Muir-Torre syndrome. This case showed greater staining for p53 (30%) and less staining for bcl-2 (5%) than the other sebaceous adenomas, a pattern of staining similar to that seen in the sebaceous carcinomas.

PCA of Sebaceous Tumors

To visualize global sebaceous tumor antibody expression patterns for the 27 samples, we generated PCA plots based on the combined data for bcl-2, Ki-67, p21, and p53 expression. A clear separation between the 8 sebaceous carcinomas versus sebaceous adenomas, hyperplasia, and sebaceomas is evident in the plot of the first, second, and third principal components in the upper right quadrant (Fig. 4), which represents 88.4% of the data. PCA also demonstrated distinct clustering of the 9 sebaceous adenomas, 6 sebaceous hyperplasias, and 4 sebaceomas, albeit in overlapping space in the first 2 principal component axes displayed (Fig. 4). Rotation of the 3-dimensional plot reveals complete separation of the benign and malignant groups from each other (data not shown). PCA thus further confirms the significant differences in expression of these 4 markers between sebaceous carcinomas and benign sebaceous lesions.

DISCUSSION

In adequate biopsies of sebaceous proliferations, immunohistochemistry is usually not necessary when histology shows typical morphologic findings. We suggest performing immunohistochemical stains to aid in the diagnosis of more atypical or borderline cases and perhaps in some cases in which the lesion is incompletely sampled in a sensitive site, such as the eyelid, and the surgeon wishes to avoid reexcision if possible. Although sebaceous neoplasms have been fairly well characterized histologically and immunohistochemically, only a few studies (most of which examined only 1 antibody) have evaluated markers that might be useful for distinguishing benign from malignant sebaceous tumors,[5,6,10] which is not a trivial issue because very small, partial biopsies from sensitive sites such as the eyelid are fairly common. Cases that histologically seem to be sebaceous adenomas may recur aggressively, and it has been postulated that all sebaceous adenomas are in fact carcinomas,[13] although this has not been confirmed by any systematic histologic, molecular, or clinical outcome studies.

We undertook this study after reviewing a case of a recurrent eyelid sebaceous tumor, which seemed histologically benign but recurred aggressively several times, eventually necessitating removal of the patient's eyelid. We sought to identify markers that could predict aggressive behavior in sebaceous tumors because they might be of significant utility in such difficult cases. Moreover, we also wanted to test the hypothesis that sebaceous adenoma and sebaceous carcinoma are indistinguishable tumors. If this is true, as some have claimed,[13] then it would follow that their immunophenotypes should be identical.

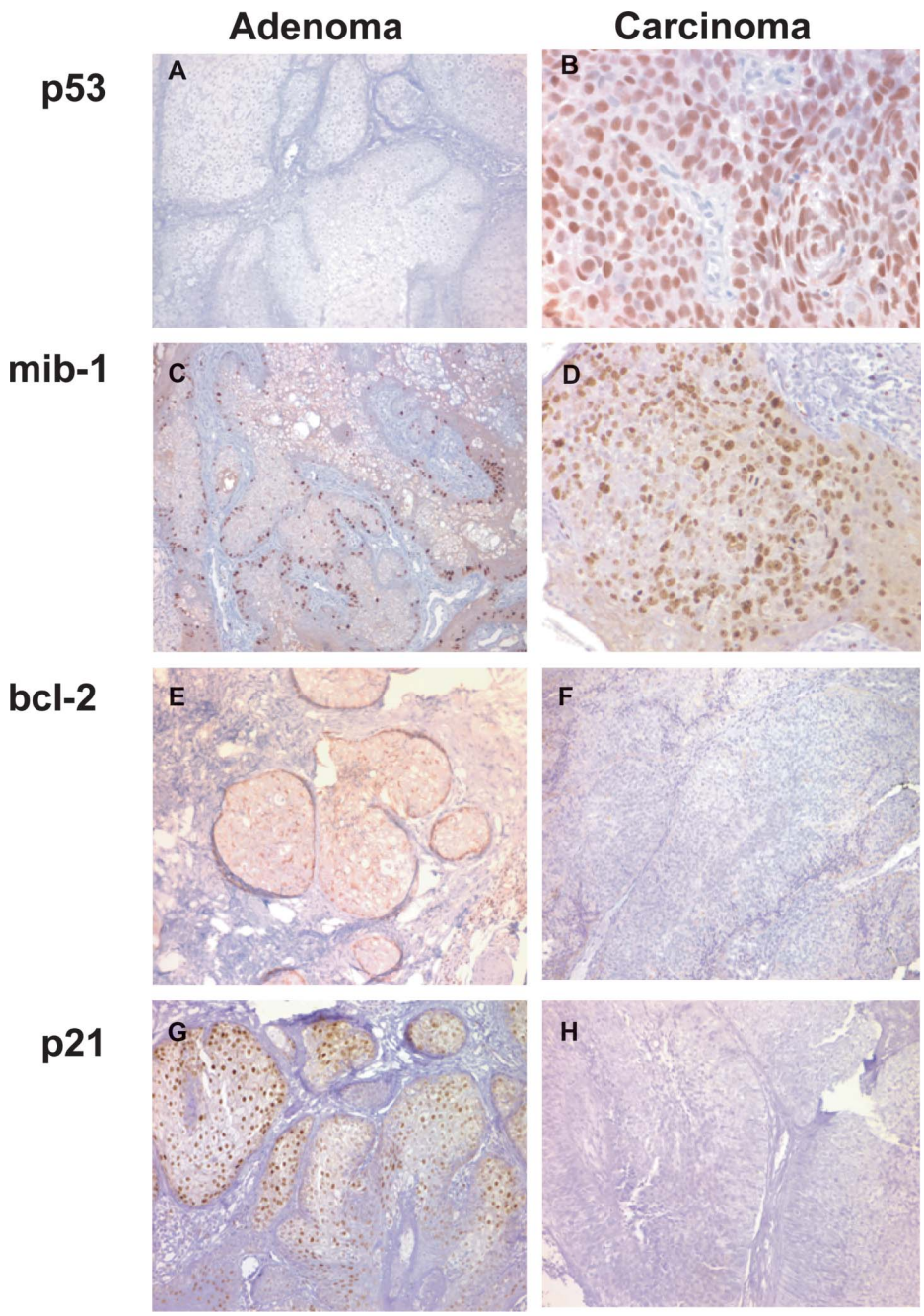

FIGURE 2. Immunohistochemical staining of sebaceous adenomas and carcinomas. A, Decreased immunostaining for p53 in a sebaceous adenoma versus (B) increased p53 nuclear staining in a sebaceous carcinoma. C, A low percentage of positive staining for Ki-67 is evident in a sebaceous adenoma compared with (D) a sebaceous carcinoma. E, Significantly greater amount of cytoplasmic staining for bcl-2 is present in a sebaceous adenoma versus (F) a sebaceous carcinoma. G, Increased nuclear expression of p21 is observed in sebaceous adenoma compared with (H) sebaceous carcinoma. (Immunohistochemical stains, various magnifications.)

Bayer-Garner et al[5] showed that sebaceous neoplasms exhibit nuclear immunoreactivity for androgen receptors and claimed that the presence of androgen receptors may be a specific marker of sebaceous differentiation. Sebaceous carcinomas tended to show less intense staining than sebaceous adenomas, sebaceomas, and hyperplasias.[5] However, the diagnostic utility of using androgen receptors is limited by the fact that other cutaneous and noncutaneous tumors (ie, up to 78% of BCCs)[18] can also express this marker.[21] Hassanein et al[6] demonstrated that the Thomsen-Friedenreich (T) antigen was expressed strongly in sebaceous carcinomas but was weaker in sebaceous adenomas and sebaceomas. These results are consistent with sebaceous adenomas and carcinomas being distinct neoplasms.

Several studies have shown that p53 expression is often increased in sebaceous carcinomas and may portend a worse prognosis.[7,8,10,12] We found a significant increase in nuclear p53 staining in sebaceous carcinomas compared to sebaceous adenomas and sebaceomas. In addition, proliferative markers, including PCNA and Ki-67 (MIB-1), are typically elevated in sebaceous carcinomas,[8,10] also similar to our findings with Ki-67, and Hasebe et al[8] showed that carcinomas with a PCNA index greater than 20% had a worse prognosis. It has also been shown that c-erbB-2 (Her-2/neu) was increased in several

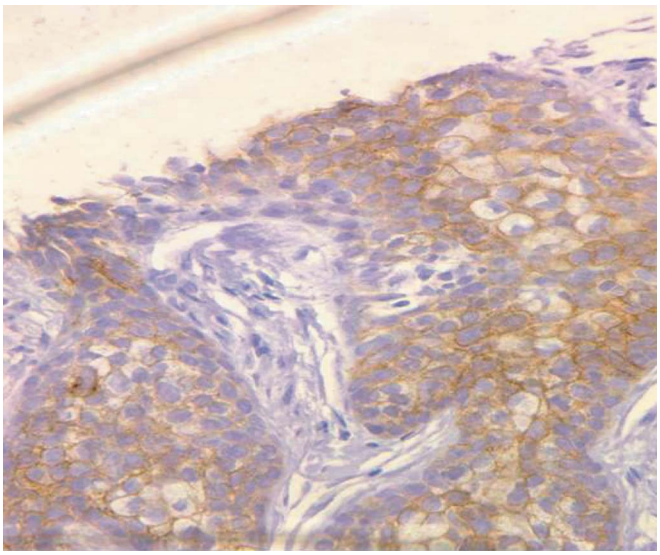

FIGURE 3. Her-2/neu immunostaining in sebaceous carcinoma. Illustration of the moderate (2+) cytoplasmic membranous staining with c-erbB-2 in a single case of sebaceous carcinoma (immunohistochemical stain, 400×).

cases of sebaceous carcinomas but was not associated with a more dire prognosis.[8,11] Bcl-2 has not been extensively studied in sebaceous neoplasms, but one study demonstrated a lack of staining in sebaceous carcinomas,[9] which is consistent with our findings of little to no bcl-2 staining in cases of sebaceous carcinoma. P21/WAF1, a nuclear tumor suppressor protein that regulates cell cycle progression, was aberrantly expressed in sebaceous carcinomas, whereas it was limited to the basaloid cells of sebaceous adenomas and sebaceomas.[10] We noticed a similar pattern of staining in our

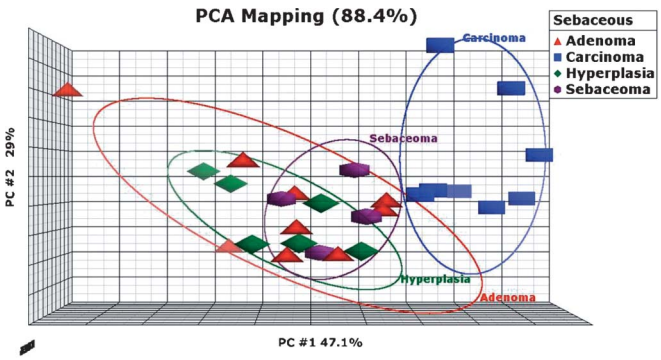

FIGURE 4. Principal components analysis (PCA) of sebaceous lesions. Depicted is a PCA map of the staining percentage data for p53, mib-1, bcl-2, and p21 immunostains for the 27 sebaceous tumor samples. Principal component (PC) 1 along the *x* axis correlates 47.1%, PC 2 along the *y* axis correlates 29%, and PC 3 along the *z* axis correlates 12.3% of the immunohistochemistry data (total correlation, 88.4%). Ellipsoids drawn by PCA show a clear separation of the 8 sebaceous carcinomas clustering separately from the 9 sebaceous adenomas, 6 sebaceous hyperplasias, and 4 sebaceomas. These 3 groups of benign lesions form closely related but distinct populations.

cases and found a significant overall reduction of this marker in cases of sebaceous carcinomas compared to the adenomas.

The major aim of this study was to evaluate a panel of 12 commercially available antibodies for their ability to distinguish benign from malignant sebaceous neoplasms. We found that the expression of several of these immunohistochemical markers can be useful in this distinction. Specifically, p53 and Ki-67 were elevated, whereas p21 and bcl-2 were depressed, in the sebaceous carcinomas compared to sebaceous adenomas and sebaceomas. These results confirm that sebaceous carcinomas are associated with increased nuclear accumulation of (presumably defective) p53, a finding common to many cancers. Decreased functional p53 and p21-mediated tumor suppression may allow for tumor progression, and loss of antiapoptotic bcl-2 may reflect lack of apoptotic sensitivity. The increase in Ki-67 staining confirms the increased proliferative activity of sebaceous carcinomas. Although any one of these markers would not provide sufficient specificity, a panel consisting of several of these antibodies may allow for distinction of sebaceous adenomas and sebaceomas from carcinomas in difficult cases. As a potential practical application of these results, we would recommend using a panel including p53, Ki-67, p21, and bcl-2 for difficult cases in which the following results would favor sebaceous carcinoma over a benign lesion: p53: greater than 10%; Ki-67: 2 or 3+; p21: less than 15%; and bcl-2: negative or less than 10%.

We did not find significant numbers of cases expressing either c-kit or Her-2/neu. The latter finding contradicts earlier studies showing higher percentages of cases staining for Her-2/neu,[8,11] but this may reflect differences in scoring of Her-2/neu staining, as well as differences in the antibodies and detection methods used. For example, Hasebe et al[8] used a polyclonal c-erbB-2 antibody from Japan, whereas Cho et al[11] used a rabbit antihuman c-erbB-2 antibody from Denmark, and scored as positive cases with 5% or greater of cells showing membrane staining. We used the US Food and Drug Administration–approved Herceptest kit (DAKO), and found only 1 of 8 cases of sebaceous carcinoma that stained weakly positive (2+) according to Herceptest scoring standards [complete membrane staining in >10% of the cells; the rest were interpreted as negative (0-1+)].

Some have claimed that all sebaceous adenomas are truly carcinomas,[13] but to our knowledge, there are no published biological or clinical studies to support this assertion. The tendency to lump these tumors may be derived from the fact that sebaceous tumors are often problematic to diagnose because of nonspecific or subtle histologic findings, and the distinction between benign and malignant lesions may be difficult.[14] However, the behavior of well-differentiated sebaceous tumors, including sebaceous adenomas and sebaceomas, is uniformly benign, with no documented metastases reported in the literature, whereas sebaceous carcinomas are aggressive and frequently metastatic.[1–3,15–17] In addition, the present study, as well as several previous immunohistochemistry studies discussed above, have shown significant differences between sebaceous adenomas and carcinomas, including differential expression of multiple proteins associated with differentiation, cell cycling, oncogenesis, and apoptosis.[5,6,10] Therefore, there is no basis for lumping sebaceous adenomas

and carcinomas together, and these tumors should continue to be distinguished clinicopathologically.

The term *sebaceoma* has received fairly widespread acceptance in the dermatopathology literature because it replaced ill-defined and confusing terms such as *sebaceous epithelioma*, which included cases of BCC with sebaceous differentiation.[19,20] Clearly, the basal cells in sebaceoma are benign, and tumors with malignant basal cells should be diagnosed as BCC (with focal sebaceous differentiation). However, there is much overlap between sebaceomas and sebaceous adenomas, and sebaceomas are likely simply a variant of sebaceous adenomas with abundant basaloid cells. Our results show that they are similar to sebaceous adenomas immunohistochemically and cluster with them by PCA analysis (and distinct from sebaceous carcinomas), thereby supporting the hypothesis that these are likely morphologic variants of sebaceous adenomas.[20]

We have confirmed that multiple markers, including p53, Ki-67, bcl-2, and p21, are differentially expressed by benign and malignant sebaceous tumors. In addition, we failed to find significant expression of c-kit or Her-2/neu proteins in most sebaceous carcinomas, indicating that immunotherapy targeting these molecules would likely not be of clinical benefit in most cases. Immunohistochemical evaluation of several markers, including p53, Ki-67, bcl-2, and p21, may be diagnostically useful in cases of incompletely sampled, difficult, or borderline sebaceous lesions.

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