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Adipophilin expression in sebaceous tumors and other cutaneous lesions with clear cell histology: an immunohistochemical study of 117 cases

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Adipophilin is a monoclonal antibody against a protein on the surface of intracellular lipid droplets, and it was recently shown to be expressed in sebocytes and sebaceous lesions. This study examines adipophilin expression in various sebaceous lesions and other cutaneous tumors with a clear cell histology that may mimic sebaceous differentiation. A total of 117 cutaneous clear cell lesions including 16 sebaceous adenomas, 25 sebaceous carcinomas, 8 basal cell carcinomas, 12 squamous cell carcinomas, 6 xanthomas, 10 xanthelasmas, 10 xanthogranulomas, 4 balloon cell nevi, 5 trichilemmomas, 8 clear cell hidradenomas, and 13 metastatic renal cell carcinomas were examined using immunohistochemistry for the expression of adipophilin. Of these 117 lesions, 42 (36%) were from the periocular region. Adipophilin was expressed in 16 of 16 (100%) sebaceous adenomas, 23 of 25 (92%) sebaceous carcinomas, 10 of 10 (100%) xanthelasmas, 9 of 10 (90%) xanthogranulomas, 6 of 6 (100%) xanthomas, and 9 of 13 (62.5%) metastatic renal cell carcinomas. The characteristic staining pattern differed between sebaceous and non-sebaceous tumors with the former showing a membranous vesicular pattern and the latter being more granular. Adipophilin expression was not seen in any of the other lesions with clear cell histology, basal cell carcinomas, or squamous cell carcinomas, including cases that had focal clear cell differentiation. Adipophilin can be valuable in an immunohistochemical panel when evaluating cutaneous lesions with clear cell histology as it identifies intracytoplasmic lipid vesicles in sebaceous and xanthomatous lesions. In periocular lesions, it is effective in helping to exclude basal cell carcinoma and squamous cell carcinoma when sebaceous carcinoma is under consideration. Adipophilin expression is not as useful for the differential diagnosis that includes metastatic renal cell carcinoma, a rare but important, diagnostic differential. The pattern of adipophilin reactivity is important to observe as membranous vesicular staining is suggestive of intracellular lipids whereas granular cytoplasmic reactivity is not.
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Sebaceous carcinoma is a relatively uncommon tumor comprising 0.05% of all cutaneous malignancies, but is the second or third most common malignant eyelid tumor in most series accounting for 2–4% of periocular tumors.[1] Local recurrence complicates 6–29% of periocular sebaceous cell carcinomas.[2–5] Regional or distal metastases affect 14–25% of patients with an associated 5-year mortality ranging from 30 to 67% according to different reports.[2,4]

Owing to its variable clinical appearance, sebaceous carcinoma mimics both benign processes, such as chalazions and blepharitis, and other malignant

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neoplasms, such as basal and squamous cell carcinomas, sometimes resulting in delayed diagnosis and suboptimal treatment.[6] Prognosis improves considerably with early diagnosis and definitive surgery.[7]

On histologic grounds alone, sebaceous carcinomas, especially those that are poorly differentiated and predominantly composed of basaloid cells and lacking conspicuous mature sebocytes, may pose a significant diagnostic challenge. In multiple studies the initial histopathologic diagnosis of such cases was incorrect in 23–77% of the cases.[8–11] Additional ancillary studies, such Oil Red O and Sudan Black IV, have been used to aid in the detection of intracytoplasmic lipids of sebaceous lesions in fresh, frozen section material. There are no immunohistochemical markers used in paraffin-embedded sections that are specific for sebaceous differentiation. Studies have shown that epithelial membrane antigen, cytokeratin 7, CAM 5.2, and androgen receptors can be used to suggest sebaceous differentiation in specific diagnostic contexts with variable success.[12–20]

A recent study investigated the use of antibodies directed against proteins associated with lipid droplets, known as the PAT or perilipin family including a monoclonal antibody to adipophilin and polyclonal antibodies to perilipin and TIP47/PP17.[17] Adipophilin is reported to be expressed in cells of lactating mammary epithelium, adrenal cortex, male reproductive system (Sertoli and Leydig cells), steatotic hepatocytes in alcoholic cirrhosis, and liposarcomas.[17,21] Mature adipocytes of fibroadipose tissue lack immunostaining for adipophilin.[21] Studies have shown these antibodies to be useful as ancillary studies to show intracellular lipid in sebaceous carcinoma. Although all three perilipin family antibodies had high specificity (adipophilin, 77%; perilipin, 100%; and TIP47/PP17, 100%), adipophilin sensitivity (88.5%) was superior (perilipin, 45.5% and TIP47/PP17, 8.3%).[17] This study suggested that adipophilin is more sensitive than Oil Red O in showing evidence of intracellular lipids in sebaceous carcinoma.[17] Additional studies have used these markers to confirm the lipid content in a variety of lesions from poorly differentiated sebaceous carcinomas arising in nevus sebaceus of Jadassohn to sebaceous epithelial-myoepithelial carcinomas of the salivary gland.[22–24]

Other cutaneous lesions with clear cell histology may represent a differential diagnostic challenge with sebaceous lesions in routine hematoxylin and eosin staining, especially in the small biopsies of eyelid or periocular areas.[25] They include basal and squamous cell carcinomas that may have histologically focal or more diffuse clear cell differentiation. It is particularly important to differentiate these entities because their behavior is generally less aggressive than sebaceous carcinoma.[5,11] Other lesions with clear cell histology, such as xanthomatous lesions, tumors originating in the outer root sheath cells of hair follicle, balloon cell nevi, and, sometimes, metastatic renal cell carcinoma can be difficult to distinguish in small biopsy specimens.

Given the potential clinical use of an immunohistochemical marker applicable to formalin-fixed paraffin-embedded sections and to provide insight relevant to this potential differential diagnostic conundrum, we evaluated the expression of adipophilin in sebaceous lesion and other cutaneous lesion with clear cell histology. The aim of this study was to determine the efficacy of adipophilin immunohistochemistry in diagnosis of sebaceous lesions, particularly its use in differentiating sebaceous lesions from other lesions with clear cell histology.

Materials and methods

Patient Cases

Archival surgical pathology material (formalin-fixed, paraffin-embedded tissue blocks and slides) from the Departments of Pathology at The University of Texas M. D. Anderson Cancer Center and Baylor College of Medicine was retrieved after Institutional Review Board approval was obtained. Under a waiver of consent, the clinical information for each subject was reviewed from the electronic medical records. All cases were reviewed and diagnoses confirmed.

A total of 117 cases were obtained and included sebaceous adenomas ($n=16$); sebaceous carcinomas ($n=25$); basal cell carcinomas, including 3 cases with clear cell differentiation ($n=8$); squamous cell carcinomas ($n=12$), including 5 cases with clear cell differentiation; xanthomas ($n=6$); xanthelasmas ($n=10$); xanthogranulomas ($n=10$); balloon cell nevi ($n=4$); trichilemmomas ($n=5$); clear cell hidradenomas ($n=8$); and cutaneous metastatic renal cell carcinoma ($n=13$). Of the 117 cases, 42 (36%) were from the eyelid and periorbital regions, including 21 sebaceous carcinomas, 5 basal cell carcinomas, 5 squamous cell carcinomas, 8 xanthelasmas, 2 xanthogranulomas, and 1 metastatic renal cell carcinoma.

Immunohistochemical Staining

Histologic sections (4-μm-thick) were placed on positively charged glass slides (ProbeOn Plus; Fisher Scientific, Pittsburgh, PA, USA). The staining was performed in a Bond Max automated immunostainer (Leica Microsystems, Bannockburn, IL, USA), with adipophilin antibody (predilute, AP125; Fitzgerald Industries International, Concord, MA, USA) with controls in parallel. No epitope retrieval was used. A polymer detection system was used, with 3,3′-diaminobenzidine tetrahydrochloride as chromogen and hematoxylin for counterstaining.

The distribution of the immunoreactivity in the neoplastic cells was evaluated independently in each of the 117 cases by at least two dermatopathologists

(DI, DAO), using semiquantitative estimation of positive cells along with overall intensity of the reactive neoplastic cells. The labeling was scored as follows: zero (0), less than 5% positive cells; one (1), 5–25% positive cells; two (2), 26–75% positive cells; and three (3), greater than 75% positive cells. The labeling intensity was tabulated as negative (0), weak (+1), moderate (+2), and strong (+3). Interobserver variation was addressed by averaging the individual values. The analysis also assessed the distribution of adipophilin expression in normal adnexal structures. Positivity was defined as membranous labeling of intracytoplasmic lipid globules (Figure 1a). For this distinction, the pattern of labeling of normal sebocytes or matures sebaceous cells in sebaceous adenomas was used as the standard. It should be noted that adipophilin is an intracellular membrane protein involved in the packaging intracytoplasmic lipids and not a specific marker of sebaceous or other type of differentiation. Granular staining (ie, uptake by keratohyalin granules and cytoplasm of macrophages) was considered nonspecific/negative (Figure 1a and b).

Statistical Analysis

The statistical association between the distribution of expression of adipophilin and type of lesion with clear cell histology was analyzed using χ^2-test and Fisher's exact test, with $P<0.05$ considered to be statistically significant.

Results

Clinical data including the diagnosis, age, gender, and anatomical site for all patients are summarized in Table 1.

The adipophilin expression is reported in Table 2. As previously described, expression of adipophilin was noted in the sebocytes of normal sebaceous glands and lipid-containing macrophages (as seen in fat necrosis).[17]

In our study, adipophilin was expressed in 16 of 16 (100%) sebaceous adenomas with a specific pattern: membranous with strong uptake at the periphery of intracytoplasmic lipid vacuoles. Of 25 sebaceous carcinomas, 23 (92%) were also labeled with a similar pattern. Interestingly, in cases of poorly differentiated sebaceous carcinoma ($n=11$), in which sebaceous differentiation could not have been reliably interpreted in hematoxylin and eosin stained sections, adipophilin highlighted the sebocytes with a strong membranous labeling of intracytoplasmic lipid droplets (Figure 2a) in 9 of 11 cases (82%). Moreover, 10 of 10 (100%) xanthelasmas, 9 of 10 (90%) xanthogranulomas, 6 of 6 (100%) xanthomas, and 9 of 13 (63%) metastatic renal cell carcinomas were also positive for adipophilin, with

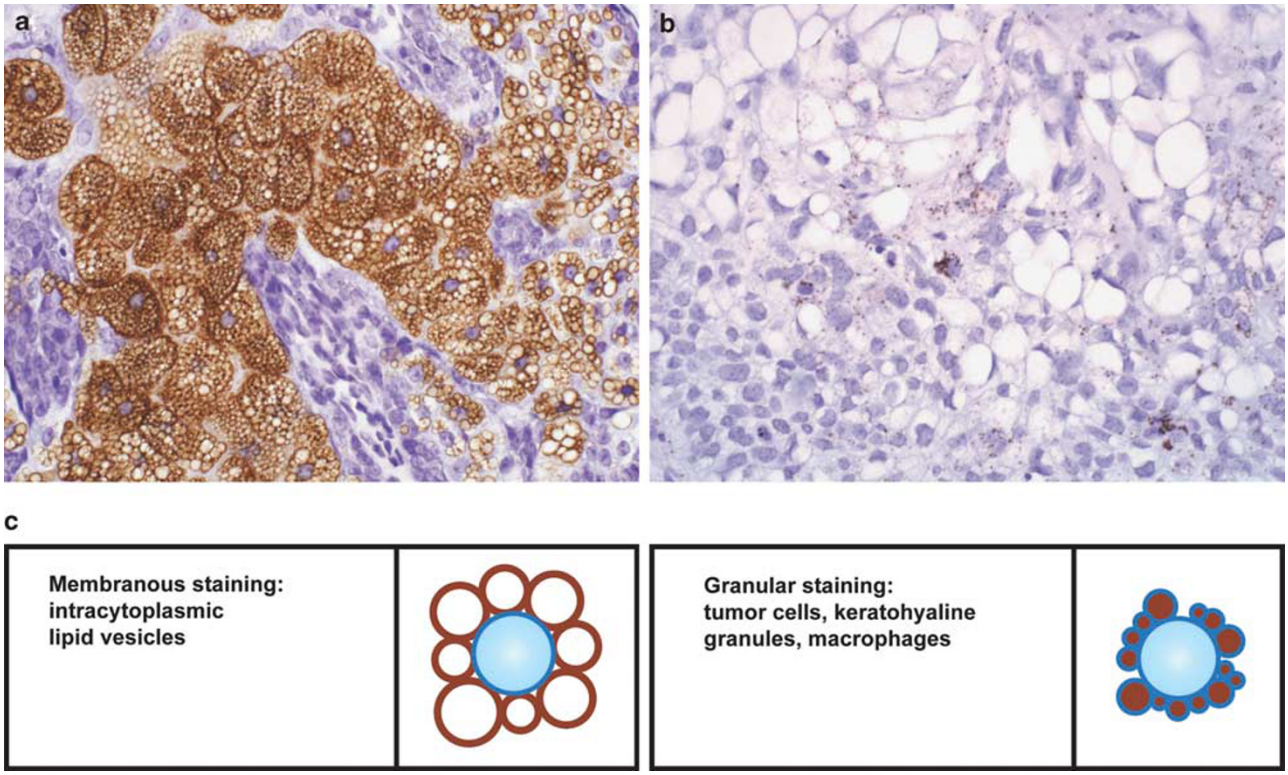

Figure 1 (**a**) Membranous staining of intracytoplasmic lipid droplets in sebaceous adenoma (original magnification, 400×). (**b**) Nonspecific uptake of adipophilin by macrophages and rare tumor cells of a basal cell carcinoma with clear cell features (original magnification, 400×). This nonspecific uptake of antibody was also seen in association with keratohyalin bodies in squamous cells. (**c**) Depiction of positive vesicular staining pattern and nonspecific granular uptake of adipophilin antibody.

Table 1 Clinical data

Diagnostic category (n)	*Age (range)*	*Sex (M:F)*	*Anatomic sites*
Sebaceous adenoma (16)	46–81 years	11:5	10 head, 1 neck, 3 upper extremity, 2 trunk
Sebaceous carcinoma (25)	36–93 years	3:2	21 periorbital region, 2 head, 1 upper extremity, 1 trunk
Basal cell carcinoma (8)	35–83 years	7:1	5 periorbital region
Squamous cell carcinoma (12)	62–88 years	5:1	5 periorbital region, 5 head, 1 neck, 1 lower extremity
Hidradenoma, clear cell (8)	31–81 years	1:1	4 head, 3 upper extremity, 1 trunk
Trichilemmoma (5)	52–74 years	4:1	5 head
Xanthelasma (10)	38–57 years	7:3	8 periorbital region, 1 nose, 1 upper extremity
Xanthogranuloma (10)	8 months–61 years	7:3	2 periorbital region, 5 head, 2 trunk, 1 lower extremity
Xanthoma (6)	9 months–67 years	1:1	2 head, 2 upper extremity, 2 trunk
Melanocytic nevus, balloon cell (4)	63–83 years	3:1	4 trunk
Renal cell carcinoma, metastatic (13)	41–79 years	9:4	6 head (3 scalp, 3 face), 1 neck, 3 upper extremity, 2 trunk, 1 lower extremity

Table 2 Adipophilin expression in sebaceous lesions and other cutaneous lesions, including lesions with clear cell histology

	Tumor cells staining (%)				*Intensity of staining*			
	Negative (%)	*1+ (%)*	*2+ (%)*	*3+ (%)*	*Negative (%)*	*1+ (%)*	*2+ (%)*	*3+ (%)*
Sebaceous adenoma ($n=16$)	0 (0)	0 (0)	0 (0)	16 (100)	0 (0)	0 (0)	0 (0)	16 (100)
Sebaceous carcinoma ($n=25$)	2 (8)	0 (0)	11 (44)	12 (48)	2 (8)	1 (4)	6 (24)	17 (68)
Basal cell carcinoma ($n=8$)	8 (100)	0 (0)	0 (0)	0 (0)	8 (100)	0 (0)	0 (0)	0 (0)
Basal cell carcinoma, clear cell type ($n=3$)	3 (100)	0 (0)	0 (0)	0 (0)	3 (100)	0 (0)	0 (0)	0 (0)
Squamous cell carcinoma ($n=12$)	12 (100)	0 (0)	0 (0)	0 (0)	12 (100)	0 (0)	0 (0)	0 (0)
Squamous cell carcinoma, clear cell type ($n=5$)	3 (100)	0 (0)	0 (0)	0 (0)	3 (100)	0 (0)	0 (0)	0 (0)
Hidradenoma, clear cell ($n=8$)	8 (100)	0 (0)	0 (0)	0 (0)	8 (100)	0 (0)	0 (0)	0 (0)
Trichilemmoma ($n=5$)	5 (100)	0 (0)	0 (0)	0 (0)	5 (100)	0 (0)	0 (0)	0 (0)
Xanthelasma ($n=10$)	0 (0)	0 (0)	0 (0)	10 (100)	0 (0)	0 (0)	0 (0)	10 (100)
Xanthogranuloma ($n=10$)	1 (10)	0 (0)	5 (50)	4 (40)	0 (0)	1 (10)	1 (10)	8 (80)
Xanthoma ($n=6$)	0 (0)	0 (0)	2 (33)	4 (66)	0 (0)	0 (0)	1 (17)	5 (83)
Melanocytic nevus, balloon cell ($n=4$)	4 (100)	0 (0)	0 (0)	0 (0)	4 (100)	0 (0)	0 (0)	0 (0)
Renal cell carcinoma, metastatic ($n=13$)	4 (31)	3 (23)	4 (31)	2 (15)	4 (31)	3 (23)	4 (30)	2 (15)

Percentage: 0, no labeling to 5%; 1+, labeling in 6–25% of cells; 2+, labeling in 26–75%; and 3+, labeling in more than 75% of clear cells in the lesion.
Intensity: 0, negative; 1+, weak; 2+, moderate; 3+, strong.

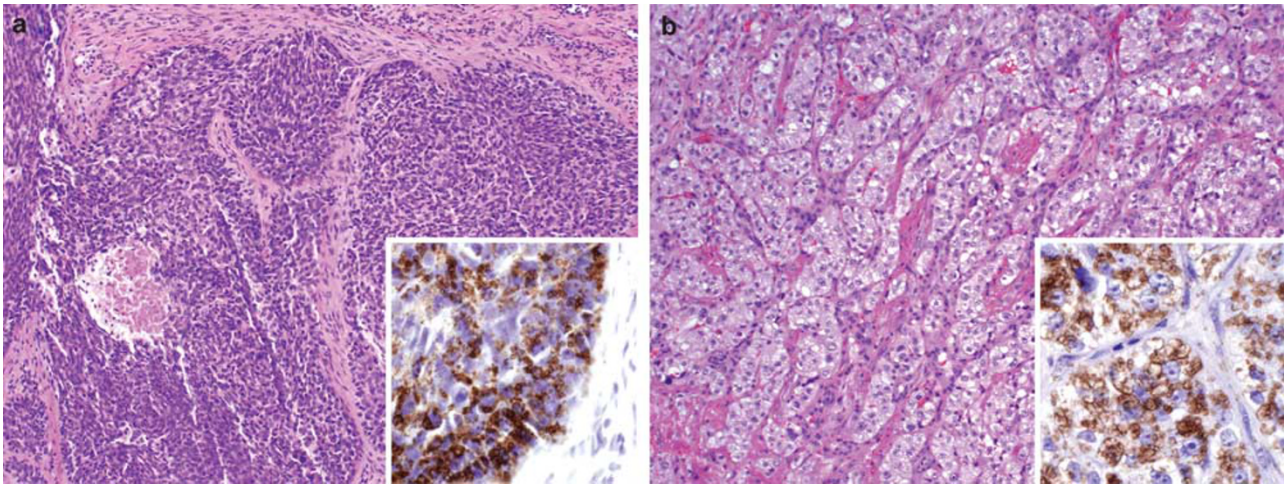

Figure 2 Poorly differentiated sebaceous carcinoma (**a**) and renal cell carcinoma metastatic to the skin (**b**) with insets strong membranous staining of intracytoplasmic lipid vacuoles by adipophilin antibody.

a similar pattern to that of sebaceous lesions (Figure 2b). Table 2 shows the distribution of adipophilin expression by grade (percentage of tumor cells staining) among each tumor type. In all the above-mentioned lesions, at least 25% of the lesional cells were positive and the intensity was

2+ or 3+. The metastatic renal cell carcinomas showed more variability; two cases had over 75% positive cells (3+), four cases were labeled with 2+ score, three cases were 1+, and four cases had less than 5% positive cells (score 0).

Expression of adipophilin with a membranous pattern of staining was not seen in any of the other clear cell lesions of the skin, including basal and squamous cell carcinomas (including in the areas of clear cell differentiation), trichilemmomas, clear cell hidradenomas, or balloon cell nevi. Interestingly, a nonspecific granular uptake of antibody was seen in adjacent macrophages, keratohyalin granules of epithelial squamous cells, and some tumor cells. Five of eight (62.5%) basal cell carcinomas (including all three cases with clear cell differentiation), two of eight (25%) clear cell hidradenomas, four of four (100%) balloon cell nevi, nine of twelve (%) squamous cell carcinomas (including all five cases with clear cell differentiation), and four of five (80%) trichilemmomas showed nonspecific granular labeling in a minority of the tumor cells (less than 25%, with a majority of cases in less than 5%). Uptake of adipophilin with similar granular pattern was also noted in macrophages, in areas of ulceration and fat necrosis. Two of the eight basal cell carcinomas had focal entrapped sebaceous glands and they were highlighted by adipophilin, with a membranous pattern. There was no staining of mature adipocytes, in the cases that contained subcutaneous or adventitial adipose tissue.

The adipophilin expression of the lesions of the eyelid or periorbital region is reported in Table 3. Adipophilin was very sensitive in detecting intracytoplasmic lipid droplets in sebaceous carcinoma of the eyelid as 19 of 21 (90%) showed either 2+ or 3+ expression. Of 21 periorbital sebaceous carcinomas, 11 were poorly differentiated, including the 2 cases that did not express adipophilin. All of the xanthomatous lesions and the metastatic renal cell carcinoma from the periorbital region labeled for adipophilin in a high percentage of tumor cells (3+ or 2+), with a pattern similar to that of the sebaceous lesions. None of the basal or squamous cell carcinomas from the eyelid showed membranous adipophilin expression of the intracytoplasmic lipid droplets. However, two basal cell carcinomas and four squamous cell carcinomas from the eyelid/periorbital region had a nonspecific granular staining pattern in less than 25% of the tumor cells. A side-by-side photomicrographic comparison of sebaceous, basal cell, and squamous cell carcinomas is shown in Figure 3, including representative hematoxylin and eosin and adipophilin stains.

Statistical Analysis

When the group of sebaceous lesions was compared with basal or squamous cell carcinomas, the differential expression of adipophilin in the sebaceous lesions was higher and strongly statistically significant ($P<0.001$).

Discussion

Sebaceous carcinoma is an uncommon but aggressive malignancy. It may mimic other benign or malignant tumors histologically, and its recognition is important for proper treatment. Traditionally, Oil Red O and Sudan Black IV have been used to identify intracytoplasmic lipids in sebaceous lesions in fresh frozen tissue. Standard permanent tissue processing extracts the intracellular lipids, rendering these approaches useless in formalin-fixed paraffin-embedded material. There is a practical need for an immunohistochemical marker that detects intracellular lipid vesicles on formalin-fixed paraffin-embedded tissue sections.

Coordination of intracellular lipid metabolism, including storage and use, is regulated by the PAT or perilipin family of lipid droplet-associated phosphoproteins, which includes perilipin, adipophilin/adipocytes differentiation-related protein, and TIP47.[21,26,27] Adipophilin is a protein present in a wide range of cells and tissues on the surface of intracellular lipid droplets.[21] Owing to the location of the protein in relation to the lipid droplets, adipophilin highlights the residual membrane proteins of the intracytoplasmic lipid vesicles. Studies have been performed to investigate such markers in tumors with sebaceous differentiation.[11,14,15,17]

In our study, we examine a series of tumors that can enter the differential diagnosis with sebaceous neoplasia for expression of adipophilin. We show vesicular staining for adipophilin in the sebocytes of normal sebaceous glands, in 16 of 16 (100%) sebaceous adenomas and 23 of 25 (92%) sebaceous

Table 3 Eyelid lesions: grading of adipophilin staining results

	Negative (%)	*1+ (%)*	*2+ (%)*	*3+ (%)*
Sebaceous carcinoma ($n=21$)	2 (10)	0 (0)	9 (43)	10 (47)
Basal cell carcinoma ($n=5$)	5 (100)	0 (0)	0 (0)	0 (0)
Squamous cell carcinoma ($n=5$)	5 (100)	0 (0)	0 (0)	0 (0)
Xanthelasma ($n=8$)	0 (0)	0 (0)	0 (0)	8 (100)
Xanthogranuloma ($n=2$)	0 (0)	0 (0)	2 (100)	0 (0)

0, no labeling; 1+, labeling in 6–25% of cells; 2+, labeling in 26–75%; and 3+, labeling in more than 75% of clear cells in the lesion.

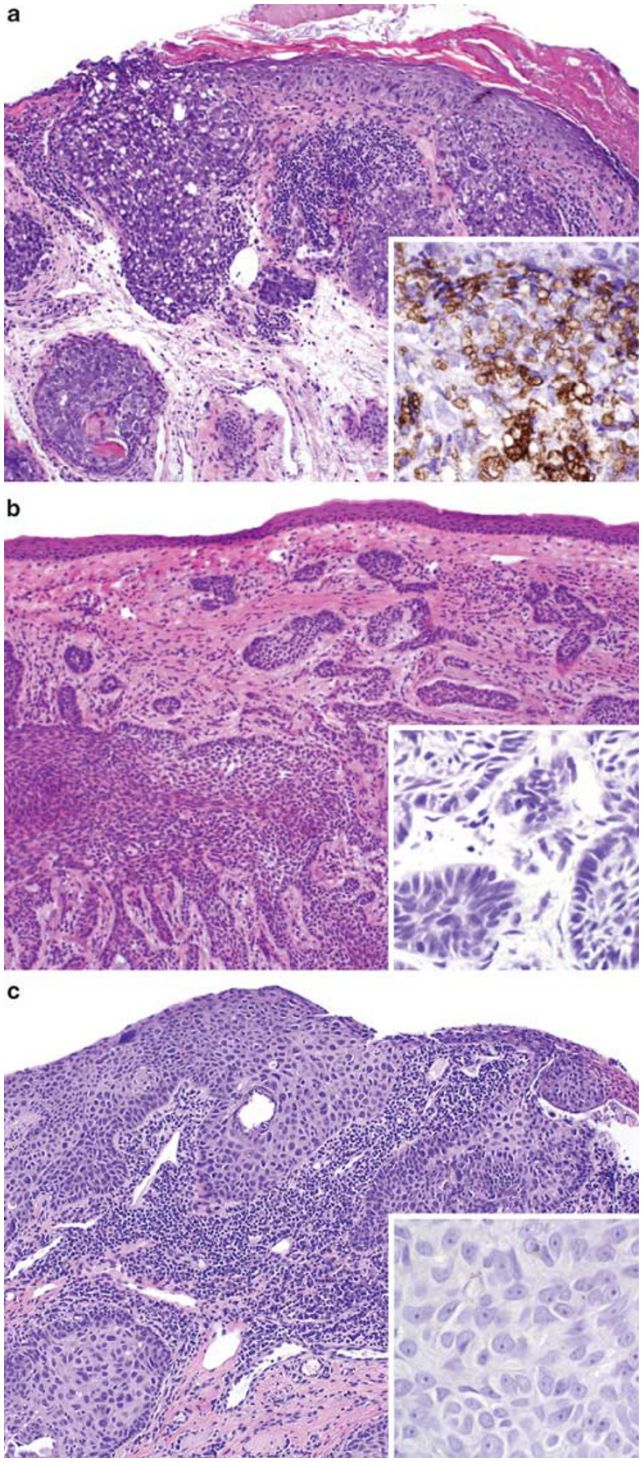

Figure 3 Hematoxylin and eosin stains with insets showing adipophilin immunostains showing the strong membranous staining of intracytoplasmic lipid in sebaceous carcinoma (**a**) compared to basal cell carcinoma (**b**) and squamous cell carcinoma (**c**).

carcinomas, including 9 of 11 (82%) cases of poorly differentiated sebaceous cell carcinomas. When the group of sebaceous lesions was compared with basal or squamous cell carcinomas, the differential expression of adipophilin was a significant discriminator ($P<0.001$). We document vesicular adipophilin expression in xanthomatous lesions and renal cell carcinomas metastatic to skin, with potentially important differential diagnostic implications. In contrast, we observed weak and focal granular labeling, that is predominantly perinuclear, in normal squamous epithelium (in keratohyalin granules and Odland bodies). Granular staining was also detected in some basal and squamous cell carcinomas, trichilemmomas, hidradenomas, and balloon cell nevi. This pattern was interpreted as nonspecific and is important to distinguish from the vesicular staining seen in sebaceous neoplasia. Muthusamy *et al*[17] noted this phenomenon and considered it as nonspecific cross-reactivity with some other intracytoplasmic antigen rather than indicating small amounts of intracytoplasmic lipids (Figure 1).

In conclusion, adipophilin is a monoclonal antibody used on formalin-fixed paraffin-embedded tissue that is helpful in the identification of intracytoplasmic lipids, as seen in sebaceous lesions. It is especially helpful in identifying intracytoplasmic lipid vesicles in poorly differentiated sebaceous carcinomas in challenging cases such as small periocular biopsy specimens. Observation of the pattern of expression is essential. Specific positivity is represented by membranous expression of intracytoplasmic lipid vesicles; focal and weak granular labeling can be observed in normal structures or tumors, but is nonspecific. Adipophilin expression is not useful for distinguishing xanthomatous lesions and metastatic renal cell carcinoma from sebaceous neoplasia.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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