Adnexal Clear Cell Carcinoma With Comedonecrosis
Clinicopathologic Analysis of 12 Cases

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Context.—Cutaneous clear cell tumors can pose a diagnostic challenge even to the experienced dermatopathologist; this is partly because of limitations of existing diagnostic categories.

Objective.—To describe a previously unrecognized, distinctive cutaneous adnexal carcinoma capable of an aggressive clinical course.

Design.—Clinicopathologic analysis of a series of 12 cases.

Results.—The patients were older individuals (median age, 71 years) with equal gender frequency. The lesions showed wide anatomic distribution with predilection for the head and neck area, especially the scalp. The lesions presented as rapidly growing, erythematous to flesh-colored, solitary papules/nodules that were capable of quickly reaching a size of several centimeters. Histologically, adnexal clear cell carcinoma with comedonecrosis was characterized by dermal proliferation of nests of epithelial cells showing distinctive zonal arrangement. The periphery of the tumor nests was formed by squamoid cells merging with centrally located clear cell areas containing foci of comedonecrosis. The lesions often showed multilobular or trabecular growth pattern and infiltrating border. Nuclear pleomorphism was variable; mitotic count ranged from 2 to 32/mm² (median, 8/mm²). No ductal, cuticular, or apocrine differentiation was seen. All cases showed expression of epithelial membrane antigen and cytokeratin 17 in clear cells, with focal carinoembryonic antigen expression in some cases. Follow-up (average, 37 months) revealed local recurrence (4 cases) and regional and distant metastases (2 cases).

Conclusions.—Adnexal clear cell carcinoma with comedonecrosis appears to be a distinctive adnexal neoplasm that has to be distinguished from more indolent squamous cell and tricholemmal carcinomas.

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Materials and Methods

The cases in our study were selected from a group of primary cutaneous carcinomas with clear cell features that defied precise classification into any existing diagnostic category. Seven cases were routine accessions from Massachusetts General Hospital and 5 cases were referrals from outside institutions, including 2 second-opinion consultations. Eight cases were initially coded as clear cell variants of squamous cell carcinomas. Diagnoses of tricholemmal carcinoma and sebaceous carcinoma were suspected in 2 cases. Four cases were provisionally classified as cutaneous clear cell carcinomas but with a comment that such lesions did not neatly fit into any current pathologic category.

Tissue sections from paraffin blocks of each case were stained for hematoxylin–eosin and periodic acid–Schiff, with and without diastase digestion. Immunohistochemical studies were performed on formalin-fixed, paraffin-embedded tissue using a standard automated streptavidin–biotin peroxidase detection system. The antibodies used, including dilutions, are detailed in Table 1.

Clinical data with follow-up information were obtained by reviewing the medical records or contacting the referring physicians or pathologists.
Table 1. Antibodies Used for Immunohistochemical Studies

<table>
<thead>
<tr>
<th>Antibody*</th>
<th>Clone</th>
<th>Dilution</th>
<th>Source†</th>
</tr>
</thead>
<tbody>
<tr>
<td>EMA</td>
<td>E29</td>
<td>Predilute</td>
<td>Ventana</td>
</tr>
<tr>
<td>CK17</td>
<td>E3</td>
<td>1:50</td>
<td>Dako</td>
</tr>
<tr>
<td>CEA</td>
<td>TF-3H8-1</td>
<td>Predilute</td>
<td>Ventana</td>
</tr>
<tr>
<td>AE1/AE3</td>
<td>1:40</td>
<td>Signet</td>
<td></td>
</tr>
<tr>
<td>CAM 5.2</td>
<td>1:5</td>
<td>Becton Dickinson</td>
<td></td>
</tr>
<tr>
<td>CK7</td>
<td>K72</td>
<td>Predilute</td>
<td>Ventana</td>
</tr>
<tr>
<td>CK20</td>
<td>Ks20.8</td>
<td>Predilute</td>
<td>Ventana</td>
</tr>
<tr>
<td>CD34</td>
<td>Q8End/10</td>
<td>Predilute</td>
<td>Ventana</td>
</tr>
<tr>
<td>S100 protein</td>
<td>Polyclonal</td>
<td>Predilute</td>
<td>Ventana</td>
</tr>
</tbody>
</table>

* EMA indicates epithelial membrane antigen; CK, cytokeratin; CEA, carcinoembryonic antigen; AE1/AE3, broad-spectrum cytokeratin; CAM 5.2, low-molecular-weight keratin; and CD34, cluster designation 34.
† Ventana, Dover, Del; Dako, Carpinteria, Calif; Signet, Madison, Wis; Becton Dickinson and Company, Franklin Lakes, NJ.

RESULTS

Clinical Features

The clinical features of the 12 cases are summarized in Table 2. There were 6 men and 6 women with an age range of 51 to 95 years (median, 71 years) at the time of diagnosis. The tumors were usually ulcerated or crusted papules, nodules, or plaques, which varied in size at the time of biopsy excision from 0.5 to 3 cm (mean, 1.4 cm) and were of variable duration. They were most commonly found on the scalp (n = 4), followed by the face (n = 3), extremity (n = 2), shoulder (n = 1), perineum (n = 1), and neck (n = 1). Clinically, the lesions were thought to be either squamous cell carcinomas, amelanotic melanomas, or ulcerated basal cell carcinomas.

Three patients had a history of organ transplantation (heart, case 2; renal, cases 4 and 8) and were receiving immunosuppressive treatment. One patient (case 11) had a concurrent renal carcinoma and transitional cell carcinoma of the bladder.

Follow-up information of 1 year or more was available for 9 patients. Recurrences developed in 4 patients (cases 4, 6, 7, and 9). The recurrent tumors grew rapidly, reaching significant size within 6 to 8 months. One patient (case 4) treated by orbital exenteration died of uncontrollable local disease. Two patients (cases 6 and 7) had regional and distant metastases to the lungs. Despite extensive surgical therapy combined with chemotherapy, one patient (case 6) had local recurrence and disseminated disease.

Histopathology

Microscopically, all tumors involved superficial-to-deep reticular dermis, with 4 lesions extending into subcutaneous fat. Surface ulceration was evident in 9 cases. At scanning magnification, the tumors showed infiltration of reticular dermis by discrete nests, lobules, trabeculae, or islands of large epithelial cells (Figure 1, A through C). The tumor aggregates showed zonal arrangement consist-

Table 2. Clinical Information*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, y/Sex</th>
<th>Location</th>
<th>Presentation</th>
<th>Size, cm†</th>
<th>Clinical Diagnosis</th>
<th>Referring/Initial Diagnosis</th>
<th>Treatment</th>
<th>Follow-up, mo</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>64/M</td>
<td>Neck</td>
<td>N/A</td>
<td>0.5</td>
<td>N/A</td>
<td>Clear cell SCC</td>
<td>Excision</td>
<td>83, NRD</td>
</tr>
<tr>
<td>2</td>
<td>68/F</td>
<td>Scalp</td>
<td>Ulcerated dome-shaped lesion</td>
<td>1.0</td>
<td>BCC amelanotic melanoma, SCC</td>
<td>Clear cell SCC</td>
<td>Excision</td>
<td>62, NRD</td>
</tr>
<tr>
<td>3</td>
<td>91/F</td>
<td>Forehead</td>
<td>Small nodule</td>
<td>0.6</td>
<td>SCC</td>
<td>Sebaceous carcinoma</td>
<td>Wide local excision</td>
<td>42, NRD</td>
</tr>
<tr>
<td>4</td>
<td>74/F</td>
<td>Eyebrow (supra-orbital)</td>
<td>Fungating tumor mass</td>
<td>2.4</td>
<td>SCC</td>
<td>Clear cell SCC</td>
<td>Excision, radiation therapy</td>
<td>18, LR, DOD</td>
</tr>
<tr>
<td>5</td>
<td>51/M</td>
<td>Scalp</td>
<td>Crusted verrucous lesion</td>
<td>1.0</td>
<td>SCC</td>
<td>Tricholemmal carcinoma</td>
<td>Excision</td>
<td>48, NRD</td>
</tr>
<tr>
<td>6</td>
<td>74/M</td>
<td>Scalp</td>
<td>Ulcerated lesion</td>
<td>1.1</td>
<td>SCC</td>
<td>Clear cell SCC</td>
<td>Excision, chemotherapy</td>
<td>18, LR, LN, and lung mets; DOD</td>
</tr>
<tr>
<td>7</td>
<td>69/M</td>
<td>Anal verge</td>
<td>Nodule</td>
<td>1.5</td>
<td>SCC with comedonecrosis</td>
<td>Clear cell SCC</td>
<td>Excision, chemotherapy and radiotherapy</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>70/F</td>
<td>Shoulder</td>
<td>Unknown</td>
<td>1.6</td>
<td>SCC, BCC, or po-rocarcinoma</td>
<td>Clear cell SCC; suspected ACCCC</td>
<td>Excision</td>
<td>Recent case</td>
</tr>
<tr>
<td>9</td>
<td>69/M</td>
<td>Hand</td>
<td>Large fungating tumor</td>
<td>3.0</td>
<td>BCC</td>
<td>Clear cell SCC; suspected ACCCC</td>
<td>Excision</td>
<td>Recent case, LR</td>
</tr>
<tr>
<td>10</td>
<td>54/F</td>
<td>Scalp</td>
<td>Nodule</td>
<td>2.0</td>
<td>SCC</td>
<td>SCC, possible pil lar tumor</td>
<td>Excision</td>
<td>24, lost to follow-up</td>
</tr>
<tr>
<td>11</td>
<td>68/M</td>
<td>Arm</td>
<td>Small nodule</td>
<td>2.5</td>
<td>SCC, pyogenic granuloma, or keratoacanthoma</td>
<td>Suspected ACCCC</td>
<td>Excision</td>
<td>30, NRD</td>
</tr>
<tr>
<td>12</td>
<td>95/F</td>
<td>Forehead</td>
<td>Elevated, hemorrhagic crusty lesion</td>
<td>1.4</td>
<td>SCC</td>
<td>Suspected ACCCC</td>
<td>Excision</td>
<td>12, NRD, DUD</td>
</tr>
</tbody>
</table>

* N/A indicates no information given or available; SCC, squamous cell carcinoma; NRD, no sign of recurrence or metastasis; BCC, basal cell carcinoma; LR, local recurrence; DOD, patient dead of the disease; LN, lymph node; mets, metastasis; ACCCC, adnexal clear cell carcinoma with comedonecrosis; DUD, patient died of unrelated disease.
† Maximum diameter.
Figure 1. A through C, The tumor shows infiltration of reticular dermis in discrete nests, lobules, tubules, or trabeculae of epithelial cells. A, Case 6; B, case 9; C, case 7 (hematoxylin-eosin, original magnifications ×2.5).

Figure 2. A through C, Zonal arrangement of tumor nests with the outer squamous and inner clear cells with centrally located degenerating tumor cells showing pattern of comedonecrosis. A, Case 2; B, case 11; C, case 4 (hematoxylin-eosin, original magnifications ×20 [A], ×10 [B], and ×40 [C]).
prominent intercellular bridges (Figure 3, A through D). Squamous pearls and single-cell keratinization could be seen in 4 cases. The squamoid areas merged with the more central zone of clear cells that occupied between 10% and 90% of the tumor volume. Smaller tumor aggregates tended to be predominantly squamoid, whereas clear cell areas were most prominent in larger tumor nodules.

Cytomorphology of clear cells varied from case to case and, to a lesser degree, within different parts of the same lesion (Figure 3, A through D). In most cases, the neoplastic clear cells had centrally placed nuclei with surrounding optically clear cytoplasm and prominent cell membranes. Less often, signet ring forms were visualized, with compressed crescent-shaped and laterally displaced nuclei. In some areas the clear cells were columnar in shape. The cytoplasmic clearing was due to accumulation of glycogen in all cases, which stained positive with periodic acid–Schiff stain in a diastase-sensitive manner (Figure 4, A through C). No koilocytic changes or any other histologic changes indicating human papillomavirus infection were seen. Evidence of intracytoplasmic lipid deposition or cytoplasmic microvacuolization, which would suggest sebaceous differentiation, was not identified in any of the cases.

All cases showed the presence of tumor necrosis forming variably sized “comedones” in the center of large tumor aggregates. In 2 patients (cases 6 and 7) the tumor necrosis was extensive, reaching geographic proportions. In some tumors, the comedones showed concentric compact keratin with retention of degenerating nuclei.

Nuclear pleomorphism could be observed in both the squamoid and clear cells and varied from case to case, but it was graded as moderate in most cases (Figure 3, A and B). Occasional bizarre pleomorphic tumor giant cells were encountered. The mitotic count ranged from 2 to 32/mm² (median, 8/mm²).

All tumors were carefully scrutinized for the presence of areas of specialized adnexal differentiation. There was no evidence of ductal, cuticular, primitive hair germ (basaloid), apocrine, pilar, pilomatrical, or sebaceous differentiation in routine sections or immunohistochemical studies in any of the cases analyzed.

Multiple sections revealed at least focal connection to the overlying epidermis in 8 cases (Figure 5, A and B). Four lesions showed multiple points of attachment of the surface. In 8 cases, areas showing in situ carcinoma could be identified (Figure 5, A). It was not apparent whether the in situ carcinoma represented a true precursor lesion.
or epidermal involvement of a predominantly adnexal or dermal tumor. There was no evidence of continuity of the tumor with a coexisting benign precursor. Lymphovascular invasion was identified in 3 cases. A mild to moderate inflammatory cell infiltrate composed of lymphocytes associated with variable amounts of neutrophils was present in the majority of cases. In one patient (case 4) there was a diffuse infiltrate of tumor nests by neutrophil polymorphs.

The surrounding supporting connective tissue stroma varied from a loose myxoid texture to dense fibrosis. Artifactual retraction of the tumor islands from the surrounding stroma was present in 4 lesions.

**Immunohistochemistry**

The immunohistochemical results are summarized in Table 3. The majority of tumors showed a unique immunohistochemical profile of a combined expression of EMA (cytoplasmic and membranous), cytokeratin 17, and, in some cases, focal staining with CEA (membranous). Expression of EMA, and in some cases cytokeratin 17, was accentuated or, in many cases, restricted to clear cell areas (Figure 6, A and B). Expression of EMA was present in all cases and was a diagnostic criterion for inclusion in the series. One case showed similar features to all the tumors but was excluded because the tumor did not express EMA. Staining with CEA was not present in all lesions. The staining seemed to be confined to the areas immediately adjacent to areas of tumor necrosis, raising doubt over its specificity (Figure 6, C through F). Artifactual or not, it was present in a sufficient number of cases to appear to be diagnostically useful. Neither EMA nor CEA staining identified ductal differentiation in any of the cases.

All tumors showed at least focal expression of cytokeratin 17 (Figure 7, A and B). Intensity of cytokeratin 17 expression was variable; however, if the internal control staining signal of normal hair follicles was strong, one would also see a similar degree of staining intensity in the tumor cells.

All cases showed expression of pancytokeratin (AE1/AE3, CAM 5.2). Expression of cytokeratin 7 was identified in only 2 cases. Immunolabeling for S100 protein, CD34, or cytokeratin 20 was negative.

**COMMENT**

We report a series of 12 cases of adnexal clear cell carcinoma with comedonecrosis (ACCCC), a distinctive and potentially aggressive tumor, characterized by squamous differentiation, clear cell changes, comedo-type necrosis, and unique immunohistochemical phenotype including expression of EMA, cytokeratin 17, and in some cases, CEA by the clear cells. This lesion has a predilection for older individuals (median age, 71 years) and occurs with equal frequency in both sexes. The most common site is the head and neck region, especially the scalp, but there is a wide anatomic distribution, including hair-bearing skin on the extremities and genital areas. Clinically, the lesions are erythematous to flesh-colored, solitary papules, nodules, or tumors, frequently ulcerated with surface scale crust. Most lesions in our series were detected early and were small, but occasionally they can reach several centimeters in diameter within several months of observation. Immunosuppression may facilitate development of this tumor; 3 of the patients in our study were transplant recipients (2 kidney transplants and 1 heart transplant).

Histologically, ACCCC is characterized by a nested, multilobular or trabecular epithelial tumor infiltrating the dermis with a poorly marginated advancing border. On biopsy, the tumor may appear predominantly dermal, but focal connection to the underlying epidermis can be ob-
The characteristic morphologic features of this tumor are variable from case to case, are conspicuous in most lesions. At low magnification, most lesions appear squamoid, with formation of occasional squamous pearls. Individual tumor aggregates show a distinctive zonal arrangement, with the outer squamoid cells merging with centrally located clear cell areas. A characteristic feature of ACCCC is comedo-type degeneration in the center of tumor nests. This pattern is most prominent in larger nests and lobules and consists of centrally located plugs containing degenerate hydropic cells, parakeratotic corneocytes, or tumor necrosis. It should be noted that not all cases showed neutrophilic debris in the center of the tumor nests as seen in coagulative necrosis, indicating that the features seen may not be entirely the result of the lack of vascular supply, but attributable to degenerative change. Because of this, we believe that terms such as comedonecrosis or comedo-type degeneration may apply.

Nuclear atypia and mitotic activity, although quite variable from case to case, are conspicuous in most lesions. The characteristic morphologic features of this tumor are complemented by consistent immunohistochemical staining, including expression of EMA, cytokeratin 17, and in many cases, CEA. Expression of EMA and CEA shows localization of the highest signal intensity to areas of clear cell morphology. Clear cell changes are due to intracellular accumulation of glycogen, as indicated by diastase sensitivity of periodic acid–Schiff staining.

As illustrated by the initial diagnoses in our cases, in routine practice, ACCCC is mostly likely to be considered as a clear cell variant of squamous cell carcinoma (SCC). Diagnoses of trichoepithelial carcinoma and even sebaceous carcinoma were also offered by experienced dermatopathologists. Histologic differential diagnosis between ACCCC and its mimics may be clinically significant as this tumor appears to behave in more aggressive fashion than typical SCC or trichoepithelial carcinoma. The incidence of metastatic cutaneous SCC has been estimated as 0.3% on sun-exposed skin\(^5\) and 2% to 3% on non–sun-exposed skin.\(^6\) Only on high-risk sites such as the ear and lip, or lesions arising as a consequence of burns, radiation, or on chronic ulceration, does the percentage of metastasizing SCC reach double figures.\(^11\)

Trichoepithelial carcinoma (malignant trichoepithelioma), as histologically defined in classic articles,\(^7,8\) is an indolent lesion with a low risk of metastasis, even though it shows nuclear pleomorphism and mitotic activity. In contrast, aggressive clinical behavior with local recurrence or metastases was observed in 4 cases of ACCCC. Two cases demonstrated metastases to regional lymph nodes and lung. Two patients died of the disease. Longer clinical follow-up will be needed to determine more precisely the clinical outcome of this tumor because the relatively short experience thus far may underestimate the number of unfavorable outcomes.

Current diagnostic classification of epidermal and adnexal neoplasms of the skin relies on the observer’s ability to identify the dominant line of differentiation. Lack of epidermoid keratinization or presence of any areas, even focal ones, showing features of typical SCC argue against epidermal differentiation in ACCCC. Expression of EMA and CEA by clear cells are consistent features of ACCCC. Immunohistochemical detection of these antigens correlates with ductal or acrosyringeal differentiation in adnexal neoplasms. Therefore, we considered a possibility of primitive eccrine or apocrine differentiation in ACCCC, which might suggest that this tumor is a variant sweat

### Table 3. Immunohistochemical Staining

<table>
<thead>
<tr>
<th>Case No.</th>
<th>EMA</th>
<th>CK17</th>
<th>CEA</th>
<th>PAN-CK</th>
<th>CK7</th>
<th>CK20</th>
<th>CD34</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>+</td>
<td>+ (focal)</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>2</td>
<td>+</td>
<td>+</td>
<td>+ (focal)</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>+</td>
<td>+</td>
<td>+ (focal)</td>
<td>+</td>
<td>+</td>
<td>-</td>
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</tr>
<tr>
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<td>ND</td>
<td>+</td>
<td>ND</td>
<td>ND</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>+</td>
<td>+</td>
<td>+ (focal)</td>
<td>+</td>
<td>-</td>
<td>ND</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>+</td>
<td>ND</td>
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<tr>
<td>8</td>
<td>+</td>
<td>+</td>
<td>+ (focal)</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
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<td>9</td>
<td>+</td>
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<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>+</td>
<td>+</td>
<td>ND</td>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>-</td>
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<td>-</td>
</tr>
</tbody>
</table>

* EMA indicates epithelial membrane antigen; CK, cytokeratin; CEA, carcinoembryonic antigen; PAN-CK, cytokeratin, broad spectrum; CD34, cluster designation 34; +, positive staining; −, negative staining; and ND, not determined.
Figure 6. A and B. Case 1. Consecutive sections showing membranous staining of clear cells by epithelial membrane antigen (EMA). In contrast, the adjacent sebaceous gland shows vacuolated pattern of staining typical of sebaceous differentiation. C through F, Case 9. Staining with carcinoembryonic antigen (CEA), which is confined to the clear cells adjacent to central necrosis. In some cases, EMA shows a similar pattern of staining but it was usually stronger and involves larger areas of the tumor nests (hematoxylin-eosin, original magnification ×20 [A]; EMA, original magnification ×20 [B]; hematoxylin-eosin, original magnification ×10 [C]; CEA, original magnification ×10 [D]; hematoxylin-eosin, original magnification ×40 [E]; and CEA, original magnification ×40 [F]).
adnexal carcinoma, such as porocarcinoma. Indeed, nested and trabecular growth, focal squamous and clear cell differentiation, comedonecrosis, and multifocal connection to surface epidermis is common in eccrine porocarcinoma. However, the tumors selected for this series showed no unequivocal evidence of ductal, cuticular, or apocrine differentiation. Importantly, ACCCC has different anatomic site distribution to porocarcinoma, which favors distant extremities and frequently arises on non–hair-bearing skin of the palm and soles. Another feature arguing against eccrine differentiation of ACCCC is lack of consistent expression of ‘eccrine’ cytokeratin 7.

We then considered the possibility that ACCCC shows follicular differentiation. Certainly, histologic features such as squamoid differentiation with focal pilar keratinization and clear cell changes are compatible with the outer root sheath (tricholemmal) differentiation. This notion is also supported by consistent cytokeratin 17 expression. This keratin is currently evaluated as a follicular/tricholemmal keratin as it is expressed in the maturing layers of the outer root sheath of the hair follicle (Figure 7, C and D). Our analysis of cytokeratin 17 staining in normal hairs and in a range of classic adnexal tumors confirms such findings (100% of follicular tumors positive; I.H.C., unpublished observations, January 2007), although we have found that it is sometimes positive in eccrine poromas (40% of cases had focal weak expression; I.H.C., unpublished observations, January 2007) and so advise interpretation of this marker as part of a panel of antibodies (notably with EMA and CEA).

Interestingly, cytokeratin 17 expression points to histologic and immunophenotypical heterogeneity of the outer root sheath, which may be important for differentiation between histogenetic lineage of ACCCC and tricholemmal carcinoma. The designation of tricholemmal carcinoma is best reserved for tumors that are architecturally similar to tricholemmoma, but with severe cytologic atypia. In contrast to ACCCC, tricholemmal carcinomas are associated with an excellent prognosis. Classic tricholemmoma and tricholemmal carcinoma show differentiation toward the suprabulbar outer root sheath, featuring prominent columnar clear cells palisading along the outer prominent basement membrane. This layer is negative for cytokeratin 17 (Figure 7, D). In contrast, cytokeratin 17 expression increases as the outer root sheath thickens and matures to-
ward the isthmus, acquiring more squamous and clear cell cytomorphology.

If ACCCC is indeed a follicular neoplasm, then it most closely recapitulates this portion of the hair follicle. The idea of follicular differentiation in ACCCC is also supported by the anatomic site, which in our series corresponded well with the density of hair follicles with the majority of tumors arising in the head and neck region and the scalp. Focal expression of EMA or CEA could also be reconciled with follicular differentiation if one considers the fact that apocrine ducts are developmentally related to hair follicles. One can also question the specificity of EMA and, especially, CEA as a marker of sweat gland differentiation in ACCCC. The staining with these markers for ACCCC certainly appears to be a useful diagnostic feature, but restriction of staining to the clear cells and the strongest signals in areas adjacent to comedonecrosis are suspicious for being a nonspecific phenomenon. It is well known that both antigens can be expressed in epithelial cells undergoing squamous differentiation or degenerative changes.

Based on the previous discussion, it seems that ACCCC has more “follicular” than sweat gland features. However, there is a significant overlap of features and it may be best to use the prefix “adnexal” to refer to these tumors. Parallels can be drawn with microcystic adnexal carcinoma, which can also show mixed follicular and sweat gland differentiation. In the original description by Goldstein et al., it was postulated to originate from a pluripotential adnexal keratinocyte capable of both follicular and sweat gland differentiation.

Our review of the literature revealed several reported cases with similar features to ACCCC. We were fortunate to review 4 of the original 5 examples of penile clear cell carcinoma, only recently described and kindly sent to us by Dr. S. Regauer (University of Graz, Austria). The authors found evidence of human papillomavirus expression in all 5 penile clear cell carcinomas. Unfortunately, we were unable to examine this in our tumors. The authors suggested that penile clear cell carcinomas were likely of eccrine differentiation. As we have discussed, it is not an unreasonable conclusion, especially if one views it from an immunohistochemical perspective, but our analysis of a larger number of cases suggests that it is not inconsistent with follicular differentiation.

We also noted no unequivocal evidence of ductal, cuticular, or apocrine differentiation in sections of penile clear cell carcinoma that were available to us. Misago and Narisawa published a case report of a similar tumor in continuity with trichoblastoma within nevus sebaceus. Dr. Misago (Saga Medical School, Saga, Japan) kindly provided the slides from his case for our review. After examination of the sections and performing additional immunohistochemical studies, we thought that it also showed features consistent with ACCCC. None of our cases occurred in the context of nevus sebaceus.

We were also intrigued by a case reported as malignant trichoepithelial carcinoma with lymph node metastases and eccrine differentiation. We were able to study skin biopsy and lymph node metastases from this lesion provided by Dr. Hoang (University of Texas, Southwestern, Dallas). This tumor showed aggressive behavior and led to systemic spread, including lymph node metastases. The cutaneous primary was histologically and immunohistochemically indistinguishable from ACCCC. However, the lymph node metastases showed substantial duct formation, consistent with sweat gland differentiation.

In addition to eccrine and trichoepithelial carcinomas, as described here, histologic differential diagnosis of ACCCC includes SCC, sebaceous carcinoma, and other primary and metastatic clear cell tumors of the skin. Histologic differentiation from invasive squamous cell carcinoma requires a high index of suspicion and awareness that not all cutaneous neoplasms showing squamous differentiation are SCC. Although clear cell SCC is a recognized variant, the characteristic combination of features, including zonal arrangement of tumor nests with squamous and clear cells areas associated with central comedo degeneration in the context of a predominantly dermal tumor, are important differentiating factors of ACCCC. Importantly, SCC can express EMA. However, in ACCCC, EMA expression is usually limited to clear cell areas. Carcinomabryonic antigen can show selective expression in keratinizing epidermis.

Histologic distinction of ACCCC from sebaceous carcinoma can be difficult. This is underscored by the fact that one of our cases was erroneously interpreted as a sebaceous carcinoma. At low magnification, some invasive sebaceous carcinomas are quite similar to ACCCC. They are characterized by a nodular or nested infiltrating growth pattern. Individual tumor nests also show zonal arrangement with inner clear cells and frequent central comedonecrosis. However, in contrast to ACCCC, the peripheral zone of tumor cells in sebaceous carcinoma, rather than being squamoid, is distinctly basaloid and primitive in histologic appearance. The clear cells in sebaceous cell carcinoma show features of sebaceous differentiation with vacuolated or bubbly cytoplasm and vesicular nuclei. If doubt remains, immunohistochemistry should support the correct diagnosis with vacuolar cytoplasmic EMA positivity in sebaceous cells, while CEA is usually negative. Furthermore, clear cell change in sebaceous carcinoma is due to intracellular fat deposition and not glycogen, which can be documented by fat stains if frozen tissue is available.

Clear cell basal cell carcinoma is very rare, with the clear cell change usually only focally present. Helpful discriminatory features include the basaloid appearance of the basal cell carcinoma coupled with retraction artifact, peripheral palisade, and stroma rich in mucin. Benign melanocytic lesions or melanoma with balloon cell change pose little diagnostic difficulty, but they should also be mentioned for the sake of completeness. The list of less common cutaneous proliferations with clear cell features is long and also includes clear cell adenocarcinomas, clear cell atypical fibroxanthoma, and the recently described clear cell mesenchymal tumor of the skin, as well as metastatic clear cell carcinoma, especially from the kidney.

In summary, we have described a group of distinctive adnexal carcinomas showing squamous differentiation, clear cell change, comedonecrosis, and immunohistochemical expression of EMA, cytokeratin 17, and in some cases,
CEA by the clear cells. The precise lineage of this tumor remains to be established, although we favor a follicular origin. These tumors appear to display potentially aggressive behavior and have to be distinguished from much more common and indolent squamous cell and tricholemmal carcinomas.

References