Primary Salivary Clear Cell Tumors—
A Diagnostic Approach

A Clinicopathologic and Immunohistochemical Study of 20 Patients With Clear Cell Carcinoma, Clear Cell Myoepithelial Carcinoma, and Epithelial-Myoepithelial Carcinoma

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Context.—Primary salivary clear cell tumors comprise an uncommonly encountered subgroup of salivary neoplasia. We hypothesize that clear cell carcinoma does not represent a “monomorphic” variant of epithelial-myoepithelial carcinoma, but is distinct in terms of histogenesis and tumor biology.

Objectives.—To compare the clinicopathologic features of 20 cases of salivary primary clear cell tumors, including 12 clear cell carcinomas (CCCs), 7 epithelial-myoeplithelial carcinomas (EMECs), and 1 clear cell myoepithelial carcinoma (CCMEC); to investigate their interrelationship with regard to myoepithelial differentiation; and to offer a diagnostic approach for distinguishing between these entities.

Design.—Retrospective and prospective identification and review of patients diagnosed with primary salivary clear cell neoplasia and review of the English language literature.

Setting.—Three academic tertiary-care hospitals.

Patients.—We identified 12 patients with CCC, 7 with EMEC, and 1 with CCMEC. Patients included 11 men and 9 women, aged 30 to 88 years (median 72.5 years).

Main Outcomes Measures.—Immunohistochemical reactivity for S100, muscle-specific actin, and calponin; ultrastructural examination when feasible; review of patient charts; and telephone interviews to establish clinical outcome.

Results.—Clear cell carcinoma has a predilection for intraoral sites, whereas EMEC has a predilection for the parotid. All 3 of the tumor types studied have a propensity for locoregional recurrence, which can manifest decades after initial surgery. There were no mortalities among patients with CCC, even after pulmonary metastasis in 2 patients, confirming the indolent nature of this group of clear cell tumors. A meta-analysis of reported cases of CCC, EMEC, and CCMEC confirmed that EMEC and CCMEC have a much greater propensity for locoregional recurrence than CCC, despite the predilection of both for a more surgically accessible site (parotid). We found no definitive evidence of myoepithelial differentiation in CCC, indicating that it is probably morphogenetically distinct from EMEC and CCMEC, both tumors with diagnostically requisite myoepithelial differentiation.

Conclusions.—The initial treatment of choice for CCC, CCMEC, and EMEC is surgical resection with negative margins. Locoregional recurrence should be treated aggressively, as it is still consistent with long disease-free intervals. The lack of myoepithelial differentiation in CCC is consistent with the concept that this tumor is histomorphogenically distinct from EMEC and that it is not merely a monomorphic variant.

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that have clear cell components. 

Table 1: Clinical Details for 20 Patients With Salivary Primary Clear Cell Tumors*

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age, y/Sex</th>
<th>Site</th>
<th>Size, cm</th>
<th>Diagnosis</th>
<th>Recurrence</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68/M</td>
<td>Parotid</td>
<td>2.5</td>
<td>EMEC</td>
<td></td>
<td>NED 6 mo</td>
</tr>
<tr>
<td>2</td>
<td>75/F</td>
<td>EMEC</td>
<td>3.5</td>
<td></td>
<td></td>
<td>NED</td>
</tr>
<tr>
<td>3</td>
<td>74/F</td>
<td>Palate</td>
<td>1.7</td>
<td>EMEC</td>
<td>Previous parotid tumor years earlier; local metastases</td>
<td>LTF</td>
</tr>
<tr>
<td>4</td>
<td>88/F</td>
<td>Parotid</td>
<td>11.5</td>
<td>EMEC</td>
<td></td>
<td>NED 2 y</td>
</tr>
<tr>
<td>5</td>
<td>63/M</td>
<td>Parotid</td>
<td>3</td>
<td>EMEC</td>
<td></td>
<td>NED 2 y</td>
</tr>
<tr>
<td>6</td>
<td>79/F</td>
<td>Parotid</td>
<td>3</td>
<td>EMEC</td>
<td></td>
<td>NED 4 y</td>
</tr>
<tr>
<td>7</td>
<td>50/M</td>
<td>Parotid</td>
<td>2</td>
<td>EMEC</td>
<td></td>
<td>NED 2 y</td>
</tr>
<tr>
<td>8</td>
<td>70/M</td>
<td>Parotid</td>
<td>2</td>
<td>CCMEC</td>
<td></td>
<td>LTF</td>
</tr>
<tr>
<td>9</td>
<td>63/M</td>
<td>Palate</td>
<td>1.4</td>
<td>CCC</td>
<td>Previous tumor 21 years earlier†</td>
<td>NED 2 y</td>
</tr>
<tr>
<td>10</td>
<td>52/M</td>
<td>Parotid</td>
<td>2.0</td>
<td>CCC</td>
<td>Recurrence 6 mo; local metastases</td>
<td>Lung metastases</td>
</tr>
<tr>
<td>11</td>
<td>71/F</td>
<td>Tonsil</td>
<td>NA</td>
<td>CCC</td>
<td></td>
<td>NED 2 y</td>
</tr>
<tr>
<td>12</td>
<td>86/F</td>
<td>Parotid</td>
<td>1.3</td>
<td>CCC</td>
<td></td>
<td>NED 2 y</td>
</tr>
<tr>
<td>13</td>
<td>77/F</td>
<td>Oral</td>
<td>1.2</td>
<td>CCC</td>
<td></td>
<td>NED 2 y</td>
</tr>
<tr>
<td>14</td>
<td>74/M</td>
<td>Base of tongue</td>
<td>1.0</td>
<td>CCC</td>
<td></td>
<td>NED 2 y</td>
</tr>
<tr>
<td>15</td>
<td>30/F</td>
<td>Palate</td>
<td>2.5</td>
<td>CCC</td>
<td>Recurrence at 7, 8, and 9 y; lung metastases</td>
<td>AWD 11 y</td>
</tr>
<tr>
<td>16</td>
<td>45/F</td>
<td>Palate</td>
<td>&lt;1</td>
<td>CCC</td>
<td></td>
<td>NED 6 mo</td>
</tr>
<tr>
<td>17</td>
<td>81/M</td>
<td>Base of tongue</td>
<td>3</td>
<td>CCC</td>
<td></td>
<td>NED 13 mo</td>
</tr>
<tr>
<td>18</td>
<td>65/M</td>
<td>Floor of mouth</td>
<td>2</td>
<td>CCC</td>
<td></td>
<td>NED 2 y</td>
</tr>
<tr>
<td>19</td>
<td>NA/M</td>
<td>Tongue</td>
<td>NA</td>
<td>CCC</td>
<td></td>
<td>NA</td>
</tr>
<tr>
<td>20</td>
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<td>Palate</td>
<td>NA</td>
<td>CCC</td>
<td></td>
<td>NED 7 y</td>
</tr>
</tbody>
</table>

* NA indicates not available; EMEC, epithelial-myoeipithelial carcinoma; CCMEC, clear cell myoepithelial carcinoma; CCC, clear cell carcinoma; NED, no evidence of disease; LTF, lost to follow-up; and AWD, alive with disease.
† Original tumor unavailable for histologic confirmation.

RESULTS

Patient demographics and follow-up data are summarized in Table 1. Twelve patients were diagnosed with CCC, 7 with EMEC, and 1 with CCMEC. Patients included 11 men and 9 women, aged 30 to 88 years (median 72.5 years). The ratio of parotid-oral cases for EMEC was 6:1, and for CCC was 1:4. Clinical information was obtained on 19 patients. One individual (patient 7) presented with concomitant Warthin tumor of the superficial parotid and EMEC of the ipsilateral deep parotid lobe. Interestingly, 5 of 19 patients (2 with CCC, 2 with EMEC, and 1 with CCMEC) were known to have remote histories of previous tumors at that same site, up to 2 decades prior to their presentation at Mount Sinai School of Medicine (Table 1, daggers). All of these tumors were previously treated surgically; however, details regarding the operations (resection vs limited excision) were unavailable. The slides or surgical reports regarding these neoplasms were from other institutions and were not available for review. It is possible that they represent other histologies, such as pleomorphic adenomas. However, the high incidence (29%) of previous tumors makes it quite likely that these cases represent previous, although unconfirmed, manifestations of the same histology. Accepting this assumption, the long intervals between the first tumor and presentation at Mount Sinai School of Medicine are consistent with recurrence rather than tumor persistence.

Prospective follow-up was achieved on 12 patients, from 3 months to 11 years (median 2 years). Total patient follow-up (prospective and retrospective) was known for 16

MATERIALS AND METHODS

We identified 268 cases of salivary tumors in the files at Mount Sinai School of Medicine (New York, NY). These cases were reviewed, and all cases with clear cell features were culled and evaluated further; 15 of these cases could be classified as primary salivary clear cell tumors. We also included 4 cases from the Department of Pathology, Henry Ford Hospital (Detroit, Mich) and 1 case from the Department of Pathology, The University of Iowa Hospital and Clinics (Iowa City). Hematoxylin-eosin-stained slides were reviewed and histochemical (periodic acid-Schiff, with and without diastase treatment, mucicarmine stain) and immunohistochemical studies were performed on formalin-fixed, paraffin-embedded sections using the labeled streptavidin-biotin-peroxidase complex method. The following antibodies were evaluated immunohistochemically: S100 protein (1:300), Dako Corporation, Carpinteria, Calif), muscle-specific actin (1:40, Dako, mouse anti-human MoB51), and calponin, (Dako, mouse anti-human, M3556). Slides evaluated for calponin were pretreated with proteinase K (Dako, 1:500 dilution) at 37°C for 10 minutes. Heat-induced epitope retrieval (0.01 mmol/L citrate buffer, pH 6.0) was performed as follows: slides were heated on a hot plate for 10 minutes at 100°C, then cooled for 20 minutes. Primary antibody incubation was performed at 1:150 dilution for 30 minutes at room temperature. Calponin is a relatively novel and sensitive smooth muscle marker, and was selected to further elucidate the relationship between CCC and EMEC. Ultrastructural studies were performed on 3 cases. Medical records were reviewed and patients were contacted for follow-up.

calponin, a novel and sensitive marker of smooth muscle phenotype. We also offer a diagnostic approach for differentiating these 3 tumors, as well as other salivary tumors that have clear cell components.

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patients, from 3 months to 28 years (median 4 years). Status of the cervical lymph nodes was known for 10 patients (5 with CCC, 4 with EMEC, and 1 with CCMEC); lymph node metastases were present in 2 (20%) of these patients (1 CCC and 1 CCMEC). If one assumes that cases with previous tumors at the same site represent unconfirmed local recurrences of the same disease, then 8 (50%) of 16 patients (4 with CCC, 3 with EMEC, and 1 with CCMEC) developed 10 local or regional recurrences and/or metastases after intervals of 0.5 to 28 years (median 7 years to first recurrence). (Patient 2 was excluded from this calculation, as the given time to recurrence was vague.) Two patients, both with CCC, developed lung metastases, which were confirmed histologically. One woman developed metastases after 4 years; she is presently disease free 5.5 years after resection of this metastasis and 9.5 years after initial presentation. The other patient developed lung metastases after 6 months. Five patients who were treated for locoregional recurrences were known to have subsequent disease-free intervals ranging from 1 to 2 years from last recurrence (median 2 years). (This number excludes patient 2 because time to recurrence was unknown.) Eight patients (6 with CCC and 2 with EMEC) remained disease free after primary therapy (0.5 to 7 years, median 2 years).

**Histology, Ultrastructure, and Immunohistochemistry**

**Clear Cell Carcinoma.**—Clear cell carcinoma appeared as islands and sheets of tumor cells with clear cytoplasm (Figure 1). The diagnosis of malignancy was substantiated by local infiltration in all cases. Tumor cells were relatively pleomorphic with high nuclear-cytoplasmic ratios and dark, condensed, eccentric nuclei. Some admixed cells were smaller and had pink cytoplasm. No hyaline-type
cells were seen. Collagen deposition was variable (Figure 2). No ductal formation was seen, but some tumor cells revealed a vague condensation reminiscent of ductule formation, albeit without true ductal lumina (Figure 3). Focal squamous metaplasia was seen in 1 case. One case was unusual in that it was also associated with an infiltrating papillary pattern and hobnail-like cells (Figure 4). (Electron microscopy in this case [Figure 5] ruled out the possibility of acinic cell carcinoma.) Lymphatic invasion could be seen in this and other cases. Perineural and osseous invasion was also evident. Necrosis and atypical mitotic figures were not seen.

Ultrastructural examination was performed in 3 cases of CCC. Tumor cells had ultrastructural features of glandular cells (luminal microvilli and intercellular desmosomes). The cytoplasm was vacuolated with residual globular or granular material consistent with leached glycogen. No cytoplasmic fat was seen. The cytoplasm also contained some mitochondria, granular endoplasmic reticulum, single ribosomes and polyribosomes, and Golgi complexes (Figure 5). No zymogen granules were identified, ruling out acinic cell carcinoma. No evidence of myoepithelial differentiation was seen in any case by ultrastructural analysis or by calponin immunohistochemistry (see “Histochemistry and Immunohistochemistry”).

Figure 5. Ultrastructural examination of clear cell carcinoma. A, Epithelial cells with cytoplasmic filopodia (original magnification ×3200). B and C, Desmosomal junctions (original magnifications ×8300).

Figure 6. A parotid epithelial-myoepithelial carcinoma growing as a bulky lobulated tumor.

Epithelial-Myoepithelial Carcinoma.—Epithelial-myoepithelial carcinomas grew in a lobulated, pseudopod-like manner (Figure 6). Podlike infiltration was common to all cases (Figure 7). The tumors were composed of cords of closely packed, cuboidal to flat ductal cells, surrounded by larger, clear, periluminal, myoepithelial-type cells (Figure 8). The clear cells varied from large and cuboidal to small and spindled. The clear cells also formed solid nests, but ductal differentiation was readily apparent by light microscopy and was accentuated by low-molecular-weight cytokeratin immunohistochemistry. Collagenous hyaline deposition was variable (Figure 9), and collagenous spheres could be seen. Necrosis usually was seen within the center of the tumor lobules. Perineural invasion could be identified, as well as osseous invasion. Atypical mitotic figures were not seen.

The bimodal ductal lumen/myoepithelial formation typical for EMEC was usually pervasive, but in 1 case from the palate (patient 3), lumen formation was focal (approximately 10%) and at the tumor periphery (Figures 10 and 11). The clear cells revealed strong S100 expression, and cytokeratin cocktail staining confirmed a ductular pattern for this case, consistent with EMEC. Therefore, the argument can be made that this tumor represents a largely monophasic EMEC, with some biphasic differentiation. Ultrastructural examination in 2 cases confirmed myoepithelial differentiation.

Clear Cell Myoepithelial Carcinoma.—The 1 case of CCMEC presented as a solid bulky tumor with a prominent clear cell component (Figure 12) and also with a prominent spindle cell component (Figure 13). The clear tumor cells were generally smaller and more uniform in size and shape than the epithelioid clear tumor cells of CCC. The spindle cells were also generally short. Hyaline deposition was prominent, and plasmacytoid hyaline cells were sparsely distributed in this case. A trabecular pattern was present focally (Figure 14). No ductoglandular formation was seen, distinguishing it from EMEC. The prominent spindled component, occasional hyaline cells, histologically distinguished this tumor from CCC. This tumor infiltrated adjacent soft tissues and bone. Necrosis was present. Electron microscopic examination was not available in this case.

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Figure 7. Low-power view of parotid epithelial-myoepithelial carcinoma demonstrating bulky infiltration (hematoxylin-eosin, original magnification ×40).

Figure 8. This bimodal tumor ductule formation is characteristic of epithelial-myoepithelial carcinoma and is not seen in clear cell carcinoma. Ductal lumina are lined by cuboidal, epithelioid, or oncocytoid cells. The abluminal myoepithelial cells are clear and epithelioid (as seen here) or spindled. A psammoma body is also evident (bottom) (hematoxylin-eosin, original magnification ×130).

Figure 9. Epithelial-myoepithelial carcinoma forming compressed ducts separated by hyaline deposition (hematoxylin-eosin, original magnification ×60).

Figure 10. Palatal epithelial-myoepithelial carcinoma. The center of this tumor is composed predominantly of spindled clear cells; however, focal ductal lumen formation (D) can be seen (hematoxylin-eosin, original magnification ×100).

Figure 11. Palatal epithelial-myoepithelial carcinoma. Obvious bimodal ductal formation is seen at the tumor periphery (hematoxylin-eosin, original magnification ×60).

Figure 12. Clear cell myoepithelial carcinoma. High-power view of clear cuboidal cells, which form the predominant tumor cell population (hematoxylin-eosin, original magnification ×400).

Figure 13. Clear cell myoepithelial carcinoma. Spindle cell component with hyaline globules (hematoxylin-eosin, original magnification ×60).

Figure 14. Clear cell myoepithelial carcinoma. A non-duct-forming trabecular pattern is seen (hematoxylin-eosin, original magnification ×40).

Histochemistry and Immunohistochemistry

Glycogen content in all of the tumors studied was confirmed by diastase-treated periodic acid–Schiff histochemistry, and lack of mucin was confirmed by mucicarmine stain (Figure 15). Strong diffuse S100 expression was seen in only 1 case of CCC (Figure 16), and weak to moderate expression was seen in 2 of the 8 cases of CCC studied. The 1 case with robust S100 expression occurred in the palate, and no ductal differentiation was seen; it was otherwise a typical hyalinizing CCC. No expression of muscle-specific actin or calponin was seen in any CCC studied (8 total). The CCMEC was strongly positive for S100 as well as cytokeratin cocktail; calponin staining was light, and no staining for muscle-specific actin was observed. With respect to EMEC, a bimodal cell population with a ductal pattern was confirmed by cytokeratin cocktail immunohistochemistry. The cleared cells variably expressed S100 and muscle-specific actin (Figure 17). Cytoplasmic calponin was detected in 2 of 4 cases of EMEC, one case staining strongly, the other weakly.

COMMENT

Historical Recognition of CCC, EMEC, and CCMEC

As we accumulate clinicopathologic, immunohistochemical, and ultrastructural experience with this rare group of salivary tumors, it is becoming increasingly evident that primary clear cell tumors (not variants of other known salivary tumors) represent a heterogeneous group of neoplasms. The entire group of primary salivary clear cell tumors had, historically, been referred to as clear cell carcinoma, clear cell adenoma, glycogen-rich adenoma, glycogen-rich adenocarcinoma, etc. In 1972, Donath et al described 8 cases of a previously unrecognized clear cell tumor of salivary gland origin, which they termed epithelial-myoepithelial carcinoma. However, it was not until 1982 that Corio and colleagues introduced this neoplasm into the English
language and expanded upon it in their report on 16 cases from the Armed Forces Institute of Pathology series. Prior to that publication, many cases of EMEC appeared in the literature as clear cell carcinoma, glycogen-rich adenoma, etc. Thus, EMEC became recognized as a distinct biphasic tumor forming ductules and glands surrounded by a variable clear cell component of myoepithelial origin with a variable hyaline background. Although these tumors can be histologically bland, the term carcinoma was advocated, as these tumors had the potential for at least local invasion if not rare metastases.

The report by Milchgrub and colleagues is important in that it first distinguished the monomorphic CCC from EMEC. In that original report, the authors described an infiltrating neoplasm forming nests and cords within a hyalinized matrix. They used the term hyalinizing clear cell carcinoma and emphasized the lack of lumen formation or biphasic nature. Hyalinization is a variable feature of CCC, and we feel that the terms clear cell carcinoma and hyalinizing clear cell carcinoma can, at present, be considered synonyms. Because CCC tumor cells were negative for S100 but positive for epithelial membrane antigen, it was proposed that CCC was primarily epithelial rather than myoepithelial in nature. By this reasoning, Dardick coined the term glycogen-rich squamous carcinoma to emphasize the epithelial nature of this tumor. In his schema, he also proposed a monomorphic variant of EMEC, thereby allowing for the classification of a non–gland-forming clear cell neoplasm with myoepithelial characteristics.

As myoepithelial cells assume a number of guises (hyaline [plasmacytoid], epithelioid, spindled, and clear), it was inevitable that a clear cell variant of myoepithelial carcinoma should also be recognized. This has been the latest group of primary salivary clear cell neoplasia to be fleshed out in the literature. Clear cell predominance among benign myoepitheliomas is rare and was seen in only 1 (2.5%) of 40 cases of benign myoepitheliomas reported by Dardick et al. Michal et al collected a series of 5 cases classified as CCMIEC. More recently, a group of 25 myoepithelial carcinomas was reported from Memorial Sloan Kettering Cancer Center. Four (16%) of these tumors were classified as predominantly clear cell type. These authors proposed that the diagnosis of myoepithelial carcinoma be reserved for tumors that are entirely composed of myoepithelial elements. Those tumors that also contained ductal elements might then be classified as (monomorphic) EMEC or, possibly, carcinoma-ex-pleomorphic adenoma.

An essential question is then as follows: how are EMEC, CCC, and CCMIEC interrelated? The observed transition between EMEC to monophasic areas would suggest that EMEC, CCC, and CCMIEC exist as a continuum of monophasic/biphasic tumors with variable myoepithelial expression. Yet, some clinical and immunohistochemical distinctions between EMEC, CCCMEC, and CCC would suggest that these tumors differ from one another.

**Diagnostic Features**

Clear cell carcinoma, by definition, contains a significant proportion of tumor cells with clear cytoplasm and does not fit into other categories of salivary neoplasia. Grossly, this tumor has been described as infiltrating and scirrhus. Microscopically, hyalinizing CCC is a low-grade carcinoma characterized by nests of clear cells in a densely amyloid-like, fibrous, hyalinizing stroma, surrounding cords, nests, sheets, and trabeculae of tumor cells. This hyalinization is not a constant feature, and some tumors may be relatively solid, and thus may be referred to as CCC. The tumor cells are characterized as being round to polygonal with clear, periodic acid–Schiff–positive cytoplasm and high nuclear-cytoplasmic ratios. The nuclei are relatively peripheral with mild pleomorphism, condensed chromatin, and inconspicuous nuclei. There is a greater overall cellular uniformity in CCC as compared to EMEC. Small areas in many tumors contain cells with eosinophilic cytoplasm; foci of squamous differentiation can be present occasionally, but true ductal lumina are not seen.

Epithelial-myoid epithelial carcinomas are grossly well delineated and firm, with infiltration into adjacent tissue. They range up to 12 cm in greatest dimension, although the average tumor size is 2 to 3 cm. Histologically, these tumors are often well circumscribed and may have a multinodular growth pattern, usually surrounded at least partially by a thick fibrous capsule. Epithelial-myoid epithelial carcinoma invariably demonstrates invasion into adjacent parenchyma. There is a general cellular heterogeneity of

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**Table 2. Literature Meta-Analysis of Clear Cell Carcinoma (CCC), Epithelial-Myoepithelial Carcinoma (EMEC), and Clear Cell Myoepithelial Carcinoma (CCMEC), Including Cases Reported in This Article**

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<thead>
<tr>
<th></th>
<th>CCC</th>
<th>EMEC</th>
<th>CCMEC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>103</td>
<td>97</td>
<td>11</td>
</tr>
<tr>
<td>Age range, y</td>
<td>1–86, median 52.5</td>
<td>42–103, median 67</td>
<td>37–78, median 64</td>
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<tr>
<td>Female-male ratio</td>
<td>1.6:1</td>
<td>2.4:1</td>
<td>1.75:1</td>
</tr>
<tr>
<td>Parotid, No. (%)</td>
<td>22/103 (21)</td>
<td>81/97 (83)</td>
<td>8/11 (72)</td>
</tr>
<tr>
<td>Oral, No. (%)</td>
<td>69/103 (67)</td>
<td>6/97 (6)</td>
<td>1/11 (9)</td>
</tr>
<tr>
<td>Submandibular, No. (%)</td>
<td>8/103 (8)</td>
<td>9/97 (9)</td>
<td>1/11 (9)</td>
</tr>
<tr>
<td>Other sites</td>
<td>Neck, 2; nasopharynx, 1; larynx, 1.</td>
<td>Nasal, 1/97</td>
<td>Maxilla, 1/11</td>
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<td>Recurrence rate</td>
<td>17%; 5 patients with 11 recurrences among 29 patients with follow-up</td>
<td>60%; 21 patients with 35 recurrences among 35 patients with follow-up</td>
<td>60%; 6 patients with 7 recurrences among 10 patients with follow-up</td>
</tr>
<tr>
<td>Time to first recurrence</td>
<td>6–252 mo (median 84 mo)</td>
<td>7–336 mo (median 36 mo)</td>
<td>0.8, 3, and 28 y</td>
</tr>
<tr>
<td>Metastatic rate, No. (%)</td>
<td>6/29 (21)</td>
<td>3/35 (9)</td>
<td>2/9 (22)</td>
</tr>
<tr>
<td>Died of disease</td>
<td>0</td>
<td>3/35 (9)</td>
<td>1/11 (9)</td>
</tr>
<tr>
<td>Time to death</td>
<td>...</td>
<td>7, 20, 28 y</td>
<td>6 y</td>
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</table>

*References included in the meta-analysis are as follows: 6–8, 10–12, 15–17, 20–30, 32–42. These data include data from the Armed Forces Institute of Pathology plus data presented by Corio et al, but without data duplication.*

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Source: Arch Pathol Lab Med—Vol 126, June 2002
EMEC, which contrasts with the relative homogeneity of CCC. Epithelial-myoepithelial carcinomas are biphasic tumors, which largely recapitulate intercalated ductule formation. They are composed of islands, large nests, or sheets of tumor cells forming ductules, which are lined by cuboidal to columnar epithelium. The abluminal aspect contains clear cells, which in turn are surrounded by dense hyalinized basement membrane material. Occasionally, foci of early squamous metaplasia can be seen within proliferating ductal structures. Rarely, proliferating spindled myoepithelial tumor cells, rather than clear myoepithelial cells, surround the ductal component. The proliferating myoepithelial component (be it clear cell or spindled) can form solid nests or sheets. The proportion and arrangement of nodular aggregates of the biphasic component and sheets of clear cells are quite variable. Occasionally, the clear cell component may predominate and the more typical biphasic component may be focal, as was seen in 1 of our cases (Figure 11). Nuclear atypia is usually minimal; however, occasional EMECs can demonstrate moderate atypia. Mitotic figures are not usually prominent (<2/10 high-power fields), although some tumors will have a mitotic rate as high as 10 per 10 high-power fields. Necrosis and perineural invasion can be present. The clear cell component contains abundant glycogen and has characteristics of myoepithelial differentiation ultrastructurally as well as immunohistochemically. The ductal lumina may, on occasion, contain mucinous material; however, intracellular mucin is not present in the clear cell component or in the ductal epithelial cells.

Clear cell myoepithelial carcinomas, like EMECs, have been described as bulky or nodular tumors. While entirely myoepithelial in composition, the clear cell component can predominate, but is often admixed with more recognizable myoepithelial elements (hyaline cells, nonclear spindled cells, and epithelioid cells). A hyalinized background is common. Michal et al described formation of rosettelike collagenous spherules. The study from Memorial Sloan Kettering Cancer Center illustrated vacuolated clear cells, which could have a signet-ring-like or lipoblast-like appearance.

How can these tumors be distinguished from one another pathologically? Figure 18 offers a schematic guide to diagnosing salivary clear cell tumors, in which we emphasize morphologic distinguishing characteristics (eg, zymogen granules by electron microscopy is specific for acinic cell carcinoma). On the other hand, perusal of this table will highlight the frustrating lack of some absolute criteria. For instance, there are no absolute immunohistochemical or ultrastructural discriminators between CCC and clear cell odontogenic carcinoma. Thus, we are brought back to the awareness that pathology is an art, and that proper diagnosis requires interpretation of the clinical presentation, histologic acumen, correlation with the immunohistochemical and ultrastructural data, and, finally, experience and intuition. As mentioned, tumor site can guide a diagnosis, as CCC has an intraoral predilection and EMEC a parotid predilection; however, this tendency cannot serve as an absolute criterion. Clear cell carcinoma tends to have weak or minimal S100 expression, but occasionally can reveal strong, diffuse S100 positivity. Therefore, robust S100 expression cannot absolutely rule out CCC. Light microscopy can best make this distinction. As mentioned, CCC has a greater cellular homogeneity than EMEC, which by definition contains a bimodal, epil-
thelial/myoepithelial population. Clear cell carcinoma may contain more "condensed" nonclear cells with pink cytoplasm, mimicking ducts, albeit lacking lumina. Focal squamous metaplasia might be seen. However, actual bilayer ductule formation is not seen in CCC and can be considered an absolute criterion for the diagnosis of EMEC. This pattern can be more obvious after cytokeratin immunohistochemistry. The pattern of invasion can be used as an adjunctive (although not absolute) criterion to aid in the differential diagnosis; CCC, especially hyalinizing CCC, can invade in small strands and nests, as opposed to the bulky lobulated pattern of invasion of EMEC. Clear cell myoepithelial carcinoma can be distinguished from CCC and EMEC by its cellular components. The clear cells of CCMEC are generally smaller and more uniform in size and shape than the epithelioid clear cells of CCC. The spindled areas, which speak for classic myoepithelioma, are densely cellular and nonclear. Hyaline-type (plasmacytoid) cells can be prominent in any myoepithelioma/myoepithelial carcinoma, but are not prominent features of CCC or EMEC.

Has the spectrum of clear cell salivary neoplasia been hereby exhausted? Perhaps not. We have recently described a sinonasal clear cell malignancy, which histologically appears almost identical to renal cell carcinoma. There was no clinical or radiographic evidence of a renal neoplasm. The ultrastructural evidence makes a compelling argument for this tumor being of salivary nonrenal origin, distinct from CCC.19

Clinical Features

Since the article by Milchgrub et al12 and reports from the Armed Forces Institute of Pathology, few other series have been reported.7,20,21 Table 2 summarizes the clinical distinctions between CCC (103 cases), EMEC (97 cases), and to a lesser extent, CCMEC (11 cases), based on cases culled from the literature and the cases reported in this article.6–8,10–12,15–17,20–30,32–42 All tumors have a female preponderance and a median age in the sixth and seventh decades of life. Patients with all tumors may develop multiple recurrences up to 2 decades after resection. Of note, CCC tends to occur at intraoral sites (65%), whereas EMEC and CCMEC tend to occur in the parotid gland (83% and 72%, respectively). Interestingly, patients with EMEC and CCMEC are significantly more likely to develop recurrences than those patients with CCC (60% and 60%, respectively, vs 17%), even though as a general rule parotid tumors are more amenable to resection and therefore less likely to recur than intraoral tumors. The metastatic rate for CCC is higher than for EMEC (21% vs 9%). No patient has died of CCC, whereas the mortality rates for EMEC and CCMEC are low (9% and 9%, respectively), but not nil.

Relationship Between CCC, EMEC, and CCMEC:
The Role of Myoepithelial Differentiation

Dardick13 subdivided CCCs into those with myoepithelial differentiation (ie, monophasic variants of EMEC) versus purely epithelial tumors, for which he used the term glycogen-rich squamous carcinoma. Our study is unique in that we employed a novel antibody against calponin, expressed in smooth muscle and myoepithelial differentiation, to investigate the issue of myoepithelial differentiation in CCC.43,44 Calponin is a 34-kd smooth muscle-specific cytoplasmic protein regulator of contraction; no analogues exist in nonmuscle cells. Its expression is developmentally regulated and appears later than expression of the structural actin and myosin proteins. Therefore, calponin is a marker of higher differentiation. Calponin has been shown to be a sensitive marker of myoepithelial differentiation in various morphologic types of neoplastic myoepithelium and in numerous benign and malignant salivary gland tumors.16,31,43,44 No calponin expression was found in the CCCs studied. In the 3 CCCs studied ultrastructurally, no overt myoepithelial differentiation (eg, dense bodies, intermediate-sized filaments, or contractile microfilaments) were found. S100 expression is not specific for myoepithelial differentiation. Therefore, our experience extends the reported data, in that CCC lacks
myoepithelial differentiation and appears distinct from EMEC and CCMEC, which have "obligate" myoepithelial differentiation. This characteristic does not negate Dardick's concept of monophasic EMEC as an entity distinct from CCC. A clear cell neoplasm that strongly expresses S100 and reveals some ductal differentiation, either by light microscopy or immunohistochemistry, could thus be classified as monophasic EMEC.

In this study, calponin was detected in only 2 of 4 EMECs with morphologic evidence of clear myoepithelial cells. This finding suggests that tissue fixation or block storage issues contributed to the lack of staining rather than insensitivity of the assay, as calponin staining is found in up to 75% of myoepithelial carcinomas. Is CCMEC the monomorphic variant of EMEC? Certainly similarities in site predisposition (preference for the parotid) and tumor biology (significant recurrence rate) would suggest a relationship. Histologically, EMEC and CCC do not contain significant populations of spindle cells, nonclear epithelial cells, or plasmacytoid cells, as can be seen in CCMEC, thereby arguing for the necessity of this third diagnostic category.

The issue of myoepithelial contribution to tumor phenotype is beyond academic interest, as it may affect tumor biology. Myoepithelial cells are known to secrete low levels of matrix-degrading proteases and an excess of protease inhibitors. This characteristic has been cited as a reason why myoepithelium-rich tumors generally grow in a bulky lobulated fashion, rather than in an insidiously infiltrating pattern, as is seen here for EMEC and CCMEC. Yet, this tendency would still not explain the propensity for observed recurrences of EMEC, compared to the more infiltrative CCC. The lack of clinical data regarding completeness of original tumor excisions precludes our offering an explanation for this phenomenon.

In summary, our experience and review of the literature regarding primary salivary clear cell neoplasia confirm a significant local recurrence rate, which may be manifest more than 2 decades after initial presentation. However, no mortalities were seen in this group, despite locoregional and distant metastases, which occurred in patients with CCC. Epithelial-myoepithelial carcinomas and CCMECs have a significantly higher local recurrence rate than CCCs, but show no propensity for distant metastases. We found no sensitive immunohistochemical marker of myoepithelial differentiation for the CCCs studied, thus favoring a histomorphogenesis distinct from that of EMECs and CCMECs.

References