Hyalinizing Clear Cell Carcinoma: Report of Eight Cases and a Review of Literature

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Received: 16 February 2009 / Accepted: 19 June 2009 / Published online: 5 July 2009
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Abstract Hyalinizing clear cell carcinoma (HCCC) is an extremely rare neoplasm with a female predominance, composed of nests of monomorphic clear cells within a hyaline stroma. This tumor often follows an indolent course and treatment includes wide surgical excision with or without adjuvant radiotherapy. We report eight cases of HCCC identified at two academic institutions in six women and two men, ranging in age from 25 to 86 years. Histologically, all cases demonstrated cords, trabeculae, and nests of monomorphic clear cells as well as cells with eosinophilic granular cytoplasm. Mild cellular atypia was occasionally seen and mitoses were very rare. Seven cases demonstrated a hyalinized stroma, and one case, a myxoid stroma. Immunohistochemically, the tumor cells were positive for epithelial markers and negative for desmin and actin. Seven cases were negative for S-100. Cells were also positive for periodic acid-Schiff and negative for mucin. The important clinicopathologic features and the differential diagnoses of HCCC, as well as a review of the literature are discussed.

Keywords Clear cell carcinoma · Salivary gland · Oral cavity · Hyalinizing

Introduction

Hyalinizing clear cell carcinoma (HCCC) is a rare neoplasm of salivary gland origin. Although previous cases

had been mentioned in the literature, it wasn't until 1994 Milchgrub et al. [1] described it as a distinct entity. In their initial case series, they described 11 cases with a female preponderance that arose in the oral cavity [1]. Since then, approximately 36 additional cases have been described in the English literature [2–22]. Histologically, this tumor is characterized by nests of glycogen-rich monomorphic clear cells within a hyaline stroma [1]. This tumor often follows an indolent course and treatment includes wide surgical excision with or without adjuvant radiotherapy [1]. Therefore, it is important to differentiate this entity from other more aggressive clear cell tumors including mucoepidermoid carcinoma, epithelial myoepithelial carcinoma, acinic cell carcinoma, odontogenic neoplasms, and metastatic tumors such as renal cell carcinoma. We report eight new additional cases of HCCC, discuss the important differential diagnoses, and provide a review of the available literature for the previously reported cases.

Materials and methods

A review of surgical pathology records at Virginia Commonwealth University Health System and Massachusetts General Hospital from 1992 to 2008 identified eight patients diagnosed with HCCC. Available clinical records, surgical pathology records, paraffin blocks, and glass slides for these patients were retrieved and reviewed.

Results

The clinical and gross features of our eight cases of HCCC are summarized in Table 1. The mean age was 66 years (range from 25 to 86 years). Of the eight cases of HCCC,

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Table 1 Clinical and gross features

Case number	Age/sex	Clinical symptoms	Location	Gross appearance	Original size of tumor (cm)	Recurrence/metastases
1	59/F	Dysphagia	Left base of tongue	Tan-grey	3	No recurrence
2	67/F	Asymptomatic	Left floor of mouth	Tan-pink, firm	2	No recurrence
3	72/F	Unknown	Anterior tongue	White, firm, well-circumscribed	1.8	Local recurrence/1 year
4	78/F	Unknown	Left cheek, buccal mucosa	Tan-pink to grey	1.7	No recurrence
5	73/M	Unknown	Left soft palate	Grey-white, rubbery	1.2	No recurrence
6	69/F	Lesions status post root canal	Left mandible	White, soft	2.5 and 1.5	Three local recurrences/1 year/5 years/6 years
7	86/M	Ulceration	Right malar region	Tan-brown, rubbery	Unknown	Two local recurrences/6 years/10 years
8	25/F	Unknown	Right orbit and lacrimal gland	Tan-grey, rubbery	4.5	No recurrence

F female, M male

Fig. 1 Hyalinizing clear cell carcinoma with characteristic hyalinizing stroma (200×, H&E)

Fig. 2 Prominent cytoplasmic clearing, HCCC (400×, H&E)

six occurred in females and two in males. Seven of eight tumors occurred within the oral cavity. One patient presented with a tumor of the lacrimal gland/orbit. Clinical symptoms at presentation varied, and ranged from asymptomatic, to dysphagia and mucosal ulceration. The mean size of the tumors was 2.3 cm (range, 1.2–4.5 cm).

Grossly, the tumors were firm to rubbery, with a white-tan to grey cut surface. Histologically, all cases demonstrated cords, trabeculae, and nests of monomorphic clear epithelial cells, as well as cells with eosinophilic granular cytoplasm (Figs. 1, 2). Seven of the cases demonstrated a background composed of a hyalinized stroma, while one case had a myxoid stroma. The tumor cells were

additionally characterized by centrally placed nuclei and inconspicuous nucleoli. Cellular atypia was mild, and mitotic figures were extremely rare. No evidence of perineural or vascular invasion, or necrosis was identified.

At least one histochemical and/or immunohistochemical stain was performed for each of the eight cases. The histochemical and immunohistochemical profiles for the eight tumors are summarized in Table 2. Tumor cells were positive for PAS (4/4) (Fig. 3), cytokeratin AE1/AE3 (4/4) (Fig. 4), polyclonal carcinoembryonic antigen (CEA) (2/2), cytokeratin CAM 5.2 (2/2), epithelial membrane antigen (EMA) (2/2), and p63 (7/8). Tumor cells were negative for desmin (0/3), smooth muscle actin (SMA) (0/6), mucin (0/3), thyroglobulin (0/2), S-100 (1/4), and calponin (1/3).

Table 2 Histochemical and immunohistochemical profile

Case no.	CK	Poly CEA	p63	EMA	CAM 5.2	S100	Desmin	Cal	Actin	TGB	PAS	Mucicarmine
1	+	+	+	+	Weak +	–	–	ND	–	–	+	–
2	ND	ND	+	ND	ND	ND	ND	ND	ND	ND	+	ND
3	ND	ND	+	+	+	–	ND	+ ^a	–	ND	ND	ND
4	+	ND	–	ND	ND	ND	ND	–	–	ND	+	–
5	+	ND	+	ND	ND	Focal +	ND	–	–	ND	ND	ND
6	ND	ND	+	ND	ND	ND	ND	ND	ND	ND	ND	–
7	ND	ND	+	ND	ND	–	–	ND	–	ND	ND	ND
8	+	+	+	+	ND	ND	–	ND	–	–	+	ND

CK cytokeratin, Poly CEA polyclonal carcinoembryonic antigen, CAM 5.2 cytokeratin CAM 5.2, EMA epithelial membrane antigen, Cal calponin, TGB thyroglobulin, PAS periodic acid-Schiff, ND not done, + positive, – negative

^a High background staining

Fig. 3 Cytoplasmic glycogen, HCCC (200×, PAS) **Fig. 4** Positive cytokeratin AE1/AE3, HCCC (200×)

The eight cases were treated with surgical excision, and one patient is known to have received adjuvant radiotherapy. Follow-up for cases ranged from one up to 10 years. Three patients developed local recurrence (two patients had multiple recurrences), with two patients initially recurring within 1 year and one patient initially recurring in 6 years. No metastases have been identified.

Discussion

Hyalinizing clear cell carcinoma was first described as a distinct entity in 1994 by Milchgrub et al. in their series of 11 patients [1]. Since then, approximately 36 additional cases have been reported in the English literature and are summarized in Table 3 [2–22]. Our series adds eight more cases of HCCC with histochemical and immunohistochemical profiles. Characteristics of the tumors in our series are very similar to the previously reported cases. A general review of the now reported 55 cases of HCCC shows a female predominance (72.7%) and an older age at diagnosis (68 years, mean). The vast majority of cases (81.8%) occurred within the oral cavity, most commonly the tongue or hard palate. Less common locations include parotid gland, nasopharynx, hypopharynx, and orbit/lacrimal gland.

Grossly, all 55 cases were described as firm, rubbery, or elastic, with varied color including white, tan, red, and grey. In cases that reported tumor size at excision, the range was from 0.5 cm up to 10 cm, with an average of 2.6 cm. Histologically, all cases demonstrated the features of HCCC with monomorphic glycogen rich clear cells in cords, nests, islands, or trabeculae within a hyalinized stroma. Fifteen cases demonstrated foci of myxoid stromal changes [1, 22]. A dense inflammatory infiltrate composed of lymphocytes and plasma cells was identified in five

Table 3 Summary features of HCCC reported in literature

Report	Age/sex	Tumor site	Gross appearance	Tumor size (cm)	CK	CK-CAM 5.2	Poly CEA	EMA	S-100	SMA	PAS
Milchgrub et al. [1]	51/F	R base of tongue	Firm, grey-white	3	+	+	–	+	–	–	+
	34/F	Tongue	Firm, tan-yellow	2.5	+	+	–	+	–	–	+
	56/F	Floor of mouth	Tan	0.5	+	+	–	+	–	–	+
	42/F	Hard palate	Firm, tan	1.5	+	+	–	+	–	–	+
	74/F	Subglottic	Firm, white	2	+	–	–	–	–	–	+
	35/F	Retromolar trigone	White, homogenous	0.6	+	+	–	+	–	–	+
	78/M	Parotid	Firm, tan-white	1.5	+	+	–	+	–	–	+
	48/M	Base of tongue	Firm, tan	2	+	+	–	+	–	–	+
	72/F	Soft palate	Tan-white	2	+	+	–	–	–	–	+
	42/F	R base of tongue	Rubbery, grey-white	1.5	+	–	+	+	–	–	+
Tang et al. [2]	77/M	R base of tongue	Tan	2.5	+	–	+	–	–	–	+
	51/F	Nasopharynx	n/a	n/a	+	n/a	n/a	n/a	–	–	n/a
	65/F	Left parotid gland	Firm, white, circumscribed	10	n/a	n/a	n/a	n/a	n/a	–	+
	67/F	Left floor of mouth	Firm tan-pink	2	+	n/a	+	+	–	–	+
	39/F	R base of tongue	n/a	n/a	n/a	+	n/a	n/a	–	–	Scant +
Bertho et al. [6]	37/F	R retromolar region	n/a	n/a	n/a	+	n/a	n/a	–	–	n/a
	51/F	Parotid gland	n/a	n/a	+	n/a	n/a	n/a	–	–	n/a
	66/F	L mandible	n/a	1.7	+	+	–	+	–	–	+
	53/F	R maxilla	n/a	2	+	+	Weak +	+	–	–	+
	53/M	L hypopharynx	n/a	2	+	+	Focal +	+	–	–	+
Ereno et al. [7]	50/M	L neck	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	69/F	L floor of mouth	n/a	1.8	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	32/M	Base of tongue	n/a	2.5	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	29/F	L cheek	n/a	2.0	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	57/M	Parotid gland	Firm, gray-white	3.2	+	n/a	+	+	–	–	n/a
Boccato et al. [9]	53/F	Palate	n/a	5	n/a	n/a	n/a	n/a	n/a	n/a	+
	40/F	L floor of mouth	Solid, gray-white	4.5	+	–	–	–	–	–	–
	48/F ^a	Hard palate	n/a	n/a	n/a	n/a	n/a	n/a	–	–	+
	48/F ^a	Hard palate	n/a	n/a	n/a	n/a	n/a	n/a	–	–	+
	48/F ^a	Tongue	n/a	n/a	n/a	n/a	n/a	n/a	–	–	+
Balakrishnan et al. [13]	35/M	Base of tongue	White-yellow, firm	3	n/a	n/a	n/a	n/a	n/a	n/a	+
	74/M	Palate	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
	57/F	R base of tongue	Firm, white, whorled	3.5	+	n/a	n/a	n/a	n/a	n/a	+
	42/F	R hard palate	Yellowish-white, firm, elastic	2.5	+	n/a	n/a	n/a	n/a	n/a	+
	66/F	Base of tongue	Milky-white, firm, elastic	4	n/a	n/a	n/a	n/a	n/a	n/a	n/a

Table 3 continued

Report	Age/sex	Tumor site	Gross appearance	Tumor size (cm)	CK	CK-CAM 5.2	Poly CEA	EMA	S-100	SMA	PAS
Meer et al. [18]	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Pujari et al. [19]	57/M	L base of tongue	Grey-white, solid	3	+	n/a	n/a	n/a	n/a	n/a	+
Angiero et al. [20]	57/F	Anterior palatoglossal arch	n/a	2	+	n/a	–	Focal +	–	–	+
Uzochukwu et al. [21]	47/F	Base of tongue	Rubbery, gray-white	4.4	+	n/a	n/a	–	n/a	–	n/a
Solar et al. [22]	34/M	Hard palate	Firm, white/red	1	+	n/a	n/a	n/a	–	–	+
	49/F	Buccal mucosa	Firm, white/red	3	+	n/a	n/a	n/a	–	–	+
	52/F	Hard palate	Firm, white/red	n/a	+	n/a	n/a	n/a	–	–	+
	65/F	Floor of mouth	Firm, white/red	n/a	+	n/a	n/a	n/a	–	–	+
	30/M	Hard palate	Firm, white/red	1.5	+	n/a	n/a	n/a	–	–	+
	85/F	R maxilla	Firm, white/red	1.2	+	n/a	n/a	n/a	–	–	+
	65/F	L maxilla	Firm, white/red	1	+	n/a	n/a	n/a	–	–	+
	60/F	Maxillary vestibule	Firm, white/red	n/a	+	n/a	n/a	n/a	–	–	+

CK cytokeratin, CK-CAM 5.2 cytokeratin CAM 5.2, Poly CEA polyclonal carcinoembryonic antigen, EMA epithelial membrane antigen, SMA smooth muscle actin, PAS periodic acid-Schiff,

n/a not available, + positive, – negative

^a Mean age reported for three cases

cases (9.1%), in which one developed lymphoid follicles with germinal centers [8, 12, 21]. Mitotic figures were identified in 18 cases (32.7%), [1, 3, 5, 6, 10–12, 16, 22]. Necrosis was identified focally in one case associated with increased mitotic activity (O'Regan et al. [15]), which had an aggressive course. In that case, the patient subsequently developed widespread metastatic disease and died within a year of diagnosis [15]. Perineural invasion was identified in approximately 20 cases (36.4%), with one case showing both perineural and perivascular invasion [1, 4–6, 11, 12, 15, 22].

Thirty-eight of 39 (97.4%) cases reported cytoplasmic glycogen by PAS stain. Only one report (2.6%) mentioned clear tumor cells to be negative for glycogen [11]. Although in most cases the tumor cells were negative for mucin, four cases were positive for focal extracellular mucin, and one case showed occasional intracellular mucin [1, 6, 12, 15]. Tumor cells in the vast majority of cases were positive for epithelial antigens including cytokeratin in 36/36 cases (100%), cytokeratin CAM 5.2 in 15/19 cases (78.9%), and EMA in 17/22 cases (77.3%). Immunohistochemical staining for polyclonal CEA was variable, with 8/20 cases (40%) showing at least focal positivity. In contrast, markers of myoepithelial origin including SMA and S-100 were negative in 43 and 37 cases, (100 and 97.3%) respectively.

No distinct morphologic characteristic such as necrosis or increased mitoses, or immunohistochemical profile, uniformly correlated with recurrence, aggressive behavior, or metastatic disease. Metastases and/or local recurrences were identified in approximately one-third of cases [1, 2, 5, 7, 8, 10, 15, 22]. Nine cases reported metastases (16.4%), five identified at the time of initial diagnosis [1, 5, 7, 8, 10, 15], one at 4 months [15], one at 3 years [8], one at 5 years [5], and one at 7 years [8]. The majority of metastases traveled to local lymph nodes and three cases showed distant metastases to the lung, with two of the three lung metastases identified at the time of diagnosis [7, 10, 15]. In the nine cases with reported recurrences (16.4%), the time span between initial diagnosis and local recurrence ranged from 11 months [5] up to 6 years [8]. It is important to differentiate HCCC from other tumors with clear cell features because of their differences in treatment and clinical outcome. These include clear cell mucoepidermoid carcinoma, epithelial-myoepithelial carcinoma, acinic cell carcinoma, some odontogenic tumors, and metastatic clear cell tumors such as renal cell carcinoma. Because HCCC is an uncommon tumor, only occasionally reported in the literature, the diagnosis can be challenging. HCCC should be considered in the differential diagnosis of tumors with the histology marked by monomorphic clear cells arranged in cords, trabeculae, or clusters surrounded by a hyalinized stroma.

In addition to the morphologic features, immunohistochemical stains may help differentiate HCCC from other tumors composed of clear cells. Review of the HCCC literature indicates that cytoplasmic glycogen is present in the neoplastic cells, as are epithelial antigens. Table 4 summarizes the immunohistochemical staining pattern of clear cell tumors in the HCCC differential diagnosis.

Clear cell mucoepidermoid carcinoma (MEC) is one of the more common malignancies of the head and neck to be considered in the differential diagnosis of HCCC (Fig. 5). The majority of mucoepidermoid carcinomas arise in the parotid gland, and characteristically have three morphologically distinct cell types: mucin-producing cells that can have the appearance of foam cells and/or goblet cells, epidermoid cells, and intermediate cells that have eosinophilic cytoplasm with round nuclei. Unlike HCCC, mucin can be demonstrated within MEC cells by mucicarmine or Alcian blue histochemistry. Immunohistochemical staining for p63 may be beneficial in differentiating MEC from some clear cell tumors [23], however, it is also positive in HCCC, and may not be helpful if used alone.

Epithelial-myoepithelial carcinoma is rare, and the tumor cells tend to show duct-like growth with a biphasic appearance. The duct-like structures are composed of eosinophilic cuboidal epithelial cells surrounded by round to spindle clear cells. The epithelial cells will stain for cytokeratin and epithelial membrane antigen (EMA). The clear cells in this tumor stain for myoepithelial markers including SMA and S-100 [24].

Acinic cell carcinoma is often infiltrative and can show different growth patterns including solid, papillary, microcystic, and follicular, and usually more than one cell type can be identified. Clear cell acinic carcinoma is fairly rare and the cells are PAS positive, but unlike HCCC, are diastase resistant [24].

Clear cell odontogenic carcinoma is an aggressive tumor and is morphologically characterized by islands of mostly clear cells surrounded by a fibrous stroma. The tumor cells possess abundant glycogen and show positivity for cytokeratin and EMA. However, unlike HCCC, clear cell odontogenic carcinoma tends to be S-100 positive [24].

Fig. 5 Cytoplasmic clearing, clear cell mucoepidermoid carcinoma of oral cavity (200×, H&E)

In addition to differentiating HCCC from other primary clear cell tumors of the head and neck, it is also important to consider metastatic tumors in the differential diagnosis. Renal cell carcinoma is commonly composed of glycogen rich clear cells (Fig. 6). However, it is often associated with hemorrhage and necrosis, and often will be positive for renal cell carcinoma antigen, CD10, and cytokeratin. Thyroglobulin and thyroid transcription factor-1 (TTF-1) can be used to identify metastases of clear cell thyroid carcinoma [24].

In summary, we report a series of eight cases of HCCC with features similar to previously reported cases. After extensive review of the literature, it is apparent that histochemical and immunohistochemical stains can be extremely helpful in distinguishing HCCC from other tumors with clear cell features. Apart from the presence of a hyalinizing stroma, HCCC is generally PAS, cytokeratin, p63, and EMA positive. Additionally, mucicarmine is useful to perform to rule out MEC, PAS and PAS with diastase to rule out acinic cell carcinoma, and SMA and S-100 to rule out clear cell epithelial myoepithelial carcinoma. If clear cell odontogenic carcinoma is in the differential, S-100

Table 4 Differential diagnosis and staining patterns of clear cell tumors of the head and neck

Tumor type	PAS	PAS-D	Mucin	CK	EMA	p63	SMA	S-100	CD10
Hyalinizing clear cell carcinoma	+	—	—	+	+	+	—	—	—
Mucoepidermoid carcinoma	+ or —	—	+	+	n/a	n/a	—	—	—
Epithelial myoepithelial carcinoma	—	—	—	+	+ or —	n/a	+	+	—
Acinic cell carcinoma	+	+	—	+	+	+	+	—	—
Clear cell odontogenic carcinoma	n/a	n/a	n/a	+	+	n/a	n/a	+	—
Renal cell carcinoma	+	—	—	+	+	n/a	—	Rare +	+

PAS periodic acid-Schiff, PAS-D periodic acid-Schiff diastase resistant, CK cytokeratin, EMA epithelial membrane antigen, SMA smooth muscle actin, n/a not applicable, + positive, — negative

Fig. 6 Cytoplasmic clearing, renal cell carcinoma (200×, H&E)

may be useful in differentiating this tumor from HCCC. Optional immunohistochemical stains such as CD10 and renal cell carcinoma antigen for renal cell carcinoma, or thyroglobulin and TTF-1 for clear cell thyroid carcinoma, can be useful if the clinical information warrants investigation of a metastasis.

The behavioral profile of our series of eight HCCC cases conformed to the relatively indolent behavior previously reported in these tumors. In a recent case series by Solar et al. [22], it was noted that 25% of cases reported in the literature had evidence of metastases. With the addition of our cases to the literature, we observed that only 16.4% of cases reported metastases. Additional cases of HCCC need to be reported to further elucidate the true behavior of this rare tumor. While surgical excision with or without radiotherapy remains the primary treatment for HCCC, we agree with Solar et al. [22] that careful observation and follow-up of these patients is warranted. It is therefore necessary to distinguish HCCC from more aggressive tumors with clear cell features to ensure proper treatment and management.

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