Int. J. Oral Maxillofac. Surg. 2017; xxx: xxx–xxx
https://doi.org/10.1016/j.ijom.2017.11.004, available online at https://www.sciencedirect.com

International Journal of Oral & Maxillofacial Surgery

Clinical Paper
Head and Neck Oncology

Hyalinizing clear cell carcinoma of salivary gland origin in the head and neck: clinical and histopathological analysis

X.-H. Yang[1,3], L. Liu[2], Y.-Y. Shi[3], Y.-J. Hu[2], Q.-G. Hu[1], P. Zhang[4,a]

[1]Stomatological Hospital, School of Medicine, Nanjing University, Nanjing, Jiangsu, China; [2]Department of Oral and Maxillofacial Surgery, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China; [3]Department of Oral and Maxillofacial Surgery and Pathology, Affiliated Hospital of Jiangsu University, Zhenjiang, Jiangsu, China; [4]Boston University Henry M. Goldman School of Dental Medicine, Boston, Massachusetts, USA**Address: Qin-Gang Hu, Department of Oral and Maxillofacial Surgery, Stomatological Hospital, Medical School of Nanjing University, 30 Zhongyang Road, Nanjing, Jiangsu 210000, China.

X.-H. Yang, L. Liu, Y.-Y. Shi, Y.-J. Hu, Q.-G. Hu, P. Zhang[4,]: Hyalinizing clear cell carcinoma of salivary gland origin in the head and neck: clinical and histopathological analysis. Int. J. Oral Maxillofac. Surg. 2017; xxx: xxx–xxx.

Abstract. Hyalinizing clear cell carcinoma (HCCC) is an extremely rare neoplasm of salivary gland origin with a low-grade indolent nature. It is difficult to distinguish from other malignant salivary gland tumours. Clinical outcomes following surgery are generally reported as good. The aim of this study was to further determine the features of HCCC. This study was approved by Medical ethics review of affiliated hospital of jiangsu university. Fourteen new cases of HCCC are reported. The clinical and histopathological data of these 14 cases were analysed alongside those of 141 cases identified in a systematic review of the literature (up to 2016). Demographic data, histopathological findings, clinical presentation, primary treatment, and outcomes were extracted. Histologically, HCCC tumour cells had a clear cell morphology with hyalinized stroma. Immunohistochemical results were positive for cytokeratins and EMA, but negative for SMA, S100, vimentin, and calponin. Twelve of the 14 patients showed EWSR1 translocation. Local nodal metastasis on presentation was present in 17.3% and the overall recurrence rate was 17.7% in the total population ($N = 155$), compared with 35.7% and 21.4%, respectively, in the new cases alone. Focal necrosis and local metastasis were identified as possibly associated with recurrence. The overall prognosis was good: only 3.8% of patients died of the disease. HCCC is less indolent than was previously thought, but overall the prognosis is good. Risk factors for recurrence may include focal necrosis and local metastasis at presentation. The best treatment for patients with HCCC is wide local excision combined with regional lymph node dissection.

Key words: head and neck; hyalinizing clear cell carcinoma; oral cancer; prognosis.

Accepted for publication 15 November 2017

Hyalinizing clear cell carcinoma (HCCC) is a rare, typically indolent neoplasm that accounts for less than 1% of all salivary gland tumours[1]. The most common sites of occurrence include the palate, base of the tongue, buccal mucosa, and floor of the

[a] Xi-Hu Yang and Liu Liu contributed equally to this work.

0901-5027/000001+07

Please cite this article in press as: Yang XH, et al. Hyalinizing clear cell carcinoma of salivary gland origin in the head and neck: clinical and histopathological analysis, *Int J Oral Maxillofac Surg* (2017), https://doi.org/10.1016/j.ijom.2017.11.004

mouth. Histologically, these tumours mainly have a clear cell morphology with hyalinized stroma. Although the use of both immunohistochemistry and histology can distinguish HCCC from the majority of other salivary gland tumours, including other clear cell carcinomas, the pathological diagnosis of HCCC remains very difficult.

HCCC was first described by Milchgrub et al. in 1994 as a rare minor salivary gland carcinoma made up of clear cells forming nests, trabeculae, sheets, and cords in a hyalinized stroma[2]. They described a tumour that occurred intraorally, predominantly in the minor salivary glands, and occurring most commonly in female patients in their fifth and sixth decades of life.

There is still controversy in the literature regarding how best to classify clear cell neoplasms of the head and neck. HCCC remains a rarely reported and rarely studied tumour, and its clinical behaviour is currently not well appreciated. The conventional view is that the prognosis of HCCC is excellent, with a minority of cases showing recurrence. Furthermore, the tumour presents a low-grade indolent nature. Histopathological findings for HCCC reported in the literature are inconsistent, so determining which reported cases are truly HCCC is challenging. Moreover, clinical and histopathological data are often incompletely reported in the literature.

The aim of this study was to perform a comprehensive review of patients with HCCC reported previously in the literature, mainly focusing on clinical and histopathological data, and to analyse these alongside 14 new patients seen at the Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.

Materials and methods

Case series

The databases of the Department of Oral Pathology, Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, were searched systematically for all HCCC of salivary gland origin during the years 2002–2012. The charts of the patients identified were reviewed for pathological diagnoses. When available, pathology slides were obtained to confirm the diagnosis of HCCC.

Immunohistochemistry

All tissue paraffin blocks were cut into 5-μm sections for standard immunohistochemical staining (IHC). After heat-induced antigen retrieval, the slides were incubated with selected antibodies at 4 °C overnight. The omission of the primary antibody served as negative control. Bound antibody was detected by Super Sensitive IHC Detection System (BioGenex, Fremont, CA, USA), according to the manufacturer's protocol. The sections were visualized with diaminobenzidine tetrahydrochloride solution (Sigma–Aldrich, St Louis, MO, USA) and counterstained with Harris haematoxylin. The staining result was determined by two independent pathologists by counting 1000 tumour cells in three 100× magnification fields; expression was further classified as low (percentage positive rate <25%) or high (percentage positive rate ≥25%).

Literature review

A comprehensive computer search of the English language literature was undertaken in the PubMed database. Search terms included ''hyalinizing clear cell carcinoma'', ''clear cell carcinoma'', ''clear cell adenocarcinoma'', ''clear cell'', and ''salivary gland tumour''. Each published case was carefully reviewed; cases were selected if the tumours were diagnosed as HCCC, or if they showed typical features of HCCC. The following data were then extracted: demographic characteristics, clinical presentation, histological features, management, and outcomes.

Statistical analysis

The data of all cases – the present case series and those reported earlier in the literature – were analysed. The statistical analysis was performed using SPSS version 17.0 software (SPSS Inc., Chicago, IL, USA).

Results

Demographic characteristics

A total of 14 patients with a diagnosis of HCCC were identified in the database review. The clinical findings are summarized in Table 1. The mean age at presentation was 53 years (range 33–82 years). Eight were female and six were male. The main clinical symptoms included a painless firm mass, ulceration, dysphagia, and bleeding. Tumours were located in the palate ($n = 6$), base of the tongue ($n = 3$), mandibular gingiva ($n = 2$), floor of the mouth ($n = 1$), hypopharynx ($n = 1$), and lip ($n = 1$). The primary tumours varied in size from 1.0 cm to 4.8 cm. Five patients (35.7%) had clinical lymph nodes on presentation. None had evidence of distant metastasis.

Treatment outcomes

All patients were treated with wide excision. Five patients underwent neck dissection at the time of resection. These patients had preoperative lymphadenopathy and furthermore exhibited histological evidence of metastasis on analysis. Four patients who had positive lymph nodes and large bulky primary disease underwent adjuvant radiation therapy. No patients underwent chemotherapy. Follow-up ranged from 3 to 7 years. Three patients (21.4%) developed local recurrence during follow-up, two of whom had multiple recurrences; this recurrence initially occurred within 1 year in two patients and at 4 years in the other. All cases of recurrence had positive lymph nodes and a large primary tumour volume. To date, no distant metastasis has been identified and no patient has died from the disease.

Histological and immunohistochemical features

Microscopically, all 14 cases demonstrated cords, trabeculae, and nests of monomorphic clear epithelial cells (Fig. 1). All of the cases demonstrated a background composed of hyalinized stroma. Twelve tumours contained smaller, polygonal cells with eosinophilic cytoplasm admixed with the clear cells. Rare mitoses were observed in four tumours (Fig. 2). Perineural invasion was identified in five tumours, and focal necrosis was identified in three tumours (Fig. 2). There was one case of recurrence among the three patients with focal necrosis, compared to only two recurrences in the remaining 11 patients.

The immunohistochemical results for the 14 tumours are summarized in Table 2. Tumour cells were positive for cytokeratin AE1/AE3 (12/12) (Fig. 3), epithelial membrane antigen (EMA) (9/9), and cytokeratins CK8 (10/10) and CK19 (6/7). Tumour cells were negative for smooth muscle actin (SMA) (0/14), vimentin (1/11), S100 (0/14), and calponin (0/12). Twelve of the 14 patients showed Ewing sarcoma breakpoint region 1 (EWSR1) translocation (Fig. 4).

Please cite this article in press as: Yang XH, et al. Hyalinizing clear cell carcinoma of salivary gland origin in the head and neck: clinical and histopathological analysis, *Int J Oral Maxillofac Surg* (2017), https://doi.org/10.1016/j.ijom.2017.11.004