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CASE REPORT

Hyalinizing Clear Cell Carcinoma of the Maxilla

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Abstract Hyalinizing clear cell carcinoma (HCCC) is a rare low-grade salivary gland tumor with distinctive clear cell morphology, accounting for < 1% of all salivary gland tumors. In the majority of cases, the tumor originates typically from the minor salivary glands in the oral cavity. A total of 155 cases of HCCCs from head and neck region have been reported in the literature until 2017, of which only 16 are of maxillary origin. Due to its low incidence, there is no clear consensus on prognostic factors and optimal treatment strategies yet. In this paper, a new case of HCCC of the maxilla is presented and its clinical and histopathological features are discussed.

Keywords Hyalinizing clear cell carcinoma · Head and neck · Maxilla · Recurrence

Introduction

Hyalinizing clear cell carcinoma (HCCC) is a rare low-grade salivary gland tumor with distinctive clear cell morphology, accounting for < 1% of all salivary gland tumors [1]. Histopathologically, it is characterized by glycogen-rich monomorphic clear cells, forming cords and nests in a hyalinized stroma. Mitotic figures are rare, with moderate nuclear pleomorphism and no evidence of necrosis [2].

In the majority of cases, the tumor originates typically from the minor salivary glands in the oral cavity. While hard palate and tongue base are the most common locations of the HCCC, it is rarely found in the nasopharynx, hypopharynx, nasal cavity, maxilla, parotid gland and lacrimal gland [3]. A total of 155 cases of HCCCs from head and neck region have been reported in the literature until 2017, of which only 16 are of maxillary origin [4]. In this paper, a new case of HCCC of the maxilla is presented.

Case Report

This case report was conducted in accordance with the Declaration of Helsinki and with approval from the Institutional Ethics Committee. Written informed consent was obtained from the patient.

A 51-year-old woman was referred to the Akdeniz University School of Medicine with a 6-month history of intermittent hemorrhage and non-healing wound at the gingiva of the right upper second tooth (lateral incisor) that developed after dental extraction for decay.

On physical examination, a 0.5 × 0.5 cm granulation tissue with an ulcerated surface was observed at the site of the extracted tooth root. A maxillofacial computed tomography (CT) scan revealed a well-defined area of bone destruction and soft tissue density in the site of extracted right upper second tooth (Fig. 1a–f). A small excisional biopsy was performed, which revealed a malignant epithelial tumor consisting of monomorphic small round cells with clear cytoplasm, but a definitive diagnosis could not be made. There was a focal but high 18 F-fluorodeoxyglucose (FDG) uptake (SUVmax = 8.23) in the

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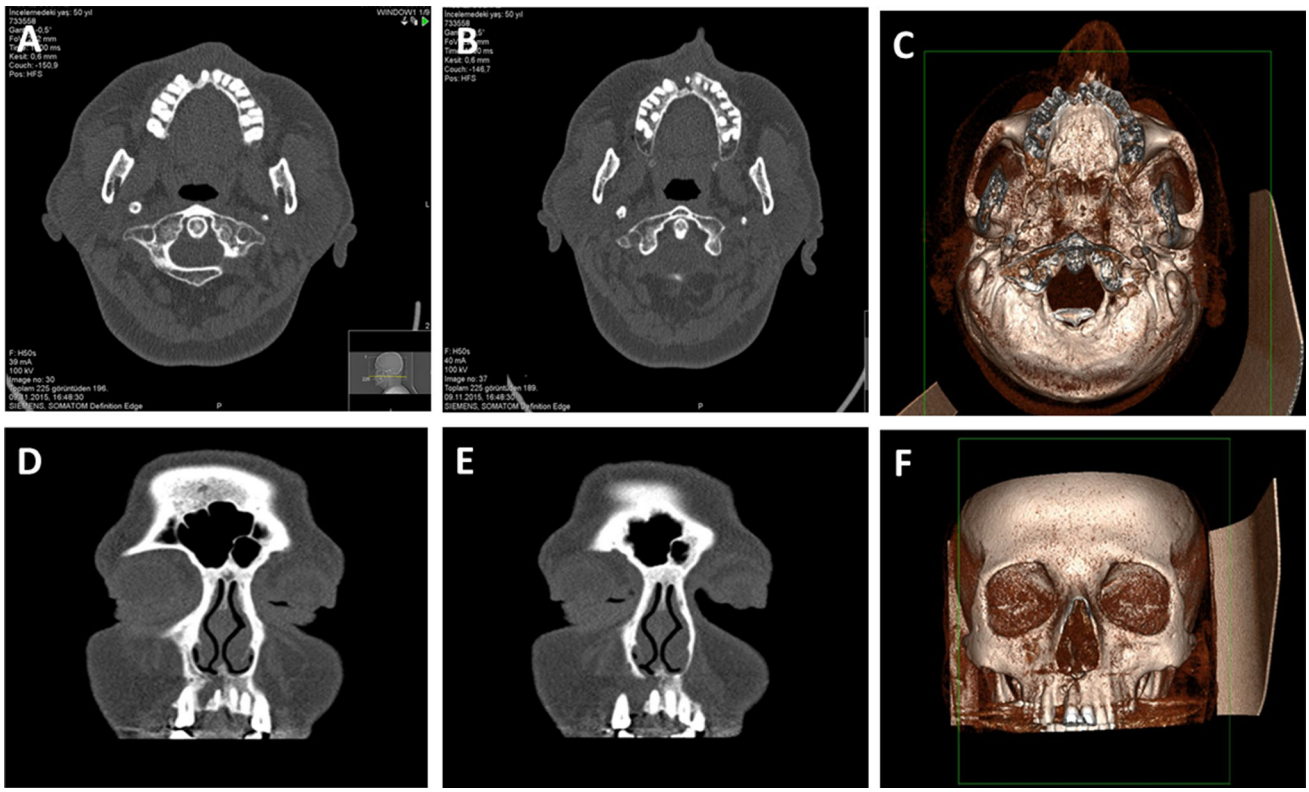

Fig. 1 Preoperative maxillofacial computed tomography view **a, b** axial plane, **c** 3-D axial plane, **d**, **e** coronal plane, **f** 3-D coronal plane

maxillary defect area in positron emission tomography combined with computed tomography (PET/CT). No other pathologic FDG uptake was noted elsewhere in the body.

The patient underwent partial maxillectomy under general anesthesia. The tumor was completely resected with the right first incisor and canine teeth (Fig. 2a–c). The maxillary defect was closed with surgical obturator prosthesis. Postoperative course was uneventful, and she was discharged home on postoperative day seven.

Monomorphic tumor cells with clear cytoplasm and round eccentric nuclei forming solid islands, nests and cords in a desmoplastic and fibrous connective tissue were detected on microscopic examination (Fig. 3a). There were a few mitotic figures. On immunohistochemical staining, the tumor showed diffuse and strong immunoreactivity for pan-cytokeratin (PanCK) and P_{63} (Fig. 3b, c). The $K\dot{I}_{67}$ proliferative index was 12%. These histological and

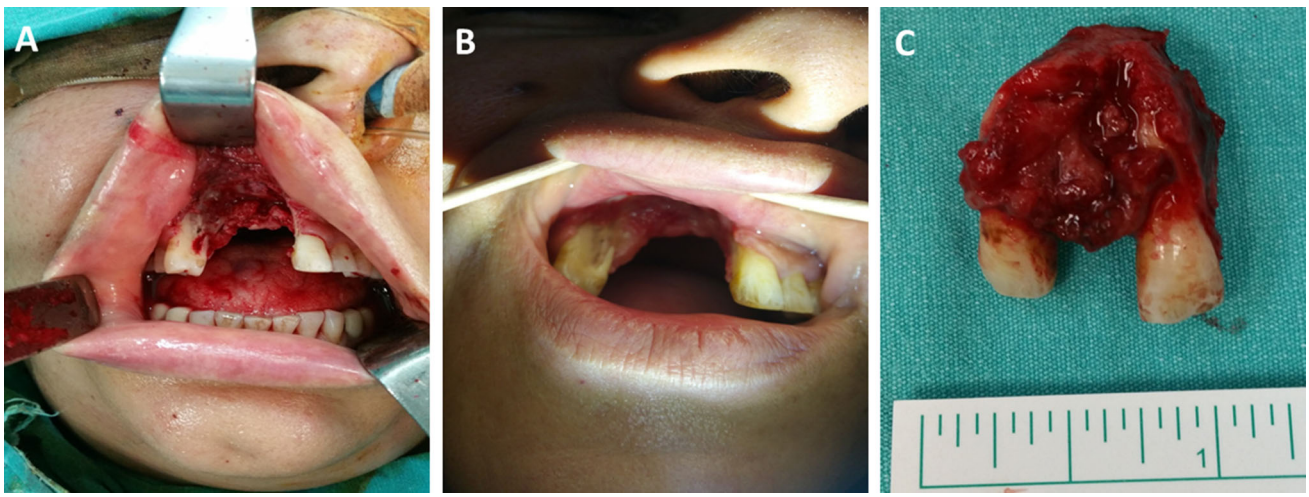

Fig. 2 **a** Postsurgical view of the maxilla, **b** view of the healed surgical site 1 month after surgery, **c** surgical specimen

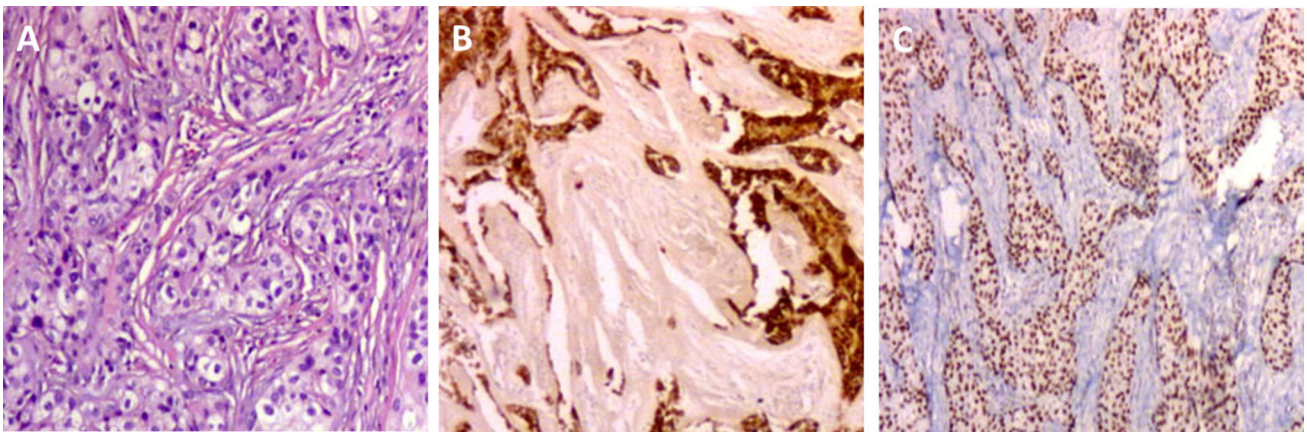

Fig. 3 Monomorphic tumor cells with clear cytoplasm and round eccentric nuclei forming solid islands, nests and cords in a desmoplastic and fibrous connective tissue. **a** Hematoxylin and eosin, (magnification, ×200), **b** Pan-cytokeratin 7 (magnification, ×200), **c** P_{63} (magnification, ×200)

immunohistochemical findings were consistent with the diagnosis of HCCC of the maxilla.

While surgical margins were negative for tumor invasion, the closest tumor-free margin distance was 4 mm. The patient did not receive adjuvant therapy and has been followed up three monthly with clinical examinations. On the 21st month of follow-up, she presented with a painful nodular lesion at the previous excision site. A paranasal CT scan revealed a well-defined soft tissue density adjacent to maxillary defect area (Fig. 4a). There was a 17 × 10 mm soft tissue mass at the anteroinferior aspect of the right maxillary sinus in paranasal magnetic resonance imaging (Fig. 4b). Following multidisciplinary tumor board counseling, a surgical re-excision was planned. The recurrent tumor was completely excised with negative surgical margins. Histopathological analysis indicated a diagnosis of recurrent HCCC of the maxilla. The patient was then put on regular surveillance with no adjuvant therapy given. At postoperative 6th month, she is alive with no evidence of disease.

Discussion

HCCC was first reported in salivary glands by Milchgrub et al. [5]. The authors described the presence of a distinct histological entity characterized by the formation of trabeculae, cords, islands, and/or nests of monomorphic clear cells that were glycogen-rich and mucin negative and were surrounded by hyalinized bands with foci of myxohyaline stroma [5]. Following similar reports, HCCC was classified as a subtype of salivary gland tumors in the World Health Organization (WHO) classification revised in 2005 and was described as a low-grade malignant epithelial tumor [6].

The microscopic features of HCCC may be difficult to distinguish from other tumors with clear cell features including mucoepidermoid carcinoma, epithelial-myoepithelial carcinoma, acinic cell carcinoma, some odontogenic tumors and metastatic tumors such as renal cell carcinoma. Immunohistochemical stains are particularly important in providing the differential diagnosis. HCCC

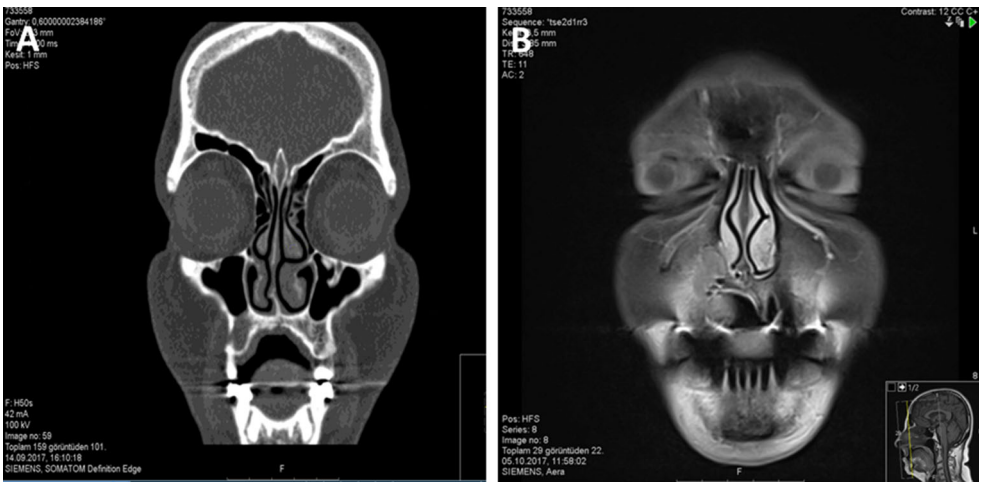

Fig. 4 **a** Paranasal computed tomography view of the recurrence on coronal plane, **b** magnetic resonance imaging view of the recurrence on coronal plane

typically shows positive staining with PanCK, P_{63} and periodic acid–Schiff (PAS); and negative staining with S-100, smooth muscle actin (SMA), glial fibrillar acidic protein and vimentin. On the other hand, differentiation of HCCC and clear cell odontogenic carcinoma, which are morphologically and molecularly similar, can only be made by different tumor localizations and clinical features [6].

HCCCs are usually reported in the fifth to seventh decades of life and are more common in women. The tumor originates from the salivary glands of the oral cavity and oropharynx in about two-thirds of the cases [3]. Patients present generally with a submucosal painless mass, but sometimes with an ulcerated mucosal lesion. Clinical symptoms often vary according to the location of the primary tumor [6]. Maxilla is an exceptional site of HCCCs, as to our knowledge only 16 cases have been reported in the literature [4]. The most common findings reported in tumors of maxillary origin are destruction of the bone, gingival hemorrhage and swinging of the teeth [7, 8]. Similar findings were also evident in our case.

HCCCs are generally considered low-grade tumors, although a few studies reported distant metastasis at presentation and poor disease outcome [9, 10]. In the most recent review of the literature, Yang et al. [4] reported that the rates of regional lymph node involvement and distant metastasis at diagnosis were 17.3% and 2.8%, respectively. Wide local excision was the most common surgical technique used, and there was no lymph node involvement on neck dissection for patients with clinically N0 necks. Seventeen percent of patients developed disease recurrence, with a median time to recurrence of 47 months (range 6–180 months). The authors concluded that overall prognosis was favorable with only 3.8% of patients died of the disease [4].

The presence of tumor necrosis, regional lymph node involvement at presentation, or surgical margin positivity has been reported to be associated with risk of disease recurrence [3, 4]. All these reported risk factors were not evident in our patient. One potential risk factor for disease recurrence in our case might be the close surgical margins, although there is no data regarding what would be the safe distance of tumor-free margin in the literature. The role of adjuvant therapy in patients with HCCC has not been clearly demonstrated due to the limited number of patients, but generally, adjuvant radiotherapy is recommended in the setting of positive lymph nodes or in case of positive surgical margins, where re-excision is not possible [3, 4].

In conclusion, this report illustrates another case of HCCC of the maxilla, followed by the review of the literature. Patients may develop disease recurrence despite lack of positive surgical margins, lymph node involvement and tumor necrosis. Thus, further studies are strongly warranted to identify the safest tumor-free margin distance in these patients.

Acknowledgment There is no financial disclosure in this study.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Standard All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

Informed Consent An informed consent was taken from the patient for being the part of research work.

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