Primary paranasal sinus hyalinizing clear cell carcinoma: a case report

Batool M. AlAli, Mohammed J. Alyousef, Ahmad Salah Kamel, Mohammad A. Al hamad, Mohammad H. Al-Bar and Roaa M. Algowiez

Abstract

Background: Hyalinizing clear cell carcinoma (HCCC) is a rare low-grade tumour of salivary glands that was first described as a distinct entity in 1994 by Milchgrub et al. EWSR1-ATF1 fusion was found to be specific for this tumour. The majority of the reported cases of HCCC arise from minor salivary glands within the oral cavity. Primary HCCC of the paranasal sinus is extremely uncommon. To our knowledge, only three cases have been reported in the English literature. Herein, we present a case of HCCC of the posterior ethmoid/maxillary sinus.

Case presentation: A 63-year-old lady who presented with a long history of epistaxis. CT scan revealed a destructive mass in the left ethmoid/posterior maxillary sinus extending to the nasal cavity. Surgical excision was done and microscopic evaluation showed a tumour composed mainly of nests of clear epithelial cells separated by fibrocellular and hyalinized septa with extensive bone destruction. The tumour cells expressed CK5/6, EMA and p63 immunohistochemically but were negative for S100 protein, PAX-8, RCC and CK7. Sinonasal renal cell–like adenocarcinomas, myoepithelial carcinoma and metastatic renal cell carcinoma were excluded by radiological and immunohistochemical studies. Fluorescence in situ hybridization analysis revealed an EWSR1 gene rearrangement. Postoperative radiation was administrated and the patient did not show recurrence or distant metastasis 4 months after the surgery.

Conclusion: Head and neck region have many tumours that demonstrate clear cell changes on histology. Thus, the differential diagnosis for HCCC is wide. Awareness of this rare entity and the possibility of it arising in unusual location is necessary. EWSR1-AFT1 fusion, a consistent finding in HCCC, can be used to confirm the diagnosis.

Keywords: Hyalinizing clear cell carcinoma, Paranasal sinuses, EWSR1-AFT1, Salivary gland, Clear cell carcinoma

Background

Hyalinizing clear cell carcinoma (HCCC), which is classified by the World Health Organization (WHO) as “Clear cell carcinoma, NOS” [1], is a rare low-grade salivary gland neoplasm with characteristic clear cells arranged in nests and cords embedded within a hyalinizing stroma. Most of the reported cases of HCCC arise from the minor salivary glands within the oral cavity, with base of the tongue and palate being the most common sites [2, 3]. HCCC of paranasal sinuses is an extremely rare tumour, and up to the best of our knowledge, only three cases have been reported in the English literature [4, 5] (Table 1). Herein, we report a case of HCCC arising primarily in paranasal sinuses in a 63-year-old woman. The diagnosis was molecularly confirmed with EWSR1 gene rearrangement.

Case presentation

A 63-year-old lady was referred from ER to the ENT department, complaining of recurrent epistaxis episodes for the past 4 years. She also has history of left sided nasal obstruction, facial pressure, yellowish nasal discharge, protrusion of left eye and anosmia. She gave history of weight loss of around 7 kg in the past 3 months associated with decrease of appetite.
Bilateral nasal endoscopic examination showed a mass that easily bleeds on touch, filling the left nasal cavity and pushing the nasal septum to the other side.

Computed tomography scan (CT) revealed a destructive mass in the left ethmoid/posterior maxillary and sphenoid sinus extending to the nasal cavity. It measured 4 × 4.5 × 6 cm, with extension posteriorly to involve the anterior superior border of the clivus, invading towards the pterygoid bone and reaching the carotid canal (Fig. 1a and b). MRI showed dural thickening lateral to the optic nerve on the left side but no clear intracranial neither periorbital extension. CT scan of chest, abdomen and pelvis were unremarkable for primary or metastatic tumour.

The tumour was treated with surgical excision; however, complete removal was not possible due to attachment to the optic nerve and carotid sheath. Post-operative radiotherapy was administrated.

Multiple soft/tan and bone fragments were received for histological examination. Frozen section was performed for diagnosis and evaluation of margin status. The frozen section diagnosis was reported as “Malignant epithelial neoplasm with prominent clear cell change”. The tumour was extending to the resection margins.

Resected tissues were then fixed in 10% buffered formalin and embedded in paraffin. Permanent hematoxylin and eosin (H&E) sections revealed an infiltrative tumour with extensive bone destruction. The tumour consisted of polygonal to round cells arranged in nests and separated by fibrocellular and hyalinized fibrous septa. Most of the cells had a clear cytoplasm while few cells exhibited eosinophilic cytoplasm especially at the periphery of the tumour. The nuclei were round, uniform and centrally located with inconspicuous nucleoli. Mitotic figures and necrosis were not present. Perineural and lymph-vascular invasion were noted (Fig. 2a-c).

The differential diagnosis based on the H&E included squamous cell carcinoma with clear cell changes, mucoepidermoid carcinoma with prominent clear cell change, metastatic renal cell carcinoma and HCCC.

Immunohistochemically, the tumour cells stained positive for EMA, CK5/6 (Fig. 2d), CEA and p63 and were negative for PAX-8, RCC, CK7, SMA and S-100 protein. FISH analysis of EWSR1 breakapart probe on paraffin-embedded tumour tissue showed evidence of a 22q12 rearrangement in 164 out of 200 (82%) of interphase nuclei scored (Fig. 2e).

### Table 1  Reported cases of paranasal sinus HCCC

| Author                        | Location                                | Age (Years) | Gender | EWSR/ Rearrangement | Treatment                                    | Follow up                  |
|-------------------------------|-----------------------------------------|-------------|--------|----------------------|----------------------------------------------|----------------------------|
| Davina Stasia Teo et al. (2015) [4] | Right ethmoid sinus extending into the nasal cavity. | 69          | Male   | Unknown              | Surgical excision                            | No recurrence after 10 months |
| Jui Lan et al. (2017) [5]     | Right maxillary sinus.                  | 48          | Male   | Positive             | Surgical excision                            | No recurrence after 9 months |
| Jui Lan et al. (2017) [5]     | Right maxillary sinus.                  | 80          | Male   | Positive             | Surgical excision + radiotherapy             | Not provided               |
| Present case                  | Left ethmoid/posterior maxillary sinuses | 63          | Female | Positive             | Surgical excision + radiotherapy             | No recurrence after 4 months |

*Fig. 1* Head CT scan. Coronal head CT scan showing a destructive lesion within the paranasal sinuses extending to the nasal cavity. The epicenter of the mass is seen within the left ethmoid/posterior maxillary and sphenoid sinus (a) with extension posteriorly to involve the anterior superior border of the clivus (b).
The histological, immunohistochemical and molecular findings were consistent with primary hyalinizing clear cell carcinoma of the paranasal sinuses.

On follow-up, the patient showed no evidence of disease 4 months after the surgery.

**Discussion and conclusions**

HCCC is an uncommon salivary gland neoplasm that is slightly predominant in women (female to male ratio = 1.6 to 1) in their seventh (26%) or sixth (20%) decade of life, with the palate and the base of the tongue being the most common sites of the tumour [2]. Occurrence in paranasal sinuses is very rare. Up to our knowledge, only 3 cases in paranasal sinuses have been reported in the English literature.

The clinical presentation varies according to the location of the tumour, and as the most common location of HCCC is the oral cavity, 74.4% of patients presented with a painless submucosal lump in the oral cavity. Mucosal ulcers, pain, dysphagia and nasal obstruction were also reported [2]. In the present case, the patient presented with epistaxis.

HCCC was first described as a distinct entity by Milchgrub et al. [6] in a series of 11 patients with a distinct salivary gland neoplasm that it is characterized
harbor a translocation t(11;19)(q21;p13) resulting in dermoid carcinoma, on the other hand, frequently these tumours, with CCOC regarded as the central or tion is the most important distinguishing criterion for CCOC by Bilodeau et al., they suggest that the loca-
cional profile to HCCC. In a study of 12 cases of entity that is identical in histology and immunohisto-
cellular carcinoma (CCOC). The latter is a recently described fibrous histiocytoma and clear cell odontogenic
not specific for HCCC; as it is also seen in other ma-
sensitivity of this test. However, this translocation is confirmed in 43 out of 45 cases. This shows the high
EWSR1-ATF1 fusion gene rearrangement was con-
In a review of HCCC by Daniele and his coworkers, HCCC from other histologically similar tumours [11].
Sensitivities of other markers are usually low [2]. Immunohistochemical profile differentiates HCCC from other primary malignancies and meta-
neoplasms in this region with clear cell changes including: squamous cell carcinoma, sinonasal renal cell–like adenocarcinomas, mucoepidermoid carcinoma, epithelial–myoepithelial carcinoma, myoepithelial carcinoma, acinic cell carcinoma and metastatic carcinoma; particularly, metastatic renal cell carcinoma which is one of the tumours that frequently metastasize to the sinonasal tract [10].

In 2011, Antonescu et al. concluded that EWSR1-ATF1 fusion is the most reliable tool to differentiate HCCC from other histologically similar tumours [11]. In a review of HCCC by Daniele and his coworkers, EWSR1-ATF1 fusion gene rearrangement was confirmed in 43 out of 45 cases. This shows the high sensitivity of this test. However, this translocation is not specific for HCCC; as it is also seen in other malignancies including clear cell sarcoma, angiomatoid fibrous histiocytoma and clear cell odontogenic carcinoma (CCOC). The latter is a recently described entity that is identical in histology and immunohistochemical profile to HCCC. In a study of 12 cases of CCOC by Bilodeau et al., they suggest that the location is the most important distinguishing criterion for these tumours, with CCOC regarded as the central or intraosseous counterpart of HCCC [12, 13]. Mucoepidermoid carcinoma, on the other hand, frequently harbor a translocation t(11;19)(q21;p13) resulting in MECT1-MAML2 fusion. This gene fusion, associated with favourable prognosis, can help in the differential diagnosis [14].

The modality of choice for treatment of HCCC is complete surgical excision with clear margins. The role of post-operative radiotherapy is still not yet proven [2]. Assessment of regional lymph nodes for metastasis is recommended [15].

Even though that this tumour is designated as low-grade, many cases were reported with lymph node, lung and even vertebral metastasis [16–18]. Histological features that may suggest a high-grade tumour include: atypical mitosis, necrosis and bizarre neoplastic cells [17, 19]. Patient follow up is recommended even if the tumour is completely excised.

In summary, we report a case of HCCC involving paranasal sinuses primarily and describe its clinical, histopathologic, immunophenotypic, and molecular cytogenetic features. Tumour cell positivity for p63, CK5/6, PAS and negativity for PAX-8, RCC, mucicarmine and PAS-D exclude mucoepidermoid carcinoma, tumours of myoepithelial origin and metastatic renal cell carcinoma.

**Abbreviations**
CCOC: Clear cell odontogenic carcinoma; CEA: Carcinoembryonic antigen; CT: Computed tomography; EMA: Epithelial membrane antigen; ENT: Ear, nose and throat clinic; ER: Emergency room; HCCC: Hyalinizing clear cell carcinoma; NOS: Not otherwise specified; SMA: Smooth muscle actin; WHO: World health organization

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BA made substantial contributions to conception and design and interpretation of data in addition to drafting the manuscript. MJ was involved in drafting and reviewing the manuscript. AS was involved in reviewing the manuscript and gave the final approval for publication. MH was involved in FISH analysis and interpretation and drafting the FISH cytogenetic part. MB was involved in patient acquisition of data and drafting of the case report part. RG was involved in obtaining radiology pictures with interpretation and drafting of the radiology findings. All authors read and approved the final manuscript.

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Author details
1Department of Pathology and Laboratory Medicine, King Fahd Hospital of
University, Khobar, Saudi Arabia. 2College of Medicine, University of
Dammam, Dammam 34212, Saudi Arabia. 3Department of Otolaryngology,
King Fahd Hospital of University, Khobar, Saudi Arabia. 4Department of
Radiology, King Fahd Hospital of University, Khobar, Saudi Arabia.

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References
1. El-Naggar AK, Chan JK, Grandis JR, Takata T, Sloatweg PJ. WHO classification
of head and neck tumours. 4th ed. Lyon: IARC; 2017.
2. Daniele L, Nikolarakos D, Keenan J, Schaefer N, Lam A. Clear cell carcinoma,
not otherwise specified/hyalinising clear cell carcinoma of the salivary
gland: the current nomenclature, clinical/pathological characteristics and
management. Crit Rev Oncol Hematol. 2016;102:55–64.
3. Chao TK, Tsai CC, Yeh SY, Teh JE. Hyalinizing clear cell carcinoma of the
hard palate. J Otolaryngol. 2004;33(5):382–4.
4. Davina ST, Linda L, Abdul Razak A, Vijayaprakas Rao R, Norkamaruzaman E.
Primary sinonasal clear cell carcinoma: case report. Med J Malaysia. 2015;
70(2):112–3.
5. Lan J, Huang SC, Chen YH, Chen WC, Lin YT, Lu YC, et al. Primary paranasal
sinus clear cell carcinoma with EWSR1-ATF1 fusion: report of two
molecularly confirmed cases exhibiting unique histopathology. Hum Pathol.
2017;63(5):139–43.
6. Milchgrub S, Gnepp DR, Vuitich F, Delgado R, Albores-Saavedra J. Hyalinizing
clear cell carcinoma of salivary gland. Am J Surg Pathol. 1994;18(1):74–82.
7. O’Sullivan-Mejia ED, Massey HD, Faquin WC, Powers CN. Hyalinizing clear
cell carcinoma: report of eight cases and a review of literature. Head Neck
Pathol. 2009;3(3):179–85.
8. Imail T, Satoh I, Matsumoto K, Ito S, Asada Y, Kato K, et al. Clear cell
carcinoma of the nasal cavity: A case report from histopathological
viewpoint. Auris Nasus Larynx. 2016;43(1):108–11.
9. Turner JR, Reh DD. Incidence and survival in patients with sinonasal cancer:
a historical analysis of population-based data. Head Neck. 2012;34(6):877–85.
10. Antonescu CR, Katabi N, Zhang L, Sung YS, Seethala RR, Jordan RC, et al.
EWSR1-ATF1 fusion is a novel and consistent finding in hyalinizing clear-cell
carcinoma of salivary gland. Genes Chromosom Cancer. 2011;50(7):559–70.
11. Bilodeau EA, Hoschar AP, Barnes EL, Hunt JL, Seethala RR. Clear cell carcinoma
and clear cell odontogenic carcinomas: a comparative clinicopathologic and
immunohistochemical study. Head Neck Pathol. 2011;5(2):101–7.
12. Bilodeau EA, Weinreb I, Antonescu CR, Zhang L, Dacic S, Muller S, et al.
Clear cell odontogenic carcinomas show EWSR1 rearrangements: a novel
finding & a biological link to salivary clear cell carcinomas. Am J Surg
Pathol. 2013;37(7):1100–5.
13. Okae M, Miyabe S, Nagatsu H, Terada A, Hanai N, Yoko i M, et al. MECT1-
MAM2 fusion transcript defines a favorable subset of mucoepidermoid
carcinoma. Clin Cancer Res. 2006;12(13):3902–7.
14. Solar AA, Schmidt BL, Jordan RC. Hyalinizing clear cell carcinoma: case series
and comprehensive review of the literature. Cancer. 2009;115(1):75–83.
15. O’Regan E, Shandilya M, Gnepp DR, Timon C, Toner M. Hyalinizing clear cell
carcinoma of salivary gland: an aggressive variant. Oral Oncol. 2004;40(3):348–52.
16. Erenco C, Grande J, Alja V, Varnoz J, Bilbao FJ. Hyalinizing clear cell
carcinoma of the hypopharynx metastasizing to the lung: a case report.
Histo pathology. 2000;37(1):89–91.
17. Newman WC, Williams L, Duvvuri U, Clump DA 2nd, Amankulor N.
Hyalinizing clear cell carcinoma with biopsy-proven spinal metastasis: case
report and review of literature. World Neurosurg. 2016;90(6):e7–e99.
18. Jin R, Caddick KJ, Irish JC, Perez-Ordonez B, Weinreb I. Recurrent
hyalinizing clear cell carcinoma of the base of tongue with high-grade
transformation and EWSR1 gene rearrangement by FISH. Head Neck Pathol.
2012;6(3):389–94.

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