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Carcinomas with clear cell features and *EWSR1* rearrangements: a report of 3 cases

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Salivary gland and odontogenic neoplasms with extensive clear cell change are rare lesions but have been increasingly characterized over the past decade. Among this heterogeneous group of neoplasms, hyalinizing clear cell carcinoma (HCCC), clear cell odontogenic carcinoma (CCOC), and clear cell myoepithelial carcinoma (CCMC) share a monophasic clear cell morphology and an *EWSR1* gene rearrangement. While HCCC is relatively well characterized, there are a limited number of *EWSR1*-reaarranged CCMC of salivary glands reported, and its clinicopathologic features in relation to HCCC and nonclear cell myoepithelial carcinoma (MC) have not been clarified. This report describes the clinical, morphologic, and immunophenotypic features of 3 carcinomas composed predominantly of clear cells and with *EWSR1* rearrangements by fluorescence in situ hybridization. A comparative literature analysis suggests that HCCC, CCMC, and nonclear cell MC of salivary glands are clinically, histopathologically, and molecularly distinct. (Oral Surg Oral Med Oral Pathol Oral Radiol 2024;138:293−300)

Primary epithelial malignancies presenting with clear cell features in the oral and maxillofacial region are usually of salivary gland or odontogenic derivation.[1] Among this heterogeneous group of neoplasms, clear cells are typically observed in hyalinizing clear cell carcinoma (HCCC),[2] clear cell odontogenic carcinoma (CCOC),[3] and clear cell myoepithelial carcinoma (CCMC).[4] It has become increasingly evident on immunophenotypic analysis that these neoplasms display a clearly definable, albeit overlapping, monophasic "lineage" of tumor differentiation.[5,6] Contrary to most epithelial malignancies these neoplasms share a fusion-driven pathogenesis, although the mechanisms by which they contribute to oncogenesis are yet to be understood.[3,7]

HCCC is a monophasic salivary gland neoplasm usually composed of clear cells in a variably hyalinized stroma.[2] Ewing sarcoma breakpoint region 1 *(EWSR1)* rearrangement has been characterized as a consistent finding in most HCCCs.[6,8,9] Application of this molecular marker over the last decade has expanded the morphologic spectrum of HCCC to include the presence of mucous cells, overt squamous differentiation as well as *EWSR1*-rearranged HCCC that may not be hyalinized or dominated by clear cells.[6] Immunohistochemistry supports squamous differentiation in HCCC, and myoepithelial markers are usually negative.[6,9] Histologically and genetically similar neoplasms arising in the jaw bones are referred to as CCOC.[3] The latter is postulated to arise from the dental lamina within bone and considered by some authors to represent an "odontogenic analogue" to HCCC,[6,10] although direct development from odontogenic rests has thus far not been demonstrated in CCOC.

In contrast to HCCC, which is well characterized in literature, carcinomas of salivary glands composed almost exclusively of myoepithelial cells represent an under-recognized entity. The neoplastic cells in myoepithelial carcinoma (MC) may display an epithelioid, spindle, hyaline and/or clear cell phenotype.[11] Of these, CCMC is a rare subtype and may arise de novo or from malignant change in a pleomorphic adenoma (PA).[12] Recent studies indicate *EWSR1* rearrangement in subsets of both CCMC and CCMC ex-PA.[4,7,13] We herein describe 3 new cases of carcinomas with clear cell features harboring *EWSR1* rearrangement, corroborating that at least a subset within the spectrum of this disease represents myoepithelial neoplasms. We also

Statement of Clinical Relevance

Accurate histopathologic characterization of myoepithelial carcinoma of salivary glands showing extensive clear cell change and dysregulation of the *EWSR1* gene is important as they appear to be associated with an aggressive phenotype with worse clinical outcomes compared to most hyalinizing clear cell carcinomas and conventional myoepithelial carcinoma.

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performed a review of the literature for similar cases to highlight the differentiating clinicopathologic profiles of these rare neoplasms.

CASE SERIES

Case 1

A 60-year-old female patient presented with a right neck swelling of >10-year duration with pain and rapid increase in size over the last 3 years. Upon clinical examination, a localized swelling was noted extending from the inferior border of the mandible to the first neck crease. There was no palpable cervical lymphadenopathy. Ultrasound showed a heterogeneous submandibular mass, measuring 35 × 40 mm with solid and cystic components. An excision of the submandibular mass was performed. The resected specimen comprised a circumscribed mass, measuring 65 × 50 × 45 mm, with a homogeneous, white, and rubbery to gritty cut surface. Histologically, the tumor had a multinodular architecture, with lobulated borders and infiltrative growth exceeding 4 mm into the surrounding tissues. The tumor cells displayed a zonal arrangement with a hypercellular peripheral rim composed of a uniform population of clear cells surrounding a hypocellular and necrotic center (Figures 1A and 1B). There were <4 mitotic figures per 10 high power fields and no perineural or lymphovascular space invasion were seen. A pre-existing PA component was not identified on the excision specimen. Immunohistochemical analysis of the tumor demonstrated positivity for AE1/AE3 (Figure 1C), p63, SOX10 (Figure 1D), and S100 in a subset of the tumor cells, while CK7 and DOG1 were negative. The findings were interpreted as CCMC. Fluorescence in situ hybridization (FISH), using break-apart probes for *EWSR1* at 22q12 with a positive cut off level for scoring at >10% of nuclei; showed an atypical, rearranged signal pattern in 93% of the tumor cells screened (Figure 2A). The remaining tumor cells screened had 1 fusion signal, likely reflecting loss of the *EWSR1* gene. There was no evidence of tumor recurrence 29-months postoperatively (Table I).

Case 2

A 55-year-old female patient presented with a 6-month history of a painful, ulcerative gingival lesion that was biopsied with a provisional clinical diagnosis of squamous cell carcinoma. Examination of the H&E-stained sections showed ulcerated stratified squamous oral mucosa with an underlying infiltrating carcinoma. The tumor cells were arranged in nests, cords and interconnected trabeculae composed predominantly of clear cells admixed with tumor cells showing pale eosinophilic cytoplasm (Figure 3A). The tumor cells were separated by bands of fibrocellular stroma and basement membrane-like material. There was minimal variation in nuclear size, nucleoli were inconspicuous, mitotic figures were infrequent and necrosis was not seen. Immunohistochemically the tumor cells were diffusely positive for CK7 (Figure 3B) and p63 (Figure 3C) with focal staining for CK5/6 (Figure 3D); and negative staining for S100, DOG1, CK20, and

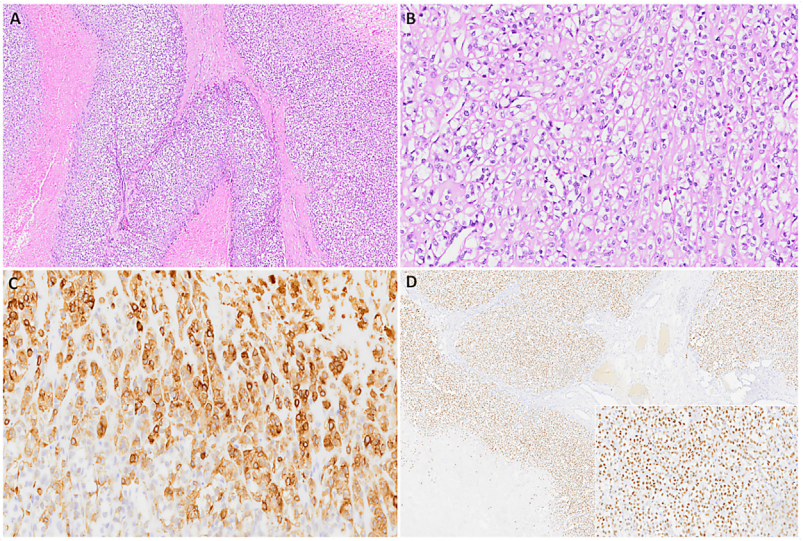


Fig. 1. Clear cell myoepithelial carcinoma. (A) Low power magnification showing confluent areas of tumor necrosis (hematoxylin and eosin [H&E]). (B) Hypercellular peripheral rim composed of large polyhedral cells with prominent clear cell morphology (H&E). Tumor cells were stained diffusely with pancytokeratin AE1/AE3 (C) and SOX10 immunohistochemistry (D). Original magnification: **A**, x 40; **B**, x 200; **C**, x 100; **D**, x 40, inset, x 400.

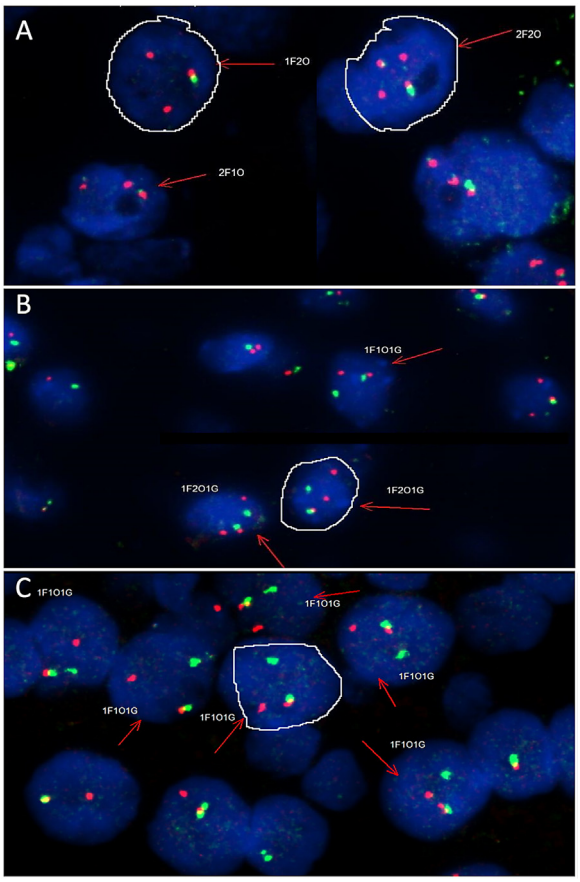


Fig. 2. *EWSR1* break-apart fluorescence in situ hybridization showing differing patterns. (A) The tumor cells showed 1−2 paired *EWSR1* signals in addition to 1−2 orange signals and no green signal, suggesting an unbalanced translocation associated with loss of the telomeric *EWSR1* probe. (B) The tumor cells had 1 paired signal, 1−2 orange signals and 1 green signal in keeping with rearrangement of the *EWSR1* gene with a variant pattern. (C) Tumor cells with a classic positive pattern of 1 paired signal, 1 orange and 1 green signal demonstrating rearrangement of the *EWSR1* gene.

PAX8. FISH studies confirmed the presence of 22q12 (*EWSR1*) gene rearrangement in all 100 cells screened, and of these positive cells 80% had a variant pattern (Figure 2B). The histopathologic differential diagnosis included a submucosal HCCC and a CCOC. Given the gingival presentation in this case the possibility of infiltration of the gingival mucosa by a mandibular CCOC, which has comparable histologic, immunophenotypic and cytogenetic features could not be excluded. Unfortunately, the patient was lost to follow-up and there were no records of further management for review (Table I).

Case 3

A 44-year-old male with a history of a malignant tumor in the region of the soft palate in 1996, presented in 2020 with a painless nonhealing ulcer adjacent to an obturator in his soft palate. An incisional biopsy was taken with a clinical differential diagnosis of traumatic ulcer or recurrent tumor. A 12 mm left submandibular lymph node was seen on a CT scan, but no uptake was demonstrated on PET scan. Sonar-guided FNA of the lymph node showed reactive features with no evidence of malignancy. An excision of the mass in the soft palate was performed, with intraoperative frozen sections to assess the surgical margins, and placement of BIPP for 3-weeks thereafter. Examination of the formalin-fixed specimen confirmed the presence of a clear cell neoplasm in the palatal mucosa. The tumor was unencapsulated and infiltrative, with an arrangement of tumor cells in sheets, nests and cords surrounded by hyalinized fibro-collagenous stroma. Individual tumor cells showed distinct cell borders and lightly eosinophilic to clear cytoplasm (Figure 4A). Nuclei were round to oval with discernible nucleoli. There were scattered mucocytes, however, epidermoid cells with

Table I. Case summaries

	Case 1	*Case 2*	*Case 3*
Age/sex	60-year-old female	55-year-old female	44-year-old male
Clinical presentation	Long-standing swelling with recent rapid growth and pain.	Painful, ulcerative mass.	Painless, nonhealing ulcer.
Location	Submandibular gland	Mandibular gingiva	Palate
Histopathology	Multinodular pattern; broad anastomosing trabeculae of large, polyhedral clear cells bordering hypocellular and necrotic centers.	Clear cells arranged in compressed cords and nests diffusely infiltrated the connective tissue stroma.	Infiltrative, malignant proliferation of clear cells arranged in sheets and islands of variable size with intervening hyalinized bands.
Immunohistochemical profile	AE1/AE3+, p63+, S100+, SOX10+; CK7−, DOG1−	CK7+, CK5/6+, p63+; S100−, SOX10 (ND), DOG1−	CK7+, CK5/6+, p63+; S100−, SOX10−, DOG1−
Molecular/cytogenetic findings	Atypical *EWSR1* rearranged signal pattern.	Atypical *EWSR1* gene rearrangement.	Classic *EWSR1* gene rearrangement.
Treatment/outcome	Submandibulectomy. NED at follow-up (29 months).	Biopsy, lost to follow- up.	Wide local excision for recurrent tumor, manifesting 24 years after the initial excision.

+, positive; −, negative; CK, cytokeratin; ND, not done; NED, no evidence of disease.

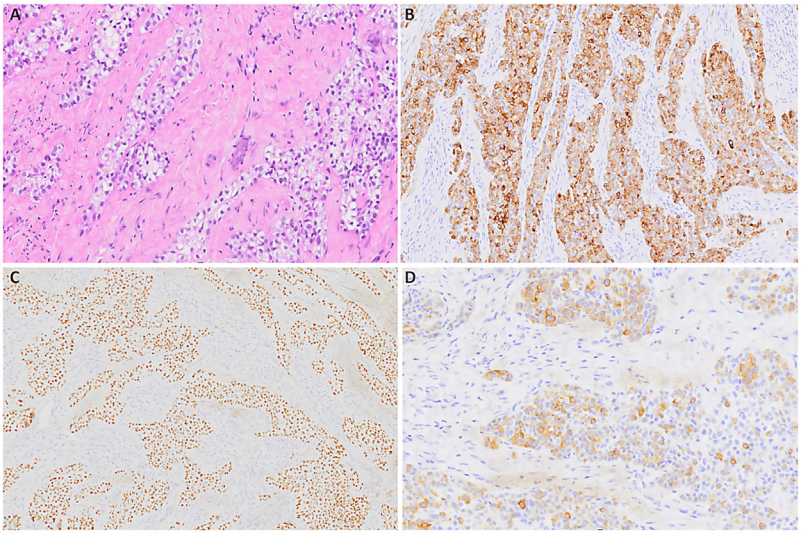


Fig. 3. (A) Hyalinizing clear cell carcinoma composed of infiltrating trabeculae of tumor cells with eosinophilic to clear cytoplasm. (B) The tumor cells are positive for CK7; p63, (C) and high molecular weight keratins CK5/6 (D). Original magnification: **A**, x 200; **B**, x 100; **C**, x 100; **D**, x 200.

abundant cytoplasm and mucous cells lining cysts were not identified. Mitotic activity was not seen and there were no features of necrosis, lymphovascular or perineural invasion. Immunohistochemically, the tumor cells expressed AE1/AE3, CK7 (Figure 4B), p63 (Figure 4C), and CK5/6 (Figure 4D). Staining for S100 protein, SOX10 and DOG1 were negative. FISH studies confirmed the presence of 22q12 (*EWSR1*) gene rearrangement in all 100 interphase nuclei that were analyzed (Figure 2C). The clinicopathologic features were considered in keeping with a recurrent HCCC. The patient is alive and without disease at 2.5-year follow-up (Table I).

DISCUSSION

EWSR1 rearrangement has thus far been described in 3 relatively rare carcinomas of the oral and maxillofacial region unified by the presence of clear cell cytomorphology. Although sharing an *EWSR1* rearrangement and clear cell phenotype there are several clinical, histopathologic, and genetic dissimilarities between CCMC and HCCC. While the oral cavity is the most common site of occurrence of HCCC, with the palate and base of the tongue accounting for most of the reported cases,[14] in several studies the parotid gland represents the most common location for both conventional MC,[11,12] and CCMC.[4] Histologically, HCCCs

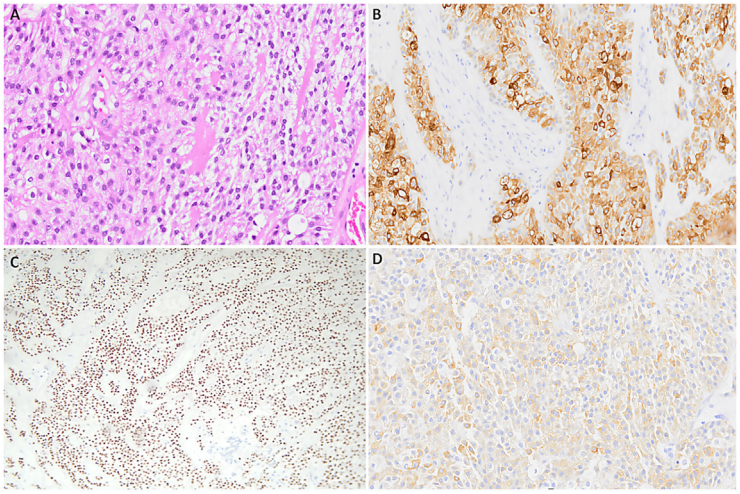


Fig. 4. (A) Recurrent hyalinizing clear cell carcinoma showing clear cells arranged in nests and separated by hyalinized bands. (B) Membranous and cytoplasmic staining for CK7. (C) The tumor cells are p63 positive and show CK5/6 expression (D). Original magnification: **A, B** and **D**, x 100; **C**, x 40.

are unencapsulated, generally poorly circumscribed and infiltrative at the margins of the tumour.[2,8] The tumor cells are arranged in sheets, cords, small nests and interconnected trabecular structures composed of cells with optically clear to pale eosinophilic cytoplasm.[2] Cellular atypia is usually mild, while mitotic activity and necrosis are rarely seen.[8,9] Hyalinization of the stroma in these tumors is as variable as the configuration of the cells which may be separated by thin fibrous septa, cellular collagenous bands, or a densely sclerotic stroma.[6] Immunohistochemically, HCCC expresses high and low molecular-weight keratins and p63, but is usually negative for S100, SOX10, SMA and calponin.[6,13,15] Genetically, most HCCC harbor a translocation involving *EWSR1* and *ATF1*.[8]

Despite the increasing frequency with which *EWSR1* dysregulation is being described in separate entities, CCMCs are rare which has resulted in few studies addressing the genetic features of this malignancy.[4,7,13] In the handful of large case series analyses on salivary gland MC that have been published to date, clear cells were infrequently encountered, either focally or rarely predominantly; with the term CCMC applied for the latter circumstance.[12,16−18] Controversies surround various aspects of salivary gland MC and the phenotypic plasticity of neoplastic myoepithelium is well known. A panel of markers demonstrating the coexpression of cytokeratin or EMA with at least 1 or 2 myoepithelial markers such as S100, SOX10, SMA, p63 CK14 or calponin is thus often required to confirm the morphologic diagnosis.[4,11,17,19] In attempt to provide characterization of the histologic subtypes of MC, we conducted a comparative clinicopathologic analysis between CCMC and nonclear cell MC arising in the salivary glands (Table II).

Current data from previous reports and our Case 1 highlights the existence of *EWSR1*-rearranged CCMC with a predilection for elderly females.[4] Skálová et al.[4] reported 25 *EWSR1* rearranged CCMCs (20 de novo and 5 MC ex-PA), all of which shared common histology showing large polyhedral tumor cells with abundant clear cytoplasm, arranged in nodules, separated by varying degrees of hyalinization and with pushing borders in most cases. While several other studies also recognize the expansile, nodular and lobulated pattern as a common characteristic of MC,[12,17] Kane and Bagwan[16] in a retrospective study of 51 cases of MC found a diffuse sheetlike growth pattern with cordlike infiltration as the predominant pattern in MC. Compared with MC of nonclear or mixed cell-type, coagulative tumor necrosis has emerged as a consistent finding in MC with clear cells.[4,20] Comparing de novo MCs versus ex-PA MCs, most CCMCs appear to arise de novo,[4] with a similar although weaker trend in nonclear cell MC.[12,16−18] There has been controversy regarding the difference in clinical outcome with respect to both the presence or absence of a PA component and tumor necrosis, however, following analysis

Table II. Clinico-pathologic comparison between *EWSR1*-rearranged clear cell myoepithelial carcinoma and nonclear cell myoepithelial carcinoma of salivary glands

	CCMC	MC
Epidemiology	Mean age at presentation of 60 years with 60% of cases in females.[4]	Wide age range, third to fifth decade usually, no sex predilection.[12,16−18]
Location	Parotid gland, followed by palate and submandibular gland.[4]	Typically occurs in the parotid gland,[12,17] slight minor salivary gland predominance in some studies.[16,18]
Histopathologic features	Multinodular growth pattern with hypercellular peripheral zone surrounding a hypocellular center and a pushing border. Composed of compact nests of clear cells divided by fibrous septa and often with prominent tumor necrosis.[4,12]	Multinodular (22%−92%),[12,16,17] or a diffuse growth pattern (8%−53%) with cord-like infiltration.[16,17] Displays a mixture of several cell types; namely spindle, plasmacytoid, epithelioid, stellate and clear cells: often with 1 dominant cell type.[12,16−18] Tumor necrosis is observed less frequently.[12,16]
Pre-existing pleomorphic adenoma (PA)	Majority are classified as de novo CCMC (80%).[4]	De novo MC is also more common than MC ex-PA (39%).[12,16−18]
Molecular profile	About one-third show *EWSR1* rearrangement,[4,7,13] accompanied by amplification of *EWSR1* locus (23%),[13] but with rare to absent fusions.[7,13] *PLAG1* fusions (33.3%) in de novo and MC ex-PA.[4,13]	*PLAG1* fusions (53%) in de novo and MC ex-PA.[7] *HMGA2* rearrangement (10%) in de novo and MC ex-PA.[7]
Clinical follow up	More frequent local recurrence (52%), nodal (24%) and distant metastasis (33%).[4] Higher risk of disease-associated mortality (38%).[4]	Reported rates of local recurrence, nodal spread, distant metastasis, and disease-related death are 38%, 18%, 23%, and 15%, respectively.[19]

CCMC, clear cell myoepithelial carcinoma; *MC*, myoepithelial carcinoma.

in a large series of cases Kong et al[17] suggested using a grading system based on the presence of tumor necrosis and a thorough search for a residual PA in the tumor to help predict clinical behavior.

At the molecular level, the frequency with which *EWSR1* rearrangement is being analyzed in histologic variants of MC of salivary glands is noteworthy, although the mechanisms responsible for the morphologic (clear cell) shift in the *EWSR1*-rearranged MC cases are not known. In some studies, *EWSR1* gene rearrangements were found to be absent in MC (de novo and MC ex-PA) of salivary glands,[8,21,22] including 3 control cases of MC with clear cells,[8] however, the cytomorphologic features were not specified in all studies.[21,22] There was neither evidence of *EWSR1* gene rearrangement in 10 spindle cell variants of MCs,[4] nor in recently reported rhabdoid and epithelioid variants of MC presenting in the maxillary sinus and tongue respectively.[23,24] Skálová et al.[4] focused on the clear cell variant of MC and detected *EWSR1* gene rearrangement in 25 of 72 (35%) "monomorphic" CCMCs. In addition, a classic FISH pattern of *EWSR1* break was accompanied by amplification of the *EWSR1* locus in 23% of cases.[13] The histologic description of the CCMC cases in the latter study are very similar to that detailed in Case 1 of this report, which further also showed an atypical *EWSR1* rearrangement pattern on FISH analysis. FISH had shown unbalanced split signals for *EWSR1* in several other *EWSR1*-rearranged neoplasms both of soft tissue,[21,25] and salivary gland including 2 of the original HCCC cases harboring *EWSR1-ATF1* fusion.[8] Owing to the proximity of the *SMARCB1* and *EWSR1* genes on chromosome 22, secondary atypical *EWSR1* FISH patterns in *SMARCB1*-deficient neoplasms often displaying rhabdoid or epithelioid morphology have been reported,[26] however, the molecular basis for this phenomenon in clear cell neoplasms of salivary gland requires further investigation.

In the study by Skálová et al.[13] the prognosis of patients with de novo CCMC and CCMC ex-PA harboring *EWSR1* rearrangement showed a trend toward worse overall survival when compared to CCMC with an intact *EWSR1* gene by FISH analysis. When tested by next-generation sequencing, however, the authors found more frequent oncogenic *PLAG1* fusions compared to *EWSR1* fusions in CCMC.[13] Similarly, data from another recent study on 40 MCs of salivary gland demonstrated *PLAG1* rearrangement in 53% of cases (de novo and MC ex-PA).[7] A recurrent *TGFBR3-PLAG1* fusion was found in 15% of tumors, while *EWSR1-ATF1* fusion was detected in 2 de novo MCs with clear cell features.[7] Taken together these findings suggest that there may exist a subset of *EWSR1*-rearranged CCMC of salivary gland with a fusion partner that is not apparent with current data or alternatively an *EWSR1* rearrangement without a productive fusion partner and where dysregulation of the *EWSR1* gene may not play a dominant role in oncogenic transformation of salivary gland myoepithelial cells.[13] Future investigations are required to gain further insight into the impact of the functional role and clinical relevance of *EWSR1* dysregulation in salivary gland CCMCs.

Despite the diverse clinical behavior of MC, increasing reports suggest a greater propensity to metastasize to distant organs rather than to regional lymph nodes.[12,17–19] By contrast HCCC is generally regarded as an indolent low-grade malignancy with an overall favorable outcome.[2,6] The optimal treatment is considered to be wide surgical excision rarely followed by adjunctive therapy.[14] Some reports suggest that delayed recurrence of disease may represent the true biologic course of HCCC,[27] with an average time to recurrence of 42.1 months.[28] This phenomenon was observed in Case 3 of this report where local recurrence manifested 24 years after the initial operation. The molecular events that underlie delayed local or regional tumor recurrence in HCCC are poorly understood as the fusion products of *EWSR1-ATF1* and *EWSR1-CREB1* are thus far considered to play a role in the initial stages of tumorigenesis by the generation of chimeric transcription factors.[29]

The identification of *EWSR1* rearrangement in HCCC currently has no prognostic value, but rather serves as a diagnostic tool to the corresponding histopathologic diagnosis.[9] The finding of the *EWSR1-ATF1* fusion in both HCCCs and a subset of CCOCs has led to the suggestion that the *EWSR1*-rearranged CCOCs are perhaps more aptly referred to as central HCCC,[3] while those cases that exhibit a soft tissue mass and involvement of the underlying bone at initial presentation may leave room for doubt regarding the exact derivation of the tumor.[10] The prognosis of CCOC is variable with most cases in the literature being reported before molecular characterization of CCOC.[30] Combined immunohistochemistry and *EWSR1* rearrangement can improve the diagnostic precision for CCOC, and as this disease entity becomes more established a clearer view of recurrence and survival rates will begin to emerge.

CONCLUSIONS

In summary, we herein described 3 rare malignant neoplasms of the oral and maxillofacial region characterized by coexpression of cytokeratin and p63, a clear cell phenotype, and *EWSR1* gene rearrangement. While most tumors that demonstrate *EWSR1* rearrangement are of uncertain lineage, those affecting the salivary glands and gnathic bones tend to show either a squamous (HCCC and CCOC) or myoepithelial (CCMC)

pattern of differentiation. Most *EWSR1*-rearranged CCMCs have been associated with worse clinical outcomes compared to other histopathologic variants of MC. Although HCCC is generally considered a low-grade tumor, the risk of delayed local recurrence warrants long-term follow up.

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DECLARATION OF INTERESTS
The authors state that there are no conflicts of interest to disclose.

CREDIT AUTHOR STATEMENT
Farzana Mahomed: Conceptualization, Writing—original draft preparation and editing, visualization. Jana de Bruin: Writing—reviewing and editing. Sizakele Ngwenya: Manuscript editing. Nikki Bouwer: Interpretation of molecular findings, visualization.

ETHICS APPROVAL
Ethics clearance certificate number: M230284.

SUPPLEMENTARY MATERIALS
Supplementary material associated with this article can be found in the online version at doi:10.1016/j.oooo.2023.11.010.

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