Case Report

Intraosseous clear cell mucoepidermoid carcinoma: A case report and evaluation

Adesh S. Manchanda, Ramandeep S. Narang, Komaldeep K. Sandhu

Department of Oral and Maxillofacial Pathology and Microbiology, Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar, Punjab, India

Abstract

Salivary gland tumours are relatively uncommon, and there exists a considerable diagnostic difficulty owing to their diverse histological features in individual lesions and the presence of a number of types and variants, in addition to overlapping histological patterns similar to those observed in different tumour entities. One such group of variations is clear cell tumours of oral cavity which constitute an assorted group of lesions that may be odontogenic or metastatic or of salivary gland origin. The clear cell variant of mucoepidermoid carcinoma is at times misleading to the clinician because of its atypical location and innocent appearance. The pathologist needs to be familiar with the molecular alterations so that there may be a strong potential to implement good treatment. Hereby, we report a rare case of intraosseous clear cell variant of mucoepidermoid carcinoma which histopathologically posed challenges due to its variable presentation, suggesting the need for histochemical stains and molecular work-up for a definitive diagnosis and a better therapeutic and prognostic insight.

Keywords: Clear cell, intraosseous, mucoepidermoid carcinoma

Address for correspondence: Dr. Ramandeep S. Narang, Department of Oral and Maxillofacial Pathology and Microbiology, Sri Guru Ram Das Institute of Dental Sciences and Research, Amritsar - 143 001, Punjab, India.
E-mail: narangraman@yahoo.com

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INTRODUCTION

Neoplasms of major and minor salivary glands are a challenge for clinicians and pathologists because they are infrequent and have a wide range of developmental, epidemiological, clinical, and histological characteristics.[1] Statistics suggest that these salivary gland neoplasms are a rare group of tumours, the annual incidence rate of which is 1 in 100,000, comprising about 3% of all head and neck neoplasms. Malignant tumours of salivary glands are infrequent and account for about 3% of all malignant neoplasms of the head and neck.[2] The neoplasm of the salivary gland usually develops in the largest of the salivary glands, the parotid glands around 75%, of which only about 20% are malignant, 15% are located in minor salivary glands of the upper digestive tract, 10% arise in the submandibular glands, and less than 1% presents in the sublingual glands.[3] The wide spectrum of histological appearance of these tumours, such as the presence of clear cells, histopathologically creates diagnostic dilemmas as well as controversies in classification of salivary gland neoplasms. Though the classification is complex, it is closely relevant to the prognostic and therapeutic aspects. Haematoxylin–eosin staining is still the gold standard method used for diagnosis; immunohistochemistry (IHC)

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can enhance the accuracy and be a helpful tool when in cases to investigate the subjects that cannot be assessed by histological examination, such as cell nature and differentiation status, cell proliferation, and tumour protein expression.[4]

The aetiology of salivary gland tumours (SGTs) is so far unknown. Putative risk factors include cigarette smoking, viral infections, genes, and so on. The only well-established risk factor is ionizing radiation. Most patients with malignant tumours of the major or minor salivary glands present with painless swelling, paraesthesia, or anaesthesia.[5]

Mucoepidermoid was first described by Masso and Berger in 1924; previously, it was termed as "mucoepidermoid tumor" and was considered to be a benign lesion and later described as a distinct pathological entity by Stewart *et al.* in 1945. World Health Organization (WHO) in 1990 classified it as a malignant neoplasm and renamed it as mucoepidermoid carcinoma (MEC).[6] Among malignant SGTs, MEC is the most frequent tumour.

MEC is a common malignant salivary gland neoplasm originating in both major and minor salivary glands. It occurs mainly in the parotid gland (89.6%), followed by the submandibular gland (8.4%). Intra-orally, it shows a strong predilection for palate.[7] It arises from the pluripotent reserve cells of the excretory ducts of salivary glands and accounts for 15% of primary carcinomas of the major and minor salivary glands. MEC occasionally has also been reported in the retromolar area, floor of the mouth, buccal mucosa, lips, tongue, lacrimal glands, bronchi, nasal mucosa, oesophagus, maxilla, mandible, liver, and so on.[8]

Some authors report that MEC is evenly distributed between sexes, but most authors report that glandular MEC is more frequent in females. The mean age at onset is in the 5th decade of life, and it is the most frequent malignant tumour in persons under 20 years of age, in whom there is a predilection for the hard palate. There is also a clear predilection for white race.[9]

MEC is caused by proliferation of secretory cells, formed by a variable proportion of mucous, epidermoid, intermediate, columnar and clear cells, often with a cystic component.[10] Clear cell neoplasm arising in the salivary gland may pose a diagnostic challenge, and several lesions including mucoepidermoid carcinoma, acinic cell carcinoma, clear cell oncocytoma, myoepithelial carcinoma, clear cell adenoma, and metastatic renal cell carcinoma should be distinguished. When clear cells predominate over other cell types, it is called as a clear cell variant of MEC. Clear cells are a rare finding in MECs, but if seen, they may occur in focal areas or may predominate large areas of the tumour, thus complicating the diagnosis.[11]

MECs are classified histologically as low-grade (48%), intermediate (13.3%), and high-grade types (38.7%) depending on the morphologic characteristics, presence of cellular atypia, number of mitotic figures, nuclear pleomorphism, perineural invasion, necrosis, and its invasive characteristics.[12] Prognosis is dependent on clinical stage, site, grading, and adequacy of surgery.

Hereby, we report a rare case of intraosseous clear cell variant of mucoepidermoid carcinoma which histopathologically posed challenges due to its variable presentation, suggesting the need for histochemical stains and molecular work-up for a definitive diagnosis and a better therapeutic and prognostic insight.

CASE REPORT

A 60-year-old female patient reported with the complaint of pain and swelling on the right side of the floor of mouth since 6 months. The swelling was sudden in onset, was small in size initially, and had gradually grown to its current size of 3 cm × 3 cm, with mild pain, which was localised, continuous, and progressive in nature. Clinically, no facial asymmetry was observed and lymph nodes were not palpable. No previous history of hospitalisation and irradiation was reported.

On intra-oral examination, it was observed that the patient was edentulous and gave a history of denture wearing since 4 years. The patient also revealed irritation due to denture wearing since past 3 months. On examination, a solitary well-defined oval-shaped swelling of size 3 cm × 3 cm, of normal colour and smooth texture, was noticed with an area of ulceration in the right side of the lingual vestibular region of the floor of mouth. The swelling extended laterally from the lingual frenum to the #44 region distally and anteriorly from the alveolar ridge to 3 cm posteriorly in the floor of mouth. The swelling was firm in consistency, tender in nature, non-fluctuant, and non-pulsatile with a mild rise in temperature.

OPG revealed a well-defined, ovoid, unilocular radiolucency on the right side of the body of mandible extending from #41 to #46 region, which portrayed a larger radiographic extent as compared to clinical evaluation. Superiorly, loss of the crestal bone was evident and the inferior border of the mandible was intact [Figure 1].

On evaluation of history, clinical, and radiographic examination, a provisional diagnosis of odontogenic cyst/tumour and a mesenchymal tumour was considered.

Histopathological examination revealed numerous oval to round cells with a clear cytoplasm and an eccentrically placed nucleus. These clear cells were present in the form of sheets, a few of which were separated by hyalinized fibrous septa [Figure 2]. A few clusters of hyperchromatic round to polygonal cells were also seen. Salivary gland acini and ducts were also present towards the periphery. Based on these findings, a diagnosis of a clear cell tumour was considered. Differential diagnosis to these findings included lesions such as minor salivary gland tumour (acinic cell carcinoma, myoepithelial carcinoma, mucoepidermoid carcinoma, salivary duct carcinoma, oncocytoma), metastatic renal cell carcinoma, clear cell odontogenic carcinoma, and the clear cell variant of calcifying epithelial odontogenic tumour.

Special staining with mucicarmine and periodic acid Schiff (PAS) was done to assess the nature of clear cells, and IHC markers were used for a confirmatory diagnosis. Although most of the clear cells were not stained for PAS or mucicarmine [Figure 3a and b], a few scattered clear cells were identified to contain mucous components and glycogen by mucicarmine and PAS, respectively, representing a rare cell cytoplasmic activity. IHC markers (CK 5 and 6, p40, p63, SMA, PCNA, bcL-2) were used for a confirmatory diagnosis. IHC showed immunopositivity for CK5 and CK6/p40/p-63/PCNA/bcL-2 and immunonegativity for SMA [Figures 4-6]. Based on these, a definitive diagnosis of the intraosseous variant of clear cell mucoepidermoid carcinoma was arrived at.

The lesion was managed surgically in accordance with treatment for malignant carcinoma. Examination of excised tissues showed similar histological features to that of pre-operative biopsy. The patient has been on regular follow-up for more than a year without any evidence of recurrence.

DISCUSSION

Primary intraosseous MEC is an uncommon lesion which was first reported and described by Leep in 1939. Waldron and Mustoe suggested that intraosseous MEC be included in the primary intraosseous carcinomas of the jaws. Pathogenesis of intraosseous MEC has been discussed extensively, and various possible origins have been considered, including (1) entrapment of the retromolar mucous glands within the mandible, which

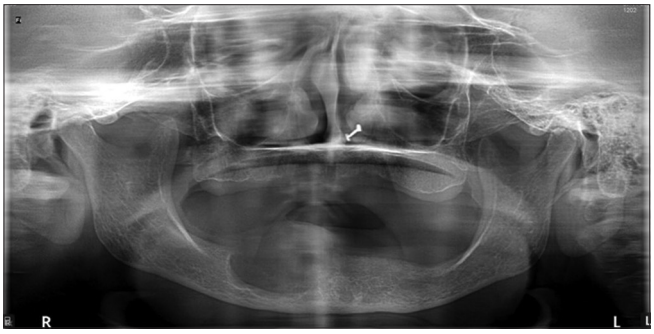

Figure 1: OPG revealed a well-defined, ovoid, unilocular radiolucency on the right side of the body of mandible extending from #41 to #46 region. Superiorly, loss of crestal bone was evident and the inferior border of the mandible was intact

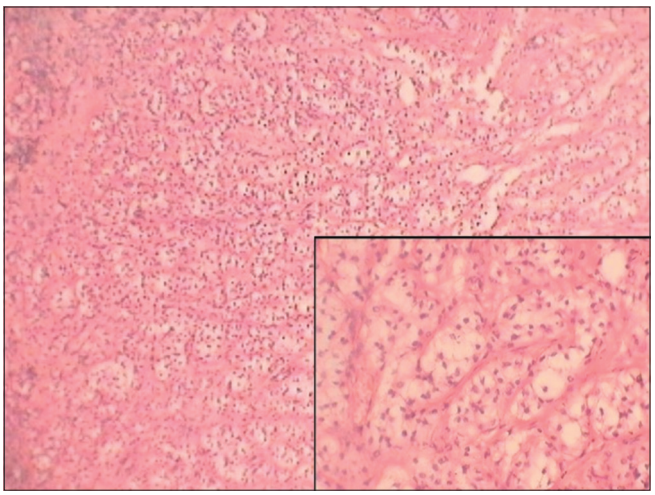

Figure 2: Histopathological examination showing numerous oval to round cells with a clear cytoplasm and an eccentrically placed nucleus. These clear cells were present in the form of sheets, a few of which were separated by hyalinized fibrous septa (H and E, ×100). The inset shows the same in H and E, ×400

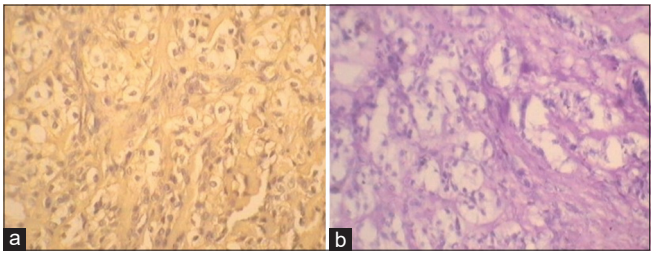

Figure 3: (a) Clear cells showing negative staining for mucicarmine (×400) and (b) PAS (×400)

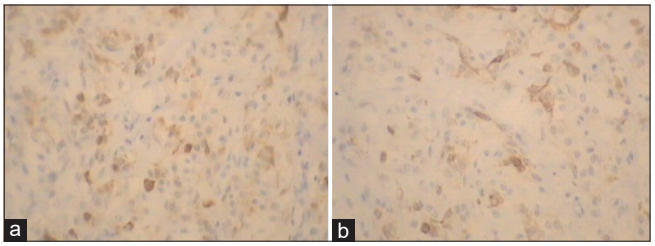

Figure 4: Immunohistochemistry showing immunoreactivity for CK 5 (a; X100) and CK6 (b; X400)

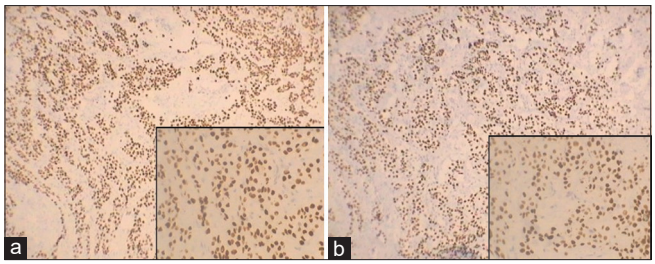

Figure 5: Immunohistochemistry showing immunoreactivity for P63 (a; X100; inset X400), P40 (b; X100; inset X400)

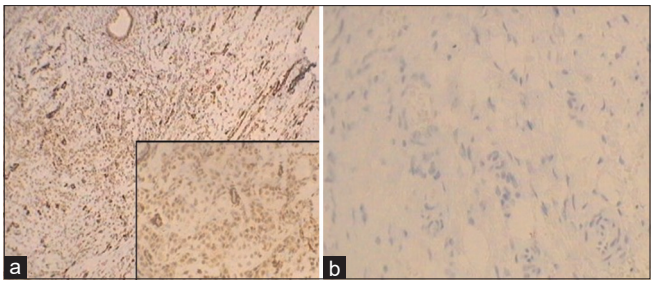

Figure 6: Immunohistochemistry showing immunoreactivity for Bcl-2 (a; X100; inset X400) and immunonegativity for SMA (b; X400)

later undergo neoplastic transformation, (2) embryonic remnants of the submandibular and sublingual glands trapped within the mandible during development, (3) neoplastic transformation and invasion from the lining of the maxillary sinus, (4) neoplastic transformation of the mucus-secreting cells from the epithelial lining of the dentigerous cyst associated with impacted third molars, and (5) neoplastic transformation of entrapped minor salivary glands within the maxilla.[13]

Diagnostic criteria for intraosseous MEC proposed by Alexander and modified by Browand and Waldron are given in Table 1.

Table 1: Diagnostic criteria for intraosseous MEC (Alexander, modified by Browand and Waldron)[14,15]

Intact cortical plate	Positive mucin staining
Radiologic evidence of bone destruction	Absence of primary lesion in the salivary gland
Histologic confirmation	Exclusion of an odontogenic tumour

Salivary gland tumours are well recognized by their wide spectrum of histological appearances. In clinical practice, the histopathological diagnosis of salivary gland tumours is made carefully through assessment of the growth pattern of tumour borders, histological architecture, cellular structure and differentiation, and components of the tumour stroma, along with the clinical information.

Clear cells, both benign and malignant, stem from a diverse group of epithelial cell types including the renal epithelium, cutaneous adnexa, salivary glands, odontogenic epithelium, melanocytes, and even mesenchymal cells which are derived from adipose and tendon sheath.

The clear cell variant of calcifying epithelial odontogenic tumour can be distinguished by a pleomorphic cellular picture having foci of calcifications and polygonal eosinophilic cell islands which are not found in MEC. Clear cells in metastatic renal cell carcinoma are positive for glycogen and lipid. A diagnosis of renal cell carcinoma can be made only by clinical evaluation of a renal primary tumour. A heterogeneous architecture and a rich dilated prominent sinusoidal vascular network and pronounced pleomorphism along with a greater amount of haemorrhage and cytological atypia should indicate the possibility of metastatic diseases like metastatic clear cell carcinoma of renal origin. However, these features were not evident in this lesion. Clear cell odontogenic carcinomas are made up of clear cells of uniform size with a delicate but well-defined cell membrane. MECs do not contain such a majority of clear cells as in clear cell odontogenic carcinoma. Intraosseous MEC should also be distinguished from cystic primary intraosseous carcinoma, where it is a squamous cell carcinoma that demonstrates a cystic component with a lumen-containing fluid or keratin and a stratified squamous epithelium showing cytological atypia.[16]

Regarding salivary gland tumours, clears cells are exhibited in pleomorphic adenoma, acinic cell carcinoma, mucoepidermoid carcinoma, myoepithelial carcinoma, adenoma, oncocytoma, and glycogen-rich squamous cell carcinoma. The clear cell variant accounts for 7.5% of mucoepidermoid carcinoma with epidermoid cells or intermediate cells suggested as the origin of clear cells using routine histological, immunohistochemical, and ultrastructural methods. Clear cells in SGT contain glycogen, epithelial mucin, mucus, lipid, or possibly fixation artifacts. It can be helpful for a definitive diagnosis to identify the contents in the clear cells by histochemical staining. The tumour containing epithelial mucin is a hallmark in obtaining a diagnosis as mucoepidermoid carcinoma. The clear cells existing only in limited areas in the tumour also contain epithelial mucin. However, a clear cell variant of the tumour is described as containing significant amounts of glycogen granules and epithelial mucin partially exists.[17] The present case exhibited only a rare cell cytoplasmic activity by mucicarmine and PAS.

Although haematoxylin–eosin (HE) staining is still the gold standard method used for diagnosing salivary gland tumour, histochemical stains and IHC can enhance the accuracy of such analysis, while its role may be limited. Various

markers have been used in an attempt at differentiating and assessing such complex salivary gland tumours as adjunct to histopathological diagnosis in general surgical pathology practice. Such markers include monoclonal antibodies to alpha-smooth muscle actin (α-SMA), smooth muscle myosin heavy chains (SMMHs), calponin, p63, Ki-67, p43, p40, c-Kit, keratin, vimentin, and S100 protein.[18] To ascertain definitive diagnosis and nature of the lesion, IHC staining in the present case showed positivity for bcl-2, PCNA, CK5, CK6, p40, and p63, while it was negative for SMA.

Cytokeratin 5/6 (CK5/6) are intermediate-sized basic keratins which are mainly expressed in keratinising (epidermis) and non-keratinising (mucosa) the squamous epithelium as well as in basal–myoepithelial cell layers of salivary glands and are also seen in benign and malignant tumours of epidermal, squamous, mucosal, and myoepithelial origins. CK 5/6 stains carcinomas from stratified epithelia and myoepithelial cells of various tissue origins; thus, it can be used as a marker for squamous cell carcinoma, myoepithelial carcinoma, basal cell carcinoma, transitional cell carcinoma, salivary gland tumours, and thymoma.[19] The present case showed CK5/6 positivity in the clear cells and the hyperchromatic cells, indicating a probability of salivary gland origin.

P63 is a member of the P53 gene family, which is involved in epithelial development, stem cell biology, and carcinogenesis and is a good myoepithelial marker for salivary gland tumours. P63 has also been reported to stain basal and myoepithelial cells of normal and neoplastic salivary gland tissues and is a useful marker to differentiate acinic cell carcinoma from mucoepidermoid carcinoma. The present case showed strong positivity for p63 staining, which ruled out clear cell variants of acinic cell and oncocytoma. Sams *et al*.[20] compared p63 expression among 31 cases of acinic cell carcinomas and 24 cases of mucoepidermoid carcinomas and found that all acinic cell carcinomas were negative for p63, while all mucoepidermoid carcinomas were strongly positive for p63. Oncocytic mucoepidermoid carcinoma can also be differentiated from oncocytoma and oncocytic carcinoma (OCC) by p63 staining patterns. It has been reported that in oncocytic mucoepidermoid carcinomas, more than 50% of the cells throughout the tumour nests were positive for p63, while only scant peripheral cells of the tumour nests in oncocytoma and oncocytic carcinoma were positive for p63. Weinreb *et al*.,[21] while comparing the positivity between OCC/oncocytoma with MEC reactivity to p63, found that in MEC, reactivity was more than 50%, while in oncocytoma/oncocytic carcinoma, it was just scanty.

Also, the stronger tendency of intermediate- and high-grade MECs to express p63 and CK 5/6 endows the immunohistochemical panel with utility in separating those cases most likely to mimic salivary duct carcinoma (SDC). In an IHC study conducted by Butler *et al*.[22] regarding differentiation of SDC with mucoepidermoid carcinoma, it was inferred that for the subset of SDCs that were incorrectly misdiagnosed as MEC, none of these tumours had more than scattered positivity with both p63 and CK 5/6. The sensitivity and specificity of p63 and CK 5/6 to identify high-grade MEC is 100%.

Protein p40 (ΔNp63), an isoform of p63, is a nuclear marker with expression in squamous, urothelial, myoepithelial/basal cell differentiation. Recent studies showed that p40 is highly specific for squamous and basal cells and has recently been proposed as a more specific marker for squamous differentiation than p63.[23] p40 is used to rule out myoepithelial carcinoma as it was not detected in either myoepithelial cells or luminal cells. p40 stains positive for oncocytoma as well as in mucoepidermoid carcinoma.

One of the most common immunohistochemical markers that characterize myoepithelial cells is smooth muscle actin (SMA). In salivary glands, α-SMA specifically recognises myoepithelial cells and does not react with the other isoforms expressed in various epithelial and non-epithelial cell types. Our case showed negativity for α-SMA, which ruled out myoepithelial carcinoma, and these findings were concurrent with the study conducted by Prasad *et al*.[24] in benign and malignant salivary gland tumours.

Bcl-2 (the B-cell lymphoma) oncoprotein is a useful marker for investigation in malignant SGTs, and its positivity in the hyperchromatic round/polygonal cells and clear cells in the present case was thought to play an important role in the antiapoptotic survival of tumour cells. Positive expression of Bcl-2 in malignant salivary gland tumours can help in predicting the behaviour of these tumours regarding their potential for aggressiveness. Namboodiripad PC[25] in a review on immunological markers for malignant SGTs concluded that there is a strong positivity for Bcl-2 in intermediate, epidermoid, and clear tumour cells of MEC.

Evaluation of PCNA expression in MEC can be used as a complementary procedure for appropriate classification of this tumour as tumours with a high grade of malignancy show a greater percentage of PCNA-positive cells than tumours with intermediate or low grade. Cardoso *et al*.[26] in their study found a significant difference in PCNA expression in high-grade MEC and intermediate- to

low-grade MECs. However, there were no differences between the intermediate and low grades. The present case showed a high positivity for PCNA, indicating towards a high grade MEC, implying a worse prognosis than low-grade tumours.

CONCLUSION

With our expanding understanding of the pathogenesis and molecular alterations in different tumour types, new targets will continue to be proposed for diagnosis, prognosis, and therapeutic applications. The pathologist needs to be familiar with the molecular alterations so that there may be strong potential to implement good treatment. Long-term follow-up is necessary as some cases suggest late local recurrences and regional metastasis or even a second primary lesion even after a decade. Despite several developments, SGTs still remain a heterogeneous group of tumours challenging both pathologists and clinicians alike.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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