CASE REPORT

Myoepithelial cell carcinoma of the oral cavity: A case report and review of literature

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ABSTRACT

Myoepithelial carcinoma (MC) is a malignant salivary gland neoplasm whose tumor cells demonstrate cytologic differentiation toward myoepithelial cells and lack ductal or acinar differentiation. It is a relatively rare tumor and many a times remains undiagnosed because of histopathological heterogeneity. It represents about 0.4–0.6% of all salivary gland tumors and 1.2–1.5% of carcinomas. It occurs predominantly in the parotid gland with a mean age of presentation being 55 years (range 14–86) with no sex predilection. MC appears to be a low grade malignancy when arising in a pleomorphic adenoma, but tends to be more aggressive and has a higher metastatic potential when arising *de novo*. The clinical behavior of MC is variable and there are no pathologic features that correlate with patients' outcome. Most tumors that display marked cytologic atypia, high mitotic activity and necrosis tend to behave aggressively. The current case is of a 42-year-old male with recurrent tumor mass in the mandibular right posterior region. The purpose of this article was to describe the clinicopathological and immunohistochemical features of intraoral MC and to discuss review of literature of this rare tumor.

Key words: Minor salivary glands, calponin, myoepithelial carcinoma

INTRODUCTION

Myoepithelial cells are an integral component of glandular epithelium present as a thin layer above the basement membrane, but generally beneath the luminal cells. Myoepitheliomas are tumors arising from myoepithelial cells lacking ductal differentiation which exhibit dual characteristics of both epithelial and smooth muscle cell. Myoepithelial tumors of the salivary gland including myoepitheliomas (benign) and myoepithelial carcinoma (MC; malignant) are a rare group of tumors. Benign myoepithelial tumors are mostly seen in extremities and head-neck region, while malignant counterparts mostly occur in the salivary gland, parotid and breast tissues.[1]

The purpose of this article was to describe the clinicopathological and immunohistochemical features of intraoral MC and to discuss review of literature of this rare tumor.

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CASE REPORT

A 42-year-old male, visited dental out patient department (OPD) with a complaint of pain and recurrent swelling in the lower jaw region since last 1 month. Past history revealed excision of swelling 3 months back, but was followed by recurrence. No histopathological report of previous excision was available. On examination, a swelling with blue black discoloration and with irregular surface was present on the alveolar ridge in place of missing 46. Swelling was soft, pedunculated, tender and measured 1 cm × 2 cm in size [Figure 1]. Clinical examination revealed no lymphadenopathy in the neck. Extraoral swelling on the right side lead to facial asymmetry and mandibular opening was normal. The patient's personal and family histories were noncontributory. The hematological tests were also within normal limits. Concurrently, patient also had multiple neurofibromas all over face and body [Figure 2].

Orthopantomogram (OPG) showed a well-defined lytic lesion in the right side of the mandible, causing erosion of the alveolar process of the mandible and the adjacent mandibular bone. The lesion extended from 45 posteriorly to the retromolar triangle. Floating tooth was noted along the superior margin of the lesion [Figure 3].

Three-dimensional computed tomography (3-D CT) of the mandible revealed a well-defined round to oval soft tissue mass measuring 6.1 cm × 5.5 cm. The mass involved the alveolar process of the mandible, retromolar region and extended buccolingually. The lesion had also caused erosion and destruction of the right mandibular canal.

With a provisional diagnosis of salivary gland tumor or odontogenic tumor, incisional biopsy was done. After the incisional biopsy, the lesion showed rapid growth, enlarging enormously in size. Within duration of 15 days; it reached up to 5 cm × 7 cm in size on the right alveolar ridge extending from 45 to 47. Swelling was bluish red in color with irregular surface, was tender and soft in consistency [Figure 4].

To rule out secondary oral involvement following a primary malignancy, esophago-gastro-duodenoscopy (EGD scopy) was done. No evidence of primary lesion was noted. Therefore, provisional diagnosis of adenocarcinoma was made.

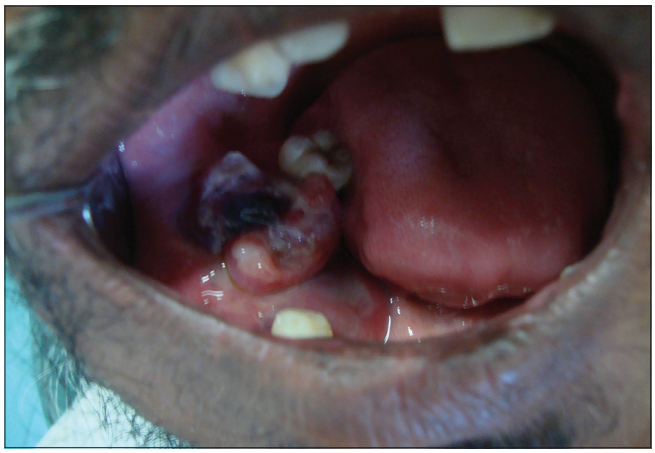

Figure 1: Soft, ulcero-proliferative growth on the lower right alveolus extending from 45 posteriorly to retromolar triangle measuring 1 x 2 cm in size.

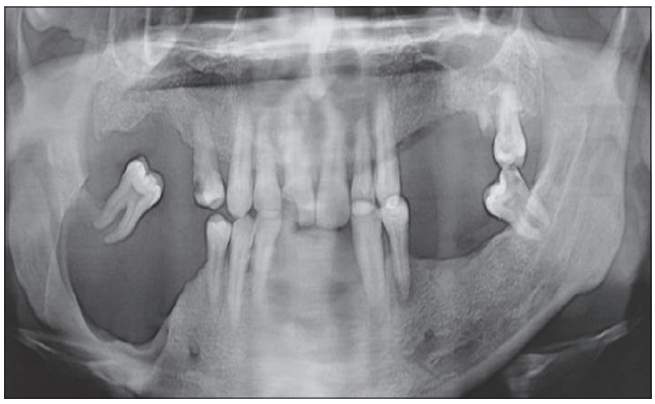

Figure 3: Orthopantomogram (OPG) showing a well-defined lytic lesion causing erosion of the alveolar process and mandibular bone. Floating tooth was also noted along the superior margin of the lesion

Histopathology

On gross appearance the tumor showed nonencapsulated, lobulated neoplasm with an off-white coarser surface without any cystic changes [Figure 5].

The tumor was predominantly cellular composed of solid sheets of cells. Lack of capsule and tumor infiltration into the adjacent tissue in the form of chords and strands could be appreciated [Figure 6]. The cells were arranged in cords, sheets and trabaculae and were separated by abundant pink, acellular and eosinophilic basement membrane-like material. Tumor cells were oval to elongated in shape, with high nuclear-cytoplasmic (N/C) ratio, vesicular nuclei and moderate amount of clear cytoplasm. Predominantly tumor cells exhibited plasmacytoid morphology. Anisonucleosis, with irregular nuclear border with increased mitotic activity of more than 3–5 per high power field was noted. In few

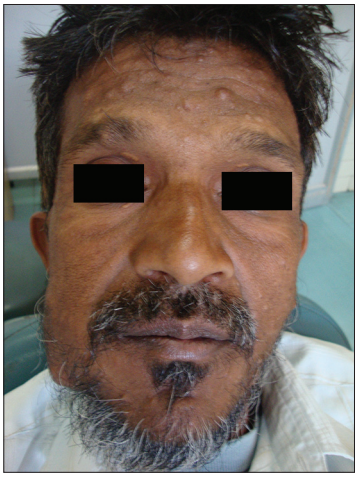

Figure 2: Extra-oral swelling present on the right side of face along with multiple neurofibromas on the face

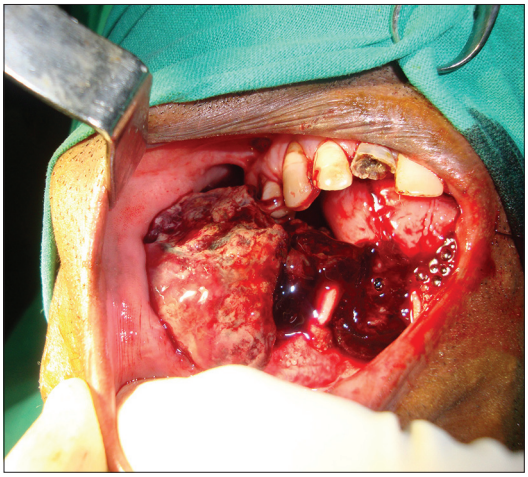

Figure 4: Rapid growth of lesion enlarging enormously after incisional biopsy

areas focal mononuclear cells are noted along with dilated and congested blood vessels [Figures 7 and 8].

Tumor cells were immunoreactive to S-100 [Figure 9], cytokeratins (CK) 5/6 [Figure 10] and CK19 [Figure 11] and calponin [Figure 12]; but epithelial membrane antigen (EMA) and p63 were negative.

Based on the above-mentioned findings, diagnosis of MC was made and patient underwent radical resection of the tumor with wide surgical margins. The postoperative histopathological diagnosis was consistent with the incisional biopsy results. One of the sections from enlarged lymph node showed subcapsular tumor infiltrates.

Hence, final diagnosis of MC locally invading and metastasizing into regional lymph nodes was made.

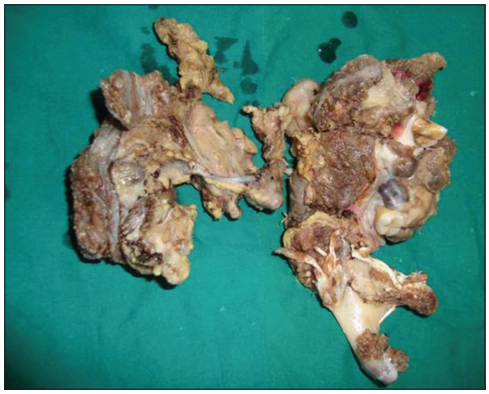

Figure 5: Excised specimen on grossing shows nonencapsulated, lobulated neoplasm with an off-white coarser surface without any cystic changes

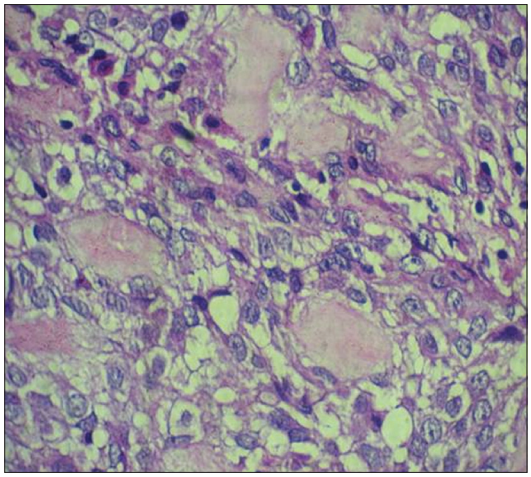

Figure 7: Photomicrograph showing the tumor cells arranged in cords, sheets and trabaculae and were separated by abundant pink, acellular and eosinophilic basement membrane-like material. Predominantly tumor cells exhibited plasmacytoid morphology. Tumor cells were oval to elongated in shape, with high nuclear-cytoplasmic (N/C) ratio, vesicular nuclei and moderate amount of clear cytoplasm. Anisonucleosis, with irregular nuclear border with increased mitotic activity of more than 3–5 per high power field was noted (H&E stain, x400)

Patient was called for regular follow-up. The lesion recurred after 8 months. Patient was not interested in any further treatment. Patient died after nearly 8 months of follow-up.

DISCUSSION

Myoepithelial cells were first described by Zimmerman in 1898. Most investigators believe it to be ectodermal in origin and are epithelial in nature. They envelop the glandular, acinar and ductal elements of various organs like breast, salivary glands and lacrimal glands. In salivary glands, the myoepithelial cells that surround the intercalated ducts are spindled in contrast to the large stellate ones that envelop the acini. Role of myoepithelial cells in various salivary gland tumors have been well-documented.[2,3]

MC also known as malignant myoepithelioma is defined as a malignant salivary neoplasm composed almost exclusively

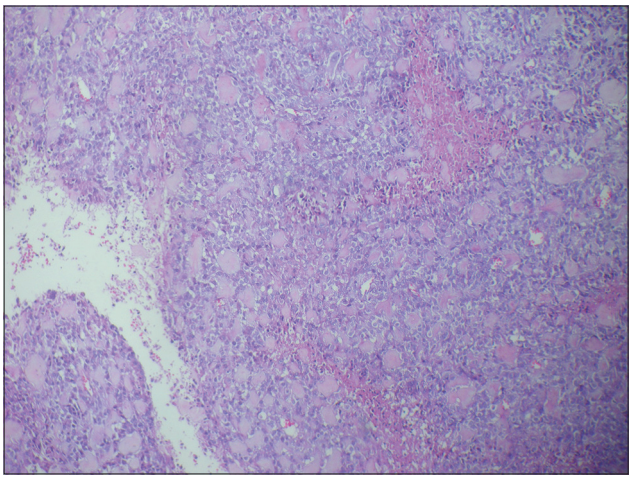

Figure 6: The tumor was predominantly cellular composed of solid sheets of cells and lack of capsule. (H&E stain, x40)

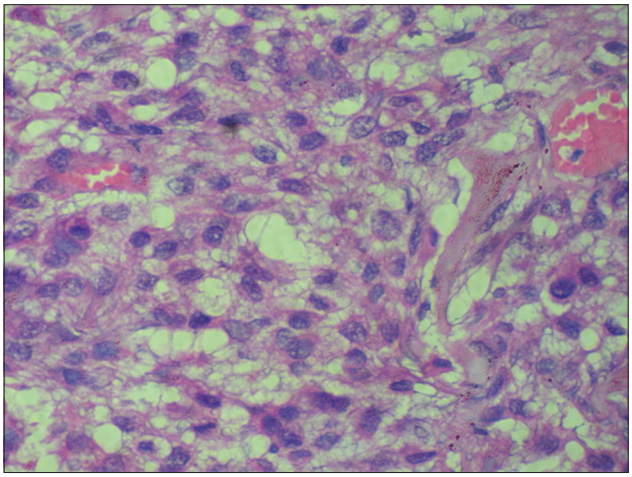

Figure 8: Photomicrograph shows tumor cells exhibiting predominantly plasmacytoid morphology. Tumor cells were oval to elongated in shape, with high nuclear-cytoplasmic (N/C) ratio, vesicular nuclei and moderate amount of clear cytoplasm. Anisonucleosis, with irregular nuclear border was seen. (H&E stain, x400)

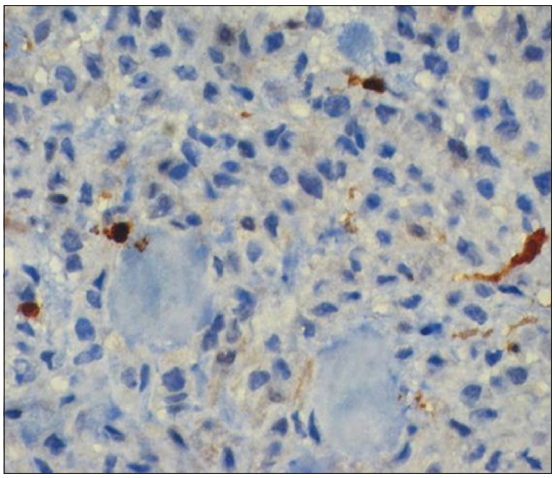

Figure 9: Few tumor cells showing – positivity to S-100 protein. (IHC stain, x400)

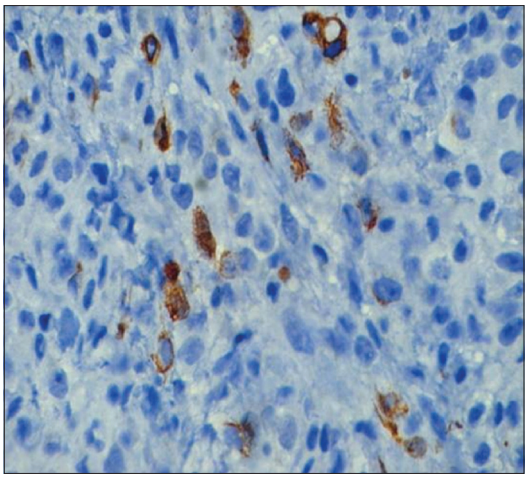

Figure 10: The tumor shows cytoplasmic positivity to CK 5/6. (IHC stain, x400)

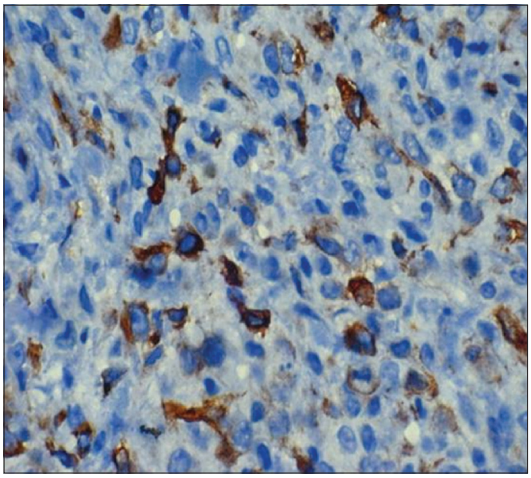

Figure 11: The tumor cells showing positivity to CK 19. (IHC stain, x400)

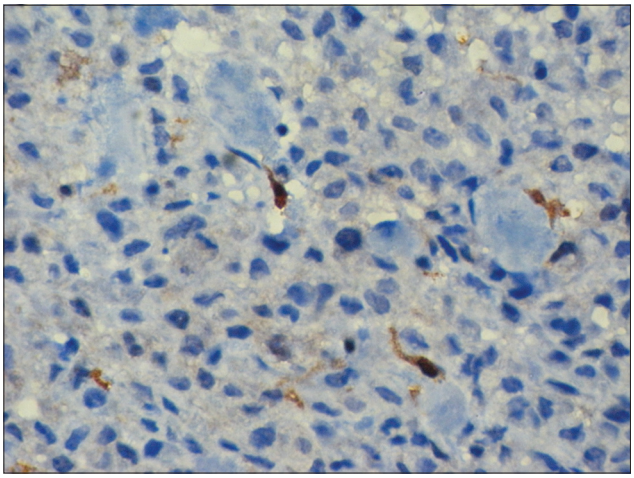

Figure 12: Focal tumor cells showing positivity for calponin. (IHC stain, x400)

of tumor cells with myoepithelial differentiation.[4] It is a relatively rare tumor, representing about 0.4–0.6% of all salivary gland tumors and 1.2–1.5% of carcinomas in recently reported large series.[5,6] It was first described by Stromeyer *et al*., in 1975 and has been included in World Health Organization (WHO) classification of salivary gland tumors since 1991.[7] The average age of patients at presentation is about 55 years (range 14–86) and the sex incidence is approximately equal. Parotid is the most common affected site, but may also affect submandibular and minor salivary glands; whereas in a series reported by Kane *et al*., minor salivary gland involvement was noted in 71% of cases; whereas, 29% of cases had major salivary gland involvement.[8] Intraorally, palate was the most frequent site of involvement followed by tongue, vestibular sulcus, retromolar region, floor of mouth, cheek and maxilla. The most common associated complaint was presence of swelling associated with surface ulceration, pain or bleeding.[9] MC may occur *de novo*, but a half or more develop in preexisting pleomorphic adenomas or benign myoepitheliomas. MC arising within a preexisting benign tumor should be suspected if there is a long history of benign parotid tumor with history of rapid growth and/or multiple recurrences in a preexisting pleomorphic adenoma with or without lymphnode metastasis. MC appears to be a low-grade malignancy when arising in a pleomorphic adenoma, but tends to be more aggressive and has a higher metastatic potential when arising *de novo*.[10]

The currently accepted diagnostic histopathological criteria for MC are exclusive or predominantly myoepithelial differentiation (both morphologic and immunohistochemical) and features of malignancy-like nuclear atypia, high mitotic rate, tumor necrosis and infiltration into adjacent tissues. Besides, the neoplastic cells must also lack ductal or acinar differentiation.[3]

Tumor cells showed various growth patterns like diffuse sheet like arrangement, multinodular, cord-like pattern separated by abundant stroma and focal areas with cribriform pattern.

Histopathological heterogenicity is a unique feature of myoepithelial cell. Different morphologic variations of tumor cells reported in order of occurrence are epitheloid, plasmacytoid, spindle, clear, stellate and mixed type.

- Epitheloid - Most predominant cells, polygonal cells, central nuclei, coarse chromatin, prominent nucleoli and pale eosinophilic cytoplasm. These cells have ill-defined cell borders and are loosely cohesive
- Plasmacytoid- Cells resembling plasma cells with hyaline stroma in varying amounts
- Spindle - Spindle-shaped cells with centrally placed elongated nuclei. Cells arranged in interlacing fascicular arrangement
- Stellate - Ovoid to short spindly with centrally placed nuclei, moderate amount of cytoplasm and indistinct cell borders. Cells arranged in sheets
- Mixed -Second most common pattern, combination of two or more cell types.

All these cell types represent different stages of myoepithelial cell differentiation.[1,8,10]

Metaplastic changes are frequent and may show squamous, chondroid or sebaceous differentiation and these cells merge with the surrounding neoplastic cells.

Mitotic figures may be scanty to plentiful and atypical mitotic figures can also be seen. Occasional presence of multinucleated and bizarre tumor giant cells can also be appreciated.[1,8,10] According to Nagao *et al*., assessment of cell proliferation activity can be used to differentiate between benign and malignant myoepitheliomas. More than seven mitotic figures/10 high power field (HPF) and/or Ki-67 labeling index >10% favors the diagnosis of MC.[11]

A universal feature of a malignant tumor is their ability to degrade the extracellular matrices. Paradoxically neoplastic myoepithelial cell augment and modify their matrix producing ability. Recent biochemical studies have shown that these tumors synthesize both basement membrane, that is, type IV collagen, laminin, fibronectin and types I and II collagen (eosinophilic appearance) and non-basement membrane components, that is, predominantly chondroitin sulfate proteoglycans (bluish grey appearance, but the latter predominates and leads to large accumulations of extracellular matrix so characteristic of this tumors. Thus, the myxoid matrix present in majority of cases reported is an invaluable clue to myoepithelial differentiation and can certainly help in confirming the diagnosis of MC.[2] Stroma is generally absent in tumors with spindle cell pattern.[8]

Tumors arising from parotid showed partial or complete encapsulation. Tumors of minor salivary gland are unencapsulated. Infiltration through the capsule into adjacent muscle or adipose tissue was noted. The tumor showed infiltration in cord-like, nodular and fascicular pattern. Few of the cases showed perineural invasion.[8]

Currently benign and malignant myoepithelioma are differentiated by cellular atypia, increased mitotic count, presence of invasive growth and tumor necrosis or their combination.[2] According to Khademi *et al*., preoperative cytological criteria for preoperative diagnosis of salivary gland myoepithelial neoplasm remained unsatisfactory and needs to be clarified.[12]

Ultrastructure

As noted by Sciubba *et al*., the character of the intermediate filaments with dense bodies within the cytoplasm of myoepithelial cells indicates anatomic comparability to actin filaments of skeletal and smooth muscles. Myoepithelial cells also contain well-formed macula adherens or desmosomes and extracellular basement membrane material.[13]

Chromosomal alterations

According to Hedy *et al.*, there are differential genomic alterations between benign and malignant myoepitheliomas of salivary gland. The recurrent gains of large genomic regions distinguish MC from their benign counterparts.[14] Inactivation of p53 protein, perhaps through mutational events, may have played an important role in the development of MC.[15]

Immunohistochemistry

Current immunohistochemical criteria for the confirmation of myoepithelial differentiation are double positivity for both cytokeratins (pan CK or preferentially basal type CK) and one or more myoepithelial markers like S-100, calponin, P63, glial fibrillary acidic protein (GFAP), maspin and actins. These tumors consistently express cytokeratin, epithelial membrane antigen (EMA), vimentin, S-100 protein and calponin. Markers like EMA, GFAP and a variety of other myogenic markers are not always positively expressed in the tumor cells and that negative staining does not necessarily exclude myoepithelial differentiation.[1,2,8-10] Prasad *et al*., in their studies confirm that α-smooth muscle actin (SMA), smooth muscle myosin heavy chain (SMMH) and calponin are specific myoepithelial markers in salivary gland tumors.[16] These antibodies are a valuable diagnostic aid in the differential diagnosis of polymorphous low grade adenocarcinoma, adenoid cystic carcinoma and pleomorphic adenoma particularly in cases where small incisional biopsy are involved and specimens that do not entirely represent the diverse morphologic patterns.

Differential diagnosis of MC includes a wide range of tumors both benign and malignant, depending on the predominant cell type.[2]

Epitheloid

Adenoid cystic carcinoma, adenocarcinoma not otherwise specified (NOS), polymorphous low-grade adenicarcinoma (PLGA), basaloid squamous cell carcinoma.

Spindle

Hemangiopericytoma, schwannoma, fibrosarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumor (MPNST).

Hyaline

Plasmacytoma, malignant melanoma, large cell lymphoma.

Clear

Epithelial myoepithelial carcinoma, hyalinizing clear cell carcinoma, mucoepidermoid carcinoma, oncocytoma, sebaceous carcinoma and metastatic renal cell carcinoma.

Thus, knowledge of diverse histopathological findings, cytokeratin positivity together with one or more myoepithelial markers or ultrastructural confirmation is deemed to make a diagnosis of malignant myoepithelioma.

Treatment and prognosis

Complete excision is the treatment of choice for myoepitheliomas.[2] Complete excision with tumor free margins with or without nodal dissection is the treatment of choice.[2,11] Local radiation therapy and chemotherapy are also needed for treating MC.[1]

Prognosis of MC is variable, approximately one-third of patients die of disease, another third have residual tumor and remaining third are disease free. Metastasis if occurs is generally seen in regional lymph nodes and at distant sites include lungs, kidney, brain and bones.[17]

CONCLUSION

Current case report and review of literature indicates that MC of intraoral minor salivary glands is generally a low grade malignancy with little propensity for regional or distant metastasis and low recurrence. But our current case showed highly aggressive tumor with regional metastasis into the lymphnodes. Patient died within 8 months of follow-up after the excision. This report discusses the concept, clinicopathological features, histopathology, immunohistochemistry, ultrastructure, genetic changes, treatment modalities and prognosis of MC. The authors suggest that a detailed knowledge of clinicopathologic and immunohistochemical findings of this lesion is mandatory for accurate diagnosis and treatment.

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