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Case Report

Mammary Analogue Secretory Carcinoma of the Buccal Mucosa: Case Report and Review of the Literature

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Abstract

Mammary analogue secretory carcinoma of salivary gland (MASC) is a recently described tumor, with small number of published cases. Less than three hundred cases have been reported in the literature and only very few of them of these cases have been reported in minor salivary glands. We present a case of a 71-years old male who was diagnosed with MASC tumor presenting in a minor salivary gland and briefly review of literature. My provisional diagnosis after careful histopathological examination of the tumor sections was either Acinic cell carcinoma or mammary analogue of secretory carcinoma of salivary gland. The final diagnosis of MASC was considered after immunohistochemical staining of tumor section with DOG-1 and mammaglobin. The gold standard for MASC diagnosis is cytogenetics, with the majority having a translocation t (12;15)(p133;q25). Although the tumor may present with different histological grading, the treatment plan could be modified in some selected cases according to the grade of the tumor.

Keywords: DOG-1; Mammary Analogue Secretory Carcinoma (MASC); Salivary Gland

Introduction

Mammary analogue secretory carcinoma (MASC) is a rare neoplasm in salivary gland that was first documented in literature by Skalova., *et al*. [1]. After that some cases of salivary gland tumors were reexamined and were found to have similar histological features as breast secretory carcinoma. Breast secretory carcinoma is a slow-growing, which is a subtype of infiltrating ductal carcinoma of the breast. It occurs primarily in young women [2].

Secretory carcinoma of the breast and MASC are associated with translocation t(12;15)(p13;q25), which is a fusion of the *ETV6* gene on chromosome 12 and the NTRK3 gene on chromosome 15. This fused gene encodes a chimeric tyrosine kinase, which plays a role in carcinogenesis as it has potential transformation activity [3]. This fusion couldn't be diagnostic for MASC as it could be also found in other tumors as acute myeloid leukemia, and congenital mesoblastic nephroma [4]. This molecular aberration can be detected by FISH using a break-apart probe for the *ETV6* gene or by reverse transcription– polymerase chain reaction using *ETV6* and NTRK3 gene-specific primers. In the context of salivary gland neoplasia, this translocation is specific for MASC. this mutation could be considered as the gold standard to reach the diagnosis of MASC [5]. Thus we usually depend mainly on immunohistochemistry to aid in reaching the final diagnosis of the cases.

Most of MASC tumors were reported in the literature as cases that were rediagnosed when they were secondarily reviewed. Old studies revealed that prior to its recognition; MASC was frequently diagnosed as a variety of other salivary gland tumors, most commonly zymogen-poor Acinic cell carcinoma and adenocarcinoma, not otherwise specified (NOS) [6].

On the other hand some of the reported cases of MASC not demonstrating *ETV6-NTRK3* fusion gene but were finally diagnosed as MASC based on the immunohistochemistry findings. According to Khurram., *et al*. immunohistochemistry can accurately diagnose MASC tumors [7]. Updating the immunohistochemical panel for the

diagnosis of MASC could potentially completely reduce the cytogenetic need in diagnosing MASC tumor [8].

Differentiation of MASC from other salivary gland tumors is aided by histological features and immunohistochemistry. The perineural invasion or lymphovascular invasion are rarely seen in MASC and also the necrostic areas are not typical [8]. MASC shows immunoreactivity for S100 and mammaglobin (70% of the time) [9] which are usually negative in acinic cell carcinoma. DOG-1 is predominantly negative in MASC but usually positive in acinic cell carcinoma. MASC of the salivary glands is a lipid-rich tumor, and adipophilin can be valuable in its identification [10].

Mammary analogue secretory carcinoma usually occurs in adults but afflicts patients across a wide age range between (13–77) years with slightly sex predilection in males. Cases of MASC affecting. Pediatric patients have also been described [11]. Most patients present with a Slow-growing, painless mass with a size of about 2 cm and with a known duration varying from 2 months to several years. Examples presenting with pain and facial paralysis have been described [12].

Seventy percent of MASC tumors are found in the major salivary glands, predominantly the parotid. Less than a quarter of the cases arise from minor salivary glands commonly of the palate [3]. Thirteen cases of MASC on the hard palate and six on the soft palate have been reported in the literature worldwide to date [13].

We present a case of a MASC tumor presenting in the minor salivary gland in the buccal mucosa. To our knowledge, this is one of the very few case reports of MASC in minor salivary gland of the buccal or labial mucosa, which was diagnosed by immunohistochemistry from an incisional biopsy and prospectively treated as a MASC tumor.

Case Presentation

A 71-years old male presented to the oral and maxillofacial surgery department in faculty of dentistry, Cairo University with a painless swelling in the right cheek (Figure 1). He elected to have the lesion evaluated due to its increase in size through few weeks ago. He reported no other symptoms.

His past medical history was free from any significant disease. He was not taking any medications, and he has no known drug allergies. He was heavy smoker for 15 years and stopped smoking for almost 20 years ago.

Figure 1

On clinical examination, it was noted that the patient had a firm, raised lesion in the right cheek with a central bluish spot located in the center of the lesion. The lesion was roughly 2.0 cm × 3.0 cm in size (Figure 2). There was no palpable lymphadenopathy on head and neck examination. The lesion was negative dental panoramic examination.

Figure 2

An incisional biopsy was performed and sent for pathology in formalin jar. The macroscopic examination of the biopsy revealed reddish white one piece specimen with dimension 1x2cm and it was firm in consistency and it was solid in cross section.

Depending on the patient history, clinical examination and radiographic examination, we could consider the clinical differential diagnosis of this case will be as malignant neoplasm due to large and rapidly increase in size swelling with short duration , mucoepidermoid carcinoma, Acinic cell carcinoma, polymorphus low grade adenocarcinoma, mammary analogue of secretory carcinoma, salivary duct carcinoma.

On hematoxylin and eosin stain, the tumor comprised of cells arranged in variable patterns as microcystic pattern, papillary pattern (Figure 4), organoid pattern (Figure 5) and glandular spaces which containing Intraluminal or intracellular colloid-like material with a "bubbly" appearance could be observed on low power (Figure 3).The tumor cells had eosinophilic granular cytoplasm with low-grade vesicular nuclei and visible (Figure 6 and 7). Nuclear pleomorphism could be detected in some cells (Figure 7). Mucous cells with vacuolated cytoplasm and scattered inflammatory cells were also found (Figure 8). A front pattern of tumor invasion to surrounding acini was also noted (Figure 3).

Figure 3

Figure 4

Figure 5

Figure 6

Figure 7

Figure 8

In Accordance with the schematic diagram for granular cell lesions in the oral cavity (Figure 9), I could consider Acinic cell carcinoma and MASC as provisional diagnosis for this case which need immunohistochemical markers as DOG-1 and mammaglobin to reach the final diagnosis (Table 1).

Acinic Cell Carcinoma	Mammary Analogue of Secretory Carcinoma
Cells have basophillic granular cytoplasm and eccentric nuclei	Cells have eosinophillic granular cytoplasm and eccentric nuclei
Different patterns of tumor	Different patterns of tumor
Positive Dog-1/	Positive mammaglobin
Negative mammaglobin	Negative Dog-1

Table 1

Figure 9

Histological examination of immunohistochemical sections revealed positive immune-expression of mammaglobin (Figure 10) and negative immune-expression of DOG-1 (Figure 11). Thus our final diagnosis is confirmed as mammary analogue of secretory carcinoma.

After considering this case as low grade MASC according to histological examination so, the treatment consisted of wide local excision of the lesion with 1 cm margins and follow up of the case was recommended to detect any local recurrence or distant metastasis.

Figure 10

Figure 11

Discussion

The exact incidence of MASC is unknown. It is reported that MASC accounts for <0.3% of all salivary gland tumors [14]. MASC involves minor salivary gland in approximately less than 25% of cases at sites including the palate, buccal mucosa, base of the tongue, and lips [11]. One case also has been reported as MASC in a lymph node with unknown primary origin. In the most recent update, there have been a total of 281 MASC cases reported in the literature, and 69 cases of MASC reported in minor salivary glands [13].

Most of the cases arise in adult age patients with average age between 50 -60 years. The tumor is very rare in children and adolescents, but only few cases have been reported [15]. MASC has been documented to have a slight male predilection with no racial predisposition [9].

The disease typically follows an indolent course. The most common presentation is a slowly enlarging and painless nodule, often detected incidentally on physical examination. There has been a report of one patient with facial paralysis from a MASC tumor in parotid gland [11].

In the current case, Low-grade salivary duct carcinoma should be considered in my differential diagnosis of this case [16]. It is also known as low-grade cribriform cystadenocarcinoma, displays intraductal proliferations of low-grade ductal cells forming anastomosing micropapillae along with cribriform and occasional solid patterns analogous to atypical ductal hyperplasia. This rare salivary gland tumor can be distinguished from MASC at low-power examination by its predominantly intraductal location. Limited extraductal invasion can, however, be seen in low grade salivary duct carcinoma [16].

Immunohistochemistry will not allow distinction between MASC and low grade salivary duct carcinoma as the later also shows strong and diffuse expression of S100 protein and mammaglobin [17]. Low-grade salivary duct carcinoma is exclusively a tumor of major salivary glands, typically the parotid, whereas MASC may also affect minor salivary gland sites. In quarry cases, the molecular studies may be useful, because no cases of low grade salivary duct carcinoma has ever been discovered to harbor the *ETV6* gene rearrangement [3].

Mucoepidermoid carcinoma, with its different population of cells as intermediate, epidermoid, and mucin-containing cells, is usually not difficult to distinguish from MASC. However, given that MASC can show mucicarmine-positive cytoplasmic mucin and focally show nuclear *p63* expression macrocystic examples of MASC may on occasion similar to cystic low-grade MEC.

Presence of at least focal epidermoid cells, more diffuse nuclear expression of p63, and negativeS100 protein expression should allow diagnosis of mucoepidermoid carcinoma [18].

In especially difficult cases identifying a *CRTC1-MAML2* fusion would be diagnostic of mucoepidermoid carcinoma [19].

Although the low-power gray-blue tumor hue of polymorphous low-grade adenocarcinoma as a result of the tumor's mucohyaline matrix and the neoplastic cell's vesicular chromatin, usually allows for the quick elimination of MASC [20] but the polymorphus low grade adeno carcinoma may co-expresses S100 protein and mammaglobin and usually occurs in minor salivary gland sites, and therefore it could easily enter into a differential diagnosis with MASC, especially on small biopsy specimens [21]. However, the lack of bubbly pink cytoplasm and frequent cordlike and whirling growth patterns of polymorphus adenocarcinoma, among other patterns, should allow its differentiation from MASC. *ETV6* gene rearrangement study may be necessary in difficult small biopsy specimens, because the *ETV6* gene is intact in polymorphus low grade adenocarcinoma [20]. In the differential diagnosis is polymorphus low grad adenocarcinoma versus MASC, the parotid location would favor MASC because parotid PLGA is extremely rare to occur in parotid gland [21].

Acinic Cell Carcinoma can be considered in my provisional diagnosis after immunohistochemical staining by DOG-1 and mammaglobin for this case. As the acinic cell carcinoma shows overlapping architectural features with MASC [1] but it differs from MASC as acinic cell carcinoma shows basophilic granular cytoplasm as containing zymogen granules. Also it shows more cytologic diversity than MASC, because serous acinar, intercalated duct–like, clear and vacuolated cells can be seen in it [18]. It should be noted that zymogen-poor and intercalated duct–rich examples of Acinic cell carcinoma exist, and it is these cases that pose the biggest diagnostic challenge with MASC. However, these cases will be negative for S100 protein and mammaglobin, unlike MASC. Conversely, strong and diffuse S100 protein and mammaglobin expression will strongly exclude Acinic cell carcinoma [18]. Further, DOG1 typically shows strong cytoplasmic immuno- expression in acinic cell carcinoma, a pattern not seen in MASC (Table 1). On the hand of molecular studies there is no case of acinic cell carcinoma has been found to harbor the *ETV6* gene [1]. Bishop., *et al*. reported that approximately 80% of extra parotid Acinic cell carcinoma needed to be reclassified as MASC on the basis of an *ETV6* translocation together with strong staining for S100 and mammaglobin [4].

So final taking in consideration that in this case the presence of microcystic, papillary and organoid tumor patterns and areas with abundant vacuolated colloid-like PAS-positive secretory material within the microcystic spaces, the tumor cells have eosinophillic granular cytoplasm and vesicular nuclei with a distinctive centrally located small nucleolus. In addition, the lack of perineural invasion, and the diffuse pattern of staining seen with mammaglobin were further features which confirming the diagnosis of MASC.

Usually if histologic, immunophenotypic, and molecular analyses of a difficult salivary gland neoplasm fail to reach final diagnosis, then a diagnosis of adenocarcinoma, NOS, ultimately a diagnosis by exclusion [18].

Griffith., *et al*. prospectively diagnosed a case of MASC based on cytogenetic study of a parotid mass fine needle aspiration (FNA), which was subsequently confirmed on final pathology [22]. The use of FNA in the diagnosis of MASC is still of questionable value [23]. Takeda., *et al*. [24] state that MASC cannot be diagnosed only from cytology alone. The histologic findings of MASC can include solid, microcystic, tubular, and papillary-cystic patterns in varying proportions [24].

There is no data available in literature showing a difference in clinical behavior or rates of regional metastasis between MASC in minor and major salivary glands. MASC may metastasize to regional lymph nodes. In one study, the rates of lymph node metastasis for MASC and acinic cell carcinoma were 17.6% (6/34) and 7.9% (3/38), respectively, with a mean disease-free survival, including death and recurrence, for MASC and Acinic cell carcinoma being 92 and 121 months, respectively [5]. Although limited in numbers, other studies have explored treatment outcomes and prognosis of both tumors and finally concluded they can be treated similarly [25].

According to The treatment of MASC in previous cases, the neck dissection is presently a surgeon preference based on clinical, radiological, and histological parameters. Sethi., *et al*. [11] reviewed 86 patients with MASC and reported 21 patients underwent neck dissections, 17 patients received postoperative radiotherapy and 2 patients received postoperative radiotherapy and chemotherapy. No reported cases of patients who had received radiotherapy without prior surgical resection [11]. One previous study done at the University of Pittsburg has reported that 4 out of 18 patients had nodal involvement were treated with neck dissections [25].

MASC usually has an overall favorable prognosis; however, high-grade transformation has been described which results in a more clinically aggressive tumor [14].

MASC tumors with necrotic areas tend to show poor prognosis and denoting high grade transformation [5].

Conclusion

We encountered a MASC tumor presenting in the region of buccal mucosa. Considering salivary gland neoplasms as Acinic cell carcinoma, mucoepidermoid carcinoma and low grade salivary duct carcinoma in my differential diagnosis. Finally my provisional diagnosis is either Acinic cell carcinoma or MASC, so immunohistochemical analysis for mammaglobin and DOG-1 stain is recommended to reach the final diagnosis.The diagnosis in this case was based on the morphology with supporting mammaglobin immuno-positive reaction and negativity to DOG-1 immunohistochemical staining suggesting MASC as final diagnosis. Due to the histopathological findings, absence of unusual morphology, and the immunohistochemical profile, the financial burden associated with cytogenetic analysis to diagnose MASC was determined to be un-

necessary. The tumor was treated by completely excision with 1 cm safety margin. No local recurrence or metastatic disease has been detected during a follow-up period of 12 months for treatment.

Conflict of Interest

The author declared that there is no conflict of interest.

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Ethical Statement

I further confirm that any aspect of the work covered in this manuscript that has involved human patient has been conducted with the ethical approval of all relevant bodies.

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