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Clinical evaluation of high grade myoepithelial carcinoma of the maxillary sinus in patients in ANMMCH, Gaya, Bihar

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Abstract

Myoepithelial carcinoma (MC) and myoepithelioma can be considered as doppelgangers, as they are difficult to distinguish due to diverse morphology and MC have infavorable outcome. Published reports suggest that MC comprise of <2% of all salivary gland carcinomas involving parotid gland most commonly. Other sites involved are palate, maxilla, nasopharynx, liver, vulva and vagina. However, this may be just a tip of the iceberg as due to increased recognition of this tumor, its incidence may be changed and may vary depending on demography. In fact, it is now believed that this tumor is the second-most common salivary gland malignancy arising from the benign adenomas. It may also arise de novo. An accurate diagnosis for MC relies on exclusive myoepithelial differentiation (morphologic and immunohistochemical [IHC]) and clear-cut tumor infiltration into adjacent salivary gland or other tissues. Bases on above findings the present study was planned for clinical evaluation of high grade myoepithelial carcinoma of the maxillary sinus in patients admitted to ANMMCH, Gaya.

The present study was planned in Department of Dentistry, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar. Total 15 cases of the myoepithelial carcinoma of the maxillary sinus were enrolled in the present study. The cases were histo pathologically confirmed cases of malignancies of nose and Para nasal sinuses are studied with regard to their clinical presentation, radiology, histopathology and treatment protocols.

The data generated from the present study concludes that the malignancies of the nose and Para nasal sinuses are an intriguing group of disorders due to the variations in their clinical presentation, histopathological diagnosis, staging and grading. The type of treatment modality also varies depending upon the aforementioned factors. The challenge lies in diagnosing the malignancy as early as possible followed by selecting an appropriate treatment option and adequate follow up.

Keywords: high grade, Myoepithelial carcinoma, maxillary sinus, etc

Introduction

Myoepithelial carcinoma (malignant myoepithelioma) is a rare salivary gland tumor composed entirely of myoepithelial cells that exhibit a dual epithelial and smooth muscle phenotype. The tumor shows wide morphologic and cytologic diversity in a similar way to its benign counterpart, myoepithelioma, with evidence of malignant change. The malignancy manifests mainly as an infiltrative growth pattern, angiolymphatic and/or perineural invasion, with a propensity for mostly distant metastasis and occasional regional lymph node involvement. Other corroborative evidence of malignancy such as necrosis and increased mitotic activity can also be seen [1].

Originally described by Stromeyer *et al* in 1975 [2], Barnes *et al* renewed interest in this rare entity in 1985 after describing 3 cases of myoepithelial carcinoma (malignant myoepithelioma) in their review of myoepitheliomas of the head and neck [3]. However, it was Dardick *et al*'s detailed descriptions of myoepitheliomas that were crucial in furthering the understanding of myoepithelial tumors [4, 5]. Their articles helped to increase the accuracy of describing ensuing reported cases of myoepithelial carcinoma (malignant myoepithelioma). In 1991, myoepithelial carcinoma was added to the second edition of the World Health Organization (WHO) classifications of malignant salivary gland tumors [6]. Many of these tumors arise as a malignant transformation in the setting of a benign pleomorphic adenoma or a benign myoepithelioma [7]. and myoepithelial carcinoma (malignant myoepithelioma) is particularly seen in association with recurrence of these benign tumors. Other such tumors arise de novo [8].

Myoepithelial carcinoma (malignant myoepithelioma) is a rare tumor with a reported incidence of 0.2% of all salivary gland tumors [9]. However, some authors contend that myoepithelial carcinoma (malignant myoepithelioma) may not be as rare as previously suggested. A lack of recognition and/or awareness of its diversity and diagnostic criteria may contribute to the relatively small number of reported cases. Different series of myoepithelial carcinoma (malignant myoepithelioma) have showed variability in sex distribution with a generally similar age range, although the pediatric age group was not represented in all the relatively large reported series.

In this context, a review by Gnepp *et al* of 70 cases of myoepithelial carcinoma (malignant myoepithelioma) from the literature, the Armed Forces Institute of Pathology (AFIP), Memorial Sloan-Kettering, and Beijing Medical University found that affected patients are usually in the sixth decade of life, with an age range of 14-86 years. The series had varying sex distribution, from equal sex distribution (1:1) to female predominance (4:1). A series of 10 cases by Nagao *et al* in 1997 showed an age range of 48-

81 years with no pediatric cases and a predominance of women over men (2:1) [10]. In 2003, Yu *et al* examined 27 cases of myoepithelial carcinoma (malignant myoepithelioma) and found a predominance of males (1.7:1), with an age range of 16-73 years [11].

No definitive etiologic factors have been identified in myoepithelial carcinoma (malignant myoepithelioma); however, p53 accumulated mutations have been reported. C-kit overexpression has also been seen in these tumors. Most reported cases of myoepithelial carcinoma (malignant myoepithelioma) arise in the parotid gland (48%-75%), followed by minor salivary glands (reported sites include the palate, cheek, gum, nasal cavity, maxillary sinus, nasopharynx, infratemporal fossa, oral cavity, base of tongue, supraglottic larynx) and the submandibular gland. Even rarer cases have been reported in the sublingual gland [7].

Most patients with myoepithelial carcinoma (malignant myoepithelioma) present with a painless mass, occasionally with a recent rapid increase in size. In this context, some authors have suggested that the tumor may remain small for a period, after which it starts growing rapidly. Symptoms vary depending on the site (eg, laryngeal location may manifest as hoarseness; a sinus location may manifest as nasal obstruction, epistaxis, pain, and headache, etc). Facial nerve involvement in parotid tumors manifests as weakness/paralysis. The average duration of symptoms before diagnosis varies from 3 months to 3 years. Myoepithelial tumors are unencapsulated soft to firm masses with infiltrative margins, although some may appear well delineated grossly. The size ranges from 2-20 cm. A multinodular appearance can be appreciated on gross examination in many of these tumors. The cut surface may show focal hemorrhage, cystic degeneration, and necrosis.

Myoepithelial carcinomas (malignant myoepitheliomas) are unencapsulated and usually multinodular in appearance, with infiltrative borders [7]. The nodules vary in size with intervening thin fibrous septae, and they can exhibit central nodular necrosis. Other less-common growth patterns include diffuse solid, trabecular, and reticular infiltrating patterns. Like all tumors with myoepithelial component, myoepithelial carcinomas (malignant myoepitheliomas) exhibit a wide morphologic and cytologic diversity that is based on 4 major types of cells similar to those seen in benign myoepithelioma: spindle, plasmacytoid (hyaline), epithelioid, and clear cell types. Many myoepithelial carcinomas (malignant myoepitheliomas) exhibit more than one cell type, but even in these, one cell type usually predominates. Other cell morphologies such as stellatelike or vacuolated cells have also been described, as well as some tumors that exhibit an oncocytic morphology. In these malignant neoplasms, however, the cell type does not appear to significantly influence a patient's survival [8].

The epithelioid cells are large polygonal cells with central ovoid or round nuclei and eosinophilic or amphophilic, sometimes focally clear cytoplasm (see the following image); these can form pseudoacini or pseudoglandular structures (not true glands). The degree of atypia of the cells varies from a surprisingly bland cytology to highly pleomorphic nuclei. Accordingly, determination of malignancy can be problematic in cases with bland morphology, particularly in small biopsy samples in which the other features of malignancy cannot be fully appreciate [12].

Infiltration into the surrounding structures and destructive growth pattern remains the most significant and unequivocal evidence of malignancy seen in malignant myoepitheliomas. The presence of angiolymphatic or perineural invasion, metastatic lesions, tumor necrosis to variable degrees [7, 8], increased mitotic activity, and marked nuclear atypia are also corroborative evidence of malignancy that are variably demonstrated among cases.

El-Naggar *et al* found that the DNA content and S-phase fraction of tumor cells are good indicators of aggressive cell behavior [13]. Nagao *et al* found that cases of myoepithelial carcinoma (malignant myoepithelioma) in their series showed an increased mitotic activity of more than 7 mitotic figures per 10 high-power fields (HPFs) or a Ki-67 L1 of more than 10% [8]. In addition, the investigators found that all those with perineural invasion had a fatal outcome, and the mitotic rate was significantly higher in the cases associated with fatal outcome than in those who survived and was generally higher than those seen in benign myoepitheliomas. Moreover, necrosis is usually seen in most cases to variable degrees.

Foci of chondroid, sebaceous, and squamous metaplasia may also be seen. Collagenous crystalloids (radially arranged, needle shaped, eosinophilic, nonrefractile fibers) have been described in myoepithelial carcinoma (malignant myoepithelioma), similar to those seen in pleomorphic adenoma and myoepithelioma. Dedifferentiated myoepithelial carcinoma (malignant myoepithelioma), in which nuclei exhibit clear high-grade undifferentiated features, including bizarre or giant cell forms with loss of myoepithelial marker expression, have also been described [7]. It is worth noting that the concept of dedifferentiation in salivary gland tumors, described initially by Stanley *et al* in dedifferentiated acinic cell carcinoma [14]. has also been described in many other salivary gland tumors, including adenoid cystic carcinoma, epithelial-myoepithelial carcinoma, and polymorphous low-grade adenocarcinoma, among others.

As described for benign myoepithelioma, some authors consider that the presence of a small component of true ductal or tubular epithelial forms (up to 5%) still qualifies the tumor to be labeled a myoepithelioma, whereas others insist on the total absence of ductal elements. This issue is probably more problematic in malignant myoepitheliomas, as many authors consider the presence of ductal elements as a qualification for considering the neoplasm "epithelial-myoepithelial carcinoma" rather than a malignant myoepithelioma. This explanation carries a lot of credibility, and it is probably better to classify cases that show ductal elements as "epithelial-myoepithelial carcinomas with predominant myoepithelial component" than to create a confused set of criteria.

Myoepithelial carcinoma (malignant myoepithelioma) mainly exhibits different types of tumor matrix: myxoid and hyalinized. Savera *et al* demonstrated myxoid matrix in all of their 25 cases, considering this finding an invaluable clue to myoepithelial differentiation [7]. Sternlicht *et al* found that neoplastic myoepithelial cells have an increased capacity to modify and augment their production of matrix (primarily chondroitin sulfate proteoglycans) [15]. As in myoepitheliomas, the electron microscopy appearance of myoepithelial carcinoma (malignant myoepithelioma) shows hybrid epithelial and myoid features, including longitudinally oriented microfilaments with dense bodies,

pinocytic vesicles, basal lamina, desmosomes, hemidesmosomes, and intermediate filaments.

As the reader reviews the various individual case reports and the larger case series, with the exception of the dedifferentiated forms, which exhibit a predictable aggressive course, judging the biologic behavior (low grade vs high grade) of different types of myoepithelial carcinomas (malignant myoepitheliomas) has been controversial and largely unknown. As noted above, myoepithelial carcinomas (malignant myoepitheliomas) can occur as ex pleomorphic adenomas or ex benign myoepitheliomas, as well as de novo.

Di Palma and Guzzo suggested that such tumors arising in the background of pleomorphic adenoma are usually low grade and that myoepithelial carcinomas (malignant myoepitheliomas) are more aggressive when arising de novo; however, others found that the clinical outcome did not follow that premise [7, 8]; Many investigators also observed no discernible histologic features that correlate with biologic behavior, as some very bland tumors had a fatal clinical course, whereas other tumors with marked atypical histologic features did not. Indeed, in a retrospective review of the clinical course of 27 cases, Yu *et al* argued that myoepithelial carcinomas (malignant myoepitheliomas) should actually be considered a high-grade salivary gland neoplasm.

Although some attempts have laid down criteria for low-grade versus high-grade myoepithelial carcinoma (malignant myoepithelioma), the best evidence so far suggests that such criteria are unpredictable when measured with the usual morphologic parameters only. In that context, Savera *et al* theorized that the unpredictable and erratic biologic behavior of myoepithelial carcinoma (malignant myoepithelioma) may be more of a reflection of the underlying biochemical secretory products of neoplastic myoepithelial cells, which are variably modified and therefore affect the biologic behavior of the tumor, regardless of the morphologic nature of the tumor [7].

Myoepithelial carcinoma (MC) and myoepithelioma can be considered as doppelgangers, as they are difficult to distinguish due to diverse morphology and MC have infavorable outcome [16]. Published reports suggest that MC comprise of <2% of all salivary gland carcinomas involving parotid gland most commonly. Other sites involved are palate, maxilla, nasopharynx, liver, vulva and vagina [17]. However, this may be just a tip of the iceberg as due to increased recognition of this tumor, its incidence may be changed and may vary depending on demography. In fact, it is now believed that this tumor is the second-most common salivary gland malignancy arising from the benign adenomas [18]. It may also arise de novo. An accurate diagnosis for MC relies on exclusive myoepithelial differentiation (morphologic and immunohistochemical [IHC]) and clear-cut tumor infiltration into adjacent salivary gland or other tissues. Bases on above findings the present study was planned for clinical evaluation of high grade myoepithelial carcinoma of the maxillary sinus in patients admitted to ANMMCH, Gaya.

Methodology

The present study was planned in Department of Dentistry, Anugrah Narayan Magadh Medical College and Hospital, Gaya, Bihar. Total 15 cases of the myoepithelial carcinoma of the maxillary sinus were enrolled in the present study. The cases were histo pathologically confirmed cases of malignancies of nose and Para nasal sinuses are studied with regard to their clinical presentation, radiology, histopathology and treatment protocols.

All the patients were informed consents. The aim and the objective of the present study were conveyed to them. Approval of the institutional ethical committee was taken prior to conduct of this study.

Following was the inclusion and exclusion criteria for the present study.

Inclusion Criteria: All patients with Histopathological confirmation of malignant neoplasms of nose and Para nasal sinuses irrespective of sex were considered for study. All patients who were immunologically competent only were included in the study.

Exclusion Criteria: Pediatric malignancies are excluded. All immune-compromised patients are excluded from the study.

Results & Discussion

Myoepithelial carcinomas are rare malignant tumors of salivary glands, characterized by exclusive myoepithelial differentiation and infiltration into surrounding tissues [9, 10]. These tumors are histologically aggressive. They may recur or even metastasize. Myoepithelial carcinomas occur most frequently in the parotid gland, followed by submandibular gland and uncommonly in minor salivary glands [19] including palate, tongue, floor of mouth, maxillary sinus, larynx [9], buccal mucosa, nasal cavity and lower alveolus. They may present clinically as a painless swelling, increasing in size over months to years [19, 21]. Sometimes, there may be history of rapid enlargement in a long standing mass. Uncommonly, they may occur in a preexisting benign tumor such as pleomorphic adenoma or benign myoepithelioma [20, 21], Myoepithelial carcinomas are extremely rare in maxillary sinus and only few cases have been reported [19, 22]. Myoepithelial carcinoma arising in a background of pleomorphic adenoma has not been previously reported in the maxillary sinus, to the best of our knowledge.

Grossly, myoepithelial carcinoma is of variable size, grey-white and firm, with cut surface showing areas of necrosis and cystic change. Tumors arising in the parotid are usually partially or completely encapsulated, while at other sites they may be unencapsulated. Histologically, they may show various patterns including multinodularity, sheets, trabeculae, nests or reticular pattern of myoepithelial cells separated by fibrovascular septa. There may be multiple nodules with hypercellular areas in the periphery and myxoid or necrotic areas in the center resembling comedo necrosis. The cellular morphology can be epithelioid, spindle cell type, stellate, plasmacytoid/hyaline, clear cell type or a mixture of two or more of these. The epithelioid variant is the most common and is characterized by polygonal cells with eosinophilic cytoplasm and central nuclei. Plasmacytoid variant shows eccentric nuclei, abundant glassy eosinophilic cytoplasm. In spindle cell variant, there are elongated bipolar cells with myoid or fibroblastic features, central nuclei, arranged in fascicles. In the clear cell variant, tumor cells show abundant pale eosinophilic to clear cytoplasm and central nuclei.

Table 1: Age of Cases and No. of Cases

Age in years	No. of cases
21-30	1
31-40	3
41-50	4
51-60	4
61-70	3
Total	15

Table 2: Frequency of presenting symptoms of sinonasal epithelial-myoepithelial carcinoma

Symptoms	No. of cases
Epistaxis	8
Nasal obstruction	9
Facial Swelling	5
Headache	1
Epiphora	0
Hyposmia	0
Vision change	0

Table 3: Site of tumor origin

Symptoms	No. of cases
Inferior turbinate	3
Maxillary Sinus	4
Nasal septum	2
Anterior ethmoid	1
Nasal cavity unspecified	3
Unknown	2
Total	10

Myoepithelial carcinoma, known as malignant myoepithelioma, is the malignant counterpart of myoepithelioma. Malignant myopithelioma has been added to the second edition of the World Health Organization's histological classification of salivary gland tumor [23]. Manuel *et al*. had previously proposed a classification system comprising de novo invasive or noninvasive pleomorphic carcinoma, invasive or noninvasive carcinoma with no pleomorphic adenoma, and true malignant mixed tumor (carcinosarcoma), which may arise alone or from a preexisting pleomorphic adenoma [24]. Myoepithelial carcinomas of the salivary gland should be classified as high-grade malignancies. Overall, the prognosis of myoepithelial carcinoma is poor [25].

EMC is a low grade malignant biphasic salivary-type tumor and the diagnosis is based on conventional light microscopy, confirmed by immune histochemical and ultrastructural investigation. Histologically, the tumor is composed of small tubules lined with two cell types: an outer layer of myoepithelial cells with clear cytoplasm surrounding an inner lining of eosinophilic cuboidal epithelial cells resembling intercalated ducts. An association has been described between epithelial –myoepithelial carcinoma and intercalated ducts hyperplasia and is suggested to be its precursor lesion because the tubular growth pattern of this tumor epitomizes this phenotype [27]. The clear cell type tumors are composed of small tubules lined by a single layer of small cuboidal cells surrounded by one or more layers of prominent clear cells [26] Although the histological appearance of EMC is usually characteristic, there may be considerable morphological variation in the form of regressive changes, Schwannoma like areas, Sebaceous differentiation, oncocytic change, and a. double clear' appearance. Thus, the disease can overlap with other salivary-type tumors and differential diagnosis from many tumors of the salivary glands is necessary [27]. The morphological features cover a wide spectrum, ranging from purely epithelial aspects such as clear cell carcinoma to the appearance of a purely myoepithelial carcinoma. The recent oncocytic variant of EMC includes oncocytoma, oncocytic papillary cystadenoma and cystadenocarcinoma [26].

Conclusion

The data generated from the present study concludes that the malignancies of the nose and Para nasal sinuses are an intriguing group of disorders due to the variations in their clinical presentation, histopathological diagnosis, staging and grading. The type of treatment modality also varies depending upon the aforementioned factors. The challenge lies in diagnosing the malignancy as early as possible followed by selecting an appropriate treatment option and adequate follow up.

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