Fine Needle Aspiration Diagnosis Of Ipsilateral Synchronous Neoplasm - Mucoepidermoid Carcinoma With Warthin Tumor In Parotid Gland

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Abstract
Warthin tumor (WT) owing to its heterogeneous appearance, biological behavior and multicentricity poses a diagnostic challenge to cytologists worldwide. We report a rare double pathology of mucoepidermoid carcinoma (MEC) with WT which was diagnosed by fine needle aspiration (FNA). Cytological smears revealed sheets of epithelial cells and small clusters of squamous cells in a background of mucoid material along with a few small groups and scattered oncocytic cells and inflammatory cells (mainly lymphocytes). In view of the cytological findings various differentials such as oncocytic lesions, benign lesions of the parotid with extensive lymphoid reaction, necrotizing sialometaplasia, WT with extensive squamous/mucoid metaplasia, metastatic squamous cell carcinoma (SCC) with or without cystic change, oncocytic variant of MEC and a possibility of a synchronous MEC with WT were considered. By means of extensive review of the smears and clinic-pathological meets as discussed below, 2 differential diagnoses were given—MEC with WT versus an oncocytic variant of MEC with “?” lymphoid (tumor response) reaction. Subsequent histopathological examination confirmed the diagnosis of MEC with WT. Recent discovery of t(11; 19) translocation generating a novel fusion gene CRTC1/MAML2 which has been demonstrated in both MEC and WT has helped in providing the missing link in confirming the genetic relatedness and proof of development of a subset of WT with concomitant MEC. The case discusses the FNA findings of a rare collision tumor (MEC with WT), its possible differentials and highlights the importance of noting the background material in a case of double pathology on FNA.

Keywords
Cytology, Mucoepidermoid carcinoma, Warthin’s tumor, Parotid, Double pathology.

Introduction
Salivary gland neoplasms owing to their heterogeneous appearance, biological behavior, multicentricity and presence of many tumor-like mimickers are diagnostically challenging on cytology. This becomes more important if a patient presents to a cytopathologist for fine needle aspiration cytology (FNA) and the predominant tumor cytology and secondary background changes (hemorrhage, mucoid material etc) overshadows the minor tumor cytology resulting in a partial or misdiagnosis. This has to be kept in mind by the cytologist in utilizing the cytological information yield in all such lesions for proper diagnosis.

In the field of salivary gland cytopathology, Warthin tumor (WT), also known as papillary cystadenoma lymphomatosum, presents with unique characteristics of multicentricity, bilateral involvement (synchronous or metachronous) and increased incidences of “double – pathology (collision tumors)”^{1,2}

We report a case of ipsilateral synchronous neoplasm; low grade Mucoepidermoid carcinoma (MEC) with WT in parotid gland,
which was diagnosed by FNA.

**Case Report**

A 30-year old male smoker, presented to the otorhinolaryngology outpatient department with a 5 year history of a painless, lemon sized, gradually increasing swelling behind the ear which extended slightly below the ear-lobule. On examination, it was a 2.5 cm x 2.0 cm, firm, non-tender mass without any discharge and appeared to be fixed to the skin and underlying structures. FNA was performed with a 22 G needle. Multiple passes were made at two different sites. The aspirate was bloody admixed with thick mucoid like material. The smears were stained with May-Grunwald-Giemsa (MGG) and haematoxylin and eosin (H & E). Cytology revealed a moderately cellular lesion with sheets and clusters of epithelial cells lying in a background of mucus and debris (Figure 1). Mostly the cells showed intracytoplasmic vacuolization with abundant cytoplasm, and nuclei exhibiting mild to moderate pleomorphism. Features of squamous differentiation were noted without any evidence of keratinization. A few scattered and small groups of oncocytic cells and inflammatory cells (mainly lymphocytes) were noted in the background, especially in the H& E slides which were partly hidden amidst the mucoid debris and predominant cellularity of MEC in MGG slides (Figure 2).

![Fig. 1: Cytological features suggesting the diagnosis of mucoepidermoid carcinoma. Moderately cellular smears with mucoid and necrotic debris in the background (MGG X 100). Inset cells showing intracytoplasmic vacuolization with abundant cytoplasm and nuclei exhibiting mild to moderate pleomorphism (MGG X 400).](image1)

![Fig. 2: Cytological findings of warthin’s tumor. The scattered oncocytic cell clusters unlike the cell morphology of the cells noted in figure 1 at the periphery (MGG X 200) with lymphocytes in the background. Inset the oncocytic cell clusters with lymphocytes in the background at higher magnification. (H& E 400X)](image2)

![Fig. 3: Histological findings of mucoepidermoid carcinoma arising with warthin’s tumor (H & E 200 X). Inset Lymphoid follicle formation with secondary germinal centre surrounded by a double layer of oncocytic epithelium (H & E 100 X).](image3)

![Fig. 4: The areas of transition characterized by cystic dilatation filled with mucoid like material. (H& E 200 X)](image4)
In view of the cytological findings, various differentials such as oncocytic lesions, benign lesions of the parotid with extensive lymphoid reaction, necrotizing sialometaplasia, WT with extensive squamous/mucoid metaplasia, metastatic squamous cell carcinoma (SCC) with or without cystic change, oncocytic variant of MEC and a possibility of a synchronous MEC with WT were considered. By means of extensive review of the smears and clinic-pathological meets as discussed below, 2 differential diagnoses were given - MEC with WT versus an oncocytic variant of MEC with “?” lymphoid (tumor response) reaction.

Specimen of parotidectomy with supraomohyoid neck dissection was received as an irregular soft tissue piece measuring 4.5 x 3.5 x 2.0 cm. Serial sections revealed a few small cystic areas along with an ill defined grayish white area. Histopathological examination revealed peripheral prominent lymphoid follicle formation with secondary germinal centre surrounding a double layer of oncocytic epithelium which supported a diagnosis of WT (Figure 3). The rest of the tumor tissue showed the histology of MEC with cystically dilated ducts and glands. The cystic spaces contained abundant eosinophilic to basophilic material and were mainly lined by mucous cells with both basaloid and cuboidal intermediate cells interspersed with mucus cells (Figure 3). Also seen were focal collections of polygonal epidermoid cells. There were certain areas of transition near these two tumor morphologies which consisted of large cystic spaces found in WT morphology filled with eosinophilic secretions; the lining epithelia exhibited evidence of hyperplasia and occasional metaplasia (both mucoid and even squamous at places) as shown in Figure 4. The lymph nodes showed no evidence of metastasis. A final diagnosis of low grade MEC with WT was given.

**Discussion**

Clinical management of salivary gland masses in present scenario is increasingly relying on radiology (having its own set of limitations) and cytopathology. Pre-operative histological biopsy or intra operative frozen sections have their own hazards and organizing problems. In contrast FNA is virtually risk free and offers enough information to plan appropriate patient management. This has virtually laid burden on the reporting desk of cytopathologist as more and more surgeons are depending upon the pre-treatment diagnosis on FNA for eventual patient management.

Synchronous tumors with WT are seen most commonly with squamous-cell carcinoma, oncocytic carcinoma, malignant melanoma, undifferentiated carcinomas, adenocarcinomas - not otherwise specified and mucoepidermoid carcinoma (MEC). (3, 4, 6)

In the present case report various differentials diagnoses as discussed above were ruled out systematically. Benign lesions of parotid with extensive lymphoid reaction such as - lymphadenoma with tumor associated lymphoid proliferation (TALP)(5), lymphoepithelial cysts and chronic sialadenitis with cystic degeneration were ruled out as all these conditions lack invasiveness and different epithelial cell types noted in the smears. Necrotizing metaplasia was ruled out as there was absence of any recognizable ductal epithelial cells in the smears examined.(7)

Employing same principle, WT with extensive squamous/mucoid metaplasia and oncocytic tumors were ruled out as the smears demonstrated admixture of different epithelial cells (especially the intermediate cells) in addition to lymphoid and oncocytic cells. Primary and metastatic SCC with or without cystic change were ruled out as extensively keratinized malignant squamous cells were not seen in the smears examined(8) Also a detailed clinical examination and patient history (including radiological work-up) failed to reveal any primary.

Oncocytic MEC is a rare low grade MEC which usually does not have lymphoid population but this possibility was also considered in the final differential diagnosis of synchronous MEC with WT as extensive lymphoid proliferation sometimes accompany malignant tumors(9)

Histopathology showed synchronous MEC and WT with certain areas of transition near these
tumor morphologies, this is consistent with often cited behavioural tendency of WT to undergo metaplastic changes and developing a low grade MEC. In recent times various molecular techniques have tried to decipher the cause, histogenesis and a possible link between these 2 entities. In this context t(11; 19) chromosomal translocation was first described in both MEC and WT. The immediate generated fusion gene MECT 1 - MAML2 was shown to be strongly associated with MEC (correlates with good prognosis) in comparison to WT.\(^{(10)}\) In a new study t(11; 19) tanslocation has been shown to generate a novel fusion transcript CRTC1/ MAML2 which has been demonstrated in both MEC and WT and providing the missing link in confirming the genetic relatedness and proof of development of a subset of WT with concomitant MEC and its malignant transformation of WT.\(^{(11)}\)

In histologically challenging cases of such synchronous lesions, molecular diagnostic tools such as in-situ hybridization (ISH) and reverse transcriptase-polymerase chain (RT-PCR) reaction can immensely help in distinguishing WT from MEC.

Other tools such as electronmicroscopy (EM) and immunohistochemistry (IHC) are also useful. On EM, WT demonstrates increased mitochondrial content whereas MEC exhibits numerous tonofilaments and mucinous granules. IHC positivity is seen for mitochondria in WT; whereas carcinoma cells of MEC show positivity for Saly-Tn. The labeling index for ki-67 is also higher in carcinoma cells of MEC than in epithelial cells of WT.\(^{(12)}\)

The case is worth reporting as, apart from discussing the cytological findings of a rare collision tumor (MEC with WT) and its differentials, it highlights the importance of noting the background material in all cytological smears (avoiding the phenomenon of seeing the trees and missing the forest). Also one should not hesitate in such cases to utilize the latest techniques of ISH, RT-PCR and IHC to reach a conclusive diagnosis.

References


