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Original Article

# Diagnostic accuracy of Fine-needle aspiration cytology in Warthin tumors

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## ABSTRACT

**Background:** Despite its well-defined histologic appearance, the often variegated cytomorphological appearance of Warthin tumor (WT) on fine-needle aspiration (FNA) may lead to an erroneous cytopathological interpretation. In the present study, the authors analyzed the potential sources of diagnostic errors and overall accuracy of FNA diagnosis of WT.

**Material and methods:** A retrospective search from saved data of the Pathology Department of S. Nijalingappa Medical College and HSK Hospital for a period of two years from June 2023 and May 2025 revealed 40 histopathologically confirmed WT cases, including 31 patients who underwent prior FNA. A comprehensive review of cytological material was undertaken to calculate the overall accuracy of FNA and to identify sources of diagnostic error.

**Results:** All tumors presented in the parotid gland and four tumors (13%) were deemed inadequate for interpretation due to insufficient material. The FNA diagnoses of WT were rendered in only 20 cases (64.5%). The remaining seven cases (22.5%) were misdiagnosed on FNA, as consistent with or suspicious for carcinoma or some other neoplastic process. The retrospective review of those tumors, which were over diagnosed on FNA showed a predominance of necrotic or cellular debris (n=6; 22%), significant epithelial metaplasia with atypia (n=4; 15%), background inflammation suspicious for tumor diathesis (n=3; 11%), spindle cells (n=1; 4%), and abundant mucin with keratinized squamous cells (n=1; 4%).

**Conclusions:** FNA is moderately accurate for diagnosing WT, with a 74% accuracy rate in the present study. Cytological misinterpretation may occur due to a lack of characteristic cytomorphological features of WT and overabundance of one or more of the following features such as, squamous metaplasia/atypia, mucoid/mucinous background, spindle-shaped cells and cystic/inflammatory debris. An adequate awareness of these potential sources of erroneous diagnoses, coupled with appropriate clinical findings, may result in a higher accuracy rate.

***Keywords:*** Warthin tumor, Cytomorphology, fine-needle aspiration, pitfalls

## INTRODUCTION

Fine-needle aspiration (FNA) is a valuable tool in the diagnosis of head and neck lesions with a proven high accuracy.[1-3] This is particularly true for salivary gland neoplasms, because FNA diagnosis guides the clinician in decision-making about the management of patients. In the vast majority of patients, careful interpretation of the cytomorphological findings renders an accurate diagnosis, allowing for conservative management of patients with benign lesions.[2] Warthin tumor (WT) (also called papillary cystadenoma lymphomatosum or adenolymphoma) is the second most common benign salivary

gland neoplasm (5-10%) and involves predominantly the parotid gland.[4-6] The tumor can present bilaterally. Patients with WT generally have a slight male predominance, and it occurs between the fourth and seventh decades of life. [2] WT has a cystic appearance with a double layer of oncocytes surrounding a lymphoid stroma. There are two main cellular components: epithelial and lymphoid. The typical features on cytology include oncocytic cells in cohesive, monolayered sheets; background lymphocytes; and amorphous, cystic debris. [2, 4] Despite its well-defined histologic appearance, the often variegated cytomorphology of WT may lead to an erroneous cytopathological interpretation. The objectives of the current study were to analyze the potential sources of diagnostic errors and examine the overall diagnostic accuracy of FNA for WT from a series of patients at a single institution.

**Materials and Methods**

A retrospective study was done in Pathology Department of S. Nijalingappa Medical College and Research Centre and Hospital for a period of two years from June 2023 to May 2025. Data obtained from departmental archieves showed 40 histopathologically confirmed WT cases, including 31 patients who underwent prior FNA. A comprehensive review of cytological material was undertaken to calculate the overall accuracy of FNA and to identify sources of diagnostic error. Smears were reviewed along with the corresponding surgical pathology slides. FNA biopsy was performed by a cytopathologist using a 23-gauge fine needle attached to a 10-mL plastic syringe and employing a Cameco gun. Slides were air dried for Diff-Quik staining, and an on-site, provisional cytopathological diagnosis was rendered on all slides. Air dried smears were stained by May Grünwald Giemsa (MGG) and alcohol fixed smears were stained by Papanicolaou (PAP) stain and hematoxylin and eosin (H&E).On review of the cytologic material, particular attention was paid to identifying the sources of diagnostic errors and correlating them with the histopathologic findings of the resected specimens.

**Results**

31 out of 40 cases had prior FNA (Graph 1). All tumors presented in the parotid gland. Four cases (13%) were deemed inadequate for interpretation due to insufficient material. WT was diagnosed in 20 cases (64.5%). The remaining seven cases (22.5%) were misdiagnosed on FNA (Graph 2) as consistent with or suspicious for carcinoma or other neoplastic process and a variety of reasons were ascribed to these misdiagnoses (Table 1). Upon careful retrospective review, the 7 cases that were over-called on FNA showed a predominance of necrotic or cellular debris (n=6 cases; 22%), significant epithelial metaplasia with atypia (n=4 cases; 15%), background inflammation suspicious for diathesis (n=3 cases; 11%), abundant mucin with keratinized epithelial cells (n=1 case; 4%), and spindle-shaped cells (n=1 case; 4%). Based on the predominance of the above mentioned atypical cytomorphological features, a number of neoplastic entities were erroneously suspected, i.e., squamous cell carcinoma (primary or metastatic), mucoepidermoid carcinoma, nerve sheath tumor, and pleomorphic adenoma. Cytomorphological features in that were diagnosed accurately as WT, the smears showed variable amounts of cellularity, ranging from barely optimum cellularity to occasional hypercellularity. There was an admixture of epithelial fragments, occasional single epithelial cells, and abundant lymphocytes noted in a granular cystic background. The epithelial cells were oncocytic in appearance with large nuclei, prominent nucleoli, and moderately abundant granular cytoplasm (Fig. 1). Neoplastic fragments had a flat, monolayered look, often with a suggestion of papillary formations. Cellular pleomorphism was minimal or absent. The background contained lymphocytes, most often as single, dispersed cells and less often appearing as crushed lymphoid tangles.

The seven cases that were diagnosed as suspicious for or consistent with carcinoma or other neoplastic processes showed a spectrum of unusual cytomorphological features. Review of the smears revealed misinterpretation due to a relative lack of the characteristic cytological features of WT (as noted above) and the overabundance of one or more of the features described below. Necrotic or cellular debris was seen in 6 specimens (22%) and appeared as thick, granular, somewhat tenacious-appearing material (Fig. 2). It not only caused cellular obscuring on the slides to a large extent but also appeared worrisome due to its content of necrotic cellular fragments, karyorrhectic nuclei, and inflammatory cells. In specimens in which carcinoma was suspected, the necrotic debris was present in significant amounts and appeared quite different from the dispersed granular and cystic background of a typical WT. Epithelial metaplasia with atypia was seen in 4 cases (15%). The cells appeared in loose fragments of 10-20 cells and less commonly, as single, discohesive, squamous cells (Fig. 3). When seen in fragments, these cells had a squamoid appearance with prominent pleomorphism and variably sized nuclei and they lacked the single, prominent nucleoli of oncocytic epithelium. The cytoplasm had a much denser quality compared with the fine granularity seen in WT. More significant was a combination of these squamoid cells and keratinized epithelium. The latter appeared as mature, orangeophilic squamous cells that were noticed mostly in loose clusters, often in a prominently granular/cystic background (Fig. 4). Occasional parakeratotic cells also were present. Overtly malignant appearing squamous epithelium, however, was not noticed. Resection specimens from these patients showed classic WT with two or more layers of oncocytic epithelium sitting on top of a lymphoid-rich stroma in addition to abundant or focal areas of squamous metaplasia (Fig. 5). Background inflammation suspicious for diathesis was present to a variable extent in 3 cases (11%) and appeared most often as a diffuse, acute inflammatory process. The inflammation and cellular debris were admixed with atypical metaplastic cells. A mucinous or mucoid background was particularly noticeable in one specimen. The mucinous material was seen diffusely coating the slides. It appeared more worrisome, however, when seen in combination with squamous metaplastic changes (Fig. 6), when the material was deemed suspicious for low-grade mucoepidermoid carcinoma. The metaplastic epithelium appeared as small fragments or as singly dispersed mature squamous cells. Spindle cells were the most unusual feature and were seen in only one specimen, in which it was believed

that they represented a nerve sheath tumor. The appearance was of numerous, tightly cohesive fragments of fusiform cells, often with uniform, wavy nuclei. This specimen lacked any identifiable epithelial component. Histologic slides from the resection showed a WT with an unusually prominent and nodular stromal cell proliferation appearing as undulating, fusiform nuclei interspersed in a loose, myxomatous connective tissue. This may be the only explanation for the presence of spindle cells in the sample from a previously performed FNA.

**Discussion**

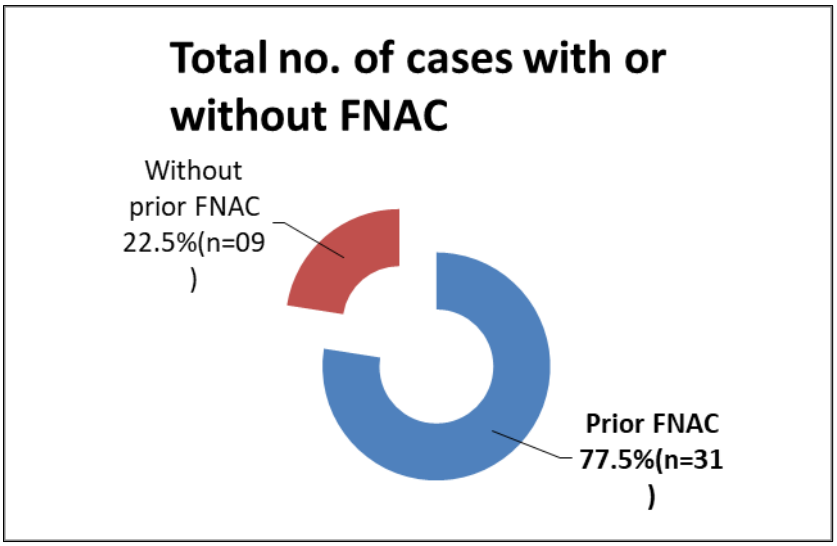
Salivary gland FNA is an established modality for preoperative evaluation of solid and cystic lesions with a high degree of accuracy. [1, 3, 5] Several studies have confirmed the utility of FNA for an accurate diagnosis of salivary gland neoplasm. One recent series examined 341 patients with salivary gland neoplasms and correlated the findings with clinical and histologic findings. [7] In that study, 88 of 91 benign epithelial tumors (97%) and 27 of 31 malignant tumors (87%) were diagnosed accurately using FNA. Seven tumors were misdiagnosed because of sampling errors (due to a cystic component) and misinterpretation of some of the rare lesions. Another large series included 841 patients with of salivary gland lesions and showed an overall accuracy rate of 97%.[3] Some of the misdiagnosed tumors included an oncocytic adenoma that was diagnosed as WT, a basal cell adenoma that was diagnosed as pleomorphic adenoma, and a low-grade mucoepidermoid carcinoma that was diagnosed as low-grade adenocarcinoma. Clearly, the overwhelming majority of these studies concluded that FNA is a valid and useful method for preoperative diagnosis of salivary gland neoplasms and helps in the broad categorization of lesions into reactive and/or inflammatory and benign versus malignant conditions. [2, 8] In the vast majority of patients, a specific and accurate diagnosis is made. However, cytopathological evaluation of salivary gland lesions may be quite difficult and challenging and often is complicated by frequent pitfalls.

An accurate FNA diagnosis may often have major therapeutic implications and may help to guide the extent of patient's surgery. [2] But some of the most common errors are a result of FNA misinterpretation of WT. In fact, this is all the more important because WT is a relatively common salivary gland neoplasm. The problems in FNA interpretation of WT may be due to a relative lack of the so-called typical or classic features of the tumor, particularly if one of the two components (epithelial or lymphoid) predominates, if sparse specimen cellularity is obscured by inflammation and/or debris, or if the atypical and/or metaplastic features outlined in this report are present. Few studies have addressed the diagnostic difficulties of WT on FNA. [9-11] The most common source of misinterpretation that has been described is squamous metaplasia in association with inflammation and degenerative/reactive changes, which mimic malignancy. [9, 10] In this setting, atypical or degenerated squamous metaplasia may be misinterpreted as squamous cell carcinoma. One study examined aspirates from 16 patients with histologically confirmed WT. [12] On review, 13 of those tumors had typical features of WT (81%). Three tumors were misdiagnosed as oncocytoma versus low-grade mucoepidermoid carcinoma, squamous carcinoma versus branchial cleft cyst, and squamous cell carcinoma. The authors of that study attributed the misinterpretations to a lack of typical features of WT and the presence of atypical squamous cells in a necrotic background, mimicking carcinoma. [12] Some investigators have suggested that squamous metaplasia in WT may be associated with a prior FNA procedure. One study examined 9 patients with WT who had squamous metaplasia arising in the parotid gland.11 of these, 8 patients had undergone a previous FNA procedure 1 to 4 months prior to surgery, and 1 patient had undergone a previous incisional biopsy. The authors of that study suggested that the pathogenesis of squamous metaplasia in these tumors most likely was vascular in origin.[11] Occasionally, extensive metaplastic and xanthomatous changes have been described in WT as a result of spontaneous infarction in the tumor, thereby highlighting the importance of an adequate sampling of the lesion.[13] Some of these changes are induced by a previous FNA procedure.[14] One study found tumor necrosis and squamous and/or mucinous metaplasia in 4 of 24 WT specimens.[15] The necrosis was noted as extensive in two tumors, producing enough architectural and cytologic atypia to simulate squamous cell carcinoma. Those authors also found that necrotic and inflammatory debris occurred within dilated tumor spaces, in the third tumor exhibiting squamous and mucinous foci, thereby suggesting low-grade mucoepidermoid carcinoma. That report suggested that tumor necrosis and metaplasia were reminiscent of necrotizing sialometaplasia of the minor salivary gland, which is believed to be ischemic in origin.[15] Squamous cells often are seen in a variety of neoplastic and nonneoplastic salivary gland lesions, such lymphoepithelial cysts, sialadenitis, pleomorphic adenomas, mucoepidermoid carcinomas, and primary and metastatic squamous cell carcinomas. Rarely, metastatic squamous cell carcinoma with cystic degeneration, particularly in a high cervical lymph node, may be diagnosed erroneously as WT with squamous metaplasia, particularly if the history of a primary squamous cell carcinoma is not available. The squamous component of the lesion must be examined carefully, along with other cellular and background components, to arrive at an accurate diagnosis. It also is prudent to remember that squamous cell carcinoma may coexist with WT; a few published reports have shown that squamous cell carcinoma actually arises from a preexisting WT. [16-23] Cytological smears may also show large, oncocytic sheets with relatively few lymphocytes and may have been misinterpreted as oncocytoma. Degenerated oncocytes in the presence of excess mucoid material may lead to an erroneous diagnosis of mucoepidermoid carcinoma. The latter was the case in one of the FNA specimens that was evaluated in our series as well as in 1 of 16 tumors that were described in another study. [9] Mucinous changes have been reported in WT, although they are less common than squamous metaplasia.[15] The misdiagnosis of a WT as a spindle cell neoplasm (nerve sheath tumor) is quite unusual and may be a unique event, as reported with regard to one of the tumors in

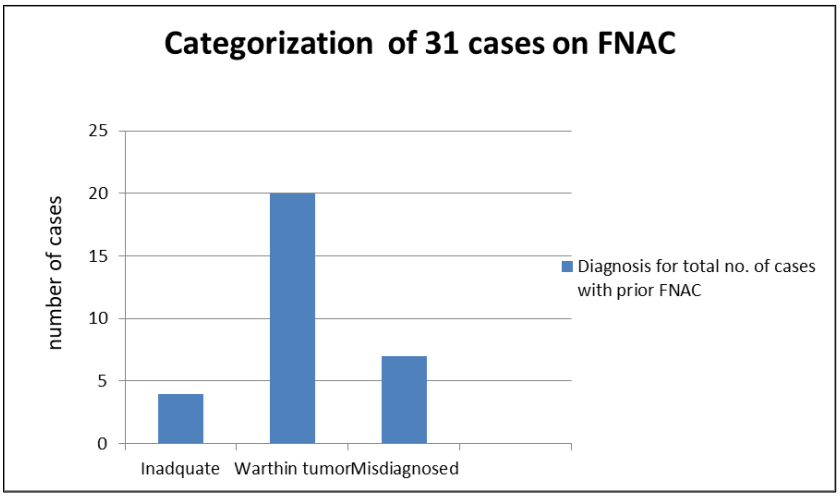
the current series. We tried to identify the source of the spindle cell fragments in the subsequent resection specimen from that particular tumor. The only unusual histologic feature was a proliferative and nodular stroma underlying the epithelium in an otherwise typical WT. The patient had undergone FNA that was performed 1 year previously at the same site, and we speculate that needling may have induced the stromal proliferation in this WT. In the current series, the diagnostic accuracy of FNA for WT was somewhat lower (74%) compared with the accuracy reported previously in another study (81%). [9]

**Table 1:** Cytomorphological features of warthin tumor causing misdiagnosedon FNAC (7 cases)

| Cytomorphologic features | N (%) (N=07) |
|---|---|
| Necrotic/ cellular debris | 06(85.8) |
| Epithelial metaplasia with atypia | 04(57.1) |
| Background inflammation suspicious for diathesis | 03(42.9) |
| Abundant mucin with keratinizing squamous cell | 01(14.2) |
| Spindle shaped cells | 01(14.2) |




**Graph 1:** Number of cases with or without prior FNAC




**Graph 2:** Categorization of 31 cases on FNAC.

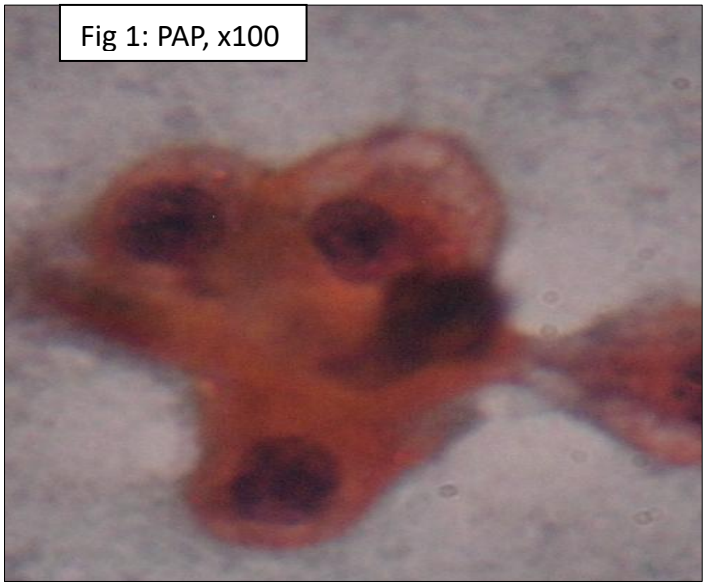



**Fig 1:** Oncocytes with large nuclei, prominent nucleoli & moderate granular cytoplasm. (PAP x100)

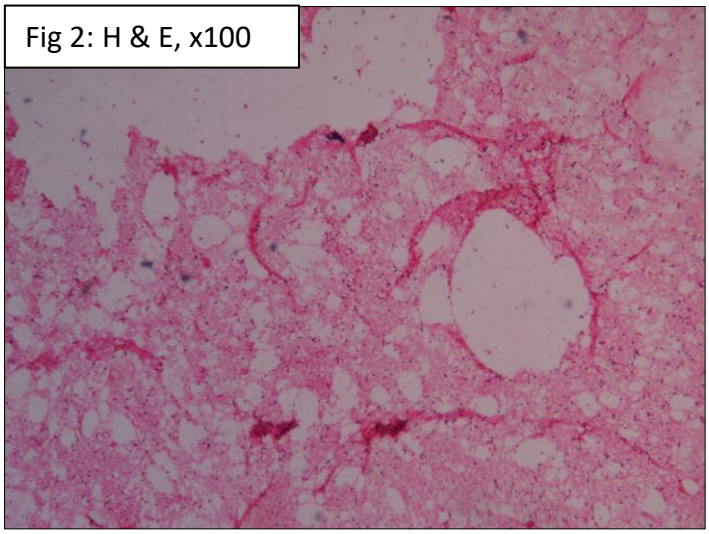



**Fig 2:** Necrotic / proteinaceous debris

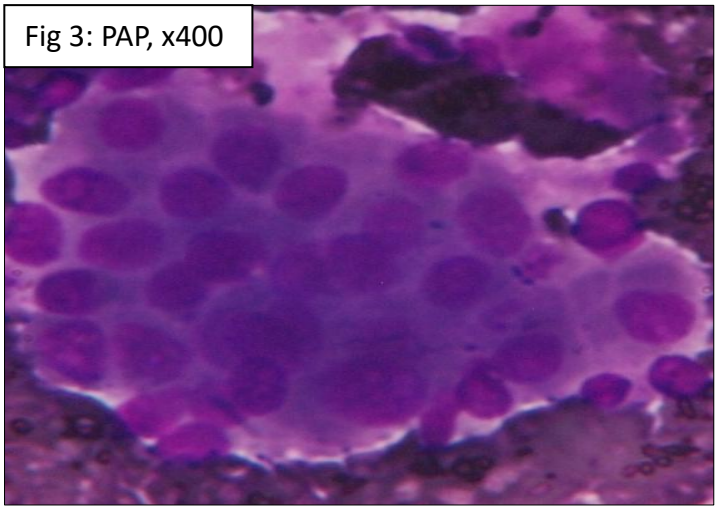



**Fig 3:** Epithelial (squamous) metaplasia with atypia

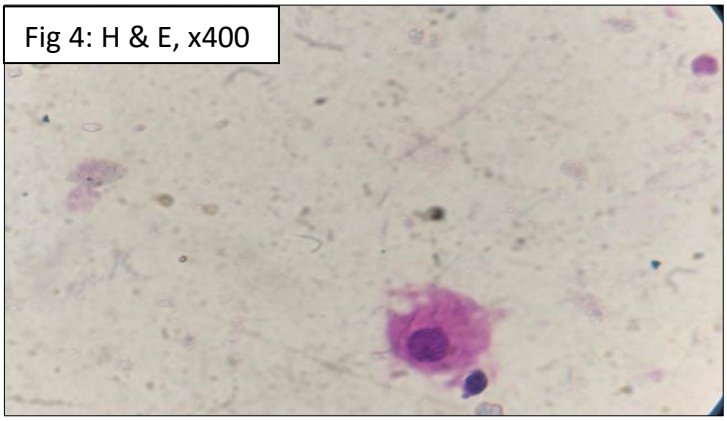



**Fig 4:** Squamous metaplasia with granular/cystic background

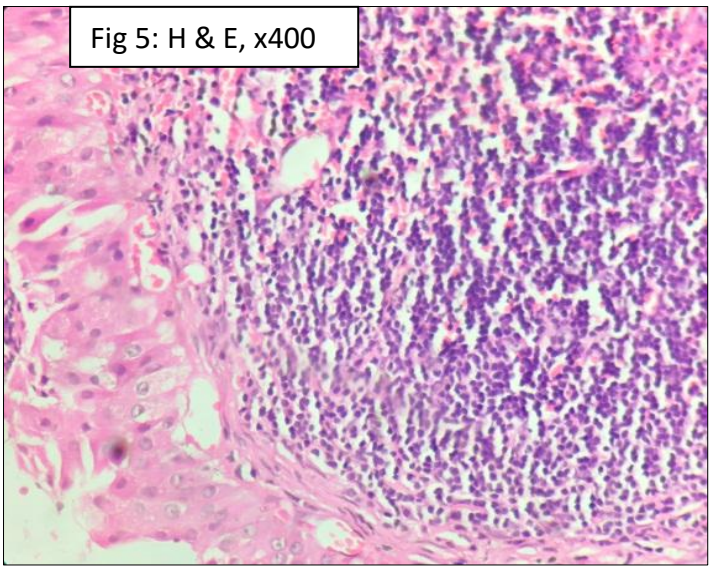



**Fig 5:** Warthins tumor histology showing bilayered oncocytic epithelium with lymphoid rich stroma

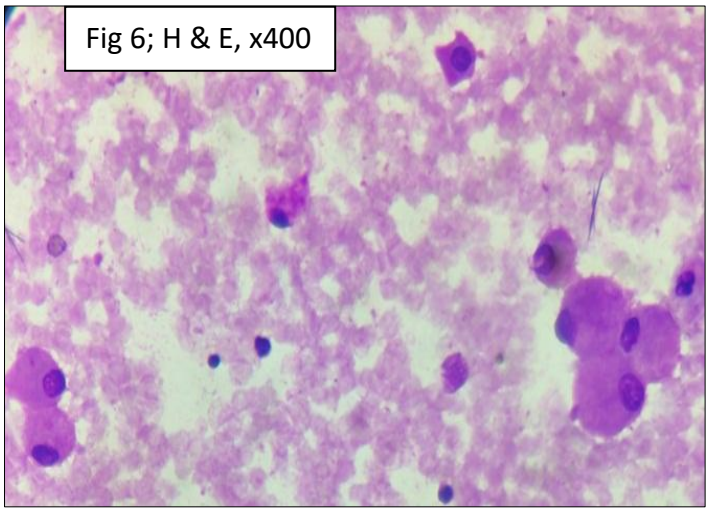



**Fig 6:** Squamous cells with mucoid background suggestive of Low grade mucoepidermoid carcinoma

## CONCLUSION

Over interpretation may occur due to an overabundance of atypical metaplastic features, necrotic background, inflammation, and/or a lack of the typical features of WT. An awareness of these potential sources of erroneous diagnoses, coupled with clinical studies, may result in a higher accuracy rate, allowing clinicians to make more appropriate therapeutic decisions in the management of patients with WT.

When in doubt, the pathologist must ask for a biopsy to rule out the other close mimics as evident from our study.\

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Conflicts of interests: The authors declare no conflicts of interest.
Author contribution: All authors have contributed in the manuscript.
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