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Original Article

Epidemiological and histopathological patterns of malignant salivary gland tumors in the Sudanese population

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ABSTRACT

Background: Malignant salivary gland tumors are rare. However, their morphological overlap and difficulty to differentiate benign from malignant makes diagnosing such diseases a challenging task. Geographical variation in distribution of these diseases is well documented in the literature. This study aims to review the histological and epidemiological variations of malignant salivary gland tumors in Sudanese patients considering the new WHO 2022 classification.

Methodology: This retrospective study included malignant salivary gland tumours in our lab spanning from the period of 2014 to 2022. Information about clinical data, habits, geographical distribution, pathological diagnosis, duration and sites of tumors were retrieved from our archives. Equivocal cases were checked by a salivary gland expert. Data analysis was performed using IBM SPSS 29.

Results: This study included 107 cases of malignant salivary gland tumours, representing 54 % of the total number of salivary gland tumours in the lab during that period. 47.7 % of the patients in this study were females and 52.3 % were males, the mean age of patients was 50 ± 15.7 years. (30 %) of the patients were from the central region of the country. The most common malignant salivary gland tumor was the Mucoepidermoid carcinoma accounting for 17 %. The palate was found to be the most common site as 38 % of malignant salivary gland tumors occurred in this site.

Conclusion: The study found a high percentage of salivary gland tumours in the Sudan suggesting geographical differentiation.

1. Introduction

Salivary gland tumours (SGT) are a histologically complex group of tumours involving an exhaustive list of variables (Rito and Fonseca, 2018; Speight and Barrett, 2020). SGTs are relatively rare tumours and account formerly 1 % of tumours in the United States, with an annual incidence of 1/100,000 per annum (“Salivary Gland Cancer Statistics | American Cancer Society,” n.d.). These tumours arise in the head and neck region, which is a sensitive region because of its proximity to vital structures and its role in the patient’s overall well-being (Speight and Barrett, 2020). Approximately 70 % of salivary gland tumours are benign (To et al., 2012). Although malignant salivary gland tumours are

very rare, they are associated with significant morbidity and increased risk of patient mortality.

Neoplasms of salivary glands arise from the stem cell population that resides in the ducts and typically gives rise to duct-lining epithelium, secretory acinar cells, and myoepithelial cells. The histology of these neoplasms is intricate due to varying ratios in which these distinct lines of differentiation may manifest (Odell, n.d.). This aspect makes salivary gland tumours one of the most challenging areas in diagnostic pathology. These tumors exhibit considerable morphological diversity and contain several overlapping features and a long list of entities, thereby presenting diagnostic challenges in histopathology practice (n.d.; Speight and Barrett, 2020).

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Geographical differences have been well documented in the literature. However, reports on malignant salivary gland tumours from the African region in general and from Sudan in particular are rare (Otoh et al., 2005). Therefore, this study aimed to highlight the specific histological findings of malignant salivary gland tumours in the Sudanese population taking into account the changes made in the new 2022 WHO classification of malignant salivary gland tumours, and compare the findings with the existing reports in the literature (Thompson et al., n.d.).

2. Materials and methods

This retrospective, cross-sectional study was performed in the Oral Histopathology Diagnostic Laboratory in the University of Khartoum. After approval of the study by the ethical board of the Sudanese medical specialization board, on the 21st of September 2022, specimen samples of malignant salivary gland tumours obtained during the period 2014–2022 were retrieved. However, the years 2019 and 2020 were not included owing to the temporary lockdown of the lab during this period. Only representative samples, either incisional or excisional, of the same patient were included in the study. Samples from non-Sudanese patients were excluded.

Clinical data were collected from the archives. Habits and geographic distributions of patients were recorded. For the purpose of this study, the 18 states of Sudan were categorised into five main geographical locations, namely, north, south, east, west, and central regions. The Northern state and River Nile state were considered north; Red Sea state, Kasala state, and Alqadarif state were considered east; Blue Nile state, White Nile state, South Kordofan state, and South and West Darfour State were considered south, and North Kordofan and North Darfour were considered west. Khartoum and Aljazeera states were considered central region of the country. Duration and sites of the tumours were recorded. Paraffin-embedded blocks were retrieved and stained using routine haematoxylin and eosin (H&E) for histological examination. The slides were examined under light microscopy. All parameters were measured twice, initially by the researcher and subsequently by the consultant histopathologist to reduce measurement bias. Diagnosis of malignancies was done according to the latest WHO 2022 classification (Thompson et al., n.d.). Controversial cases were reviewed by an expert in salivary gland pathology. Immunohistochemistry and molecular studies were performed in selected cases.

2.1. Data analysis

IBM SPSS version 29 was used for entering the data, calculating frequency, percentages and data distribution. The mean and standard deviation of the age of participants and duration of tumour was calculated.

3. Research results

During the 7-year period of the study, a total of 107 cases of malignant salivary gland tumours and 90 benign tumours were diagnosed at the Oral Histopathology Laboratory of the Faculty of Dentistry, University of Khartoum. The malignant salivary gland tumours therefore accounted for 54 % of the total number of salivary gland tumours. Of the 107 cases, 47.7 % were women and 52.3 % were men, with a ratio of 1:1.1. The age of the patients ranged from 8 years to 85 years, with a mean age of 50 ± 15.7 years. Ninety-seven patients 90.7 % did not report any oral habits, six 5.6 % patients were snuff dippers, and four 3.7 % patients were smokers.

According to the geographical location of the patients, a major proportion (31 patients, 30 %) was from the central region of the country, followed by the western region (18 patients, 17.4 %) (Fig. 1).

Twenty-one malignant tumours were recognized by the latest WHO 2022 classification (Thompson et al., n.d.). Our study found 14 different

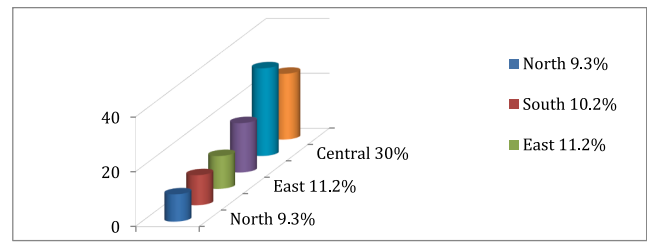


Fig. 1. Distribution of cases according to geographical location.

malignant tumours (Table 1). Mucoepidermoid carcinoma was the most common malignant tumour and accounted for 17 % of the tumours. This was followed by polymorphous adenocarcinoma, which represented 15.9 % of the tumours. The 18 cases of mucoepidermoid carcinoma were further graded into low, intermediate, and high according to the Auclairs grading system, with 56 % tumours graded as low, 28 % as high, and 17 % as intermediate.

The durations of these lesions were variable as in some patients, it was as high as 10 years, whereas in others, it was as low as 1 month; the mean duration was 27 ± 33.86 months. The vast majority of malignant salivary gland tumours (65.4 %) occurred in the minor salivary gland, with the palate being the most common site that affected 38.3 % of the patients. The most commonly affected major salivary gland was the parotid gland, which accounted for 20.6 %. The most common tumours affecting this gland were myoepithelial carcinoma and ductal carcinoma, with a percentage of 18.2 % for each tumour.

Of the 107 cases of malignant salivary gland tumours, 30.8 % showed perineural invasion (PNI), 33 patients in number. Moreover, 60 % of the tumours exhibiting PNI were of the adenoid cystic carcinoma type. The tumour was recurrent in 16 (15 %) patients. The most common tumour exhibiting recurrence was carcinoma ex pleomorphic adenoma, with a recurrence rate of 42.9 %.

In this study, controversial cases were reviewed by a head and neck pathology expert. One of the rare tumours found in this study was the case of a 34-year-old man with a fungated palatine mass. The morphology was indicative of monomorphic salivary type carcinoma with prominent nesting and neuroendocrine-like features not quite fitting any entity. Immunohistochemical studies were performed, and the results were negative for MUC4-NUT-P63, PAN-Trk-S100-SOX10, and mamoglobin and positive for NR4A3/NOR1 (40 % of the nuclei were positive). Molecular testing was performed using RNA sequencing with the Tru sight panel of Illumina. The results confirmed the presence of CRTCL1:MAML2 fusion; hence, the patient was diagnosed with a mucoacinar variant of mucoepidermoid carcinoma, which is very rare. Because of its distal intercalated duct/acinar phenotype, it was first

Table 1
Distribution of cases according to tumour type.

| Different entities seen in the study | | |
|--------------------------------------|-----|---------|
| Tumour type | N | Percent |
| Mucoepidermoid carcinoma | 18 | 17 |
| Polymorphous carcinoma | 17 | 15.9 |
| Adenoid cystic carcinoma | 15 | 14.0 |
| Ductal carcinoma | 13 | 12.1 |
| Myoepithelial carcinoma | 11 | 10.3 |
| Acinic cell carcinoma | 9 | 8.4 |
| Epithelial myoepithelial carcinoma | 8 | 7.5 |
| Ca ex Pleomorphic Adenoma | 7 | 6.5 |
| Basal cell adenocarcinoma | 4 | 3.7 |
| Adenocarcinoma NOS | 1 | 0.9 |
| Secretory carcinoma | 1 | 0.9 |
| Intraductal carcinoma | 1 | 0.9 |
| Sialoblastoma | 1 | 0.9 |
| Hyalinizing clear cell carcinoma | 1 | 0.9 |
| Total | 107 | 100.0 |

thought to be a hybrid tumour of mucoepidermoid carcinoma and acinic cell carcinoma. The tumour exhibited acinar morphology and was positive for NOR4, but molecular analysis revealed the presence of a CRTC4-MAML2 fusion gene. Hence, the tumour was concluded to be a variant of mucoepidermoid carcinoma with acinar features (Bunde et al., 2021).

Another interesting case in this study was a 50-year-old man with a swelling in the soft palate extending to the posterior wall of the pharynx. The patient was previously diagnosed to have mucoepidermoid carcinoma, and after revision, was reclassified as mucinous myoepithelial carcinoma. Mucinous myoepithelial carcinoma is a rare variant of myoepithelial carcinoma, with only 14 cases reported in the English literature. This carcinoma is characterized by pools of mucin resembling mucinous carcinoma. (Yang et al., n.d.) (Fig. 2 and Fig. 3).

4. Discussion

The incidence of salivary gland tumours has been reported to be influenced by geographical and racial factors (Boukheris et al., 2009; Bradley and McGurk, 2013; Vuhahula, 2004). Data on malignant salivary gland tumours in Africa in general and Sudan in particular are scarce in the literature.

During the study period, a total of 90 cases of benign tumours and 107 cases of malignant tumours were identified from the total number of salivary gland tumours presenting to the lab. This translates to a percentage of 54 % for malignant tumours. Previous published studies from the country reported a high ratio of malignancy too, a hospital-based study conducted in 2018 demonstrated a malignancy percentage of 48.3 % (Abdulghani, n.d.). Studies from other African countries such as Uganda and Nigeria showed a similar relatively high malignancy ratio of 46.6 % and 53.3 % respectively (Lawal et al., 2015; Vuhahula, 2004). This finding contradicts accounts from other regions of the world such as the UK, Poland and Brazil which show a significantly lower ratio of malignant salivary gland tumours of 14 %, 29.7 %, 20.5 % respectively (Gontarz et al., 2021; Lawal et al., 2015; Nascimento et al., 2020).

In this study, malignant salivary gland tumours were found to be more common in men than in women. This finding is in line with reports from Uganda, Nigeria, UAE, Jordan, and the USA (Al Sarraj et al., 2015; Boukheris et al., 2009; Lawal et al., 2015; Ma'aita et al., 1999; Vuhahula, 2004).

The mean age of patients in this study was found to be 50 ± 15.7 years, which is low when compared with the mean ages of those from Western and Asian nations, where malignant tumours were common in patients aged >60 years (Alsanie et al., 2022; Boukheris et al., 2009; Gontarz et al., 2021; Lukšić et al., 2012; Taghavi et al., 2016). However, the results agree with reports from other African countries such as

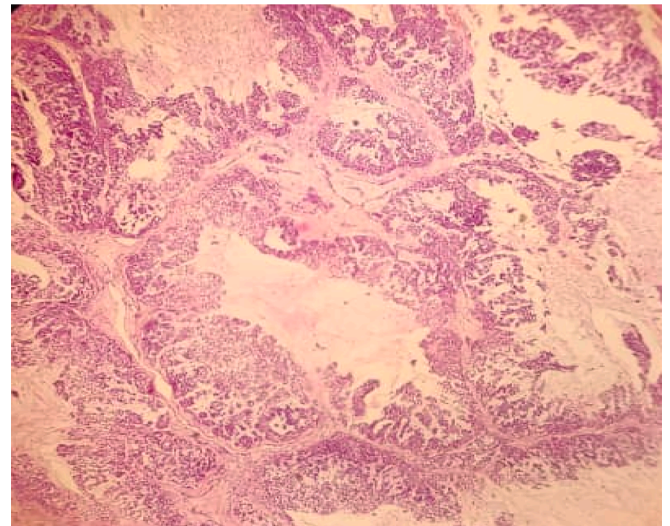


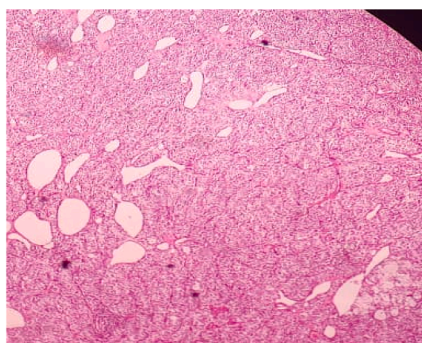
Fig. 3. Magnification: $\times 4$, H&E stained section of mucinous myoepithelial carcinoma show myoepithelial cells with signet ring morphology and pools of mucin.

Nigeria, Uganda, and Cameroon (Ochicha et al., 2009; Sando et al., 2016; Vuhahula, 2004). The youngest patient in our study was an 8-year-old child who was diagnosed with sialoblastoma and even had a metastatic lymph node.

A previous study from Sudan has proposed that the use of toombak could be a possible etiological factor and a potential reason for the observed surge in cases in the country (Idris et al., 1995). In this study, 90.7 % of the patients did not report any oral habits, six patients (5.6 %) were snuff dippers, and four patients (3.7 %) were smokers. Hence, according to the findings of this study, a causative association between malignant salivary gland tumours and toombak is very unlikely. The findings of this study are in line with a similar study by Ali (2018), which found no significant association between oral habits and the incidence of salivary gland tumours.

Regarding the geographical distribution of the patients, a high proportion of the patients (30 %) were from the central region of the country, namely, Khartoum and Aljazeera states, followed by the western region, from which 18 patients (17.4 %) hailed. The increased prevalence of patients from the central region can be attributed to the fact that they have a greater access to healthcare centres. The high number of patients from the western region is a finding that should be investigated.

A



B

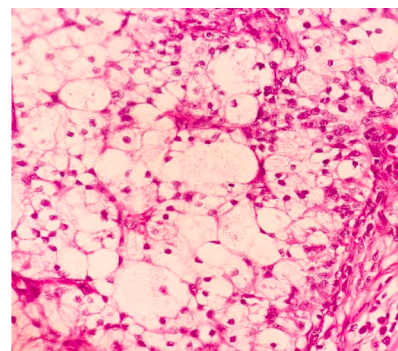


Fig. 2. (A) Magnification $\times 4$ H&E stained section shows a monomorphic salivary type carcinoma with prominent nesting and neuroendocrine like features consistent with mucoacinar variant of myoepithelial carcinoma. (B) Magnification $\times 40$ shows a nest of clear to amphophilic cells with lymphocytic infiltrate.

In this study, mucoepidermoid carcinoma was noted to be the most common malignant salivary gland tumour. This finding is consistent with reports from Jordan, KSA, UAE, and other Western countries (Al Sarraj et al., 2015; Alsalem et al., 2022; Bradley and McGurk, 2013; Ma'aïta et al., 1999). However, it is contrary to findings from other African countries reporting adenoid cystic carcinoma to be the most common type (Alsanie et al., 2022; Lawal et al., 2015; Sando et al., 2016; Vuhahula, 2004).

Mucoepidermoid carcinoma was diagnosed in patients with a mean age of 38.5 years. This finding is well documented in the literature as it is known that mucoepidermoid carcinoma is the commonest salivary gland malignancy in patients <30 years of age (Rutt et al., 2011).

The mean duration of the tumours before diagnosis was approximately 27 months. The relatively late presentation of patients is likely due to low patient awareness about these diseases. Hence, public health authorities should conduct programs to enhance patients' awareness about these diseases, especially because most of these tumours are painless in the early stage. Sudan has been classified by the International Monetary Fund as a low-income country. Therefore, the low socioeconomic status of most of these patients makes seeking healthcare an additional burden.

The vast majority of malignant salivary gland tumours included in this study were in the minor salivary glands, with the palate being the most frequent location. This finding is consistent with those from other studies in Sudan (Abdulghani, n.d.; Fahal et al., 1993). Nonetheless, previous studies from other countries have observed that the parotid gland is the most common site (Boukheris et al., 2009). The difference between African and Western populations regarding the proportion of the affected site has been documented in several African studies (Lawal et al., 2015; Ochicha et al., 2009; Otoh et al., 2005; Vuhahula, 2004). The reason for this phenomenon remains unclear. Reports from Egypt have suggested that malnutrition affects the contents of salivary glands ("SALIVARY GLAND TUMOURS IN EGYPT AND NON-WESTERN COUNTRIES - PubMed," n.d.).

The most common tumours affecting the parotid gland were myoepithelial and ductal carcinomas, with the parotid gland being the site of occurrence in approximately 36 % of myoepithelial carcinomas and 38 % of ductal carcinomas. In the literature, ductal carcinoma has been reported to be a rare but aggressive variant of salivary gland malignancy accounting for approximately 2 % of all salivary gland tumours. The percentage observed in our study was alarmingly higher than that in previous reports (12.1 %).

PNI is considered a route of tumour dissemination (Huyett et al., 2018; Liu et al., 2020). This neurotropism has been attributed to the release of surface adhesion molecules by the tumour (Oates et al., 2006). In this study, 60 % of the malignant tumours that exhibited PNI were adenoid cystic carcinomas, a finding well documented in the literature, followed by carcinoma ex pleomorphic adenoma and polymorphous adenocarcinoma (Liu et al., 2020).

The malignant salivary gland tumour carcinoma ex pleomorphic adenoma showed the highest recurrence rate, whereas mucoepidermoid carcinoma was the tumour with the highest number of recurrences. In 2019, Alraddadi et al. from KSA conducted a study on recurrence in malignant salivary gland tumours; they found mucoepidermoid carcinoma to be the most common salivary gland tumour showing recurrence. The researchers concluded that the initial presentation of the patient with advanced stage of salivary gland cancer, was associated with recurrence of salivary gland malignancy (Alraddadi et al., n.d.).

4.1. Conclusion

- Demographic variations exist in the presentation of malignant salivary gland tumours. This study has shown an increased incidence of these tumours in the African population, with aggressive types being highly prevalent and complicated by late presentation, thus leading to poor prognosis in many patients.

4.2. Recommendations

- Further studies on salivary duct carcinoma in Sudanese patients and its possible etiological factors are recommended.
- The occurrence of rare histological variants of salivary gland malignancies in Sudanese patients warrants the funding of genetic studies for possible unique findings that might have an impact on the diagnosis and management of these tumours in the future.

Author statement

The author named in this manuscript confirm that this work is original and that they have all read and confirmed the contents, they also confirm that no artificial intelligence has been used to write it is content whatsoever.

Ethical considerations

Ethical approval was obtained from Ethical Review Board at the Sudanese medical specialization Board and university of Khartoum. Information was treated with confidentiality, and no patient name was used, only the serial number. The authors of this manuscript certify that the using of data in this study complies with the guiding principles for experimental procedures as set forward by the declaration of Helsinki. This is a retrospective review of data submitted to biopsy services for routine diagnostic workup. No special changes were made just for this research. Also the scientific material found within this abstract has not been presented in any other conference or journal.

CRediT authorship contribution statement

Yassmin Abdalla Mustafa Mohamed: Conceptualization. **Hagir A. Mahmoud:** Conceptualization. **Fatima Abdalmonim Abdelrahman Eltahir:** Data curation. **Abeer Hemedan Mohammed Ahmed:** Data curation. **Yousif Osman Yousif:** Supervision.

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