Mammary analogue secretory carcinoma: An Indian experience of a novel entity

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ABSTRACT

Aims: To explore clinical, histopathological and immunohistochemistry (IHC) features of mammary analogue secretory carcinoma (MASC) with systematic literature review. Setting and Design: Hospital based cross-sectional study. Subjects and Methods: The data of all cases of MASC diagnosed over a period of 1 year i.e., from July 2017 to July 2018 were retrieved. The haematoxylin and eosin (H and E) sections, and IHC sections were studied. A strict histological and recently updated criteria were applied and patients with a confirmed diagnosis of MASC were included in the study. A systematic literature review was conducted by searching the PubMed and National Centre for Biotechnology Information database. Statistical Analysis Used: Microsoft Excel 2010. Results: The present case series is 27⁸ in the English literature and 1⁰ case series describing its histopathology in the Indian literature. The mean age of presentation is 43 years. Female preponderance was found i.e., M:F ratio of 0.5. Conclusion: Histopathology and if necessary, followed by IHC is required for the confirmation of diagnosis of MASC. We should be aware about this recently described entity which is usually mistaken for other low grade salivary gland carcinomas like Acinic cell carcinoma (AcCC) and Mucoepidermoid carcinoma (MEC). The knowledge about its typical morphology, high degree of suspicion and IHC confirmation with both S-100 and Mammaglobin help in precise diagnosis.

KEY WORDS: ETV6-NTRK3 gene fusion, mammaglobin, mammary analogue secretory carcinoma

INTRODUCTION

Mammary analogue secretory carcinoma (MASC) of the salivary gland is a recently described entity that has just been established in the new WHO classification of head and neck tumours (4ᵗʰ edition, 2017). It has a synonym: Secretory carcinoma. Breast and salivary glands are derived from the same embryonic ectoderm exhibiting same ductulo-acinar architecture. MASC has similar histopathology and IHC features to Secretory carcinoma of breast, hence named so. Secretory carcinoma was first documented in salivary glands in 2010 by Skalov et al. in a series of 16 cases.

There are about 279 cases reported since then according to a major review by Khalele et al., of which 1% cases were Indian i.e. three cases, all these were single case reports. Apart from this large review five more single case reports and one case series comprising of three cases by Oliver et al. were reported in the literature. Also, out of three cases of cytology case series by Oza et al. only one was considered by Khalele et al. in his major review. The above-mentioned data made the count of total number of reported cases of MASC as 289. Again out of these five case reports, four are Indian cases making the total count of MASC cases reported in India to eight. To the best of our knowledge this is overall the second Indian case series of MASC and the first case series of MASC discussing its histopathology in the Indian literature. The first done by Oza N. et al. being a cytology study.

SUBJECTS AND METHODS

This study comprises three cases of MASC diagnosed over a period of 1 year (from July 2017 to July 2018). All cases were documented; detailed clinical information was recorded from the case sheets. This included their age and sex of the patients, and site of biopsy. All three tumours were resected, and pathological examination was...
performed on representative fixed-tissue samples embedded in paraffin and stained with H and E. Frozen section was performed in case 2.

Haematoxylin and eosin stained sections were studied and the following histological features were evaluated:

- Circumscribed or infiltrative
- Lobulated growth pattern with fibrous septa
- Microcystic/solid, tubular, follicular, and papillary-cystic structures with distinctive luminal secretion
- Tumour cells with eosinophilic granular or vacuolated cytoplasm with small, uniform nuclei
- Presence of secretory zymogen cytoplasmic granules
- If any high grade transformation present and
- Special stains-Diastase resistant PAS positivity.

Subsequently, IHC was done. The following antibodies were used: CK, EMA, Vimentin, S-100, Mammaglobin, p63, GCDFP, ER, and PgR.

Strict histological and recently updated criteria were applied and patients with a confirmed diagnosis of MASC were included in the study.

Genetic profile: Molecular study for ETV6-NTRK3 gene fusion was done in the first two cases by RT-PCR. Positive results were obtained in both.

**Systematic review**

A systematic literature review was conducted by searching the PubMed and National Centre for Biotechnology Information database using the keyword search term “Mammary analogue secretory carcinoma”, “Mammary analog secretory carcinoma” and “MASC”, and the Medical Subject Heading term Mammary analogue secretory carcinoma. All case series of MASC cases published hitherto were included. Excluded were reports published in a language other than English, and without an English-language abstract. This yielded a total of 26 publications. This analysis included gender, age at diagnosis and tumor site (whether parotid or other).

Ethics: The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 2000.

The survival metanalysis was not done since it's a recently described entity with only few cases published with follow-up.

**RESULTS**

It was between the periods July 2017 to July 2018, three cases of MASC were diagnosed. The clinical characteristics of the three cases are summarized in Table 1. On systematic review, it was found that the present case series is 27th in the English literature, overall the second Indian case series of MASC, and the first case series of MASC discussing its histopathology in the Indian literature. The first done by Oza N. et al. being a cytology study.

The mean age of presentation was 43 years. There was a female preponderance i.e., M:F ratio of 0.5. Most predominant symptom was painless preauricular swelling. Average size was 3.06 cm. All three cases involved the parotid gland.

FNAC could be done in the first two cases. Cytology was a pitfall in both the cases. H and E stained cytosmears showed cell clusters in an arborizing pattern with vascular core, microcystic spaces. The cells were polygonal with abundant eosinophilic or vacuolated-bubbly cytoplasm and with bland nuclei. A provisional impression of salivary gland neoplasm possibly a low grade carcinoma was made. The differential diagnosis considered in case 1 were low grade MEC (Mucoepidermoid carcinoma), and AciCC (Acinic cell carcinoma). While the differentials considered in case 2 were cellular pleomorphic adenoma, and low grade carcinoma (AciCC MEC). In the second case because of dilemma on FNAC between benign and malignant lesion, frozen section was done and it was reported as low grade salivary gland neoplasm. Following that, total parotidectomy with SOHND (Supra-omohyoid node dissection) was done since the lesion was located in the deep lobe of parotid gland.

In the first and third cases superficial parotidectomy was performed.

The gross and histopathological features of all the three cases are summarized in the table below [Table 2]. The extracellular material was PAS positive and was resistant to diastase digestion in all the cases [Figure 3].

IHC profile of all the cases was same. The tumour cells expressed CK, EMA, Vimentin, Mammaglobin and S-100. The tumour cells did not express p63, GCDFP, ER and PgR [Figure 4].

Molecular study for mutation ETV6-NTRK3 was done in the first two cases by RT-PCR, and both of them showed positive results.

| Case No. | Age (year of diagnosis) | Sex | Site | Symptoms | USG |
|----------|-------------------------|-----|------|----------|-----|
| 1        | 40 years (2017)         | Female | Left parotid region | Painless swelling 4 × 3 cm | Left parotid well defined lobulated complex, solid and cystic lesion measuring 4.5 × 3.8 cm. |
| 2        | 38 years (2018)         | Male | Left parotid region | Painless swelling 3.5 × 2.8 cm | Oval hypoechoic lesion in deep lobe measuring 3.5 × 2.8 cm |
| 3        | 51 years (2018)         | Female | Left parotid region | Gradually increasing painless swelling 4.8 × 4 × 2 cm | Hypoechoic mildly vascular lesion in superficial lobe with exophytic component causing disruption of tragus |
All three cases are in regular follow up. No disease or recurrence is noted in case 1 and 3, after 1 year and 4 months of surgery, respectively. While the case 2 turned up with local recurrence, ipsilateral cervical lymph node metastasis and widespread metastases to lungs and brain after 7 months of surgery.

Few of the previous case series on MASC are summarized in the table below: [Table 3].

**DISCUSSION**

The periodic reassessment of even well-established entities is a necessary exercise that improves diagnostic accuracy. It is especially true when new entities like MASC are introduced.
Tumours of salivary gland are rare and have an incidence of 3 per 100000 people.\textsuperscript{[22]} MASC accounts for <0.3% of all salivary gland tumours.\textsuperscript{[23]}

Secretory carcinoma is generally a low grade salivary gland carcinoma characterized by morphological resemblance to mammary secretory carcinoma and ETV6-NTRK3 gene fusion.\textsuperscript{[1]}

Secretory carcinoma was first documented in salivary glands in a 2010 study by Skalova \textit{et al.}, who reported first case series of 16 cases and described their morphology and immunoprofile in detail. They reviewed the cases retrospectively and concluded that most of these cases were initially reported as zymogen poor AciCC or Cystadenocarcinoma NOS.\textsuperscript{[2]}

There are about 279 cases reported since then according to a major review by Khalele \textit{et al.}\textsuperscript{[3]} of which 1% cases were Indian i.e., three cases, all these three cases were single case reports. After this large review seven more cases have been reported in the English literature, making the count of total reported cases of MASC as 289. To the best of our knowledge, this is the first case series of MASC discussing its histopathology in the Indian

\begin{table}[h]
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\hline
\textbf{Study (year)} & \textbf{No. of cases} & \textbf{M: F ratio} & \textbf{Mean age (yrs.)} & \textbf{Mean size (cm)} & \textbf{Site (Parotid/others)} & \textbf{Recurrence} \\
\hline
Skalova (2010)\textsuperscript{[2]} & 16 & 1.2 & 46 & 2.1 & P13/O3 & 3 cases \\
Chiosea (2012)\textsuperscript{[6]} & 10 & 4 & 45.5 & NA & NA & NA \\
Connor (2012)\textsuperscript{[7]} & 7 & 6 & 40 & 1.8 & P2/O5 & NA \\
Wollenberg (2013)\textsuperscript{[8]} & 20 & NA & NA & NA & NA & NA \\
Griffith (2013)\textsuperscript{[9]} & 6 & 52 & 43.7 & 1.72 & P4/O2 & None \\
Bishop (2013)\textsuperscript{[10]} & 5 & 1.5 & 52 & 1.9 & P4/O1 & 1 case \\
Jung (2013)\textsuperscript{[11]} & 13 & 1.6 & 46.4 & 1.77 & P11/O2 & 3 cases \\
Majewska (2014)\textsuperscript{[12]} & 7 & 2.5 & 51.4 & 2.8 & P6/O1 & 2 cases \\
Ito (2015)\textsuperscript{[12]} & 14 & 0.75 & 39 & 2.6 & P9/O5 & NA \\
Kawahara (2015)\textsuperscript{[13]} & 8 & 3 & 46 & NA & P7/O1 & NA \\
Luk (2015)\textsuperscript{[14]} & 9 & 1 & 36 & 2.2 & P9 & NA \\
Projetti (2015)\textsuperscript{[15]} & 10 & 0.6 & 38 & 1.3 & P8/O2 & NA \\
Shah (2015)\textsuperscript{[16]} & 19 & 0.58 & 45 & NA & P16/O3 & NA \\
Stevens (2015)\textsuperscript{[17]} & 14 & 0.75 & 55.3 & NA & P9/O5 & NA \\
Khurram (2016)\textsuperscript{[18]} & 11 & 1 & 51 & NA & P6/O5 & NA \\
Oza (2016)\textsuperscript{[19]} & 3 & 0.5 & 23.3 & 2.6 & P3 & None \\
Hsieh (2016)\textsuperscript{[20]} & 14 & NA & NA & NA & NA & NA \\
Din (2016)\textsuperscript{[21]} & 11 & 1.4 & 27.5 & 4.4 & P7/O4 & 3 cases \\
Oliver (2017)\textsuperscript{[22]} & 3 & 2 & 48.3 & 1.5 & P2/O1 & NA \\
\hline
\end{tabular}
\caption{Previously reported studies on MASC}
\end{table}
literature and overall second case series of MASC.\textsuperscript{[5]} The first study in the Indian literature is a cytopathology study.

Most of the diagnoses in these previous studies are derived from the retrospective review of institutional archives of other salivary gland tumour diagnoses.

The mean age of presentation in the previous reviews ranged from 27.5 to 53.3 years. The mean age of presentation according to the WHO 2017 classification of Head and Neck tumours is 46.5 years.\textsuperscript{[10]} The mean age in our case series is 43 years.

There is no gender predilection according to WHO 2017 Classification of Tumours of Head and Neck.\textsuperscript{[1]} Among the 25 publications, 40\% of the studies showed male preponderance, 24\% showed female preponderance while there is M: F ratio of 1:1 in 24\% of the studies. In our case series there is a female preponderance (Male: Female ratio of 0.5:1).

The MASC clinically presents as a painless slow-growing mass in the pre-auricular region, which was seen in all the cases of our study. This entity is diagnosed mainly in the major salivary glands with 70\% being in the parotid gland and 7\% in the submandibular gland. This has also been found in minor salivary glands of lip, soft palate, hard palate, base of tongue and buccal mucosa.\textsuperscript{[24]}

The cytomorphology includes cohesive epithelial cells and/or papillary fragments or dispersed cells, sometimes with cystic debris. The neoplastic cells are phenotypically epithelial, with abundant and variable, granular to vacuolated, eosinophilic to clear cytoplasm and single nuclei.\textsuperscript{[9]} Before its first description in 2010 which it was classified as a ‘zymogen-poor’ Acinic cell carcinoma (AcCC). The cytological distinction between AcCC and MASC is very difficult because of overlapping features.\textsuperscript{[6]} Cytology was a diagnostic pitfall in both the cases of present study. Also, of the 12 FNAC cases described in the literature, only one received an accurate initial diagnosis of MASC.\textsuperscript{[8,10]}

On histopathological examination of H and E stained sections reveal a circumscribed or partially encapsulated tumour displaying a lobulated growth pattern with fibrous septa and is composed of microcystic/solid and tubular structures. The macrocystic pattern with abundant homogeneous secretion is also seen. The tumour cells have bland vesicular round to oval nuclei, with finely granular chromatin and distinctive centrally located nucleoli. Abundant eosinophilic homogeneous secretions in microcystic and tubular spaces is seen. Glandular secretion gives a positive periodic acid-Schiff (PAS) reaction before and after enzyme digestion.\textsuperscript{[1]}

On IHC, MASCs are characteristically positive for Pan CK (AE1/AE3 and CAM5.2), CK7, CK19, EMA, Vimentin, MUC1, MUC4, STAT5a S100 protein and mammaglobin. Most cases are DOG1, ER, and PgR, p63, CK20, Her2, SMA, and calponin negative.\textsuperscript{[1]} GCDFP is variably expressed. One important caveat is that, as with immunostaining in general, strong S-100 positivity must be used in the appropriate morphologic context. One has to remember that other ductal tumours are also strongly S100 positive.\textsuperscript{[23]} Another marker of interest and routine availability is mammaglobin. Mammaglobin is a member of the uteroglobin family of proteins that was initially described to be restricted to breast tissue.\textsuperscript{[26]} Skalova and colleagues have shown that all MASCs were positive for mammaglobin in keeping with their breast counterparts. As both breast and salivary glands are similar, it is not surprising that a ‘mammary specific’ marker is also expressed in salivary tissue and can be used to support the diagnosis of MASC.\textsuperscript{[5]}

MASC has a characteristic genetic profile, it harbours a recurrent translocation t(12;15)(p12;q25), which results in fusion of the ETV6 gene on chromosome 12 and the NTRK3 gene on chromosome 15. This fusion has not yet been demonstrated in any other salivary gland tumours.\textsuperscript{[1]} It encodes a chimeric oncoprotein tyrosine kinase that activates the Ras-MAP kinase and phosphatidylinositol-3-kinase-Akt pathways.\textsuperscript{[27]} This chimeric tyrosine kinase activates cell proliferation and increases survival of tumour cells playing a fundamental role in its oncogenesis.\textsuperscript{[12]} ETV6 rearrangement may be detected from paraffin-embedded tissue by break-part FISH, or the fusion transcript can be detected by reverse transcriptase-polymerase chain reaction.\textsuperscript{[10]} In case1 and 2 of our study we performed RT-PCR and ETV6 rearrangement was detected. There is no consensus among experts on whether documentation of the ETV6 rearrangement is absolutely required to make the diagnosis of MASC without molecular testing in cases that are classic from a morphologic and immunophenotypic standpoint. However, in cases that depart from the typical features of MASC in some way either high grade transformation or unusual immunostaining pattern ETV6 rearrangement studies should be done.\textsuperscript{[10]}

Due to its overlapping features on histopathology, MASC can be easily misinterpreted for various other low grade salivary gland carcinomas and Pleomorphic Adenoma. Main differential diagnoses are discussed in the table below: [Table 4]

Though there are three other salivary gland neoplasms which express S-100 and Mammaglobin i.e., salivary gland duct carcinoma, Adenocarcinoma NOS and Low grade cribriform carcinoma, these can be easily ruled out. Both Salivary gland duct carcinoma and adenocarcinoma NOS are high grade neoplasms of which Adenocarcinoma NOS is a diagnosis of exclusion. Salivary gland duct carcinoma has comedo necrosis and apocrine cells expressing PSA, Her2 and androgen receptors.\textsuperscript{[11]}

MASC is usually an indolent salivary gland malignancy. High clinical stage and high-grade transformation are the main adverse prognostic factors. MASC has relatively favourable prognosis, usually do not infiltrate the surrounding tissue.\textsuperscript{[3]} Exceptional examples can exhibit a highly infiltrative growth pattern, brisk mitotic activity, significant nuclear atypia, and/or necrosis that warrant a higher grade. Indeed, Skalova et al.\textsuperscript{[23]} and Jung et al.\textsuperscript{[11]} reported 4 examples of MASC with high grade transformation, a phenomenon that is well recognised in other low grade salivary
gland carcinomas. Lymph node metastases are reported in as many as 25% of cases, but distant metastases are rare. Case 2 of our study presented with local recurrence, ipsilateral cervical lymph node metastasis and widespread brain and lung metastases 7 months after the surgery, probably due to high grade transformation.

Clinical stage at diagnosis is the most accurate predictor of prognosis. Treatment protocols are tentative due to limited cases published with follow up.

As for low grade salivary gland carcinoma the standard treatment is radical surgical resection. Lymph node dissection is recommended only for T3T4 stage and patient with clinical nodal disease. The value of Post-operative RT is unclear due to the paucity of treatment specific survival data. Post-operative RT is reserved for close margins (<5 mm), T3T4 stage, incomplete excision and/Peri-neural invasion.

Chemotherapy has very limited role and is given in distant metsateatis only.

Although MASC revealed a capacity for an aggressive course, the ETV6-NTRK3 translocation might provide a potential therapeutic target.

Overall, there is no conclusive evidence that MASC should be treated any differently than other low-grade malignant salivary gland cancers.

CONCLUSION

At present, it is a challenge to differentiate MASC from other salivary gland neoplasms on the basis of clinical features, imaging and routine histopathological study. Histopathology with the aid of appropriate immunohistochemistry can help in the correct diagnosis of this low grade carcinoma and thus help in the management.

Our institution has encountered 3 cases of MASC in the last 1 year. Though cytology was a diagnostic pitfall, HPE along with IHC aided in the diagnosis. Like Bishop said MASC is not as rare as it was previously believed. As experience with MASC has grown its clinical histologic spectra have become increasingly in focus. We should be aware about this recently described entity which is usually mistaken for other low grade salivary gland carcinomas like AciCC and MEC. Knowledge about its typical morphology, high index of suspicion and IHC confirmation with S-100 and Mammaglobin help in a precise diagnosis.

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Conflicts of interest

There are no conflicts of interest.

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