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Original Research Article

Challenges in Diagnosis and Treatment of Mammary Analogue Secretory Carcinoma of Salivary Glands – Our Experience

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Abstract

With the recent WHO classification listing atleast 40 histological types of salivary gland tumors, their pathological diagnosis remains a challenge.

Mammary analogue secretory carcinoma (MASC) is a recently described tumor of salivary glands. As its name suggests, it bears a striking resemblance to secretory carcinoma of the breast. Both the tumors are currently defined by the presence of a balanced translocation, t(12;15) (p13;q25) creating a *ETV6-NTRK3* fusion gene. Histologically, MASC is often confused with other malignancies such as acinic cell carcinoma, mucoepidermoid carcinoma and adenocarcinoma, not otherwise specified. Immunohistochemistry and molecular studies play a crucial role in differentiating MASC from its mimickers. This distinction is important because of differences in their biological behavior.

We describe our experience with mammary analogue secretory carcinoma over a three-year period, all of our cases being diagnosed only on histology of the excised tumor. Diagnosis was confirmed by the presence of characteristic histological features together with strong positivity for S-100 and mammaglobin on immunohistochemistry. The challenges faced in diagnosing and treating this tumor has been discussed.

Keywords: Parotid Neoplasms; Immunohistochemistry; In Situ Hybridization, Fluorescence; Polymerase Chain Reaction

Introduction

Mammary analogue secretory carcinoma (MASC) is a recently described tumor of salivary glands. As its name suggests, it bears a striking resemblance to secretory carcinoma of the breast. Both tumors share the underlying genetic basis, a balanced translocation, t(12;15) (p13;q25) creating a *ETV6-NTRK3* fusion gene.[3] Owing to its

rather non-specific features, MASC can be easily mistaken with primary adenocarcinoma, acinic cell carcinoma and mucoepidermoid carcinoma on cytology and histopathology. Differentiating MASC from these mimickers, however, is important because of differences in their biological behaviour. Immunohistochemistry and molecular genetic analysis remain the cornerstone of making this distinction. We describe our experience with mammary analogue secretory carcinoma over a three-year period. We encountered four patients Diagnosis in these cases was confirmed by the presence of characteristic histological features together with strong positivity for S-100 and mammaglobin on immunohistochemistry. The challenges faced in diagnosing this tumor have been discussed. Although MASC generally follows the behaviour of a low-grade malignancy, recurrences have been uncommonly reported in literature. Even high-grade transformation or dedifferentiation has been very rarely reported. One patient in our series had tumor recurrence 2 years after primary surgery. In view of paucity of literature on this entity, long term follow-up is recommended.

Observations and Results

We encountered four patients with mammary analogue secretory carcinoma over a three-year period. The mean age at presentation was 45.5 years. While 3(75%) of them were localised in the parotid gland, one (25%) was present in submandibular gland. All patients underwent evaluation with fine needle aspiration cytology (FNAC) and MRI. FNAC was suggestive of acinic cell carcinoma in 3 (75%) patients, while the type of malignancy could not be ascertained in 1 patient with submandibular gland tumor. MR imaging revealed T2 hypointensity in 2 (50%) patients and T2 hyperintensity in 2 (50%) cases. All the tumors showed heterogeneous post-contrast enhancement. The pre-operative evaluation has been summarised in Table 1.

Table 1: Clinical characteristics and preoperative evaluation.

S.no.	Age/ Sex	Salivary gland	FNAC	MRI
1.	60/M	Parotid	Acinic cell carcinoma	• Mass within both superficial and deep lobes of parotid gland • Iso to hypointense on T1W image • Heterogeneously hyperintense on T2W image with a necrotic component postero-medially • Heterogeneous enhancement on post-contrast T1W image • Recurrence – Hyperintense on T1, hyperintense on T2 with heterogeneous contrast enhancement; extending from skin, subcutaneous tissue into deep retromandibular region
2.	35/M	Submandibular	Low grade malignancy of uncertain type	• Submandibular tumor abutting SMG with obliteration of fat plane • T1 – Central hypointensity (necrotic) with peripheral hyperintensity and post-contrast enhancement

				• T2 - Hyperintense
3.	42/F	Parotid	Acinic cell carcinoma	• Bulky left parotid gland with T2 hypointensity and ill-defined heterogeneously enhancing area within.
4.	45/M	Parotid	Acinic cell carcinoma	• Mass in superficial lobe; hyperintense on both T1 and T2 with intense central enhancement and mild peripheral enhancement.

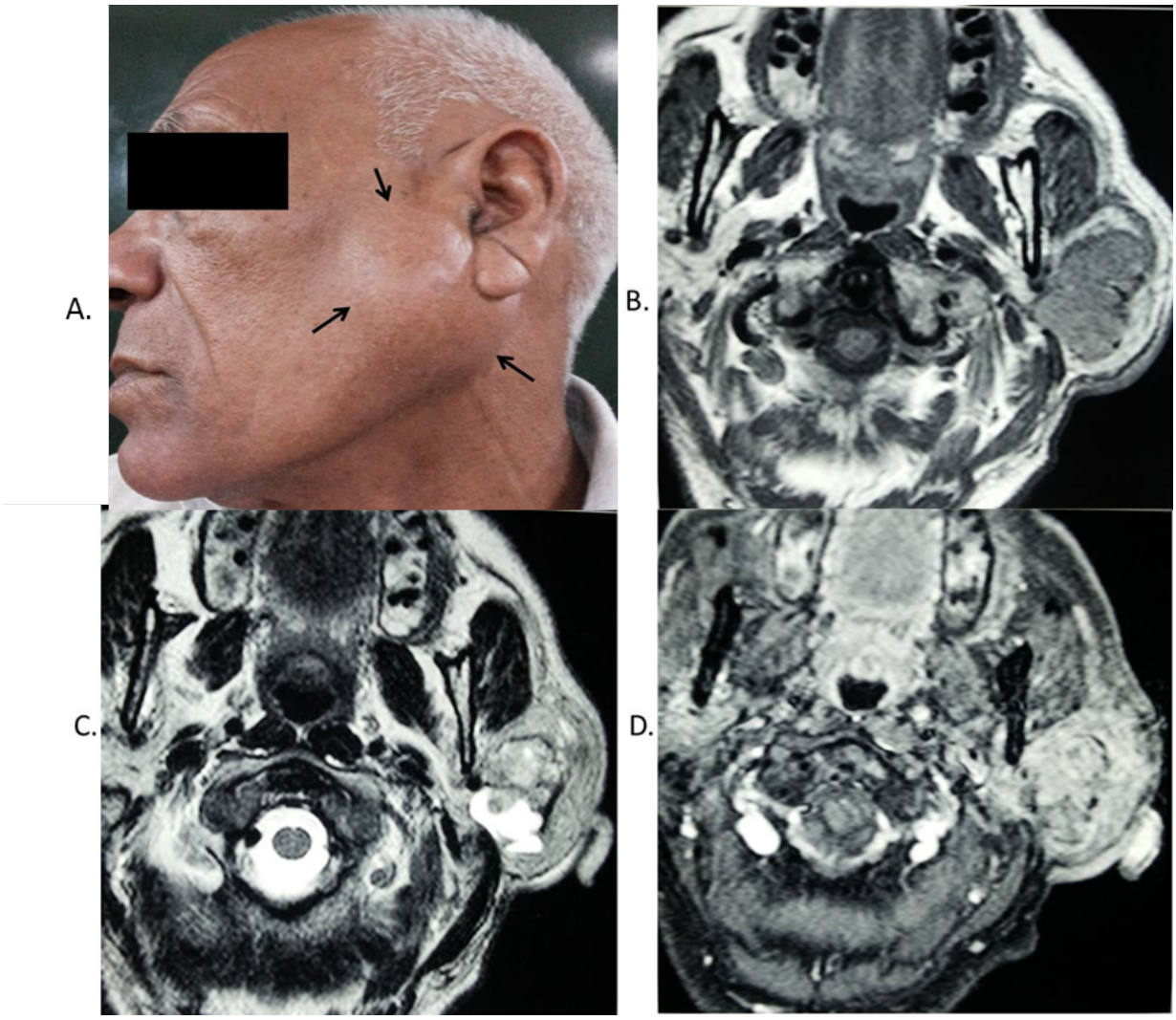

Figure 1: A. Left parotid swelling MR Imaging showing bulky left parotid gland with 3 X 3.8 X 5 cm lesion involving both lobes. B. Isointense on T1W image C. Heterogeneously hyperintense on T2W image with a necrotic component postero-medially D. Heterogeneous enhancement on post-contrast T1W image.

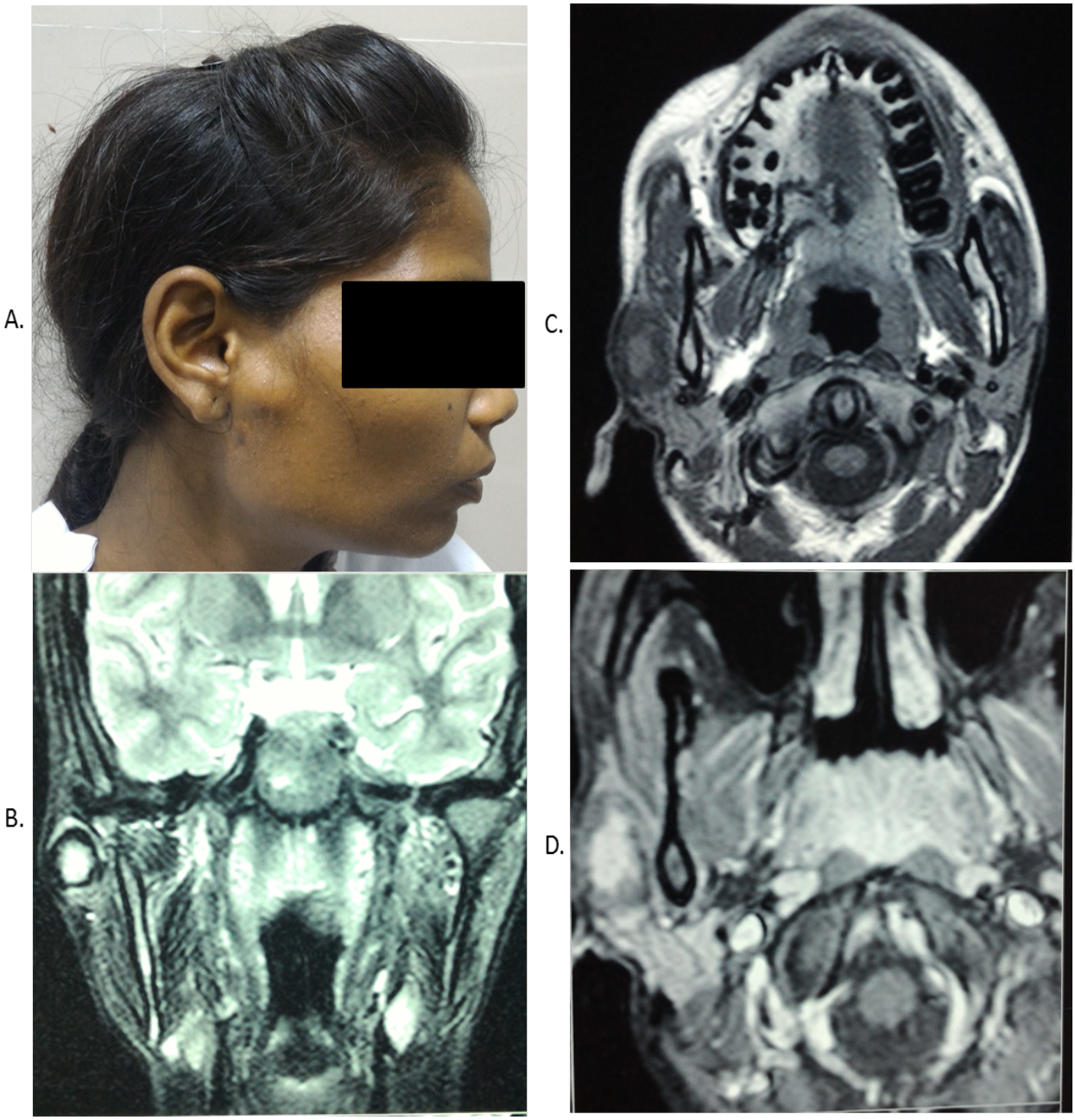

Figure 2: A. Right parotid swelling MR imaging shows well-defined lesion in superficial lobe of right parotid gland. B. Hyperintense on T1 with hypointense rim C. Hyperintense on T2 with hypointense rim D. Heterogeneous post-contrast enhancement

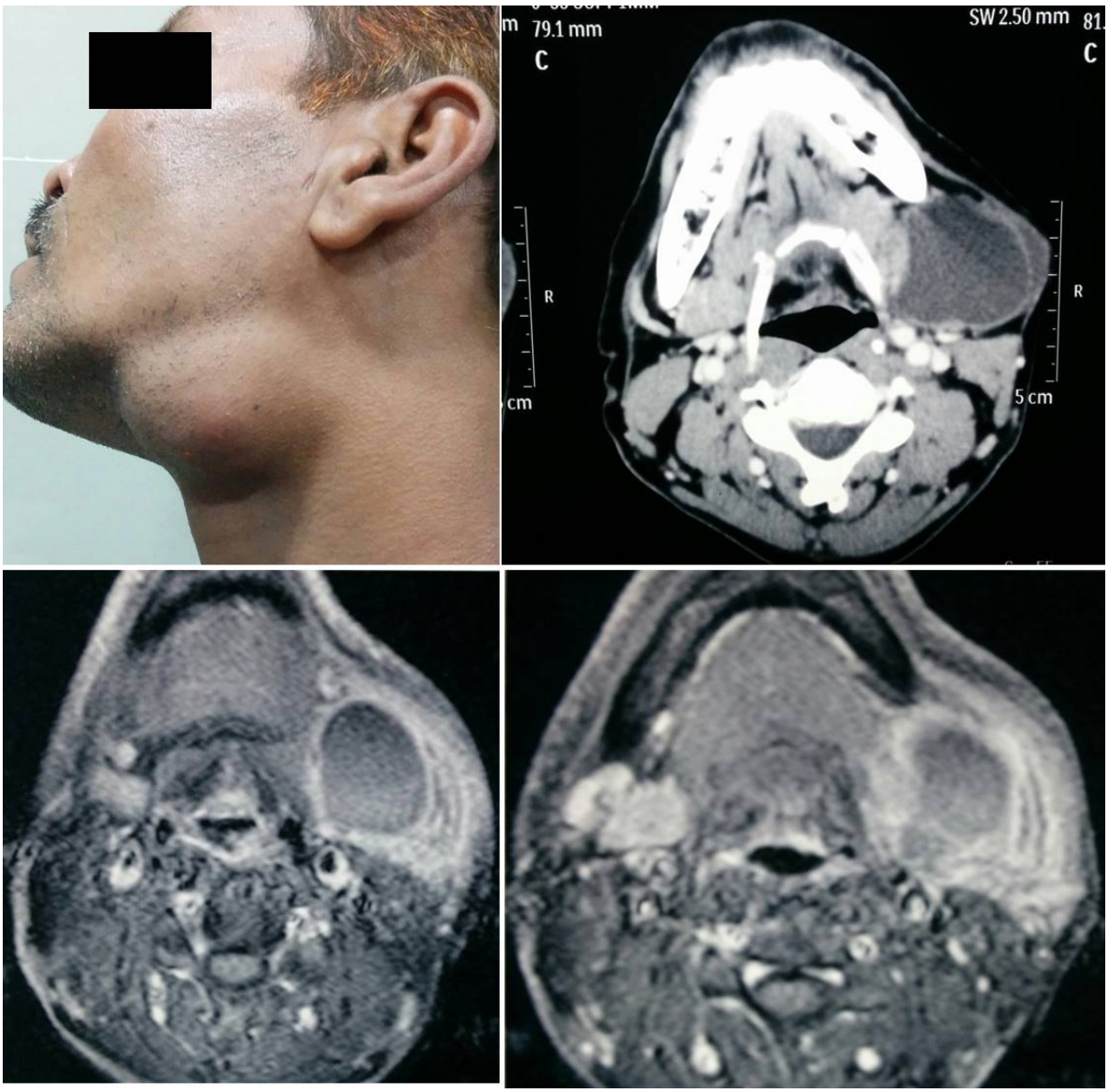

Figure 3: Left submandibular swelling. CT scan showing hypodense, multiloculated cystic mass lesion in the left submandibular region and abutting submandibular gland. MRI showing peripheral enhancement and s was hypointense on T1W image and hyperintense on T2W image with peripheral post-contrast enhancement and obliteration of fat plane between the tumor and submandibular gland.

All four patients underwent surgical excision of the gland – Total conservative parotidectomy in 2 (50%), superficial parotidectomy in 1 (25%) and submandibular gland excision in 1 (25%). Diagnosis of MASC was made on histopathology of the excised specimens owing to the characteristic morphology and immunohistochemistry findings, which have been summarised in Table 2. S-100 and mammaglobin positivity was found in all tumors (100%).

None of the patients underwent adjuvant post-operative radiotherapy in view of low-grade nature of the tumor and absence of any high-risk pathological features. 1 (25%) patient developed recurrence of the tumor after 2 years along with features of Frey's syndrome. He underwent revision

parotidectomy with tensor fascia lata interposition along with post-operative adjuvant radiotherapy. All the other patients have been free of recurrences so far, the minimum follow-up period being 2 years.

Table 2: Summary of treatment, histopathology and follow-up

S.no	Primary treatment	Adjuvant treatment	Diagnosis of MASC		Recurrence	Treatment after recurrence
			Morphology	IHC		
1	Total conservative parotidectomy	Nil	Tumor cells in cystic, tubular, trabecular, cribriform and papillary patterns with moderate amount of eosinophilic and vacuolated cytoplasm. Moderate nuclear pleomorphism and occasional mitotic activity	S-100, mamma globin and pan-CK	After 2 years	Revision total parotidectomy followed by EBRT
2	Submandibular gland excision	Nil		S-100, mamma globin	Nil at 3 years	-
3	Total conservative parotidectomy	Nil		S-100, mamma globin	Nil at 2 years	-
4	Superficial parotidectomy	Nil	Morphology +	S-100, mamma globin	Nil at 2 years	-

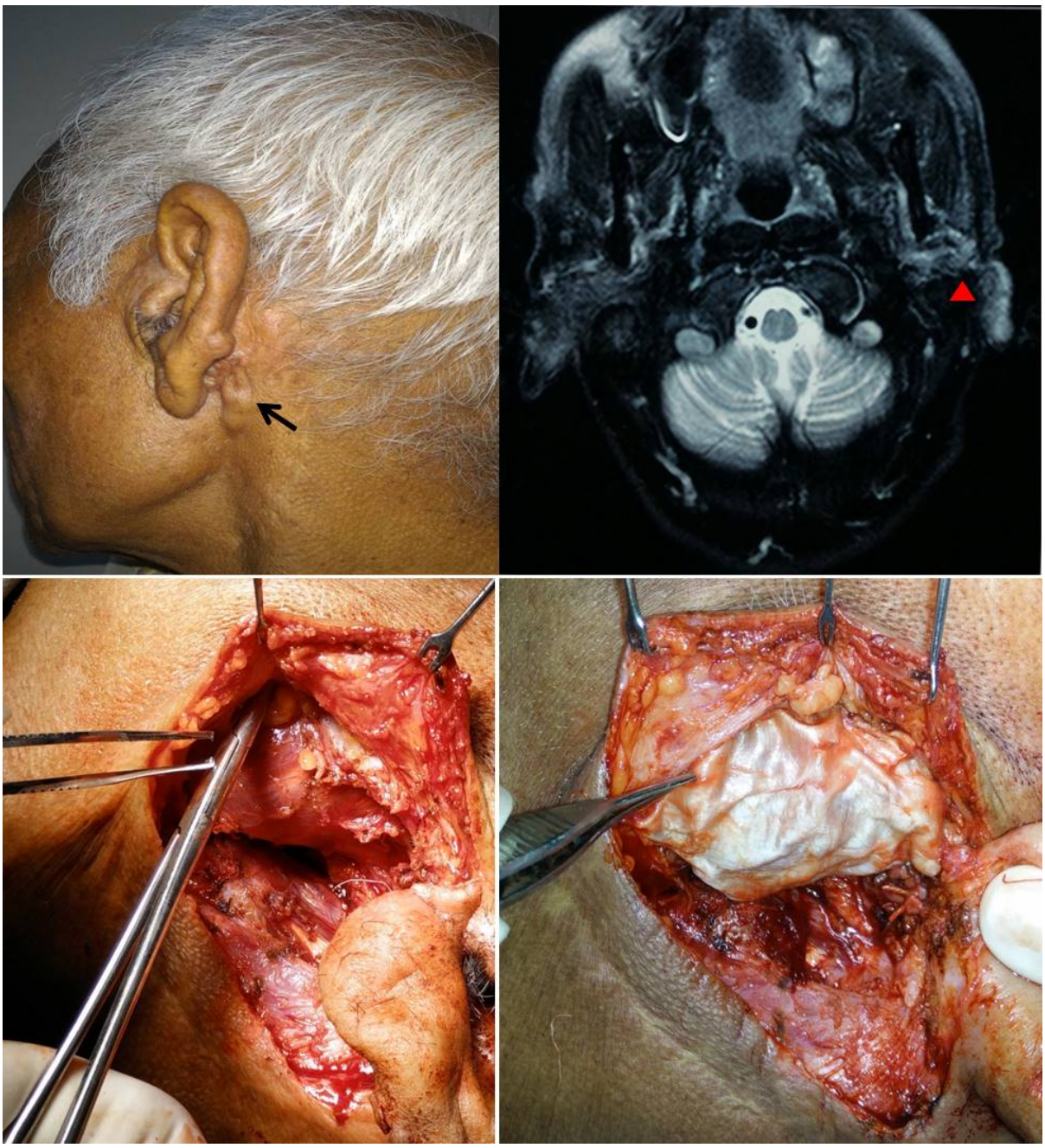

Figure 4: Two years post-operative. Nodular skin swellings over previous scar (*arrow*). MRI showing T2 hyperintense lesion extending from skin, subcutaneous tissue into deep retromandibular region (*arrowhead*). Intraoperative picture showing excision of recurrence followed by tensor fascia lata interposition.

Discussion

Secretory breast carcinoma is a rare and invasive type of breast cancer. It was first recognised in a series of seven children as "juvenile breast carcinoma" by McDivitt and Stewart.[1] It was subsequently reported in adults and was renamed as "secretory breast carcinoma" by Tavassoli and Norris based on its histopathological characteristics, that is, cells containing vacuolated cytoplasm and presence of intracellular and extracellular secretory material. [2] This tumor is currently defined by the presence of a specific genetic

alteration, t(12; 15) (p13; q25), which leads to the fusion of the *ETV6* gene on chromosome 12 with the *NTRK3* gene on chromosome 15 encoding for a chimeric tyrosine kinase [3].

In 2010, Skalova *et al* published a series of 16 salivary gland tumors with histomorphologic and immunohistochemical features reminiscent of secretory carcinoma of the breast, including the presence of aforementioned genetic alteration. They chose to designate this new entity as "Mammary analogue secretory carcinoma of salivary glands (MASC)" [4].

MASC is not the first salivary gland tumor to be shown to have a biological or morphological counterpart in a mammary gland neoplasm. Other examples include adenoid cystic carcinoma, mucoepidermoid carcinoma, acinic cell carcinoma, salivary duct carcinoma and pleomorphic adenoma. This is not surprising given the shared embryological (ectodermal) origin and histological (exocrine) organization of the mammary and salivary glands [5].

Since its first description, about 134 MASC cases have been reported till 2014 [6]. Luo *et al* observed a slight male predilection in these cases (M: F = 1.2:1). Among these tumors, 91 occurred in parotid, 11 in submandibular gland, 29 in minor salivary glands, and 2 in unspecified area [6]. Our limited series also showed a predilection for parotid gland and male gender.

The clinicopathological features of MASC are now well recognized. These features include tumor cells with oval to round nuclei with vesicular to finely granular chromatin and a single distinct nucleolus. Tumor cell cytoplasm is eosinophilic and vacuolated. Architectural growth patterns are varied and include microcystic, tubular, solid, macrocystic, papillary and pseudopapillary patterns. Intraluminal secretions ranging from light pink to colloid-like is also usually present. These characteristic features have been confirmed in numerous series and reports [4,7,8].

After it was first described, several pathological studies have been conducted which have identified MASC retrospectively among cases that were previously diagnosed as acinic cell carcinoma (ACC), mucoepidermoid carcinoma (MEC), or adenocarcinoma/cystadenocarcinoma, not otherwise specified (ADC-NOS) [4,7,9,10].

MASC bears a striking morphological resemblance to ACC. Both tumors show a variety of overlapping architectural patterns (microcystic, follicular, papillary-cystic). Moreover, MASC cells can resemble a variety of cell types seen in ACC, that is, intercalated duct-like, vacuolated, non-specific glandular, clear cells [11]. However, a major point of distinction between the two entities is the presence of distinct blue-purple zymogen granules in ACC [7]. Accordingly, ACC should no longer be diagnosed based only on cytological architecture. The absence of zymogen granules should prompt the pathologist to consider MASC as the possible alternative.

Although MASC may resemble mucoepidermoid carcinoma (particularly its oncocytic variant) in mucin production and eosinophilia, it lacks the squamoid cells and abundant mucocytes that are characteristic of MEC. Moreover, the papillary architectural pattern with transgressing vessels is more characteristic of MASC [12]. As for adenocarcinoma, not otherwise specified, its definition entails that a specific histological entity such as MASC must be excluded before making a diagnosis of ADC-NOS. Our study also demonstrated the similarity between MASC and ACC, 3 of our cases being diagnosed as ACC on fine needle aspiration cytology.

Immunohistochemistry (IHC) and molecular studies play a vital role in distinguishing MASC from its morphological mimickers. On IHC, MASC is consistently positive for

cytokeratin 7, cytokeratin 18, S-100 protein, vimentin, mammaglobin, and STAT5a, generally in a diffuse and strong fashion. Smooth muscle actin and calponin are consistently negative [4,8,11]. The characteristic genetic alteration of MASC may be detected either by break-apart ETV6 fluorescent in situ hybridization (FISH) or by detecting the ETV6–NTRK3 fusion transcript by reverse transcription-polymerase chain reaction (RT-PCR) [11]. Currently, molecular confirmation is considered the gold standard for the diagnosis of MASC.

Patel *et al* reported that 60% of polymorphous low-grade adenocarcinomas (PLGA) and 13.3% of adenoid cystic carcinomas showed significant positivity for mammaglobin and S-100, and cautioned against the use of only immunohistochemistry for diagnosing MASC, in the absence of molecular confirmation [13]. However, in a review of 19 cases by Shah *et al*, they found that morphology together with immunohistochemistry highly correlated with the *ETV6* gene rearrangement. They concluded that molecular confirmation is not required to diagnose every MASC; only in cases with atypical histological features, intraoral tumors (given the predilection of PLGA) or with areas of high-grade transformation, molecular confirmation should be sought.14 We did not perform molecular analysis in our patients. Molecular studies are often time-consuming and limited by their high cost and low availability. We agree with Shah *et al*. contention that molecular studies be limited to cases with atypical pathological features [14]. Accordingly, the diagnosis in all our patients was established by presence of typical histological features in addition to characteristic immunohistochemistry.

MASC generally follows the behaviour of a low-grade malignancy. The overall survival is similar to that of ACC [15]. Metastasis to lymph nodes, lymphovascular and perineural invasion can occur [16]. Most of the patients live free of disease after treatment. In Luo *et al*'s literature review of 134 cases, 17 patients experienced local recurrence, four experienced distant metastases, and only 6 patients died of disease [6]. The first patient in our series suffered from recurrence only after 2 years. Although the other patients have been recurrence-free, the paucity of literature at this time dictates that these patients be followed for a prolonged period. It must be stressed that a clinician should always have a high index of suspicion for recurrence in salivary gland tumors. Our case merely had nodular skin swellings over the previous scar when he presented to us for gustatory sweating, which could easily have been mistaken for fibrosis/hypertrophic scar. One must have a low threshold for investigating a patient for recurrence by FNA cytology and imaging.

High-grade transformation of MASC is rare and reported in only four recent cases.16, 17 All were composed of two distinctive areas with classic low-grade microcystic appearance in one area and well-demarcated, high-grade solid nests in other areas. Interestingly, one case was originally reported as monomorphic adenoma [16] and the other as dedifferentiation of ACC [17].

At this time, there is no conclusive evidence to say that MASC should be treated any differently than other low-grade malignant salivary gland tumors. Thus, radical surgical resection of the involved gland should be the initial treatment of choice. The value of post-operative radiotherapy (PORT) is unclear due to the paucity of treatment-specific survival data. Similar to other low-grade malignancies, PORT should be reserved for close margins, incomplete resection, perineural invasion, advanced (T3-T4) tumors and recurrences. Accordingly, the recurrent parotid MASC in our series underwent PORT while the others only underwent surgical resection.

Conclusions

MASC is a recently described malignant salivary gland tumor that mimics the histology and genetics of secretory carcinoma of the breast. MASC must be distinguished from its morphological mimickers. Characteristic histological features together with immunohistochemistry are diagnostic in most cases. Molecular confirmation is required in select situations. Radical surgical resection remains the treatment of choice. PORT is reserved for indications similar to other low-grade malignancies. One must have a high index of suspicion for recurrences and a prolonged follow-up period is warranted. Further research is needed to understand the clinical behaviour and prognostic significance of MASC.

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