Review Article

Secretory carcinoma of salivary gland – A systematic review of pediatric case reports and case series

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Abstract

Aim: Mammary analog secretory carcinoma (MASC) is a new pathological entity of salivary gland origin recognized as Secretory Carcinoma (SC) in the WHO 2017 classification. Pediatric cases of MASC were reviewed systematically from 2010 to 2019.

Materials and Methods: Databases were searched from 2010 to 2019 for pediatric case reports and case series, excluding retrospective studies. A total of 12 manuscripts were reviewed for clinical, histological and immunohistochemical findings.

Results: A total of 13 pediatric cases (11 case reports and 1 case series of 2 cases) of MASC in pediatric patients were found. The youngest reported age was 5 years. The common site was parotid gland usually presenting as a slowly growing firm, painless mass.

Conclusion: MASC should be considered in the differential diagnosis of salivary gland tumors in pediatric population, especially from parotid gland. Extended research on such recent entities with more inputs from new cases reported in literature may outstretch the possibilities of therapeutic fusion inhibition in future.

Keywords: Mammary analog, pediatric case reports, pediatric case series, salivary gland, secretory carcinoma

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INTRODUCTION

Mammary analog secretory carcinoma (MASC) is a neoteric salivary gland tumor with genetic, histologic and immunophenotypic equivalence to Secretory Carcinoma (SC) of the breast. This novel pathological entity was acknowledged in the WHO 2017 classification as SC.[1] Less than 300 cases have been published so far, more prevalent in parotid gland and minor salivary glands.[2]

SC of the breast, a variant of mammary ductal carcinoma, was described by McDivitt and Stewart. As the synchronous mention goes as juvenile breast cancer, it is predominant in 3–15 years and less frequent in the elderly. Studies reported that the molecular pathogenesis of SC of the breast is chromosomal translocation of t (12;15), (p13; q25), resulting in fusion of transcriptional regulator gene ETV6 with membrane receptor kinase NTRK3. Fusion gene promotes oncogenesis through activation of RAS-MAP pathway and phosphatidylinositol 3-kinase-protein kinase B pathway, by tyrosine kinase causing increased cell proliferation and survival of tumor cells. Identical translocations were documented in myelogenous leukemia,

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infantile fibrosarcoma and congenital mesoblastic nephroma in the past. At present, cases of MASC have been reported in thyroid gland.[3-5]

Skalova *et al*. in 2010 explored matching histological, immunohistochemical and genetic translocations from archives of salivary gland tumors by fluorescence *in situ* hybridization (FISH), reverse transcriptase-polymerase chain reaction (RT-PCR) and described them as MASC. They were earlier reported as zymogen-poor acinic cell carcinoma/adenocarcinoma NOS, low-grade cystadenocarcinoma. They reported 16 such cases, 13 from parotid and 3 from minor salivary glands of buccal mucosa, upper lip and palate, respectively.[3-5]

MASC clinically presents as a slow-growing, asymptomatic, non-aggressive mass, with male predominance in the age group of 21–75 years (mean – 46 years). Vast majority of cases were reported in parotid gland and minor salivary glands of buccal mucosa, palate and palate. Size of the slow-growing mass varies between 0.7 and 5.5 cm (mean-2.1 cm).[3-5]

Macroscopically, the tumor is, unencapsulated, well circumscribed, firm to rubbery in consistency, gray white to brown on cut surface with variable cystic component. The microscopic presentation is, heretogeneous with various patterns. Low-grade tumor cells with eosinophilic cytoplasm and vesicular, oval-to-round nuclei, central nucleoli and fine granular chromatin are most commonly reported. Various patterns include solid, microcystic, tubular, glandular and papillary–cystic. Microcysts and tubular spaces are filled with bubbly, colloid-like Periodic acid-Schiff (PAS) +ve secretion.[3-7]

Histochemical studies prove to be a confirmatory tool next to FISH and RT-PCR considering the economic resources for FISH. MASC shows positivity for S100, vimentin and mammaglobin. Other positive markers include pan-cytokeratin (AE1–AE3 and CAM5.2), EMA, CK7, CK8, CK18, CK19, GATA3, SOX10, Muc1, Muc4, STAT5A and GCDFP15. The cells show negative staining for basal cell and myoepithelial cell markers such as p63. Some cases have reported p63 positivity in areas of peripheral staining suggestive of intraductal component of MASC.[7]

Molecular detection by FISH remains the gold standard as fusion gene has not been reported so far in any other salivary gland tumor. Novel ETV6-non NTRK3 fusion and ETV6-X gene fusion other than exon5-exon15 have been delineated. These atypical junctions may correlate to densely hyalinized fibrous septa, thick fibrosclerotic stroma and infiltrative histologic features.[7]

MASC is reported to rarely metastasize, though lymphovascular, perineural, extraglandular invasion and necrosis may prevail. Cases of high-grade transformation have been documented.

Management ranges from excision to neck dissection based on aggressiveness. Surgical exploration through neck dissection with/without postoperative radiotherapy and chemotherapy is being followed as a treatment modality. Preoperative radiotherapy was not considered in the sequelae. ETV6 may serve as a therapeutic target in inhibition of gene fusion. *In vitro* studies suggest inhibitors of insulin-like growth factor-1 might block the translocation between ETV and NTRK.[8]

Thereby, behavior and presentation of MASC in an adult patient as reported in the literature have been abridged to analyze the distinguishing features of MASC in pediatric patients. This systematic review was put forward to address the clinical, histopathological and immunohistochemical presentation of pediatric cases of MASC.

MATERIALS AND METHODS

Data sources

Databases such as PubMed, Crossref, Cochrane, Science Direct and Google Scholar were searched for keywords, namely SC, mammary analog, pediatric cases using Boolean operators AND/OR in various combinations using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Search strategy

Case reports from 2010 to 2019 were extracted and duplicates were removed. Only case reports and case series were included, retrospective studies were excluded. Case reports of more than 18 years of age were excluded. Case reports of MASC of skin, nasal cavity, lungs and thyroid were excluded. Studies in language other than English were excluded.

RESULTS

Following the initial search using Medical Subject Headings (MeSH) terms, 18 articles from PubMed, 2 from Crossref, 3 from Cochrane, 3 from Science direct and 16 from Google Scholar were obtained [Figure 1]. The manuscripts were filtered based on the inclusion and exclusion criteria following which a total of 13 cases (11 case reports and 1 case series of 2 cases) were evaluated according to the objectives of the study [Table 1].

Table 1: Overview of reported pediatric cases of SC

Author/year	Age/sex	Size/site/ duration	Clinical presentation	Histopathological presentation	Immunohistochemical finding	Treatment and follow up
Rastatter *et al*., 2012[9]	14 years/ female	4 cm/4 months/ right parotid	Asymptomatic, slowly enlarging	Papillary, microcystic with bubbly secretions	S100+	Parotidectomy with right selective neck dissection-12 months postoperative-uneventful
Hwang *et al*., 2014[10]	13 years/ male	3 years/left parotid	Asymptomatic mass	Microcystic, tubular with focal papillary. Focal infiltration to surrounding tissue	S100+/CK19+/ vimentin+/CK5/6-/ p63−/CEA−/DOG1−/ alpha-1-antichymotrypsin 1−	Excision-8 months postoperative-uneventful
Woo *et al*., 2014[11]	14 years/ male	1.5 cm/1 year/left parotid (history/ of atypical teratoid rhabdoid tumor at the age of 3 years)	Persistent firm, mobile mass with left frontal branch involvement	Microcystic, tubular, solid	Vimentin +/S100+/ EGFR+/DOG1−/p63−	Superficial parotidectomy with facial nerve dissection
Keisling 2014[12]	5 years/ female	4 months/right buccal mucosa	Persistent mass	Solid sheets of tumor cells	Vimentin +/AE1/AE3+/ CK7+/CK14−/DOG1−	Excision. Further excision recommended, patient was lost to follow-up
Inaba 2015[6]	15 years/ female	1 year/left parotid	Slowly enlarging mass	Multinodular, hyalinized stroma, microcystic and tubular pattern	S100+/GCDFP15+/ Mammaglobin+/ER-/PgR−/ HER−/p63−	Parotidectomy, symptom free 40 months postop
Quattlebaum *et al*., 2015[13]	15 years/ female	3 cm/several months/left parotid	Slowly enlarging, fixed, firm mass	Microcystic, papillary	S100+/CK19+	Superficial parotidectomy with facial nerve dissection
Joshi *et al*., 2015[14]	15 years/ male	20 cm/18 months/right parotid	Asymptomatic, firm progressive mass	Microcystic with lipid containing vacuoles. Tiny aggregates of epithelial cells were seen	S100+/CK7+/CK19+/ vimentin +/EMA +/ GCDFP15+/CD10+/CK20−/ PR−/SMA−/DOG1−/ CD34−/CEA−	Total parotidectomy with facial and spinal accessory nerve
Oza *et al*., 2016[15]	9 years/ female	1 cm/3 months/ right parotid	Asymptomatic mass	Microcystic, tubular, solid patterns	S100+/mammaglobin +/ CK7+DOG1−/p63−	Parotidectomy
Oza 2016	16 years/ female	2 cm/8 months/ right parotid	Painless swelling	Microcystic, tubular, solid patterns	S100+/mammaglobin +/ CK7+/DOG1−/p63−	Parotidectomy
Ngouajio *et al*., 2017[16]	14 years/ male	3 cm/several months/left parotid	Progressively increasing, firm, immobile mass	Microcystic, solid, tubular patterns	S100+/mammaglobin +	Superficial parotidectomy with selective neck dissection. Disease free 14 months postoperative
Shukla *et al*., 2018[17]	17 years/ male	3 cm/18 months/ left parotid	Nontender, firm mass	Solid, tubular, cystic, papillary architecture	S100+/mammaglobin+/ EMA+/pan CK+/DOG1−/ ER−/PR−/SMA−/Her2neu−/ GCDFP1−/calponin−	Parotidectomy. Disease free 7 months postoperative
Chen *et al*., 2018[18]	12 years/ female	2 cm/2 months/ right parotid	Firm, tender mass	Microcystic	S100+/GATA3+/ CK7+/p63−/actin−/ calponin−/DOG1−	Superficial parotidectomy. Planned for close follow-up for 5 years
Shigeta *et al*., 2018[19]	7 years/ male	5 cm/1 year/left parotid	Slowly enlarging mass	Microcystic	S100+/mammaglobin+/ GCDFP15+/vimentin+/ CAM5.2+	Superficial parotidectomy. 20 months postoperative disease free

CK: Cytokeratin, EMA: Epithelial Membrane Antigen, GCDFP: Gross Cystic Disease Fluid Protein, PR/PgR: Progesterone Receptor, SMA: Smooth Muscle Actin, CEA: Carcinoembryonic Antigen, ER: Estrogen Receptor, EGFR: Epidermal Growth Factor Receptor

DISCUSSION

Salivary gland neoplasms constitute 2% to 6% of all head-and-neck cancers. Pediatric salivary gland malignancies are reported to be <5%.[20] Secondary salivary gland malignancies arising postradiation are the most common in children and constitute 6% of all secondary pediatric malignancies. Mucoepidermoid carcinoma is reported to be the most prevalent pediatric secondary salivary gland malignancy.[21]

SC of the salivary gland shares morphological, immunological and molecular profiles with SC of the breast which may be attributed to both having tubuloacinar exocrine glands. Despite these analogous criteria, difference in clinical behavior is observed as salivary gland SC is most common in 21–75-year-old male patients as compared to 3–15-year-old female cases in SC of the breast.[22]

Of the 13 pediatric cases evaluated, the mean age was 12.7 years ranging from 5 to 17 years, with a M: F ratio of 1:1.2. The sex predilection was not compatible with the published reports of adult cases. This may be attributed to the limited number of pediatric cases reported. Of 13 pediatric cases, 12 were from parotid and 1 from buccal mucosa. Vast majority of adult cases were also from

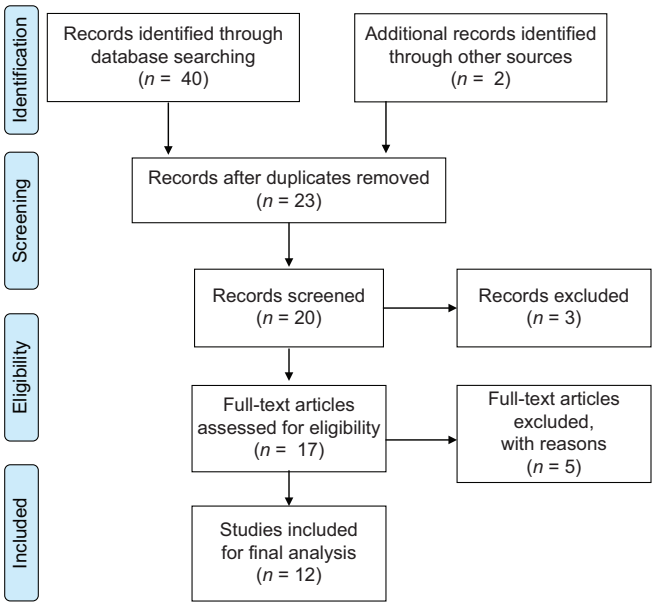

Figure 1: Data extraction as per PRISMA guidelines

parotid. The smallest size of SC among 13 cases was 1 cm and largest was 20 cm, both from parotid. The mean size of SC from adults is 0.7 to 5.5 cm. Location of the tumor may also contribute to the size. Clinical presentation was asymptomatic, painless mass with indolent course, also consistent with the adult literature. Only one pediatric case had SC arising as a secondary malignancy from treated atypical teratoid rhabdoid tumor.

Fine-needle aspiration cytology was performed in 6 cases of 13 and advanced imaging techniques were performed as a diagnostic aid in all 13 cases. Histologically, microcystic, tubular and solid patterns with eosinophilic bubbly secretions were the most common patterns in pediatric cases too. Lymph node metastasis and perineural invasion are also important features of SC with aggressive course. High-grade transformation of SC has not been reported in pediatric population though observed in adults.

Management of SC is yet to be well documented as most of the studies are retrospective. Parotidectomy was the treatment of choice in pediatric cases as compared to surgical management with/without postoperative chemotherapy and radiotherapy in the management of adult SC. Postoperative follow-up details were available for 7 cases. Sparsity of clinical data with respect to management and long-term follow-up of pediatric SC can add up to the need for therapeutic target in near future.

However, the review has certain limitations such as evidence selection bias where studies with statistically significant outcomes were only published and retrospective studies, studies with only abstracts were not included in the study.

CONCLUSION

The diagnosis of SC in pediatric cases is challenging due to the paucity of cases reported. SC should be considered in the differential diagnosis of salivary gland tumors in pediatric population, especially from parotid gland. Although pediatric clinical, immunologic and histological presentation is similar to the adult literature published so far, extended research on such recent entities with more inputs from new cases reported in literature may outstretch the possibilities of therapeutic fusion inhibition in future.

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Conflicts of interest
There are no conflicts of interest.

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