SECRETORY CARCINOMA OF SALIVARY GLAND – A SYSTEMATIC REVIEW OF PEDIATRIC CASE REPORTS AND CASE SERIES

V Vasanthi1, R Ramadoss2

1Lecturer, Department of Oral Pathology and Microbiology, SRM Dental College, 2Professor, Department of Oral Pathology and Microbiology, Saveetha Dental College, Chennai, Tamil Nadu, India

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,

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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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, heterogeneous 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 fibroelastic 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].
Vasanthi and Ramadoss: Secretory carcinoma – Pediatric case reports and case series

DISCUSSION

Salivary gland neoplasms constitute 2% to 6% of all head-and-neck cancers. Pediatric salivary gland malignancies are reported to be <5%. 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.

SC of the salivary gland shares morphological, immunological and molecular profiles with SC of the breast which may be attributed to both having tubuloacinereous 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.

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 the age of 3 years.)

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 | 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 | 13 years/ male | 3 years/left parotid | Asymptomatic mass | Microcystic, tubular with focal papillary, Focal infiltration to surrounding tissue Microcystic, tubular, solid | S100+/CK1 9+ | Excision-8 months postoperative-uneventful |
| Woo et al., 2014   | 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 | Solid sheets of tumor cells | Vimentin+/CAM5.2+/GCDFP1 5+/CK1 9+/p63−/CEA−| Superficial parotidectomy with facial nerve dissection |
| Keisling 2014      | 5 years/ female | 4 months/right buccal mucosa | Persistent mass | Multinodular, hyalinized stroma, microcystic and tubular pattern | S100+/GCDFP1 5+/Mammaglobin+/ER−/PgR−/HER−/p63− | Parotidectomy, symptom free 40 months postop |
| Inaba 2015         | 15 years/ female | 1 year/left parotid | Slowly enlarging mass | Multinodular, hyalinized stroma, microcystic and tubular pattern | S100+/GCDFP1 5+/Mammaglobin+/ER−/PgR−/HER−/p63− | Total parotidectomy with facial and spinal accessory nerve |
| Quattlebaum et al., 2015 | 15 years/ female | 3 cm/several months/left parotid | Slowly enlarging, fixed, firm mass | Microcystic, with lipid containing vacuoles. Tiny aggregates of epithelial cells were seen | S100+/CAM5.2+/GCDFP1 5+/CK1 9+/p63−/CEA− | Superficial parotidectomy with selective neck dissection. Disease free 14 months postoperative |
| Oza et al., 2016   | 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 |
| Ngouajo et al., 2017 | 14 years/ male | 3 cm/several months/ left parotid | Progressively increasing, firm, immobile mass | Microcystic, solid, tubular patterns | S100+/mammaglobin+/Vimentin+/CAM5.2+ | Superficial parotidectomy, planned for close follow-up for 5 years |
| Shukla et al., 2018 | 17 years/ male | 3 cm/18 months/ left parotid | Nontender, firm mass | Solid, tubular, cystic, papillary architecture | S100+/mammaglobin+/EMAT1+/pan CK+/DOG1−/ER−/PR−/CEA−/CD34−/CAM5.2+ | Superficial parotidectomy, planned for close follow-up for 20 months postoperative disease free |
| Chen et al., 2018   | 12 years/ male | 2 cm/2 months/ right parotid | Firm, tender mass | Microcystic | Vimentin+/CAM5.2+ | Superficial parotidectomy, planned for close follow-up for 5 years |
| Shigeta et al., 2018 | 7 years/ male | 5 cm/1 year/ left parotid | Slowly enlarging mass | Microcystic | Vimentin+/CAM5.2+ | Superficial parotidectomy, planned for close follow-up for 5 years |

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
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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