Mammary Analogue Secretory Carcinoma of the Parotid Gland as a Secondary Malignancy in a Childhood Survivor of Atypical Teratoid Rhabdoid Tumor

Jennifer Woo · Raja R. Seethala ·
S. Joseph Sirintrapun

Received: 19 April 2013 / Accepted: 22 July 2013 / Published online: 7 August 2013
© Springer Science+Business Media New York 2013

Abstract We report the first case of mammary analogue secretory carcinoma (MASC) arising as a secondary malignancy in a 14 years old child with a history of atypical teratoid rhabdoid tumor (ATRT). Although MASC and ATRT are both rare malignancies, they do not share the same genetic and molecular profiles. MASC is a salivary malignancy characterized by a t(12;15)(p13;q25) translocation, resulting in an ETV6-NTRK3 fusion product encoding for a tyrosine kinase. ATRT is a highly malignant pediatric tumor characterized by a chromosome 22 mutation in the hSNF5/INI1 gene, encoding for a chromatin remodeling protein. Additionally, although mucoepidermoid carcinoma has been described as a secondary malignancy post-therapy for head and neck tumors, MASC has only been reported as a primary malignancy. Our patient was treated with a complete resection of his left sided ATRT at age 3 followed postoperatively with chemoradiotherapy. At age 14 he underwent a parotidectomy for his 1 year history of a left sided preauricular mass and was subsequently diagnosed with MASC. We not only report a case of two rare malignancies in one patient, but also the first case of MASC arising as a secondary malignancy.

Keywords Mammary analogue secretory carcinoma · Parotid gland · Atypical teratoid rhabdoid tumor

Introduction

Major salivary gland malignancies are rare in the pediatric population with <5 % of malignancies seen in children. Of these, the most common histological type is mucoepidermoid carcinoma (MEC) followed by acinic cell carcinoma (AciCC) [1]. Most pediatric salivary gland malignancies occur as secondary cancers arising post-radiation and constitute 6 % of all secondary pediatric malignancies. Mucoepidermoid carcinoma is described as the most common of these secondary cancers [2].

Mammary analogue secretory carcinoma (MASC) is a recently described malignancy affecting both adult and childhood populations. MASC has so far been reported as a primary malignant tumor of rare incidence. We describe the first known development of MASC arising as a secondary post-radiation malignancy in a 14 years old child with a history of atypical teratoid rhabdoid tumor (ATRT) resected at age 3. This is a child with a history of two rare malignant neoplasms.

Case Report

Clinical Presentation

A 14 years old boy with a history 11 years prior of ATRT of the left temporoparietal lobe presented to the ENT clinic with a 1 year history of a left sided preauricular mass. Initially, a computerized tomographic scan demonstrated a 2 × 2 cm fluid collection with rim enhancement in the anterior left parotid. Because the mass persisted on follow-up examinations, a fine needle aspiration biopsy (FNAB) was performed revealing clusters of atypical epithelial-appearing cells with eccentric nuclei, nuclear enlargement

J. Woo (✉) · R. R. Seethala · S. Joseph Sirintrapun
School of Medicine, Wake Forest University, Winston-Salem,
NC, USA
e-mail: jennifer.susan.woo@gmail.com

and small nucleoli, suggestive of a salivary neoplasm, though further classification was not possible.

On physical examination 2 months after FNAB, the 1.5 cm firm mobile mass remained persistent. Notably, the patient developed left frontal branch weakness and an absence of left-sided forehead creases. The rest of the facial nerve was intact. There was no palpable lymphadenopathy on neck exam. Further radiographic evaluation with an MRI revealed a $1.0 \times 1.7 \times 1.9$ cm mildly enhancing preauricular subcutaneous soft tissue mass which was inseparable from the anterior parotid gland. In light of this mass with newly developed facial nerve involvement and a remote history of ATRT, the patient underwent a left superficial parotidectomy with facial nerve dissection for further evaluation and treatment.

Surgical Management

Dissection of the main trunk of the left facial nerve was accomplished and a 2 cm firm mass was palpable in the superficial lobe of the parotid gland. The mass had a discolored tan appearance and was intimately associated with at least three branches of the upper division of the left facial nerve. To facilitate resection, the proximal end of the facial nerve upper division was sacrificed. A cable nerve graft was then anastomosed with the facial nerve defect using the left great auricular nerve. The postoperative course was unremarkable and the patient was discharged within 2 days.

Results

Pathological Evaluation

The superior resection of the left parotid mass showed a well-circumscribed tumor with a tan variegated appearance. Sections showed a tumor with pushing borders and microcystic, tubular, and solid growth patterns (Fig. 1a). The tumor cells were monotonous with granular and vacuolated amphophilic cytoplasm (Fig. 1b). There was abundant extracellular mucin production within luminal structures as confirmed by mucicarmine staining. No perineural invasion was appreciated on the main tumor specimen or the additional facial nerve branch excisions. A PAS stain before and after diastase treatment showed no evidence of true zymogen granule formation. An immunohistochemical panel revealed positive tumoral staining for vimentin (strong), S100 (strong diffuse) and EGFR (weak). The tumor showed no staining for p63 which highlighted only perilesional cells. A DOG-1 stain was negative.

Additionally, the slides and blocks from the patients ATRT were retrieved and re-reviewed. The tumor showed

confluent nests and solid sheets rather than glandular or rosette formation. The tumor comprised of medium-sized pleomorphic cells with abundant vacuolated eosinophilic cytoplasm and prominent nucleoli (Fig. 1c). As confirmation of the ATRT, INI1 staining was performed on that specimen and showed loss of protein staining (Fig. 1d).

Molecular Evaluation

Fluorescence in situ hybridization (FISH) for *ETV6* rearrangement was performed on both the salivary tumor and the ATRT utilizing a *ETV6* (12p13) break-apart probe (Abbot Molecular, Des Plaines, IL, USA) (Fig. 2). Rearrangement was positive in the salivary tumor and negative in the ATRT.

Discussion

Radiation therapy is estimated to incur a 10–20-fold risk of secondary malignancy within the pediatric population [3]. The cumulative probability of a secondary malignancy ranges from 3.3 to 12 % at 20 years [4, 5]. In children, salivary gland tumors occur more frequently after post-radiation therapy. Although pediatric neoplasms of the salivary glands are rare, approximately one-quarter to one-half of salivary neoplasms are malignant [2]. Of these, the most common histological type is MEC. It is reported that survival of pediatric patients with major salivary gland carcinomas is generally favorable with a 5-year overall survival of over 90 % [6].

Our patient is a 14 years old male who developed MASC years after resection of ATRT at age 3. To date, this is the first report of MASC developing post-radiation therapy.

Mammary analogue secretory carcinoma is a recently described tumor entity which historically had been designated as AcicC. Genetically, it is characterized by a t(12;15)(p13;q25) translocation, resulting in an *ETV6-NTRK3* fusion product encoding for a tyrosine kinase. This malignancy shares the same translocation as breast juvenile secretory carcinoma, infantile fibrosarcoma, and congenital mesoblastic nephroma [7]. Histologically, MASC is locally invasive with microcystic architecture, low-grade nuclei, and granular pink vacuolated cytoplasm. It stains positively for S-100 and vimentin, as demonstrated in our patient. The characteristic *ETV6-NTRK3* rearrangement can be detected via FISH and is used as confirmation for MASC diagnosis. MASC has been reported in ages ranging from 14 to 77 years as a primary malignant tumor with a slightly male predominance and a predilection for the parotid gland [8]. Although given its rarity, the prognostic relevance of recognizing MASC is not entirely clear, a comparative

Fig. 1 H & E sections of the MASC demonstrate a monotonous salivary gland tumor with pushing borders and microcystic, tubular, and solid growth patterns (**a**), as well as granular and vacuolated amphophilic cytoplasm (**b**). Sections of the ATRT showed confluent

nests and solid sheets of medium-sized pleomorphic cells with abundant vacuolated eosinophilic cytoplasm and prominent nucleoli (**c**). INI1 immunostains showed loss of protein staining, confirming the diagnosis (**d**)

Fig. 2 Fluorescence in situ hybridization (FISH) for *ETV6* rearrangement was performed on the salivary tumor and was positive for rearrangement, confirming the diagnosis of MASC

analysis of MASC and AciCC suggested a slightly worse mean disease-free survival (92 months) compared to AciCC (121 months). However though this difference has not been proven to be statistically significant [9].

The concurrent occurrence of MASC with yet another rare tumor, ATRT, is unique. However we also document that these two tumors as expected, arise from distinctive molecular pathways.

Atypical teratoid rhabdoid tumor (ATRT) is a highly rare and malignant pediatric brain tumor comprising approximately 2–3 % of pediatric brain tumors and 10 % of CNS tumors in infants [10]. Unlike the t(12;15) translocation found in MASC, ATRT is generally characterized by inactivating deletions and mutations affecting the *hSNF5/INI1* tumor suppressor gene on chromosome 22 encoding for a chromatin remodelling protein. A translocation event on 22q11.2 can also be involved in the pathogenesis of malignancy in addition to the more commonly found

biallelic mutations and deletions [11]. Histologically, ATRT is composed of rhabdoid cells which are characterized by a medium-size, round to oval shape with distinct borders, eccentric nuclei, and prominent nucleoli [12]. Immunohistochemical staining can display a wide range including the presence of vimentin, epithelial membrane antigen, smooth muscle actin, and glial fibrillary acid protein. ATRT can be confirmed by loss of nuclear immunostaining for INI1 protein as confirmed with our case [11]. Treatment for ATRT includes complete resection and chemoradiotherapy, however prognosis remains dismal even despite optimal surgical and medical therapy. Survival occurs in <20 % of patients at 12 months from diagnosis [12].

Despite seemingly disparate pathogeneses for MASC and ATRT, the potential for MASC to arise as a secondary malignancy post therapy is still hypothetically plausible. There are several examples of secondary malignancies of the head and neck region whereby translocation rearrangement is the mechanism of pathogenesis. One example is MEC, the most common malignant salivary tumor. MEC does occur post-radiation therapy and is the most common secondary salivary malignancy. MEC is associated with a translocation t(11;19)(q21;p13) involving the MECT1 and MAML2 genes [13]. Radiation-associated papillary thyroid cancer (R-PTC) is another example with rearrangements of the RET gene. It has been shown that RET translocation partners like the H4 gene are in close spatial continuity during interphase. With radiation induced breakage enabling rearrangement between RET and H4, this results in the RET/PTC1 fusion gene seen in R-PTC [14]. A similar mechanism is possible with MASC, where the ETV6-NTRK3 fusion product is the result of similar spatial continuity during interphase.

In summary, we report a novel case of MASC arising as a secondary malignancy subsequent to treatment of an ATRT. We have shown that both tumors have a distinct morphologic and molecular phenotype suggesting that the development of MASC after this ATRT may be instead similar to the development of other secondary malignancies post therapy. Although MASC and ATRT are rare, this case draws attention to the growing importance of cytogenetics and molecular characterization in the diagnosis of newly defined tumor entities.

References

1. Shapiro NL, Bhattacharyya N. Clinical characteristics and survival for major salivary gland malignancies in children. *Otolaryngol Head Neck Surg.* 2006;134:631–4.
2. Cheuk DKL, Shek TWH, Chan GCF, et al. Parotid acinic cell carcinoma in a long-term survivor of childhood acute lymphoblastic leukemia. *Pediatr Blood Cancer.* 2006;50(3):636–9.
3. Kaste SC, Hedlund G, Pratt CB. Malignant parotid tumors in patients previously treated for childhood cancer: clinical and imaging findings in eight cases. *AJR Am J Roentgenol.* 1994;162:655–9.
4. Mike V, Meadows AT, D'Angio GJ. Incidence of second malignant neoplasms in children: results of an international study. *Lancet.* 1982;2:1326–31.
5. Myer CMIII. Second primary malignancies of the head and neck in children. *Am J Otolaryngol.* 1995;16:415–7.
6. Kupferman ME, de la Garza GO, Santillan AA, et al. Outcomes of pediatric patients with malignancies of the major salivary glands. *Ann Surg Oncol.* 2010;17:3301–7.
7. Skalova A, Vanecek T, Sima R, et al. Mammary analogue secretory carcinoma of salivary glands, containing the ETV6-NTRK3 fusion gene: a hitherto undescribed salivary gland tumor entity. *Am J Surg Pathol.* 2010;34:599–608.
8. Connor A, Perez-Ordóñez B, Shago M, Skalova A, Weinreb I. Mammary analog secretory carcinoma of salivary gland origin with ETV6 gene rearrangement by FISH: expanded morphologic and immunohistochemical spectrum of a recently described entity. *Am J Surg Pathol.* 2012;36(1):27–34.
9. Chiosea SI, Griffith C, Assaad A, et al. Clinicopathological characterization of mammary analogue secretory carcinoma of salivary glands. *Histopathology.* 2012;. doi:[10.1111/j.1365-2559.2012.04232.x](https://doi.org/10.1111/j.1365-2559.2012.04232.x).
10. Coccé MC, Lubieniecki F, Kordes U. A complex karyotype in an atypical teratoid/rhabdoid tumor: case report and review of the literature. *J Neurooncol.* 2011;104:375–80.
11. Bikowskaa B, Grajkowskab W, Jóźwiak J. Atypical teratoid/rhabdoid tumor: short clinical description and insight into possible mechanism of the disease. *Eur J Neurol.* 2011;18:813–8.
12. Macdonald TJ. Aggressive infantile embryonal tumors. *J Child Neurol.* 2008;23:1195.
13. Clauditz TS, Gontarewicz A, Wang CJ, Münscher A, Laban S, Tsourlakis MC, Knecht R, Sauter G, Wilczak W. 11q21 rearrangement is a frequent and highly specific genetic alteration in mucoepidermoid carcinoma. *Diagn Mol Pathol.* 2012;21(3):134–7.
14. Nikiforova MN, Stringer JR, Blough R, Medvedovic M, Fagin JA, Nikiforov YE. Proximity of chromosomal loci that participate in radiation-induced rearrangements in human cells. *Science.* 2000;290(5489):138–41.