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CASE REPORTS

Salivary Gland NUT Carcinoma with Prolonged Survival in Children: Case Illustration and Systematic Review of Literature

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Abstract

NUT (midline) carcinoma is a rare, highly aggressive, poorly differentiated carcinoma that characteristically harbors a rearrangement of the *NUTM1* gene. Most of these tumors occur in adolescents and young adults, arise from the midline structures of the thorax, head, and neck, and are associated with extremely poor outcomes. Rare cases originating from salivary glands have been reported with clinicopathologic features comparable to NUT carcinoma of other sites. Outcome studies regarding this subgroup are currently lacking. We report a case of NUT carcinoma arising in a submandibular gland of a 12-year-old boy. Diagnosis was confirmed by fluorescence in situ hybridization demonstrating fusion of the *BRD4* (19p13.12) and *NUTM1* (15q14) gene loci. A systematic review of all previously reported salivary gland NUT carcinomas (n = 15) showed exclusive occurrence of pediatric cases (n = 6) in males compared to adult patients (n = 9, male: female = 1:2; $p < 0.05$). The median survival was 24 and 4 months for pediatric and adult patients, respectively (95% confidence interval was 8–24 and 1–7 months, respectively; $p < 0.01$). The 1-year overall survival was 67% for pediatric and 11% for adult patients. Among all NUT carcinomas, pediatric salivary gland tumors may represent a distinct clinical subset associated with male predilection and comparatively prolonged survival.

Keywords NUT · *BRD4-NUTM1* · Salivary gland tumor · Pediatric · Survival

Introduction

NUT (midline) carcinoma is a rare variant of poorly differentiated carcinoma defined by translocations involving the *NUTM1* gene on chromosome 15q14 [1–3]. The *NUTM1* gene is most commonly fused to the Bromodomain and Extra-Terminal (BET) family genes *BRD4* gene on chromosome 19p13.12, and less frequently to the *BRD3* gene on chromosome 9q34.2 or the *NSD3* gene on chromosome 8p11.23 [1, 3, 4].

Originally considered to be restricted to the midline head and neck structures or mediastinal region in young individuals, NUT carcinomas now are identified in patients of all ages, affecting males and females equally, and can rarely arise outside of midline locations. Outcomes are almost universally dismal, with most patients presenting with advanced primary tumors and distant metastases [3–5]. Overall survival (OS) does not appear to correlate with gender, tumor site, histology, or lymph node involvement [5, 6]. Response to conventional chemotherapy is poor. However, new treatment strategies involving small-molecule BET inhibitors and

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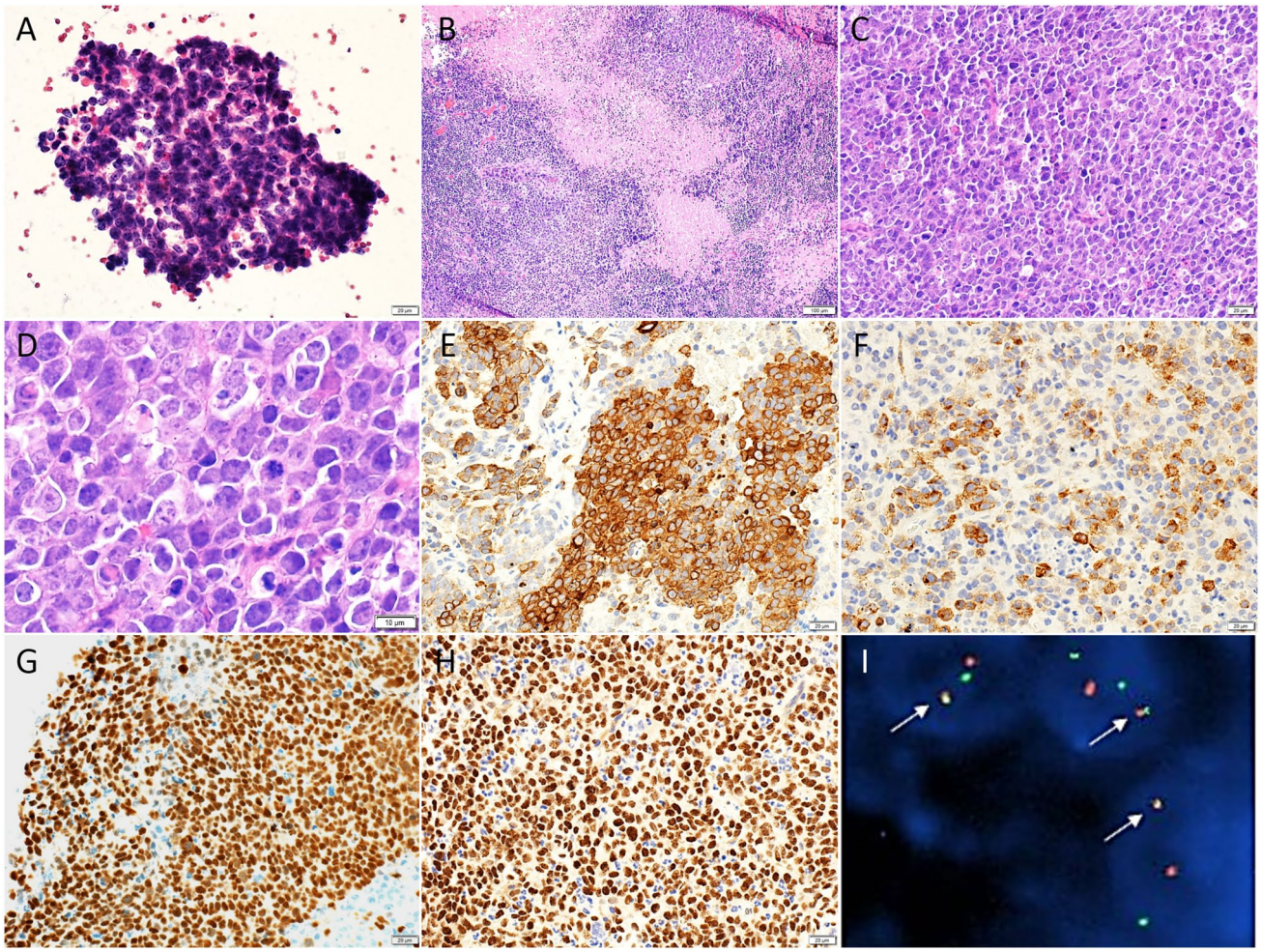

Fig. 1 Histologic, immunohistochemical and molecular cytogenetic findings of the initial biopsy tissue. **a** Touch preparation showing a cluster of cohesive poorly differentiated cells. **b** Frequent areas of geographic tumor necrosis. **c** Tumor cells demonstrating a predominantly solid growth pattern. **d** Poorly differentiated tumor cells with scant to moderate, eosinophilic and occasionally dense cytoplasm, moderate pleomorphism, and brisk mitotic activities. **e** Pan cytokeratin (AE1/AE3) stain showing diffuse and variably strong immunoreactivity in the poorly differentiated cells. **f** A subset of tumor cells strongly positive for synaptophysin with granular cytoplasmic staining. G, p63 stain showing patchy but strong nuclear immunoreactivity. **h** NUT stain showing diffuse and strong expression in tumor cell nuclei. **i** Representative interphase nuclei illustrating tightly juxtaposed orange (*BRD4*) and green (*NUTM1*) signals (arrows) indicative of *BRD4-NUTM1* fusion

histone deacetylase inhibitors are currently in development and hold promise [7–9]. Prompt enrollment of patients with early, treatable NUT carcinoma into clinical trials requires early diagnosis by recognition of the clinicopathologic features and a high degree of suspicion.

Salivary gland is an unusual site for NUT carcinoma. To the best of our knowledge, 14 cases of salivary gland NUT carcinoma (5 pediatric and 9 adult) have been reported in the literature [6, 10–19]. Here, we describe the clinicopathologic features and autopsy findings of a sixth pediatric case arising from the submandibular gland. A systematic review of the reported cases demonstrated male predilection and significantly prolonged OS in the pediatric group.

Case Report

An 11-year-old male presented with an enlarging and painful mass at the angle of the left mandible for 2 months. Physical examination showed a large, complex, firm mass extending downward from the angle of the left mandible without evidence of cellulitis of the overlying skin and soft tissue. Lymph nodes in the submental region and the left posterior triangle of the neck were enlarged. Computed tomography (CT) with contrast enhancement of the neck showed a partially necrotic lesion in the left submandibular space measuring 5.5 × 5.4 × 5.1 cm, as well as a separate 3.6 × 3.2 × 3 cm mass deep to the left sternocleidomastoid muscle. The

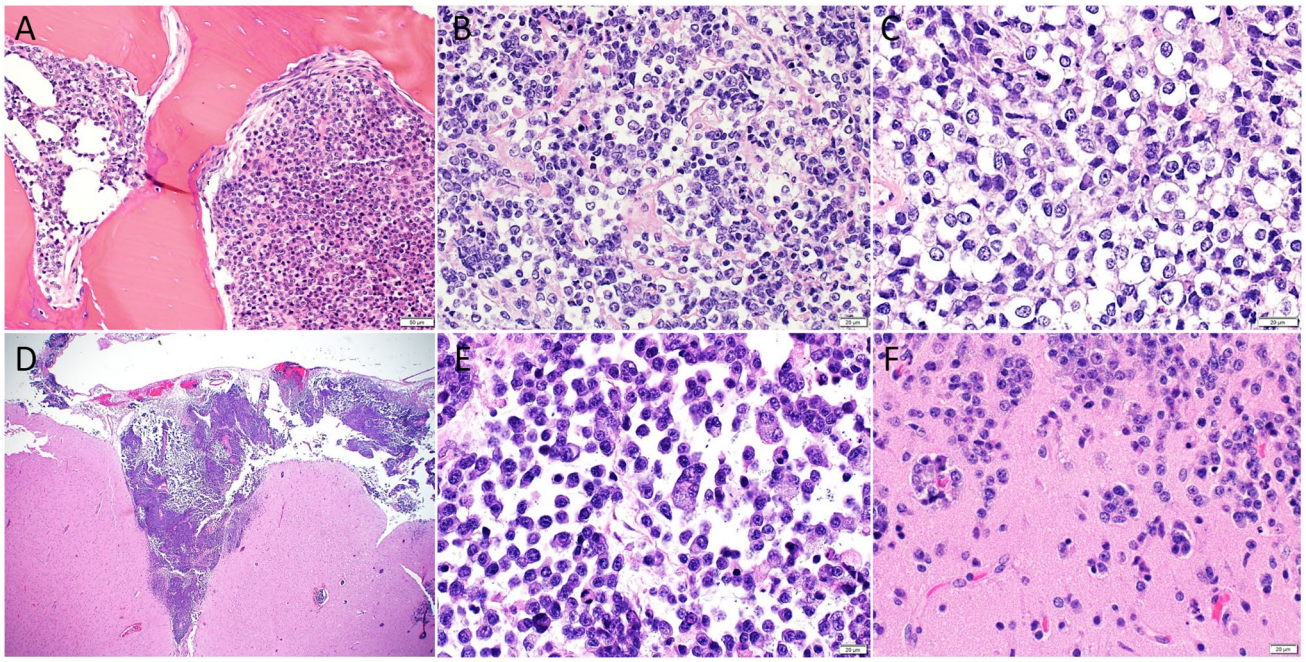

Fig. 2 Histologic features of metastatic disease. **a** Cribriform plate involvement by aggressive local invasion. **b** Sagittal suture metastasis showing a pseudoalveolar and nested pattern. **c** Tumor cells focally exhibiting prominent clear cytoplasm and vesicular chromatin. **d** Representative area showing extensive leptomeningeal carcinomatosis with superficial invasion into brain parenchyma. **e** Discohesive tumor cells in leptomeningeal spread. **f** Tumor cells breaking through the Virchow–Robin spaces and demonstrating an infiltrative growth pattern

clinical and radiologic findings were suggestive of a malignant neoplasm originating from the left submandibular gland with nodal involvement.

An incisional biopsy of the large mass was performed. Microscopic examination showed cohesive sheets of medium-sized round blue tumor cells intimately associated with a reactive lymphoid process in the background of extensive necrosis. The tumor cells exhibited scant to moderate cytoplasm, mild nuclear pleomorphism, evenly dispersed chromatin, inconspicuous nucleoli, and abundant mitotic figures of both typical and atypical forms (Fig. 1a–d). Squamous differentiation was lacking. The tumor cells exhibited strong but patchy immunoreactivity for AE1/AE3 (Fig. 1e), CK19, CK5/6 and CAM 5.2. The tumor cells were also positive for synaptophysin (Fig. 1f), p63 (patchy, Fig. 1g), CD99, INI-1 (retained nuclear expression), Bcl2 and S-100 (patchy). Negative stains included GFAP, epithelial membrane antigen (EMA), chromogranin A, CD56, NB84, CD34, smooth muscle actin, desmin, myogenin, Melan-A, HMB-45 and CD117. Epstein–Barr virus-encoded small RNAs (EBER) in situ hybridization was negative. Based on the histologic features and immunohistochemical profile, a preliminary diagnosis of poorly differentiated carcinoma was made, with NUT carcinoma and myoepithelial carcinoma being considered more likely on the differential diagnosis. Subsequent fluorescent in situ hybridisation (FISH) study for the *BRD4* and *NUTM1* spanning probe set was positive, confirming the diagnosis of NUT carcinoma (Fig. 1i). FISH studies for rearrangement of the *EWSR1* locus seen in some myoepithelial tumors and the *SS18* locus in synovial sarcomas were both negative. A retrospective NUT immunostain showed diffuse and strong nuclear positivity in tumor cells (Fig. 1h).

Imaging studies demonstrated metastatic disease in the liver, brain and bone. A magnetic resonance imaging (MRI) of the brain revealed dural enhancement with a 0.6 × 1.8 cm nodule over the left frontal lobe. Approximately 2 weeks after the initial biopsy, chemotherapy was initiated with vorinostat (180 mg/m^2/dose on days 1–5 and 8–12), paclitaxel (250 mg/m^2/dose on day 1) and cisplatin (50 mg/m^2/dose on days 1 and 2). Restaging after two cycles of chemotherapy demonstrated a mixed response. There was 50% reduction in size of the primary tumor, but new metastatic bony sites emerged in the spine associated with back pain. The chemotherapeutic regimen was then changed to ifosfamide (1800 mg/m^2/dose on days 1–5), etoposide (100 mg/m^2/dose on days 1–5) and vorinostat (180 mg/m^2/dose on days 1–5 and 8–12). The patient received four cycles of this chemotherapy regimen with partial response at the primary and metastatic sites including resolution of PET avidity. He subsequently underwent resection of the primary tumor with a modified left radical neck dissection. Pathologic

Table 1 Summary of clinicopathologic features and molecular findings of all reported salivary gland NUT carcinomas in children and adults

Case	Age/sex	Location	Size (cm)	Histologic features	Immunohistochemistry	EBER ISH	Molecular	TMN stage	Outcome	References
1	15/M	Parotid	1.5	Loosely cohesive sheets of undifferentiated basaloid cells, squamoid islands, cartilage, reactive lymphocytic infiltrate	NUT + (carcinoma cells and chondroid cells), CAM5.2 +, p63 +, CD56 +, SYN-, Ch-A-, SMA-, calponin-, desmin-, CD99-, CD34-	Negative	*NUTM1-BRD4* (FISH)	T1N + M0	AWOD (7 m)	den Bakker
2	15/M	Submandibular	2.5	Cohesive sheets of undifferentiated basaloid cells, squamoid foci	NUT n/a, AE1/AE3 +, CAM5.2 +, p63 +, S-100 + (patchy), CD117 + (patchy), CD56-, SYN-, Ch-A-, SMA-, calponin-, CD34-	Negative	*NUTM1* (FISH)	T2N + M0	AWD (3 m)	Ziai
3	12/M	Parotid	2.4	Cohesive sheets/nests of poorly differentiated basaloid cells, desmoplasia, no squamoid foci	NUT +, AE1/AE3 +, p63 +, S-100-, SYN-, Ch-A-, CD99-, CD56-, SMA-, desmin-, CD34-, WT1-	N/A	N/A	T2N + M0	DOD (24 m)	Park
4	9/M	Sublingual	N/A	Poorly differentiated small cells	NUT +, p63 +, cytokeratin +, CK7 +, SYN-, CD99-, Fli-1-, SMA-, desmin-, myogenin-	N/A	N/A	TxN + M0	AWOD (6y)	Storck
5	9/M	Parotid	3	Monomorphic malignant cells	NUT +, cytokeratin +, SYN-, S-100-, CD99-, SMA-, MSA-, GFAP-, myogenin-, CD34-	N/A	N/A	T2N + M0	AWOD (8 m)	Storck
6	11/M	Submandibular	5.5	Cohesive sheets of small blue round cells, no squamoid foci, reactive lymphocytic infiltrate	NUT +, AE1/AE3 +, CK5/6 +, CK19 +, CAM5.2 +, p63 + (patchy), SYN +, CD99 +, S-100 + (patchy), EMA-, GFAP-, Ch-A-, CD56-, SMA-, desmin-, myogenin-, CD34-, HMB45-, CD117-	Negative	*NUTM1-BRD4* (FISH)	T3N + M1	DOD (8 m)	Current case
7	32/M	Parotid	3.8	Poorly cohesive large cells	NUT +, p63 +, AE1/AE3 +, SYN +, CD56 +	N/A	*NUTM1-BRD4* (FISH)	T2N0M0	DOD (4 m)	Vulsteke
8	40/F	Sublingual	4	Poorly cohesive basaloid cells, squamoid islands	NUT +, p63 +, AE1/AE3 +, CK7 +, CK5/6 +, SYN-, Ch-A-, CD56-, S100-, TTF1-, HER2-, p16-	Negative	*NUTM1-BRD4* (FISH)	T2N0M0	DOD (5.5 m)	Andreasen
9	21/F	Parotid	5	Poorly cohesive basaloid cells	NUT +, p63 +, AE1/AE3 +, EMA +, SYN-, Ch-A-, CD56-, S100-, CD99-	Negative	*NUTM1-BRD4* (RT-PCR)	T3N + M0	DOD (2 m)	Klijanienko
10	26/M	Sublingual	3	Poorly cohesive large cells	N/A	N/A	*NUTM1-BRD4* (FISH)	T2N + M0	DOD (1 m)	Seim
11	39/M	Parotid	3.6	Poorly cohesive large cells, squamoid islands	NUT +, p63 +, AE1/AE3 +, CK7 +, SYN-, Ch-A-, CD56-	Negative	*NUTM1-BRD4* (FISH)	T2N2bM0	DOD (7 m)	Agaimy

Table 1 (continued)

Case	Age/sex	Location	Size (cm)	Histologic features	Immunohistochemistry	EBER ISH	Molecular	TMN stage	Outcome	References
12	35/M	Parotid	N/A	Poorly cohesive basaloid cells, squamoid islands	NUT + , p63 + , AE1/AE3 + , SYN-, Ch-A-, CD56-	Negative	*NUTM1*(FISH)	TxN + M0	AWD (3 m)	Agaimy
13	55/F	Parotid	9	Poorly cohesive basaloid cells, squamoid islands	NUT + , p63 + , AE1/AE3-, SYN-, Ch-A-, CD56-	Negative	*NUTM1-BRD4* (FISH)	T3N + M0	DOD (7 m)	Agaimy
14	29/F	Submandibular	4	Poorly differentiated small cells	NUT + , p63 + , cytokeratin + , p16 + , EMA + , calponin + , vimentin + , SMA-, S100-, SYN-, Ch-A-, CD56-, CD117-	Negative	N/A	T1N2aM1	AWD (20 m)	Cho
15	21/F	Parotid	N/A	N/A	NUT + , AE1/AE3 +	N/A	*NUTM1-BRD4* (RT-PCR)	TxN + M0	DOD (3 m)	Lemelle

M male, *F* female, *SYN* synaptophysin, *Ch-A* chromogranin A, *SMA* smooth muscle actin, *MSA* muscle specific actin, *EBER ISH* Epstein–Barr virus-encoded small RNAs in situ hybridization, *AWOD* alive without disease, *AWD* alive with disease, *DOD* died of disease, *N/A* not available, *m* months

examination showed residual NUT carcinoma with extensive therapy effect (< 5% tumor viability), negative surgical margins, and 5 out of 32 lymph nodes positive for metastatic NUT carcinoma. Within 2–3 weeks after surgery, the patient experienced rapid growth of tumor at the primary site. During the following two months, the patient developed new and progressive tumor recurrence in the left submandibular region, left orbit, right parietal bone, and leptomeninges, most extensively in the posterior fossa. The patient did not demonstrate response to salvage chemotherapy with cyclophosphamide, topotecan and vorinostat. He received palliative radiation therapy and died 8 months after initial presentation from progressive disease.

Autopsy of the head and neck showed an 8 × 6 × 5 cm left submandibular recurrent tumor and a 7 × 6 × 2 cm tumor involving the left orbit and cranial bones (Fig. 2a). Intracranially, there was a 5 × 3 cm, hemorrhagic epidural metastasis extending from the superior sagittal sinus and eroding into the parietal bones. Tumor cells focally exhibited a pseudoalveolar and nested growth pattern (Fig. 2b) and prominent clear cell change (Fig. 2c) in the epidural location. The leptomeninges were grossly thickened with tan discoloration, and microscopically showed diffuse leptomeningeal carcinomatosis (Fig. 2d, e). Although the cerebral and cerebellar parenchyma appeared to be normal on gross examination, superficial cortical infiltration by carcinoma was evident microscopically, involving both frontal lobes, right temporal lobe, cerebellum and the brainstem (Fig. 2f).

Discussion

NUT carcinomas of probable or possible salivary gland origin are rare. Herein the clinicopathologic characteristics (including molecular alterations) of all reported cases (Table 1), and noted differences in sex and outcomes between the pediatric and adult groups are summarized. A systematic analysis comparing the parameters between these two groups (Table 2) showed all pediatric patients were male (6/6) while the male-to-female ratio was 1:2 in adults ($p = 0.028$). There was no statistically significant difference by all tumor characteristics, including size, type of salivary gland, primary tumor stage, lymph node involvement, and distant metastasis, although pediatric patients tended to have to smaller mean tumor size at presentation (3 cm in children versus 4.6 cm in adults). Molecular data was available in 3 of 6 pediatric and 8 of 9 adult cases, with 2 pediatric and 7 adult cases known to have *BRD4-NUTM1* translocation. A Kaplan–Meier analysis demonstrated significant prolonged OS in pediatric patients compared to adults (Fig. 3, $p = 0.0014$), with longer median OS time (24 versus 4 months) and higher 3-month (100% versus 67%), 7-month (83% versus 11%), and 1-year (67% versus 11%)

Table 2 Comparison of salivary gland NUT carcinoma in pediatric and adult population

Characteristics	Pediatric (n = 6)	Adult (n = 9)	*p* value*
Demographics			
Age, mean, range (y)	11.8, 9–15	33.1, 21–55	–
Male:female ratio	6:0	3:6	0.028
Tumor characteristics			
Size, mean, range (cm)	3.0, 1.5–5.3	4.6, 3.0–9.0	–
Parotid:submandibular:sublingual	3:2:1	6:1:2	–
Higher tumor stage (≥ T3)	20% (1/5)	29% (2/7)	–
Lymph node metastases	100% (6/6)	67% (6/9)	–
Distant metastases	17% (1/6)	11% (1/9)	–
Survival analysis			
Median survival (m), 95% CI	24, 8–24	4, 1–7	0.001
3-month OS	100% (6/6)	67% (6/9)	–
7-month OS	83% (5/6)	11% (1/9)	–
1-year OS	67% (2/3)	11% (1/9)	–

OS overall survival, *CI* confidence interval

*Fisher's exact test and log-rank test were used for male:female ratio and survival curve analysis, respectively

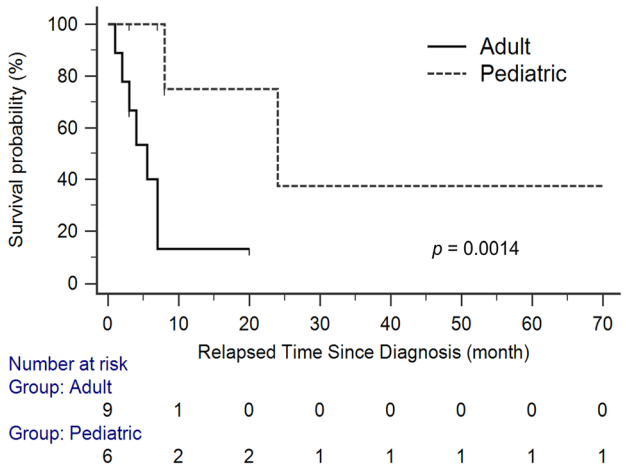

Fig. 3 Kaplan–Meier survival analysis of patients with salivary gland NUT carcinoma. The probability of overall survival is estimated for adult (age ≥ 21; n = 9) and pediatric patients (age < 21; n = 6). Log-rank test was performed to compare the survival distributions of these two groups

Table 3 Survival of patients with NUT carcinoma of salivary gland, head and neck, and all locations

Location	# of cases	Median survival (m)
Salivary gland (current study)	15	7 (95% CI 3–24)
Pediatric	6	24, (95% CI 8–24)
Adult	9	4, (95% CI 1–7)
Head and neck (Chau)	40	9.7 (range 6.6–15.6)
All locations (Bauer)	54	6.7 (range, 0.7–228 +)
All locations (Lemelle)	12	4.7 (95% CI 2.1–17.7)

CI confidence interval

OS rates (Table 2). Compared to the median OS time for NUT carcinomas of all ages and locations (4.7–6.7 months) [5, 6] and head and neck region only (9.7 months) [20], pediatric patients with salivary gland NUT carcinoma appears to have a better prognosis (Table 3). However, the results of this study must be interpreted cautiously due to the small sample size. Assembly of a much larger cohort of pediatric cases with molecular information will be necessary to draw more definitive conclusions.

Classifying a small round blue cell neoplasm in the head and neck region can be challenging. Due to its rarity and non-midline location, salivary gland NUT carcinoma may be an underrecognized diagnostic consideration in the differential diagnosis of any poorly differentiated salivary gland tumor. In fact, NUT carcinoma in general has been confused with squamous cell carcinoma, NOS, poorly differentiated carcinoma, NOS, thymic carcinoma, sinonasal undifferentiated carcinoma, Ewing sarcoma, or classified as undifferentiated epithelioid/round cell malignant neoplasms, creating significant diagnostic challenge [21–27]. If present, foci of squamous differentiation, often abrupt, can be helpful in distinguishing NUT carcinoma from most small round blue cell tumors. However, it is not uncommon for NUT carcinoma to lack any morphologic evidence of squamous differentiation (such as the current case), especially in biopsies or specimens of small size. Some tumors may exhibit features mimicking myoepithelial carcinoma with myxoid matrix, and rarely mesenchymal differentiation as described in one pediatric salivary gland NUT carcinoma [11]. Immunohistochemically, expression of cytokeratins, EMA, myoepithelial markers, and CD99 in NUT carcinoma overlaps with myoepithelial carcinoma and Ewing sarcoma. Fortunately, NUT

IHC has been proven to be a relatively sensitive (87%) and highly specific (nearly 100%) tool for the diagnosis of NUT carcinoma, demonstrating diffuse and strong nuclear reactivity with a speckled pattern [22]. Recently, NUT immunoexpression and *NUTM1* rearrangements have also been described in tumors with a favored diagnosis of sarcoma [28–30]. An alternative to NUT IHC is molecular analysis to detect rearrangement of *NUTM1* gene using FISH, reverse-transcriptase polymerase chain reaction (RT-PCR), cytogenetics, or next-generation sequencing-based approaches. A reciprocal translocation between *NUTM1* and *BRD4* genes can be demonstrated in up to 70% of NUT carcinomas by molecular analysis. *NUTM1* has also been shown to be fused to *BRD3* or *NSD3,* and rarely to *ZNF532, ZNF592* or *CIC* [3, 30, 31]. In the current study, *BRD4* was the only identified *NUTM1* fusion gene partner for the subset of cases reviewed (9/15) for which molecular assessment capable of identifying partnerships was performed. Interestingly, it has been suggested that *NSD3*- or *BRD3-NUTM1*-positive tumors may be associated with significantly better overall survival than those with *BRD4-NUTM1* [3]. Molecular analysis to identify specific fusion partner to *NUTM1* therefore may be of potential clinical relevance.

In summary, salivary gland NUT carcinomas are rare, diagnostically challenging, and probably underrecognized due to overlapping histopathologic features with other poorly differentiated neoplasms. Among all patients with NUT carcinoma, children with salivary gland origin may represent a distinct subset with male predilection and better overall survival.

Author Contributions All authors contributed to material preparation, data collection and analysis of the case report. Literature review and analysis were performed by Huiying Wang and Jiancong Liang. The first draft of the manuscript was written by Huiying Wang and Jiancong Liang. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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