

Case Report

# Pediatric Oral/Maxillofacial Soft Tissue Sarcomas: A Clinicopathologic Report of Four Cases

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## Keywords

Soft tissue sarcoma · Children · Oral/maxillofacial region

## Abstract

Pediatric soft tissue sarcomas of the oral/maxillofacial region are rare neoplasms that present significant difficulty with respect to treatment and local control measures. We report four cases of pediatric oral/maxillofacial soft tissue sarcomas from our tertiary care pediatric hospital and emphasize the rarity of these malignancies and the challenges encountered in treating these lesions, and suggest areas for further research. We conclude that multimodal therapy and interdisciplinary cooperation are paramount to successful management of these lesions.

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Published by S. Karger AG, Basel

## Introduction

Sarcomas are a heterogeneous group of malignancies that are generally identified as arising from mesenchyme-derived tissue [1]. Soft tissue sarcoma (STS) account for only about 12% of all pediatric head and neck cancers, with a small minority in the oral/maxillofacial (OMF) region [2]. These tumors present significant challenges for local control due to the proximity and radiosensitivity of regional anatomic structures [2]. These challenges highlight the importance of coordination between various medical subspecialists in planning and executing treatment and local disease control measures. With a multidisciplinary and multimodal approach to management and local control, preservation of function has become a realistic goal of therapy [3].

Our search revealed no published case series that offer a synthesized view of their diagnosis, pathology, treatment, and outcomes. We report four pediatric cases of STS involving the OMF region, highlighting difficulties inherent in managing these lesions, the needs for multimodal therapy and improved risk stratification strategies.

## Methods

The tumor registry at Nationwide Children's Hospital was screened for cases of STS occurring in the OMF region from 2000 to 2015 in accordance with a protocol approved by the Institutional Review Board. Patients with primary lesions in other head and neck sites were excluded.

## Case 1

A 2-year-old Caucasian boy presented with a right upper lip mass and ipsilateral cervical lymphadenopathy. Biopsy of primary site and lymph node excisional biopsy were followed by gross total surgical resection. Pathologic examination showed a tumor composed of solid nests and sheets of monotonous, small malignant cells with cytologic features suggestive of rhabdomyosarcoma (RMS). Mitotic figures and karyorrhectic tumor cells were frequent, and several areas of geographic necrosis were present. Immunohistochemical staining showed diffuse desmin reactivity in the tumor cytoplasm, and myogenin reactivity in more than 95% of tumor nuclei, supporting the diagnosis of alveolar RMS (fig. 1a, b). There were no sites of metastatic disease on pre-therapy evaluation, and the patient was categorized as clinical group II, stage 1, intermediate risk. He received chemotherapy with vincristine, dactinomycin, and cyclophosphamide (VAC) with radiotherapy for local control (41.4 Gy in 23 fractions). Complete response was seen with no evidence of disease at end-of-therapy evaluation.

Thirteen months after the original diagnosis, a left frontal lobe mass was discovered and resected. This demonstrated similar pathological findings to his original tumor. Molecular studies were performed and demonstrated a fusion of the *PAX3* and *FOXO1* genes. He received chemotherapy with vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide, and intrathecal chemotherapy. Local control was achieved with 45 Gy radiotherapy in 25 fractions.

Twenty months later, a solitary right leg mass was resected, and pathology confirmed relapsed alveolar RMS. He received cyclophosphamide and topotecan and underwent autol-

ogous hematopoietic stem cell transplantation with a preparatory regimen of vincristine, melphalan, and thiotepe. He remained in remission for 8 months until he developed right eye swelling and was found to have an orbital mass; this was partially resected and redemonstrated alveolar RMS. He again received radiotherapy (44.6 Gy in 25 fractions). Four months later, he developed a left lung nodule which was biopsied and confirmed disease relapse. He received lung radiation with 10 Gy but ultimately succumbed to his disease 5 weeks later, 46 months from his original diagnosis.

### Case 2

A 13-year-old Caucasian girl presented with a 2 × 2.5 × 3 cm right masseter muscle mass which was completely resected. Pathologic examination showed a tumor composed of small nests of small round cells infiltrating skeletal muscle and adipose tissue. The cells showed scant eosinophilic cytoplasm, with cytologic features suggestive of RMS, similar to Case 1. Immunohistochemical staining confirmed this impression, showing focal desmin reactivity (fig. 1c, d). There was no metastatic disease on staging evaluation. She was diagnosed with alveolar RMS, clinical group II, stage 1, intermediate risk. She received chemotherapy with VAC as well as radiation therapy (41.4 Gy in 23 fractions) and was in remission at the end of therapy. She had a complete response and continues to be in remission at her last follow-up 102 months from her original diagnosis.

### Case 3

A 4-year-old Caucasian girl presented with a 3 × 2 cm left-sided maxillary mass, which was partially resected. Pathology demonstrated a variably cellular tumor composed of poorly differentiated round to spindle cells with myxoid stroma. The nuclei showed moderate pleomorphism, and mitotic figures were frequent. Immunohistochemical staining showed strong cytoplasmic desmin reactivity, and myogenin reactivity was seen in less than 50% of the tumor nuclei, supporting the diagnosis of embryonal RMS (fig. 1e, f). There was no metastatic disease on staging evaluation. She was diagnosed with group III, stage 3, intermediate-risk embryonal RMS. She underwent radiation therapy with a dose of 50.4 Gy in 28 fractions and also received chemotherapy with VAC.

Four months later, she developed a local recurrence in the same area, which was again completely resected. She received additional radiotherapy with 30 Gy in 15 fractions, as well as further chemotherapy with vincristine and ifosfamide/etoposide. Ten months later, she developed a third local recurrence, for which she underwent a gross total resection, radiation therapy at a dose of 10 Gy, and chemotherapy with topotecan. Eight months later (42 months after primary diagnosis), she developed metastatic disease in her lungs and died due to complications of pneumonia.

### Case 4

A 4-year-old Caucasian boy presented with a rapidly enlarging tongue lesion. Microscopically, sections demonstrated a densely cellular tumor composed of poorly differentiated spindle cells with areas containing epithelial elements (fig. 1g, h). Many dilated and

branching vascular spaces were present, and focal areas were less cellular with myxoid stroma. Mitotic figures were abundant. Immunohistochemical staining was negative for desmin and myogenin. Pancytokeratin and epithelial membrane antigen stains showed reactivity in many spindle cells, and highlighted the epithelial elements. RT-PCR testing identified a fusion of the *SS18* and *SSX1* genes, confirming the diagnosis of synovial sarcoma. No evidence of metastatic disease was identified on pre-therapy evaluation. He underwent a gross total resection of the lesion with reconstruction of his tongue using fasciocutaneous left radial forearm free flap. Due to airway safety concerns, a tracheostomy tube was placed at the same time and was subsequently removed 2 weeks later. Radiation therapy after surgical resection was deferred despite narrow negative margins due to concern for associated morbidity. He completed chemotherapy with 6 cycles of ifosfamide and doxorubicin and continues to be disease-free 36 months after his original diagnosis.

## Discussion

We report four cases of STS occurring in the OMF region at a tertiary care pediatric center over a 15-year period. The broad differential diagnosis of lesions in the OMF region is described in [table 1](#). The rarity of STS in this region and the preponderance of RMS noted at our institution are consistent with data from larger epidemiological studies [3]. Pathology showed overlapping poorly differentiated features, demonstrating the importance of immunohistochemistry and molecular testing in confirming the diagnoses. The diagnostic accuracy of fine-needle aspiration cytology for primary diagnosis and recurrences have been reported in tumors of the OMF region with a sensitivity of 96.2% and specificity of 99.4% [4].

These four cases highlight several important multidisciplinary aspects of managing these patients, primarily the difficulty associated with local control of malignancies in this region. Cases 1 and 3 endured multiple local and distant recurrences. Case 3, in particular, demonstrates the difficulty of achieving adequate local control. Current recommendations include optimizing surgical resection even at metastatic sites; however, this is generally not feasible with widely metastatic disease.

Radiation therapy, however, is readily utilized for metastatic sites and as well as grossly resected disease with positive margins. With the advent and precision of new technologies, there is an increasing interest in proton beam radiotherapy as it has been shown to have utility in the treatment of head and neck malignancies [5]. The primary advantage is the ability to spare surrounding normal tissues from unintended irradiation. For patients with oropharyngeal cancer, decreased symptoms of dysphagia and xerostomia have been reported [6]. A head-to-head comparison of intensity-modulated photon therapy with intensity-modulated proton therapy is ongoing, and the results from this trial will quantify the clinical benefit to patients from the reduction of dose to nontarget tissues [7]. Fewer than 20% of RMS are resected with negative margins [8], and radiation therapy has a well-known role in the management of RMS. Coordination between surgeons, oncologists, and radiation oncologists with consideration of modality with least morbidity is of the utmost importance as demonstrated in Case 4.

It is not surprising that the two patients (Cases 1 and 3) who suffered multiple episodes of recurrent disease ultimately succumbed to their disease. Additionally, the three cases with RMS are examples of the heterogeneous outcomes observed in intermediate-risk RMS [8] and highlight the need for better risk stratification methods for these patients. The tumor in

Case 1 was positive for the *PAX3/FOXO1* fusion gene product, which is known to be a poor prognostic marker [9]. Yet without integration of *PAX3/FOXO1* into stratification algorithms, he was considered to have intermediate-risk disease. Preliminary gene expression profiling work in pediatric RMS has been performed [10], and further studies are currently underway attempting to better understand the biological implications for risk stratification in RMS in particular and STS in general [11].

Our four cases represent a large case series of pediatric OMF STS, reinforcing the rarity and the spectrum of these malignancies. Individual pediatric case reports have reported rare OMF STS tumors such as leiomyosarcoma [12], alveolar soft part sarcoma [13], and fibrosarcoma [14]. We highlight the various presentations, approaches to management, and distribution of STS in the OMF region, and challenges faced to achieve satisfactory local control.

### Statement of Ethics

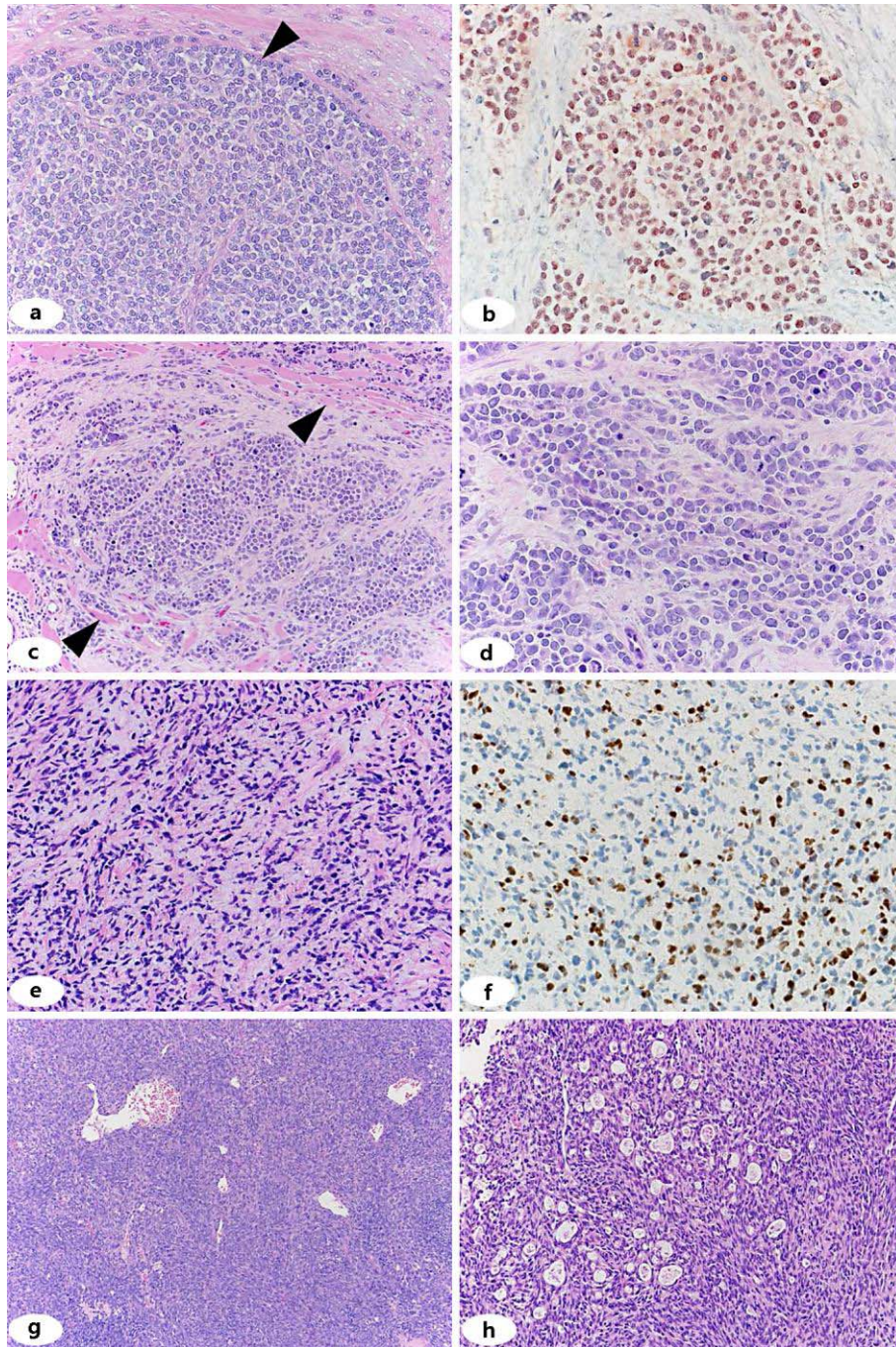
The authors have no ethical conflicts to disclose.

### Disclosure Statement

The authors have no conflict of interest to report.

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**Fig. 1.** Histologic and immunohistochemical features of OMF sarcomas. Case 1 shows solid nests of tumor cells with round nuclei and scant eosinophilic cytoplasm (**a**, 40× objective magnification). Linear arrangement of the tumor cells was focally seen at the edges of the nests of tumor cells (**a**, arrowhead). Immunohistochemical staining for myogenin demonstrated reactivity in nearly all tumor nuclei (**b**, 40× objective magnification). Biopsies of Case 2 show nests of tumor cells infiltrating skeletal muscle (**c**, arrowheads, 20× objective magnifications). The tumor cells show round nuclei and frequent single cells undergoing mitosis or karyorrhexis (**d**, 40× objective magnification). Case 3 shows spindle cells in a myxoid matrix and relative nuclear pleomorphism compared with Cases 1 and 2 (**e**, 40× objective magnification). Myogenin immunohistochemical staining highlights less than half of the tumor nuclei (**f**, 40× objective magnification). The tumor cells of Case 4 show spindle cells arranged in short curved fascicles with scattered dilated and branching vascular spaces (**g**, 10× objective magnification). Focal areas of the tumor demonstrate intermixed epithelial elements (**h**, 20× objective magnification).

**Table 1.** Differential diagnosis of soft tissue masses of the mouth and face in children

Congenital	Infectious	Benign	Malignant
Dermoid cyst	Lymphadenitis	Angiofibroma	Angiosarcoma
Hemangioma	Odontogenic infection	Dermoid cyst	Alveolar soft part sarcoma
Lymphangioma	Parotitis	Hemangioma	Lymphoma (Hodgkin's vs. non-Hodgkin's)
	Periorbital/orbital cellulitis	Inclusion cyst	Dermatofibrosarcoma protuberans
	Soft tissue cellulitis/abscess	Keloid	Epithelioid sarcoma
		Lipoma	Langerhans cell histiocytosis
		Lymphangioma	Malignant fibrous histiocytoma
		Neurofibroma	Malignant peripheral nerve sheath tumor
		Pilomatrixoma	Neuroblastoma
		Squamous cell papilloma	Rhabdomyosarcoma
			Synovial sarcoma
			Salivary gland neoplasms
			Undifferentiated sarcoma