Sclerosing Rhabdomyosarcoma: Presentation of a Rare Sarcoma Mimicking Myoepithelial Carcinoma of the Parotid Gland and Review of the Literature

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Abstract Sclerosing rhabdomyosarcoma (SRMS), a recently characterized variant of rhabdomyosarcoma, can pose a significant diagnostic challenge given its rarity and its histological similarity to other malignancies. SRMS is characterized by dense hyalinized or sclerosing collagenous matrix and a pseudovascular pattern of growth. SRMS shares histologic similarities with several mesenchymal tumors including: leiomyosarcoma, osteosarcoma, chondrosarcoma, angiosarcoma, and sclerosing epithelioid fibrosarcoma. We herein report a case of SRMS mimicking a myoepithelial carcinoma of the parotid gland. The tumor contained small, spindled, and epithelioid tumor cells lining pseudovascular spaces within a dense hyalinized stroma. Initial stains for keratins, S100 and p63 were negative. However the tumor cells showed desmin and myogenin positivity. The tumor was negative for FKHR gene rearrangements and showed no MDM2 gene amplification. This is the second case of SRMS to be diagnosed in the parotid gland highlighting the potential for misdiagnosis as a primary salivary gland epithelial malignancy.

Keywords Sclerosing rhabdomyosarcoma · Parotid gland · Myoepithelial carcinoma · FKHR rearrangement · Immunohistochemistry

Introduction

Primary sarcomas of the salivary glands are rare but as with epithelial malignancies, sarcomas also occur most commonly in the parotid gland [1]. Rhabdomyosarcoma (RMS) is the most common type of sarcoma, comprising 3 % in one literature review conducted by Cockerill et al. [1]. Not surprisingly, parotid rhabdomyosarcomas are more common in the pediatric age group with a median age of 7 years [1].

In 2000, a new variant of RMS characterized by abundant hyaline sclerosis and a pseudovascular growth pattern was described by Mentzel and Katenkamp [2] who named it “sclerosing, pseudovascular rhabdomyosarcoma” subsequently shortened to ‘sclerosing rhabdomyosarcoma’ (SRMS) by Folpe et al. [3] in their report of four additional cases. Since these early reports a total of 42 cases of SRMS have been described in the English literature of which 22 have occurred in adults (≥ 18 years old) [2–20]. From the limited number of cases of this rare malignancy, it appears that SRMS has a predilection for the extremities and the head and neck. In contrast to embryonal and alveolar types of rhabdomyosarcoma, which occur mostly in children and adolescents, SRMS occurs over a broad age range with a bimodal distribution with cases in children and older adults.

Sclerosing rhabdomyosarcoma is characterized by a moderately cellular proliferation of small, round to spindle-shaped cells with scant cytoplasm admixed with prominent hyalinized stroma [3]. As the original name would indicate, the tumor cells often line spaces within the stroma imparting vascular appearance [2]. Although occasional cases of SRMS will demonstrate histologic evidence of overt skeletal muscle differentiation with rhabdomyoblasts and strap cells, most cases require confirmation with

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Fig. 1 Coronal (a) and axial (b) views of computed tomography (CT) scan with contrast of the head and neck. The CT demonstrates an indistinctly bordered (arrows) mixed attenuation lesion with hypervascularity in the left face at approximately the parotid gland

immunohistochemical studies using markers of skeletal muscle differentiation (e.g., desmin, myogenin, and MyoD1 proteins) [15].

Sclerosing rhabdomyosarcoma raises a broad histologic differential diagnosis, which includes angiosarcoma, extraskeletal osteosarcoma, chondrosarcoma, sclerosing epithelioid fibrosarcoma as well as carcinomas. Specifically, in the head and neck, salivary malignancies are the main diagnostic considerations. The first reported case that presented in the parotid gland had an appearance of myoepithelial carcinoma [12] and another case occurring in the masseter muscle focally mimicked adenoid cystic carcinoma [19]. We herein report the second case of SRMS of the parotid gland, discuss the differential diagnosis, and review the current English literature regarding this rare sarcoma variant.

Case Presentation

A 36-year-old Latino man presented with a 2-month history of pain while chewing in the left face accompanied by numbness of the left lip and jaw. The patient confirmed light alcohol consumption, denied tobacco use, and his medical history was unremarkable. Physical examination was remarkable for a mass in the left parotid gland region. Computed tomography (CT) scan of the neck with contrast demonstrated a 2.6 cm × 1.9 cm mixed hyper- and hypo-attenuated lesion within the superficial lobe of the parotid gland with indistinct borders (Fig. 1). The growing mass displaced branches of the left external carotid artery. Ancillary findings from the CT scan included normal appearing right parotid, submandibular, and sublingual glands. No cervical lymphadenopathy was noted. A fine

needle aspirate (FNA) was diagnosed as ‘epithelial neoplasm, compatible with pleomorphic adenoma and described as bland epithelial cells, dyshesive myoepithelial cells and scattered metachromatic stroma (Fig. 2).’

Surgical resection was subsequently performed. Initially, a left superficial parotidectomy with facial nerve preservation was planned, however intraoperatively, the tumor was noted to be rather infiltrative, extending deep to the superficial parotid gland and facial nerve into the parapharyngeal space, prompting a total parotidectomy. Despite the more aggressive surgical approach, the tumor in the parapharyngeal space could not be entirely resected.

Gross examination of the surgical specimen demonstrated a tan-purple, firm, mass involving the entire parotid gland. Sections showed a moderately cellular infiltrative tumor with small ovoid to spindle cells with scant cytoplasm embedded in an abundant hyalinized stroma (Fig. 3a, b). Occasional cells had a plasmacytoid appearance. The tumor was clearly infiltrative into adipose tissue and demonstrated extensive perineural invasion. Only scant residual parotid gland tissue could be identified. In many areas, the hyalinized stroma formed cylinders reminiscent of those seen in salivary tumors such as adenoid cystic carcinoma. In other areas, the stroma enveloped single tumor cells in a manner reminiscent of osteoid, though no mineralization was noted. The tumor cells organized into strands and cords with central pseudolumina reminiscent of vascular spaces. The mitotic index was 13 mitoses per 10 high power fields (400×). No rhabdomyoblasts or strap cells were identified. Immunohistochemical studies were performed and the antibodies used are listed in Table 1. Although the initial impression was a myoepithelial carcinoma, epithelial markers (AE1/AE3, p63, and CAM5.2) and myoepithelial markers (S-100 protein, calponin, and

Fig. 2 Fine needle aspiration (FNA) was reported as “epithelial neoplasm, consistent with pleomorphic adenoma.” The tumor is composed of small *blue cells* with little to no cytoplasm mimicking the appearance of dyshesive myoepithelial cells. The stroma in this

case was hyalinized rather than fibrillary but was not present on the Diff-Quik stained smears to evaluate for metachromatic staining. **a** Papanicolaou stain (×400) and **b** Diff-Quik (×400)

Fig. 3 Morphologic and immunohistochemical features. **a, b** Section of the tumor showing the moderate cellularity composed of small blue cells with scant amphophilic to eosinophilic cytoplasm between prominent hyalinized trabeculae and cylinders of stroma reminiscent of a salivary type tumor. Hematoxylin-eosin (H&E), original

magnification ×200. **b** Hematoxylin-eosin (H&E), original magnification ×400. **c** Immunohistochemical stain showing strong diffuse cytoplasmic expression of desmin, original magnification ×400. **d** Focal individual cells demonstrated strong nuclear staining with myogenin, original magnification ×400

smooth muscle myosin) were negative and only smooth muscle actin demonstrated weak reactivity, essentially excluding this diagnosis. On the other hand, desmin

showed diffuse strong cytoplasmic reactivity (Fig. 3c), and myogenin (Fig. 3d) showed scattered strongly positive tumor cells. CD31 and CD34 were negative as were EMA

Table 1 Antibodies used for Immunohistochemistry

Antibody	Company	Clone	Dilution
Pankeratin AE1/AE3	Dako, Carpinteria, CA	AE1/AE3	1:100
Pankeratin CAM 5.2	BD, Franklin Lakes, NJ	CAM 5.2	1:100
p63	Thermo, Waltham, MA	4A4	1:200
S-100	Dako, Carpinteria, CA	Polyclonal	1:500
Calponin	Dako, Carpinteria, CA	CALP	1:50
Smooth muscle myosin	Dako, Carpinteria, CA	SMMS-1	1:800
Smooth muscle actin	Cell Marque, Rocklin, CA	IA4	Predilute
CD31	Dako, Carpinteria, CA	JC70A	1:40
CD34	Ventana, Oro Valley, AZ	QBEnd/10	Predilute
EMA	Cell Marque, Rocklin, CA	E29	Predilute
MUC-4	Invitrogen, Carlsbad, CA	1GA	1:100
Desmin	Ventana, Oro Valley, AZ	DE-R-11	Predilute
Myogenin	Cell Marque, Rocklin, CA	F5D	Predilute

and MUC1. Fluorescence in situ hybridization for *FKHR* (Vysis Dual Color Break Apart FISH Probe Kit, Abbott Molecular, Abbott Park, Illinois) rearrangements and *MDM2* (Aquarius Pathology probes, Cambridge, United Kingdom) amplification were negative. Based on the overall histologic appearance, immunophenotype and results of molecular studies the diagnosis of SRMS was made.

Since the tumor was incompletely excised, the patient was referred to an oncologist for adjuvant chemotherapy and radiation therapy. The patient was placed on a rhabdomyosarcoma combination chemotherapy regimen: vincristine, actinomycin-D, and cyclosporine (VAC regimen). Currently, the patient is alive without evidence of disease after 6 months of follow up.

Discussion

We herein report the second case of SRMS occurring in the parotid gland and the forty-third case overall. Figure 4a, b summarize key epidemiologic features of this rare variant [2–20]. The most common sites of presentation of SRMS are the extremities and the head and neck (Fig. 4a). SRMS has a wide range of ages of presentation (<1–79 years) and a bimodal age distribution (Fig. 4b). A large proportion of cases are diagnosed in the first and second decades or around the fifth decade. There is a roughly even gender distribution with perhaps a small male predilection (56 %).

The understanding of the relationship of SRMS to other variants of rhabdomyosarcoma is still evolving. Karyotypic analysis and genome wide single nucleotide polymorphism arrays have been performed on eight cases and usually harbor a complex karyotype with whole chromosome gains and losses [4, 7, 9, 11, 18]. Other molecular changes that have been detected in SRMS include a PIK3CA exon 20

mutation in one case and amplification of the region including *MDM2* in two cases [4, 9]. Rearrangement of the *FKHR* gene has only been detected in one of fourteen previously tested SRMS (which in fact questions the validity of classification as SRMS in this case) in the literature and was negative in the current case [6] arguing against a relationship with alveolar rhabdomyosarcoma which carries *FKHR* translocations in ~80 % of cases [21]. These findings, combined with the pattern of immunohistochemical studies with myogenin and MyoD1, had been used to support the inclusion of SRMS as a subtype of embryonal rhabdomyosarcoma [7, 11, 17, 18]. However, the difference in age distribution and unique appearance raised concerns about this categorization. Currently, the new 4th edition of the WHO classification of Tumors of Soft Tissue and Bone created a provisional category combining SRMS with spindle cell rhabdomyosarcoma (which was also previously included under embryonal rhabdomyosarcoma) [22]. The basis for this recategorization appears to be mainly a result of morphologic overlap between these variants [2, 8, 13, 15, 17, 23]. Since follow up data for SRMS are limited, and provisional categorization has only recently been established, we can only speculate on the prognostic significance of this entity. Summary of the follow up data for cases of SRMS imply this sarcoma may follow an intermediate to aggressive course. Of the 29 cases with reported follow up data, 19 patients experienced recurrence or metastasis. The mean disease-free and overall survival was merely 17 and 40 months, respectively. Of the seven patients that died of disease, six were adults (≥ 18 years of age).

The appearance of SRMS poses challenges on both cytologic and surgical specimens. Furthermore, a head and neck location raises unique differential diagnostic considerations. Specifically, as in this case, aspirate smears from a SRMS will likely be mistaken for a primary salivary

Fig. 4 Site (a) and age distribution by decade (b) of published cases (including our case) of SRMS. It is clear that sclerosing rhabdomyosarcoma has a predilection for the extremities and head and neck. SRMS is most commonly diagnosed in the first decade of life with a

second mode centered around the fifth decade. The age distribution is a unique facet of sclerosing relative to embryonal and alveolar rhabdomyosarcoma variants

gland neoplasm. The stromal characteristics raise considerations ranging from cellular pleomorphic adenoma to myoepithelioma/myoepithelial carcinoma, basal cell salivary tumors (adenoma and carcinoma), and even adenoid cystic carcinoma. While clinical and radiologic characteristics may help in terms of predicting likelihood of malignancy, it would be very difficult to establish a diagnosis of SRMS on FNA without a high index of suspicion and immunohistochemical studies. Even on surgical resection, akin to the previously reported parotid SRMS [12], this current case had a striking resemblance to a myoepithelial carcinoma. Myoepithelial carcinomas have a diverse morphologic spectrum and can indeed have cytenuclear features and abundant hyaline stroma that mimic SRMS to the extent that immunohistochemical markers are required even on surgical resection specimens. Other salivary malignancies such as adenoid cystic carcinoma [19], epithelial-myoeplithelial carcinoma, and basal cell adenocarcinoma may also have similar areas of sclerosis and a pseudovascular appearance, but these entities also have a ductal component (i.e., they are biphasic), which eliminates them from consideration.

Even when a true sarcoma diagnosis is raised as a possibility, SRMS must be distinguished from other sarcomas including: angiosarcoma, osteosarcoma, and sclerosing epithelioid fibrosarcoma. The original term used for this tumor was “sclerosing pseudovascular rhabdomyosarcoma” indicating the histologic overlap in appearance with angiosarcoma [2]. In these cases the lining of the tumor cells along the hyalinized stroma with central spaces gave the impression of complex vascular channels [2, 3]. Additionally many of these reports describe the presence of papillary structures in these spaces. However, angiosarcomas are negative for desmin, myogenin and MyoD1, and are CD31 and CD34 positive. Of note, however, SRMS can rarely show CD34 positivity [12]. The hyalinized stroma of SRMS may occasionally resemble [3], though it lacks the mineralization, expected in osteosarcoma. However, mineralization of the

stroma, which is present in osteosarcomas, has never been reported in SRMS. Sclerosing epithelioid fibrosarcoma is also a differential diagnostic consideration for SRMS [3, 13, 17]. However, these tumors, a subset of which are thought to be related to low-grade fibromyxoid sarcoma, exhibit EMA and/or MUC4 positivity [24]. Ultimately, desmin, myogenin and/or MyoD1 positivity will confirm rhabdomyosarcomatous differentiation. Desmin typically demonstrates strong and diffuse cytoplasmic reactivity in SRMS. The immunohistochemical reactivity pattern seen with myogenin is generally seen as focal, weak, and nuclear as is seen in embryonal rhabdomyosarcoma and in contrast to the generally strong diffuse nuclear pattern seen in alveolar rhabdomyosarcoma. While we did not perform immunohistochemical studies for MyoD1, this has been shown to be strong and diffuse in SRMS [3].

In summary, we have described the second case of SRMS presenting in the parotid gland. This case highlights the challenge, both on fine needle aspiration and surgical resection, in distinguishing a true mesenchymal neoplasm such as this one from a primary epithelial salivary tumor. Even within the mesenchymal tumor category, SRMS shows overlap with several entities such as osteosarcoma, angiosarcoma, and sclerosing epithelioid fibrosarcoma. Approaches to these dilemmas necessitate the use of ancillary studies. Current classification of this variant with respect to other rhabdomyosarcoma variants is evolving, though currently, this is considered within the spectrum of spindle cell rhabdomyosarcoma.

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