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Low-Grade Fibromyxoid Sarcoma Featuring an Unusual *EWSR1-CREB3L2* Gene Fusion: Report of a Rare Case Arising in the Parotid Gland

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Abstract

Low-grade fibromyxoid sarcoma (LGFMS), also known as Evan's tumor, is a fibroblastic tumor with a deceptively bland morphology but a high metastasizing potential and late recurrence. It presents clinically as a slowly growing mass in the deep soft tissue of extremities and trunk. Morphologically, it shows a biphasic pattern with alternating fibrous and myxoid areas, whorling growth pattern, hypocellularity, and bland fibroblasts with curvilinear or arcuate vessels in between. Collagen rosettes with central hyalinization is a helpful feature but not specific. MUC-4 is the most sensitive immunostain in LGFMS. The majority of cases harbor a gene fusion in *FUS-CREB3L2*. Herein, we present a 23-year-old female patient with a slow growing painless mass in the left parotid gland, which was later diagnosed as LGFMS. Involvement of the head and neck region by LGFMS is uncommonly encountered. To date, only two cases within the parotid gland have been described.

Keywords

- low-grade fibromyxoid sarcoma
- Evan's tumor
- parotid gland
- MUC-4

Introduction

Primary sarcomas are rarely encountered in the head and neck, accounting for ~1% of all malignancies in such a region.[1] Rhabdomyosarcoma, Ewing sarcoma, synovial sarcoma, Kaposi sarcoma, and angiosarcoma are the most frequent sarcomas in the head and neck. LGFMS is relatively rare among other sarcomas, first described by Evans in 1987.[2] It predominantly affects proximal extremities, trunk, and to a lesser extent, abdominal cavity, retroperitoneum, and mediastinum. Although the overall age range is wide (3–78 years), young to middle-aged individuals are typically affected with a median of 34 years.[3] Slight male predilection has been noted with a male to female ratio of ~3:1.[3] Morphologically, it is characterized by bland-looking spindle cells that may be confused with other benign spindle cell lesions such as fibroma and fibromatosis. The majority of the cases show the cytogenetic hallmark of LGFMS t(7;16)(q33;p11). It has been shown that local recurrence and distant metastasis in the first 5 years after excision reaches up to 10% and 5% of patients, respectively. To date, only 26 cases of LGFMS involving the head and neck have been reported.[4] Herein, we report a case of LGFMS in the parotid gland of a 23-year-old female patient. Up to our knowledge, only two cases have been found in the parotid gland in the English literature.[5,6]

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Case Presentation

A 23-year-old female patient with a known medical history of systemic lupus erythematosus presented to the clinic complaining of a slowly growing mass in the left side of the neck for the last 2 years. Physical examination showed a well-defined, painless, firm mass, which was confined to the left parotid gland. Facial nerve function was preserved and there were no palpable cervical lymph nodes. Computed tomography (CT) of the neck showed a $3.0 \times 2.8 \times 2.0$ cm well-defined left parotid mass with heterogeneous enhancement (►Fig. 1). Fine-needle aspiration (FNA) yielded a moderately cellular sample with scattered basaloid cells arranged in loosely cohesive groups and single cells. The cells had a variable amount of cytoplasm with nuclei demonstrating bland round-to-oval shape, hyperchromasia, and smooth contours. A few small fragments of a magenta-colored fibrous stroma were seen (►Fig. 2). It was reported as a basaloid salivary neoplasm favoring pleomorphic adenoma. Classification of this FNA as Milan System category IV warranted the patient to undergo a left superficial parotidectomy, in which a $3.7 \times 2.8 \times 2.0$ cm well-circumscribed, tan-white, homogenous, firm mass was identified. Microscopically, a well-circumscribed neoplasm was separated from the surrounding normal salivary parenchyma by a thin fibrous capsule. The tumor showed a biphasic morphology composed of hypocellular collagenous areas with an abrupt transition to hypercellular myxoid areas. Tumor cells were spindled, bland-looking, and arranged in short fascicles. Arcades of arteries with a hemangiopericytoma-like morphology were seen in the background. There were ill-defined collagen rosette-like areas that showed central hyalinized fibrosis cuffed by tumor cells (►Fig. 3). A rare mitotic figure was seen. Immunohistochemistry (IHC) showed immunoreactivity of tumor cells to vimentin, CD99, and MUC-4, while negative for pancytokeratin, p63, smooth muscle actin, desmin, S100, SOX-10, EMA, BCL-2, CD34, and β-catenin. MUC-4 immunostain positivity is shown in ►Fig. 4. K_i-67 proliferation index was low at ~2%. Based on the histomorphology and immunophenotype, LGFMS was favored. FISH analysis for *FUS* gene rearrangement was negative. Next-generation sequencing (NGS) revealed high quality of *EWSR1-CREB3L2* gene fusion. The overall findings were consistent with LGFMS.

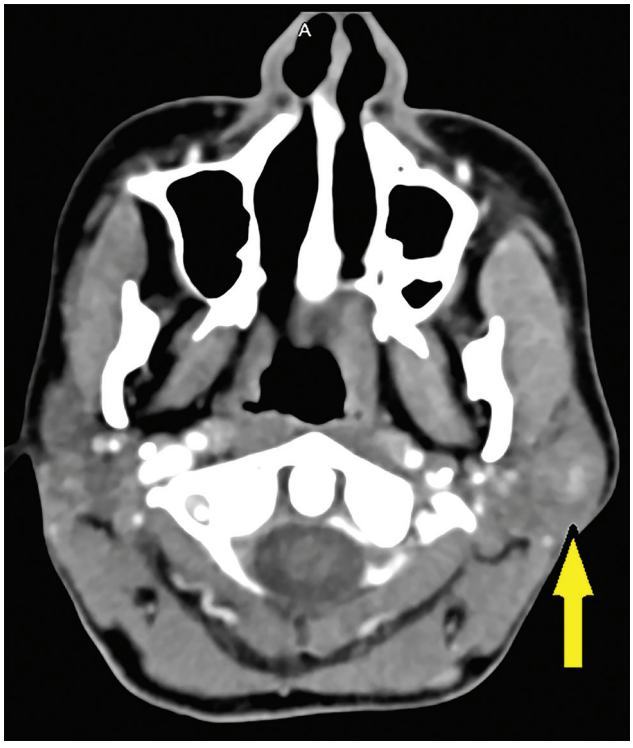

Fig. 1 Neck CT showing the left parotid mass (arrow).

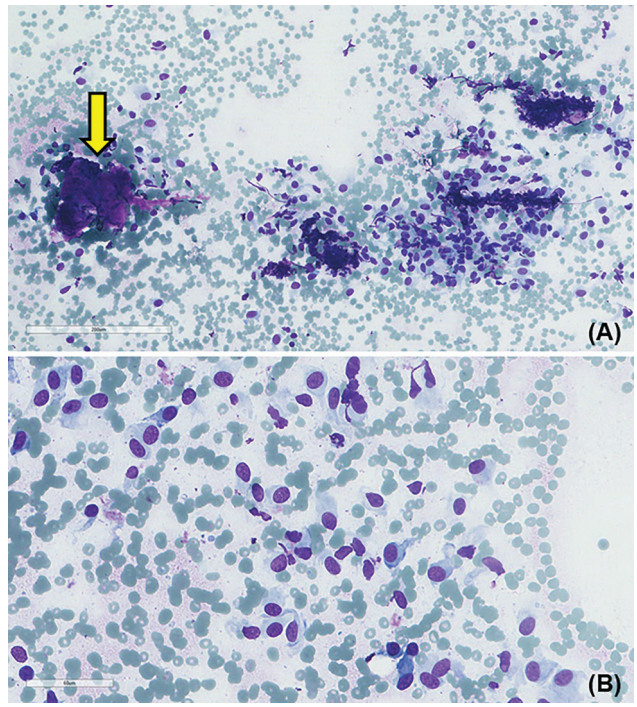

Fig. 2 FNA findings (Diff Quik). (**A**) Basaloid cells and a small fragment of fibrous stroma (arrow) (original magnification ×200). (**B**) Bland spindle cells with a moderate amount of cytoplasm (original magnification ×400).

Discussion

LGFMS is now classified by the World health Organization (WHO) Soft Tissue and Bone Tumors, 5th edition as a malignant fibroblastic neoplasm.[7] In 1997, it was termed a hyalinizing spindle cell tumor with giant rosettes (HSCTWGR) by Lane et al, and thereafter was considered a distinctive type of LGFMS.[8] It typically affects middle-aged adults (median: 34 years) but the age-range is wide (3–78 years).[3] Slight male predominance is noted.[3] Commonly, it involves proximal extremities and trunk, and to a lesser extent central body sites such as the abdominal cavity, retroperitoneum, and mediastinum. In children, superficial soft tissue involvement might be seen.[9] However, LGFMS involving the head and neck region is very rare with only 27 cases in the English literature to date (►Table 1).[3–6,10–22] Of these, only two cases have been found in the parotid gland. Botev et al reported a giant

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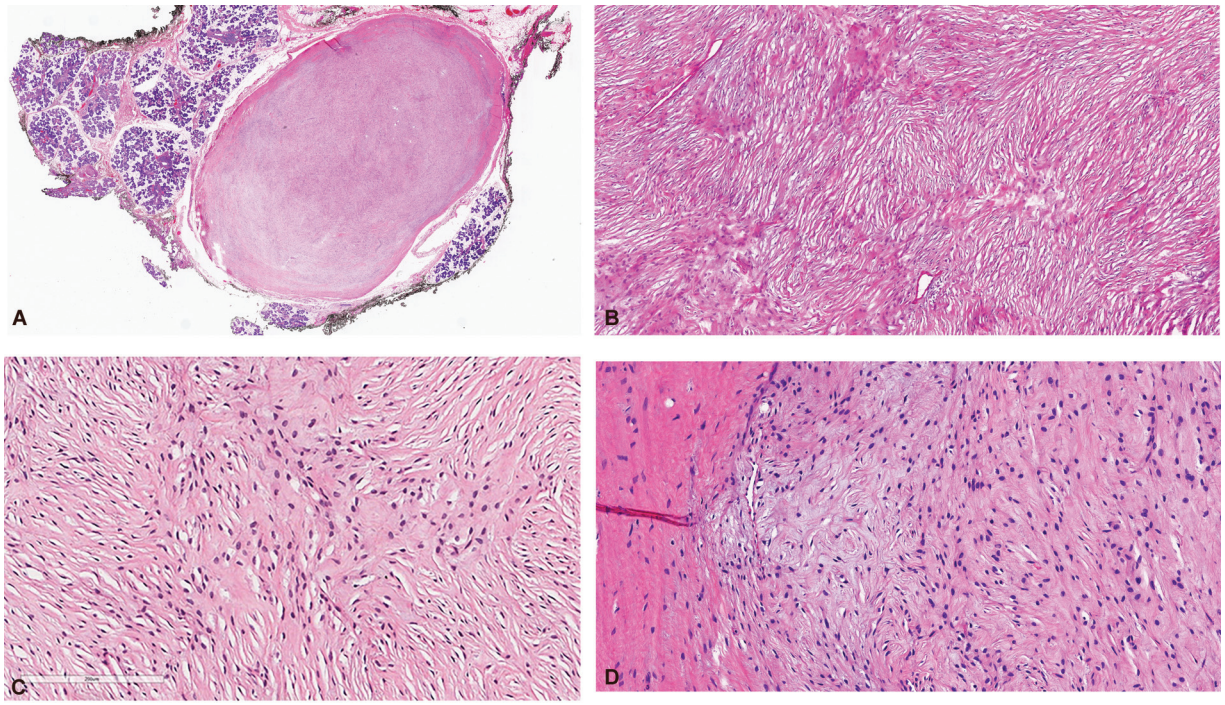

Fig. 3 Histologic findings of LGFMS. (**A**) Panoramic view of a well-defined tumor within parotid gland (H&E*, original magnification ×20). (**B**) Hypo- and hypercellular areas in a whorling pattern with scattered elongated vessels and vague collagen rosette-like arrangement (H&E*, original magnification ×40). (**C**) Bland spindle cells in a fibrous stroma (H&E*, original magnification ×200). (**D**) Myxoid areas (H&E*, original magnification ×200) *Hematoxylin and eosin.

sarcoma of the parotid gland in a 57-year-old woman with histologic features consistent with LGFMS. However, neither MUC-4 immunostain nor molecular studies were done at that time.[5] The second case was described in a 5-year-old Nigerian boy who presented with a large rapidly growing parotid mass, clinically mimicking Burkitt lymphoma. FNA was inconclusive but a tissue biopsy showed LGFMS. Similar to Botev's case, MUC-4 and molecular testing were not performed. In addition to surgical excision, this boy received radiation therapy and is in good condition after 5 months' follow-up.

It is extremely challenging to diagnose LGFMS in the parotid gland, given the unusual location, indolent nature of the clinical presentation, and non-specific FNA findings. Therefore, surgical intervention is required to render a definitive diagnosis. Compute tomography (CT) scan and T2-weighted magnetic resonance imaging (MRI) studies typically show nonspecific features including a well-delineated, relatively low-density to isodense tumor and heterogeneous low-to high-signal intensity, respectively. On FNA, cytomorphologic findings typically show a cellular smear composed of spindle cells with uniformly elongated bland nuclei, inconspicuous nucleoli, and a variable amount of wispy cytoplasm. No significant pleomorphism or increased mitosis is seen. The favored diagnosis, based on location, is pleomorphic adenoma, which cannot be ruled out solely based on cytologic findings. Nevertheless, histomorphologically, the tumor is composed of collagenous hypocellular areas and more cellular myxoid nodules. The tumor cells are bland, spindled, sometimes plump, and they grow in short fascicles or in a whorling pattern. Mitotic figures are generally absent. Arcades of small vessels and arteriole-sized vessels with perivascular sclerosis and hemangiopericytoma-like patterns are occasionally seen. In ~30% of cases, the characteristic collagen rosettes with hyalinized collagen centers cuffed by epithelioid tumor cells are present, which were not typical in our case.

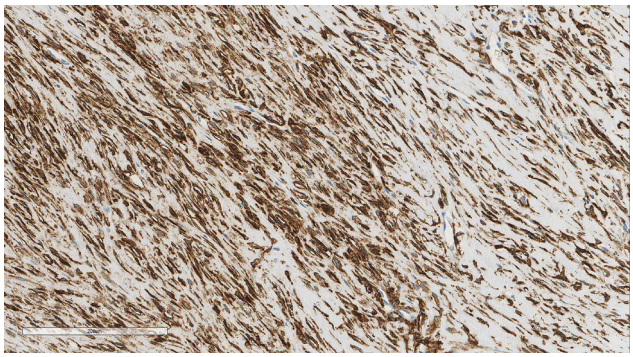

Fig. 4 MUC-4 immunostain showing diffuse strong staining (original magnification ×200).

The differential diagnosis of bland spindle cell lesions is broad due to shared histologic features, including benign and low-grade malignant tumors such as perineuroma, neurofibroma, schwannoma, fibromatosis, solitary fibrous tumor, LGFMS, sclerosing epithelioid fibrosarcoma (SEF), and myxofibrosarcoma. The giant collagen rosettes are relatively unique to LGFMS but not seen in all cases. Myxofibrosarcoma typically displays more pronounced cellular pleomorphism. Panels of IHC stains are usually performed to rule in/rule out the above diagnoses. In our case, MUC-4 showed a diffuse

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Table 1 Summary of LGFMS cases in the head and neck region[3–5,7,10–24,26]

Case number	Author	Patient age/gender	Site	Tumor size (cm)	Treatment
1	Botev et al[5]	57/male	Parotid gland	17	En bloc resection and postoperative radiotherapy
2	Lee et al[6] (Poster presentation only)	5/male	Parotid gland	15	Excision followed by external beam radiotherapy
3	Tang et al[10]	2/male	Cheek	8	Complete resection
4	Papadimitriou et al[11]	4/male	Mandible	4	Curettage
5	Wu et al[12]	4/female	Angle of jaw	Unknown	Resection
6	Abe et al[13]	84/female	Temporal region	3	Complete resection
7	He et al[14]	14/male	Cheek	8	Complete resection
8	Chaudhuri et al[15]	35/male	Mandible	3	Complete resection
9	Cowan et al[4]	6/male	Posterior cervical spine	NA	Complete resection
10	Cowan et al[4]	43/female	Facial skin	NA	Complete resection
11	Cowan et al[4]	45/male	Mandible	NA	Complete resection
12	Cowan et al[4]	73/male	Larynx	NA	Complete resection
13	Rao et al[16]	18/female	Orbit	2.4 cm	Fractionated stereotactic EBRT
14	Toroa et al[17]	57/female	Parapharyngeal space	8 cm	Complete resection
15	Evans et al[3]	9/male	Neck	NA	NA
16	Evans et al[3]	26/male	Neck	NA	NA
17	Rekhi et al[18]	69/male	Neck	NA	NA
18	Rekhi et al[18]	31/male	Face	NA	NA
19	Rekhi et al[18]	27/male	Jaw	NA	NA
20	Viswanathan et al[19]	57/male	Anterior neck	NA	NA
21	Tang et al[10]	1/male	Cheek	NA	NA
22	Merchant et al[20]	NA	Head/neck	NA	NA
23	Merchant et al[20]	NA	Head/neck	NA	NA
24	Merchant et al[20]	NA	Left maxillary sinus	NA	NA
25	Merchant et al[20]	NA	Sternocleidomastoid muscle	NA	NA
26	Guillou et al[21]	22/male	Neck	NA	NA
27	Prieto-Granada et al[22]	41/male	Supraclavicular	NA	NA

Abbreviation: NA, not available.

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strong cytoplasmic staining. CD99 and vimentin were positive, while pancytokeratin, p63, SMA, S100, SOX10, CD34, bcl-2, EMA, and β-catenin were completely negative in tumor cells.

The main differential diagnosis in this case is SEF as it shows clinical, morphologic, and immunophenotypic overlap with LGFMS. SEF is a rare fibroblastic neoplasm with an aggressive behavior. They both express MUC-4 positivity by immunohistochemical stain. Previously, it was thought that the presence of microscopic foci of LGFMS-like areas, common MUC-4 positivity, and *FUS* gene rearrangements point toward a close inter-connection with LGFMS. However, subsequent studies have shown that SEF is a genetically distinct entity from LGFMS. The predominant genetic alteration in SEF is *EWSR1-CREB3L1* gene fusion with only a minority of cases showing FUS-CREB3L2 fusions.[23,24] The distinction between the two is of clinical importance, as SEF tends to be more aggressive with shorter survival rate, higher metastatic potential, and greater propensity to involve deep soft tissues and bones.

Molecular testing is considered the most specific modality for diagnosing LGFMS, given its two distinct chromosomal translocations. More than 90% of LGFMS harbor the t(7;16)(q34;p11), resulting in *FUS-CREB3L2* gene fusion.[23] Around 10% of cases display t(11;16)(p11;p11) that result in the *FUS-CREB3L1* gene fusion.[23] Only rare cases were found to harbor an *EWSR1-CREB3L1*gene fusion.[23] Our patient surprisingly was found to have a high-quality *EWSR1-CREB3L2* gene fusion, which has never been reported previously in pure LGFMS in the English literature.[23] Nonetheless, *EWSR1-CREB3L2* has been found in pure SEF and rarely in hybrid LGFMS/SEF.[23,24]

The mainstay of the management is surgical, including local excision, radical surgery, wide en bloc resection, or compartmental resection.[10] The rule of other adjuvant therapeutic modalities such as chemotherapy and radiotherapy is still controversial. Despite the fact that the risk of local recurrence and metastasis are low during the first 5 years, long-term follow-up showed higher rates. Based on a study performed by Evans on 33 cases of LGFMS with a long-term follow-up, recurrences, metastases, and death from disease were seen in 64%, 45%, and 42% of patients, respectively.[3] Our patient showed no clinical or radiologic evidence of recurrence or metastasis after a 3-year follow-up.

Conclusions

LGFMS occurring in the parotid gland is exceptionally rare. The diagnosis is difficult, given the nonspecific radiological, clinical, cytologic, and histomorphological findings. Ancillary studies, including IHC and molecular studies, must be conducted to reach a definitive diagnosis. Given the high risk of local recurrence and metastasis, long-term follow-up is warranted.

Availability of Data and Material

All data regarding this case is available at our department as actual slides or digitally as photos and soft copies.

Consent for Publication

All authors read and approved the manuscript.

Ethical Approval

All study procedures were performed in accordance with the Declarations of Helsinki, 1964.

Authors' Contributions

D.M.A. wrote the initial manuscript. M.M.P. collected the data and revised the submitted manuscript.

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None.

Conflict of Interest

None declared.

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