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Low-grade fibromyxoid sarcoma of the parapharyngeal space: A case report and review of the literature

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A B S T R A C T

This paper reports a rare case of Low-grade fibromyxoid sarcoma (LGFMS) that occurred primarily in the parapharyngeal space, in a 57-year-old woman. To the best of our knowledge, this is the first case of LGFMS arising from the parapharingeal space reported in the literature. Primary sarcomas of the head and neck region are very rare, accounting for approximately 1% of malignancies in this region. LGFMS is a distinctive type of soft-tissue sarcoma that was first described by Evans in 1987. LGFMS may be included in the differential diagnosis of tumors of the parapharyngeal space, and especially among the bland-looking spindle cell lesions. Despite its bland-looking morphology, this sarcoma should be recognized to avoid confusion with other bland-looking benign spindle cell lesions. Radical surgical resection with clear margins, is the treatment of choice of LGFMS. Despite its bland-looking histologic appearance, it is characterized by a malignant behavior with high rates of local recurrence and metastatic spread. For these reasones, all patients with LGFMS are recommended for long-term follow-up.

1. Introduction

Primary sarcomas of the head and neck region are very rare, accounting for approximately 1% of malignancies in this region [1,2]. Low-grade fibromyxoid sarcoma (LGFMS) is a distinctive type of soft-tissue sarcoma that was first described by Evans in 1987 [3] and subsequently by Fletcher and colleagues [4]. Despite its bland-looking histologic appearance, it is characterized by a malignant behavior with high rates of local recurrence and metastatic spread [5]. Due to its bland-looking morphology, it might be confused with other benign spindle cell lesions and undertreated. The age distribution in the cases reported in the literature, ranges from childwood to the eighth decade [6–9]. Male and female are approximately equally affected. LGFMS primarily occurs in the soft tissues of the extremities and trunk, with only few cases reported in the head and neck region [5,6,9,10]. Molecularly, it is characterized by a traslocation of chromosomes 7 and 16, leading to the gene fusion product *FUS/CREB3L2* [11–13] or, less frequently, to *FUS/CREB3L1* [14]. However, occasional cases of LGFMS lacking *FUS* rearrangements have been reported [15–17]. Immunohistochemical analyses, showing a diffuse and strong cytoplasmic expression of MUC4, are extremely helpful in confirming the morphological suspicion [8]. The most striking morphologic features of LGFMS include alternating myxoid and fibrous areas, prominent curvilinear or branching/plexiform vasculature [18] and collagen pseudorosettes [9]. The neoplastic cells vary from spindle-to stellate-shaped cells.

We herein report a rare case of LGFMS that occurred primarily in the parapharyngeal space. To the best of our knowledge, this is the first case of LGFMS arising from the parapharingeal space reported in the literature so far.

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1.1. Presentation of case

A 57-year-old woman presented with painless, slowly-expanding mass in the right side of the neck. The mass had first appeared one year before the surgical consultation. The patient denied pain, and did not exhibit any weight loss or other constitutional symptoms. The patient also denied smoking, alcohol consumption and using drugs. Physical examination revealed asymmetry of the neck, with firm and non-tender mass in the right side of the neck, measuring 8 cm × 4 cm with clear border and moderate hardness. No enlarged lymph nodules were palpated on the neck. Tongue dyskinesia and oral mucosal diseases were absent, the lateral pharyngeal wall showed no distension, and mouth opening was not limited. She was subjected to an ultrasound examination of the neck and ultrasound-guided needle biopsy. The biopsy result demonstrated a "benign chondroma". So, a Computed tomography (CT) with and without contrast, was considered the appropriate investigation.

CT showed a large, well-circumscribed, hyperdense mass that measured approximately 8 cm × 3 cm X 4 cm, involving the right parapharyngeal space, with dislocation of the major vessels posterolaterally (Fig. 1, and Fig. 2). The mediastinal computed tomogram and electrocardiogram (EGC) were normal, and the results of routine laboratory tests were within reference ranges. A fine-needle aspiration biopsy showed rare short spindle cells without nuclear atypia and bloody background. Mitoses or necrosis were absent. The possibility of a spindle cell lesion, likely benign, was suggested, but surgical excision was mandatory for a correct diagnosis.

After the complete systematic examination, complete excision of the mass was performed with the patient under general anesthesia. The tumor was resected with a right cervical antero-lateral approach, using a vertical incision on the skin projection of the anterior margin of the sternocleidomastoid muscle. After the exposure and the lateral retraction of the muscle, the tumor was easily exposed. The mass was well circumscribed and, was blunt dissected along the carotid artery and jugular vein. Post-operatively, the patient was free of symptoms and discharged on day 5 after the operation with no complications. After the final histological results, the staging was completed with a whole body PET/CT scan. In relation to stage (T2b,N0,M0,G1) and the low degree of malignancy and, characteristic of this type of neoplasm, after the consultations of the oncologist and the radiotherapist, the indication for adjuvant therapies was excluded and the patient started a strict follow-up planned with: clinical examination every 3 months for the first 2 years, associated with an neck ultrasound every 3 months for the first 2 years and a CT of the neck once a year for the first 3 years. And a whole body PET/CT scan once a year for the first 5 years. At the time of the submission of this paper, the patient has been followed 2 years after the surgery with no evidence of tumor recurrence (Fig. 3). She will continue the follow-up.

The surgical specimen was submitted for histological examination in neutral-buffered 10% formalin, dehydrated using standard techniques, embedded in paraffin, cut to 5 μm, and stained with hematoxylin and eosin (H&E). Gross examination showed a well-circumscribed, nodular mass, measuring 8cm in greatest diameter. The cut surface showed a homogeneous mass, firm in consistency and whitish in color. Histological examination showed clear margins. The tumor appeared as a well circumscribed fibro-myxoid mass (Fig. 4A). Notably fibrous areas were alternating with myxoid areas (Fig. 4B). Tumor was composed of bland-looking spindle cells arranged into short intersecting fascicles (Fig. 4C). Tumor vasculature was represented by capillary-like blood vessels with branching or curvilinear configuration (Fig. 4D). A striking feature was the presence of variably-sized pseudorosettes composed of hyalinized collagen surrounded by a palisade of neoplastic cells (Fig. 4E). Immunohistochemistry, performed with the labeled streptavidin–biotin peroxidase detection system, revealed diffuse expression of vimentin and MUC4 (Fig. 4F), and focally of EMA. No immunostaining was obtained with the following antibodies: α-actin, desmin, myogenin, CD34, pancytokeratins, S100 protein, GFAP, p63, STAT6. Based on morphological and immunohistochemical features, the diagnosis of "*low-grade fibromyxoid sarcoma*" was rendered.

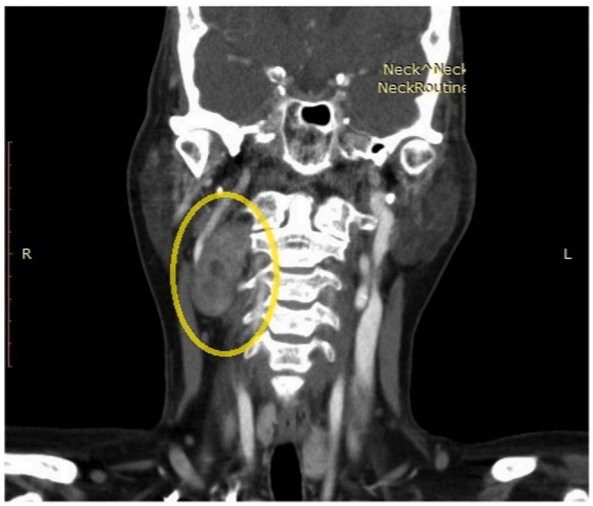

Fig. 1. Coronal and axial CT scans showing the mass in the right parapharyngeal space.

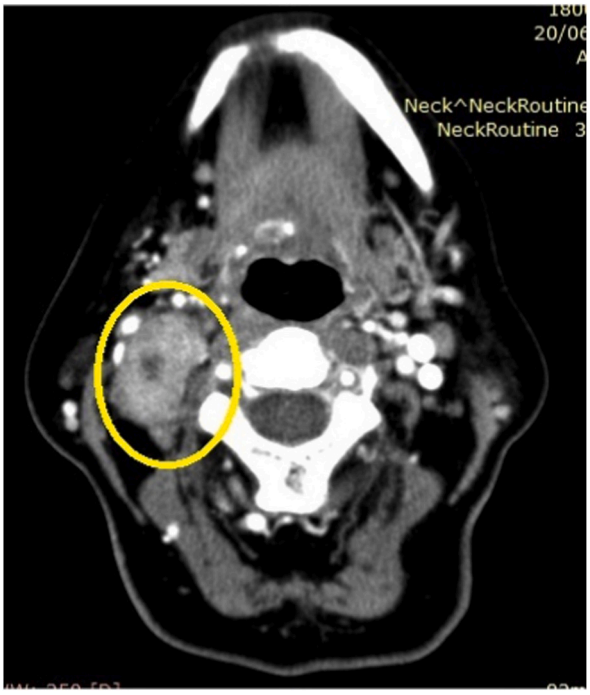

Fig. 2. Coronal and axial CT scans showing the mass in the right parapharyngeal space.

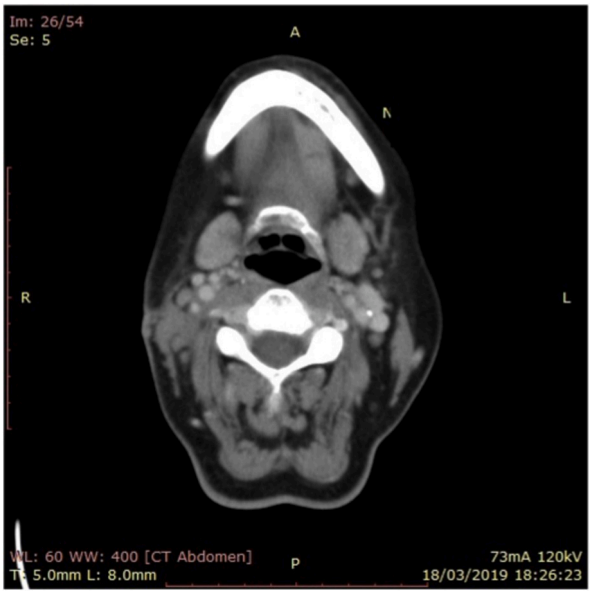

Fig. 3. Axial CT scan, 2 years after surgery.

2. Discussion

LGFMS of the head and neck is exceedingly rare. It may occur in the maxilla [19], the palate [20], the mandible [21,22], the cheek [23,24], the sternocleidomastoid muscle [25], the masseter muscle [26], the parotid gland [27], the external auditory canal [28] and the neck [5,29]. We herein report the first case of LGFMS occurring in the parapharyngeal space. The diagnosis was histologically based. Tumor was composed of bland-looking spindle cells arranged into short fascicles or whorls with alternating myxoid and fibrous areas and branching vasculature. Notably our case showed the characteristic collagen pseudorosettes consisting of a central core of collagen surrounded by a palisade of neoplastic cells. In the past tumors with predominant collagen pseudorosettes that obscured the

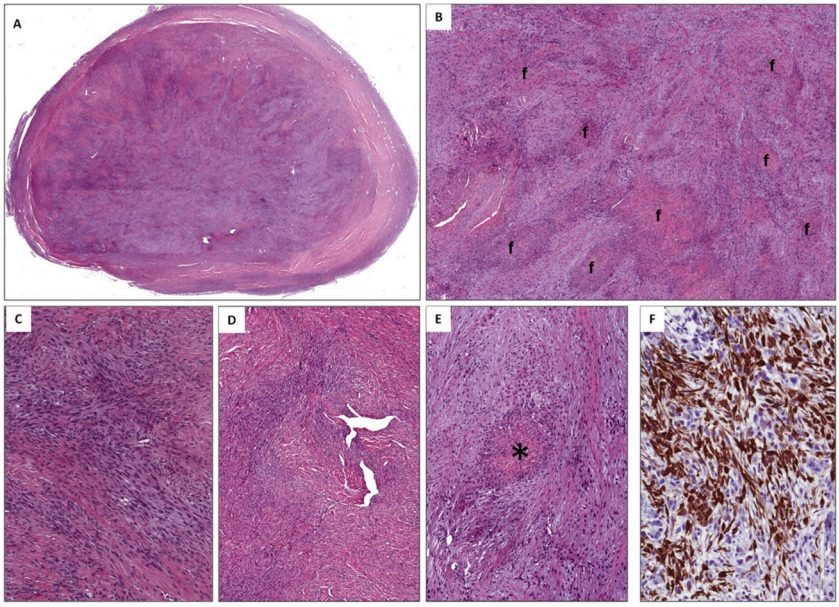

Fig. 4. Histological features of low-grade fibromyxoid sarcoma. Hematoxylin and eosin stain. (A) Low magnification showing a well circumscribed tumor mass. (B) Alternating myxoid and fibrous areas (f) are noticed at low-magnification. (C) Tumor is composed of bland-looking spindle cells arranged into short fascicles. (D) Notably capillary-like blood vessels with branching configuration are seen. (E) Collagen pseudorosettes (*) with surrounding palisade of neoplastic cells were scattered throughout the tumor. (F) Neoplastic cells were stained with MUC4.

underlying neoplastic spindle cell component, had been labeled "hyalinizing spindle cell tumor with giant rosettes" and considered as a distinct entity [30,31].

Although in the past there were no reliable immunomarkers for diagnosis of LGFMS, actually commercially available antibodies against MUC4 are helpful in confirming its diagnosis. In this regard it has been shown that this sarcoma is characterized by the overexpression of the MUC4 protein by means of immunohistochemistry. MUC4 is a high-molecular weight transmembrane glycoprotein that is normally expressed on many epithelial surfaces, including respiratory and colonic ones, where it plays a protective role and participates in cell growth. In our case the diagnosis was confirmed by a diffuse expression of MUC4 and focal staining for EMA (Epithelial Membrane Antigen) which is positive in about 50% of cases [18]. When dealing with a tumor exhibiting the typical morphology of LGFMS, but lacking MUC4 expression, ancillary molecular analyses (RT-PCR or F.I.S.H.) should be performed. In this regard it is well known that the chimeric *FUS/CREB3L2* gene is specific for LGFMS. Although little is known about the mechanisms causing the translocations of chromosomes 7 and 16, the detection of such a fusion gene, consistently associated with this specific sarcoma, has contributed significantly to the precision with which this tumor may be diagnosed. Recently, an alternative molecular aberration has been identified which was confirmed by DNA sequencing of reverse transcriptase-polymerase chain reaction products and fluorescence in situ hybridization: *EWSR1/CREB3L1* gene fusion. Interestingly, the *EWSR1/CREB3L1* gene fusion has been reported in sclerosing epithelioid fibrosarcoma (SEF) which also shares overlapping morphologic features with LGFMS.

In our case the histological diagnosis was challenging in that the parapharyngeal space is an unexpected site of occurrence for LGFMS. However the identification of the diagnostic morphologic clues was crucial for a correct interpretation. The differential diagnosis included a wide spectrum of bland-looking spindle cells lesions. Among these lesions those that can mimic LGFMS are mainly: nodular fasciitis, perineurioma, desmoid-type fibromatosis and solitary fibrous tumor. Unlike LGFMS, nodular fasciitis, a benign self-limiting myofibroblastic proliferation-exhibits brisk mitotic activity, cell culture appearance but it lacks MUC4 expression. Perineurioma, a benign peripheral nerve sheath tumor, may share some morphological and immunohistochemical (EMA expression) features with LGFMS. However perineurinoma is composed of spindle cells with long bipolar cytoplasmic processes, and usually lacks a significant myxoid stroma and MUC4-immunoreactivity. Unlike LGFMS, desmoid-type fibromatosis is composed of long fascicles, variably intersecting, it is stained with β-catenin (80%) and MUC4-negative. Lastly solitary fibrous tumor, unlike LGFMS, shows a prominent branching vasculature and is stained with STAT6 antibodies, along with the lack of MUC4 expression.

The reported techniques in the literature include local excision, radical surgery, wide en bloc resection, compartmental resection. Surgical resection with clear margins appears as the treatment of choice of LGFMS. The role of chemotherapy and radiotherapy as adjuncts to surgical intervention remains unclear. The potential for late recurrences and metastatic spread is high. For this reason all patients with LGFMS are recommended for long-term follow-up. Our patient is well with no evidence of local recurrence after 2 years of diagnosis, and she will continue the follow-up.

3. Conclusion

The present paper suggest to include LGFMS in the differential diagnosis of tumors of the parapharyngeal space, and especially among the bland-looking spindle cell lesions of the parapharyngeal space. Despite its bland-looking morphology, this sarcoma should be recognized to avoid confusion with other bland-looking benign spindle cell lesions. The distinction of LGFMS from its potential mimickers is crucial, given the high rate of local recurrence and metastatic potential.

Declaration of competing interest

All authors disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work.

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