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ORIGINAL PAPER

Low-Grade Fibromyxoid Sarcoma of the Head and Neck: A Clinicopathologic Series and Review of the Literature

Morgan L. Cowan[1] · Lester D. Thompson[3] · Marino E. Leon[4] · Justin A. Bishop[1,2]

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Abstract Low-grade fibromyxoid sarcoma (LGFMS) is a deceptively bland malignancy with potential for late recurrence and metastasis, which usually occurs in the deep soft tissues of the extremities and trunk. Most LGFMSs harbor a characteristic gene fusion of *FUS-CREB3L2*, and recently MUC4 immunostaining has been found to be highly sensitive and specific for the diagnosis. We present a dedicated series of head and neck LGFMS, including the first reported laryngeal case, as well as a review of reported head and neck cases. The surgical pathology archives of our three institutions were searched for cases of LGFMS arising within the head and neck, and four cases were identified. The H&E slides were reviewed, and immunohistochemistry were performed for pancytokeratin, p63, p40, EMA, S100 protein, β-catenin, actin, CD34, and MUC4. The patients were 6, 43, 45, and 73 years old (mean 41.8 years) and included three males and one female. The tumors were located in the posterior cervical spine, facial skin, mandible, and larynx. The tumors were treated with surgical excision, and all four had histologic features typical for LGFMS including alternating myxoid and fibrous areas with prominent curvilinear vasculature. All tumors were MUC4 positive (100%), 2/4 (50%) were p63 positive, 1/4 (25%) showed focal EMA positivity; all 4 were negative for pancytokeratin, p40, S100 protein, β-catenin, actin, and CD34. LGFMS is a low grade sarcoma that rarely develops in the head and neck. Due to its rarity, a pathologist may not consider LGFMS in the differential diagnosis of spindle cell neoplasms within the head and neck. Immunohistochemical staining is helpful, but stains should be selected carefully to avoid misdiagnosis.

Keywords Low-grade fibromyxoid sarcoma · MUC4 · Head and neck sarcoma · p63 · p40

Introduction

Primary sarcomas of the head and neck region are rare tumors, comprising <1% of primary malignancies in this region [1]. Primary head and neck sarcomas affect both adults and children. Some of the most frequently encountered sarcomas include rhabdomyosarcoma and Ewing sarcoma in children and young adults, and rhabdomyosarcoma, synovial sarcoma, Kaposi sarcoma, and angiosarcoma in older adults [2, 3]. Primary head and neck sarcomas commonly involve the scalp, face, and nasal cavity, while the larynx and upper airway are more unusual sites [1, 4, 5]. The prognosis is related to the tumor type and extent of resection, which is often incomplete due to anatomic restrictions [5].

Low-grade fibromyxoid sarcoma (LGFMS) is a deceptively bland malignancy with potential for late recurrence and metastasis [6]. LGFMS typically affects young adults, although children and older adults are also affected [7–9]. LGFMS occurs most commonly in the deep soft tissues of

✉ Morgan L. Cowan
mcowan6@jhmi.edu

[1] Department of Pathology, The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Pathology 401, Baltimore, MD 21287, USA

[2] Department of Otolaryngology-Head and Neck Surgery, The Johns Hopkins University School of Medicine, 600 North Wolfe Street, Pathology 401, Baltimore, MD 21287, USA

[3] Department of Pathology, Southern California Permanente Medical Group, Woodland Hills, CA, USA

[4] Department of Anatomic Pathology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL, USA

the proximal extremities and trunk, with only isolated head and neck cases reported [7, 9–14]. Most LGFMSs harbor a characteristic gene fusion of *FUS/CREB3L2*, and recently MUC4 immunostaining has been found to be highly sensitive and specific for the diagnosis [15, 16]. We present a dedicated series of head and neck LGFMS, including the first reported laryngeal case.

Methods

The surgical pathology archives of The Johns Hopkins Hospital, H. Lee Moffitt Cancer Center, and Southern California Permanente Medical Group were searched for cases of LGFMS arising within the head and neck. Hematoxylin and eosin stained slides were reviewed and immunohistochemistry was performed on an automated immunostainer for CK (pck-26, Ventana, pre-diluted), p63 (4a4, BioCare, pre-diluted), p40 (BC28, BioCare, 1:100), EMA (E29, Ventana, 5 mL/5mcg), S100 protein (4C4.0, Ventana, pre-diluted), muscle specific actin (HHF35, Ventana, pre-diluted), β-catenin (Transductinon Laboratories, 1:1000), CD34 (QBE-10, Ventana, 5 mL/5 mcg), and MUC4 (EPR9308; ABCAM; 1:400 dilution). All available clinical and follow-up information was reviewed.

Results

Four head and neck LGFMSs were identified, of which three cases were external consultations (Table 1). The patients ranged from 6 to 73 years in age (mean 41.8 years) at the time of diagnosis and included three males and one female. The tumors were located in the posterior cervical spine, facial skin, mandible, and larynx. One patient had a history of radiation to the tumor bed more than 10 years prior for excessive bone growth following trauma. All of the tumors were treated with wide surgical excision. Histologic examination showed the typical features of LGFMS. At low power, three of the tumors were poorly circumscribed, while one was fairly well demarcated. The tumors were characterized by alternating myxoid and fibrous areas with areas of prominent curvilinear or plexiform vasculature (Fig. 1a, b). The tumor cells contained monotonous, hyperchromatic nuclei with only rare mitoses (Fig. 1c). While none of the tumors exhibited the so-called "giant rosettes" that can be seen in LGFMS, three tumors had areas of whorled tumor cells suggesting early rosette formation (Fig. 1c).

By immunohistochemistry, all tumors were diffusely and strongly MUC4 cytoplasmic positive (Fig. 2a). Additionally, 2/4 (50%) were diffusely p63 nuclear positive (Fig. 2b), and 1/4 (25%) showed focal EMA cytoplasmic positivity (Fig. 2c). All four were negative for p40 (Fig. 2d), CD34, β-catenin, cytokeratin, muscle specific actin, and S100 protein. Follow up information was available for only two patients. One patient was disease-free at 12 months post-excision. The other patient was alive 10 months after surgery with multiple sub-centimeter pulmonary nodules too small to biopsy and enlarged post-tracheal and jugular chain lymph nodes (up to 1.4 cm) suggesting disseminated disease.

Discussion

LGFMS is an uncommon sarcoma with a known propensity for late recurrence and metastasis. Young adults are primarily affected, with mean reported ages ranging from late 3rd to 4th decades. Despite the metastatic potential of these tumors, even decades after the initial resection, patients can survive for many years with metastatic disease [7, 8, 11]. LGFMS primarily occurs in the soft tissues of the extremities, but cases have been reported involving the thoracic cavity, abdomen and bowel, and perineum [17–19].

Characteristic morphologic features of LGFMS include the alternating myxoid and fibrous areas with prominent arching vasculature and bland tumor cells. Tumors may also have collagen rosettes. Initially, tumors displaying these collagen rosettes were described separately due to an apparent benign clinical behavior, named *hyalinizing spindle cell tumor with giant rosettes* [20]. However, subsequent studies revealed the metastatic potential of these tumors and suggested they were within the spectrum

Table 1 Clinical features of head and neck low-grade fibromyxoidsarcomas

Case	Age (years)	Sex	Location	Presentation	Treatment
1	6	M	Posterior cervical spine	Slow-growing lump in neck	Surgery
2	43	F	Facial skin	Facial mass	Surgery
3	45	M	Mandible	Prior radiation to area following trauma	Surgery
4	73	M	Larynx	Laryngeal mass	Surgery

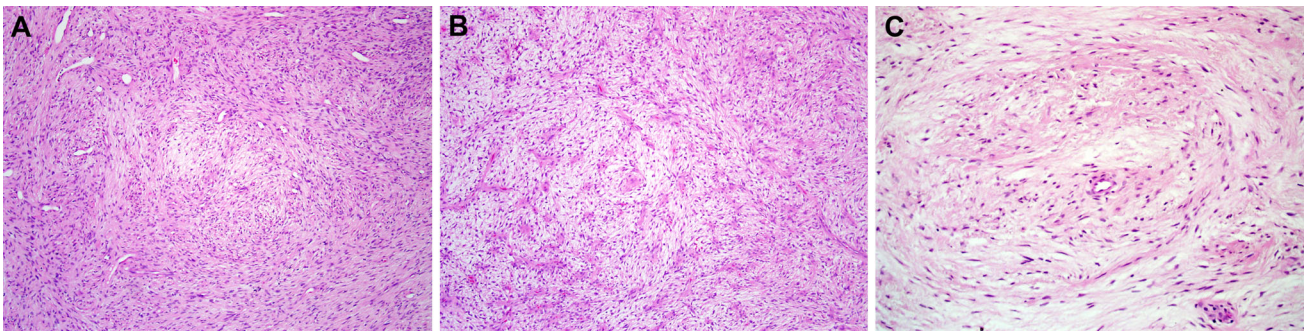

Fig. 1 **a** Low-grade fibromyxoid sarcoma characteristically exhibits alternating fibroblastic and myxoid zones at low-power (hematoxylin and eosin, X100). **b** In the more myxoid areas, a plexiform arrangement of delicate curvilinear vessels are noted (hematoxylin and eosin, X100). **c** In other areas, the tumor cells are arranged in characteristic whorls. The tumor cells are elongated and hyperchromatic, without pleomorphism or mitotic activity (hematoxylin and eosin, X200)

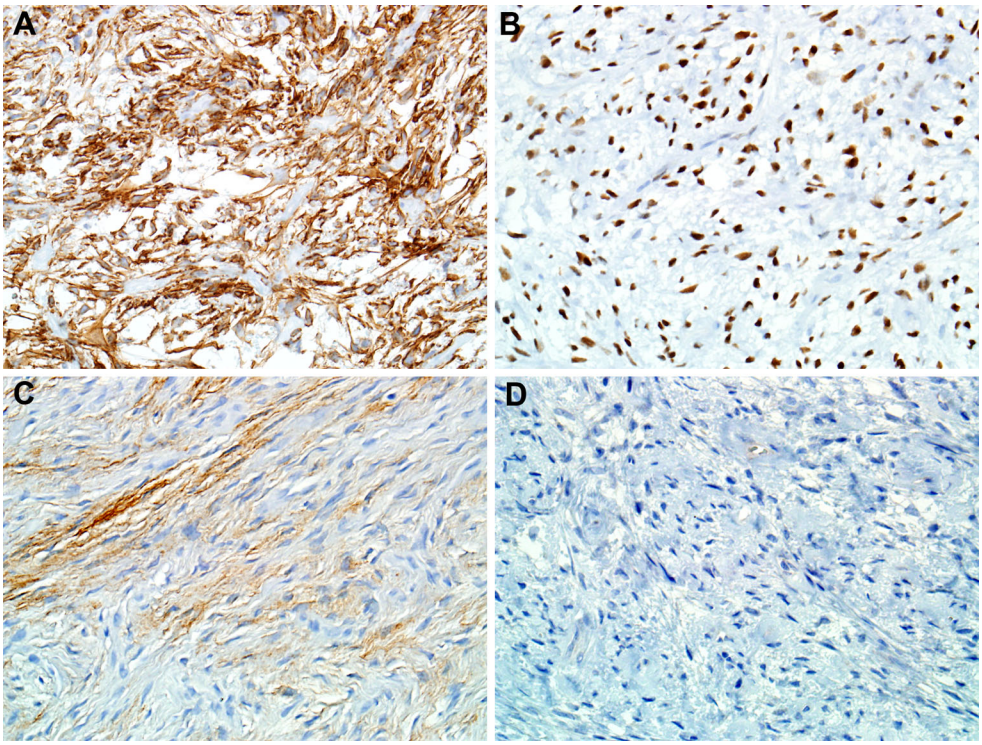

Fig. 2 **a** All three cases of low-grade fibromyxoid sarcoma were strongly positive for MUC4 (MUC4 immunohistochemistry, X400). **b** Two cases were diffusely positive for p63. **c** One case was focally positive for EMA, findings that could raise concern for the possibility of a sarcomatoid carcinoma (p63 and EMA immunohistochemistry, X400). **d** All cases of LGFMS were negative for p40, the more specific isoform of p63 (p40 immunohistochemistry, X400)

of LGFMS [7, 8]. Further, molecular studies identified the same chromosomal translocation as LGFMS [21].

Immunohistochemically, LGFMS may be positive for EMA, CD99, and bcl-2. Rarely LGFMS reacts with CD34 and SMA. LGFMS is generally negative for S100, desmin, caldesmon, cytokeratin, and CD117 [10, 22]. Recently, MUC4 has been shown to be a sensitive and specific marker for LGFMS, with 100 % of tested LGFMS MUC4 positive and most other spindle cell neoplasms in the differential, including desmoid tumor and perineurioma, nonreactive [15]. Although these earlier studies showed universal positivity in LGFMS, there are now reports of MUC4 negative tumors with the characteristic morphological features of LGFMS and molecular analysis

Table 2 Previous reported LGFMS in the head and neck

Case	Age (years)	Sex	Location	Outcome (if known)	Reference
1	26	M	Neck	Multiple recurrences, alive at 44 years	Evans, 1993 [9]
2	3y10 m	M	Jaw	Local recurrence after 3 months; local recurrence and concomitant lung metastasis after 15 years with surgery and radiation; NED 2 ½ years later	Papadimitriou, 1997 [13]
3	36	M	Left anterior neck	NED at 55 mo	Lane, 1997 [20]
4	N/A	N/A	Head/neck	N/A	Folpe, 2000 [7]
5	N/A	N/A	Head/neck	N/A	Folpe, 2000 [7]
6	N/A	N/A	Head/neck	N/A	Folpe, 2000 [7]
7	N/A	N/A	Head/neck	N/A	Folpe, 2000 [7]
8	22	M	Neck	NED at 38 months	Guillou, 2007 [10]
9	N/A	N/A	Sternocleidomastoid muscle	N/A	Marglani, 2007 [12]
10	N/A	N/A	Left maxillary sinus	N/A	Merchant, 2009 [33]
11	N/A	N/A	Head/neck	N/A	Merchant, 2009 [33]
12	N/A	N/A	Head/neck	N/A	Merchant, 2009 [33]
13	1y10 m	M	Cheek	NED after 6 months	Tang, 2010 [14]
14	57	M	Anterior neck, mimic thyroid nodule		Viswanathan, 2010 [34]
15	27	M	Jaw	NED after 22 months	Rekhi, 2011 [11]
16	31	M	Face	N/A	Rekhi, 2011 [11]
17	69	M	Neck	2 recurrences after 10 years	Rekhi, 2011 [11]
18	26	M	Neck	Multiple recurrences treated with excision, NED at 44 years	Evans, 2011 [8]
19	9	M	Neck	Multiple recurrences, followed by radiation after last; lung and chest wall metastases at 25 years treated with multiple resections; died of metastatic tumor at 42 years	Evans, 2011 [8]
20	41	M	Supraclavicular	N/A	Prieto-Granada, 2015 [30]

N/A Information was not available, *NED* No evidence of disease

demonstrating the *FUS-CREB3L2* rearrangement. MUC4 is not 100 % specific, and other tumors may stain with MUC4, including synovial sarcoma (30–90%) and sclerosing epithelioid fibrosarcoma (SEF, 78%) [15, 23]. In practice, the morphologic features of LGFMS generally do not overlap with synovial sarcoma and thus unlikely the tumors would be in the same differential diagnosis. The distinction with SEF may be troublesome since a subset of SEF has *FUS* translocations and it has been suggested that these tumors are related to LGFMS [8, 9].

Molecularly, LGFMS is characterized by a translocation of chromosomes 7 and 16, leading to the fusion product *FUS/CREB3L2* (t(7;16)(q32–34; p11) is the most common in 90% of cases) or *FUS/CREB3L1* (t(11;16)(p11; p11)) [16, 24–26]. However, a lack of *FUS* gene rearrangement should not be used to exclude the diagnosis of LGFMS, as occasional cases of LGFMS have been reported which lack *FUS* rearrangements and instead harbor an *EWSR1-CREB3L1* fusion [27, 28]. Interestingly, the *EWSR1-CREB3L1* gene fusion is more commonly reported in sclerosing epithelioid fibrosarcoma (SEF) which exists on an overlapping morphologic spectrum with LGFMS and similarly exhibits frequent MUC4 positivity [29–31].

A review of the previous literature on LGFMS yielded only 20 head and neck cases of over 400 total, many as part of earlier series or case reports (Table 2). Notably, several recent larger series of LGFMS did not identify any cases in the head and neck region [4, 5]. Many authors did not specify the location beyond "head/neck". Of the eight cases that did specify a more detailed location, only two involved deep anatomic locations: one in the left maxillary sinus and the second in the anterior neck which clinically simulated a thyroid nodule [32, 33]. Outcomes that were reported found one patient died of disease after

42 years, and four patients had recurrences and/or late metastases.

Spindle cell neoplasms in the head and neck present a unique set of diagnostic challenges. In particular, spindle cell "sarcomatoid" squamous cell carcinoma (SCSCC) should top the differential diagnosis, especially in older individuals. In one study, 70% of spindle cell lesions in the head and neck were spindle cell squamous cell carcinoma [34]. SCSCC sometimes contain a collagenous or myxoid background and deceptively bland areas, but the cells usually display pleomorphism and increased mitoses at least focally, which would not be expected in LGFMS. The presence of surface squamous dysplasia or a conventional epithelial component is very helpful in identifying SCSCC. In the absence of an epithelial component, immunohistochemistry may be helpful. SCSCC may be positive for epithelial markers, such as cytokeratin AE1/AE3, EMA, p63, p40, and CK5/6, however, only about 70 % of SCSCC react with these epithelial markers [35, 36]. Some SCSCC also express mesenchymal markers, such as CD99, bcl-2, S100 protein, and SMA [35, 37–39]. Interestingly, two tumors in this series of LGFMS were diffusely p63 reactive and one was EMA reactive, further blurring the distinction between mesenchymal and epithelial differentiation. Usually, p63 and/or EMA positivity suggests the diagnosis of SCSCC. Fortunately, it has been recently shown that while half of LGFMS may be p63 reactive, the more specific ΔNp63 isoform of p63 (p40) appears to be consistently negative in LGFMS [40]. Therefore, the immunohistochemical panel should be carefully selected to avoid misinterpretation by including several epithelial and mesenchymal markers.

The presence of alternating loose and pale areas in a spindle cell neoplasm without overt cytologic malignancy would raise the differential diagnosis of peripheral nerve sheath tumors, especially schwannoma and neurofibroma. However, these tumors should exhibit S100 protein and SOX10 staining while LGFMS is consistently non-reactive with S100 protein and SOX10 [10, 41]. Other entities in the differential diagnosis include myofibroblastic tumors and fibromatosis. Myofibroblastic tumors, such as myofibroma or inflammatory myofibroblastic tumor (IMT), will be reactive with actins, while LGFMS is non-reactive. While fibromatosis may show prominent vasculature, the pattern is not that of the vascular arcades seen in LGFMS, and LGFMS will be β-catenin negative, while fibromatosis shows a strong nuclear reaction.

In summary, LGFMS is a low grade sarcoma that may rarely develop in the head and neck. Due to its rarity, a pathologist may not consider LGFMS in the differential diagnosis of spindle cell neoplasms within the head and neck. Awareness of LGFMS and its characteristic histologic features should be considered in the differential diagnosis of a head and neck spindled cell tumors, with MUC4 immunostaining an easy study to help confirm the diagnosis.

References

1. Bentz BG, Singh B, Woodruff J, et al. Head and neck soft tissue sarcomas: a multivariate analysis of outcomes. Ann Surg Oncol. 2004;11:619–28.
2. Barosa J, Ribeiro J, Afonso L, et al. Head and neck sarcoma: analysis of 29 cases. Eur Ann Otorhinolaryngol Head Neck Dis. 2014;131:83–6.
3. Peng KA, Grogan T, Wang MB. Head and neck sarcomas: analysis of the seer database. Otolaryngol Head Neck Surg. 2014;151:627–33.
4. Tajudeen BA, Fuller J, Lai C, et al. Head and neck sarcomas: the UCLA experience. Am J Otolaryngol—Head Neck Med Surg. 2014;35:476–81.
5. Tejani MA, Galloway TJ, Lango M, et al. Head and neck sarcomas: a comprehensive cancer center experience. Cancers (Basel). 2013;5:890–900.
6. Evans HL. Low-grade fibromyxoid sarcoma. A report of two metastasizing neoplasms having a deceptively benign appearance. Am J Clin Pathol. 1987;88:615–9.
7. Folpe AL, Lane KL, Paull G, et al. Low-grade fibromyxoid sarcoma and hyalinizing spindle cell tumor with giant rosettes: a clinicopathologic study of 73 cases supporting their identity and assessing the impact of high-grade areas. Am J Surg Pathol. 2000;24:1353–60.
8. Evans HL. Low-grade fibromyxoid sarcoma: a clinicopathologic study of 33 cases with long-term follow-up. Am J Surg Pathol. 2011;35:1450–62.
9. Evans HL. Low-grade fibromyxoid sarcoma. A report of 12 cases. Am J Surg Pathol. 1993;17:595–600.
10. Guillou L, Benhattar J, Gengler C, et al. Translocation-positive low-grade fibromyxoid sarcoma: clinicopathologic and molecular analysis of a series expanding the morphologic spectrum and suggesting potential relationship to sclerosing epithelioid fibrosarcoma: a study from the French Sarcoma Gro. Am J Surg Pathol. 2007;31:1387–402.
11. Rekhi B, Deshmukh M, Jambhekar NA. Low-grade fibromyxoid sarcoma: a clinicopathologic study of 18 cases, including histopathologic relationship with sclerosing epithelioid fibrosarcoma in a subset of cases. Ann Diagn Pathol. 2011;15:303–11.
12. Marglani O, Commons S, Lamothe A. Radiation-induced low-grade fibromyxoid sarcoma of the sternocleidomastoid muscle. J Otolaryngol. 2007;36:E73–5.
13. Papadimitriou JC, Ord RA, Drachenberg CB. Head and neck fibromyxoid sarcoma: clinicopathological correlation with emphasis on peculiar ultrastructural features related to collagen processing. Ultrastruct Pathol. 1997;21:81–7.
14. Tang Z, Zhou Z, Lv C, et al. Low-grade fibromyxoid sarcoma: clinical study and case report. J Oral Maxillofac Surg. 2010;68:873–84.
15. Doyle LA, Möller E, Dal Cin P, et al. MUC4 is a highly sensitive and specific marker for low-grade fibromyxoid sarcoma. Am J Surg Pathol. 2011;35:733–41.
16. Panagopoulos I, Storlazzi CT, Fletcher CDM, et al. The chimeric FUS/CREB3l2 gene is specific for low-grade fibromyxoid sarcoma. Genes Chromosomes Cancer. 2004;40:218–28.
17. Park IJ, Kim HC, Yu CS, et al. Low-grade fibromyxoid sarcoma of the colon. Dig Liver Dis. 2007;39:274–7.
18. Jakowski JD, Wakely PE. Primary intrathoracic low-grade fibromyxoid sarcoma. Hum Pathol. 2008;39:623–8.

19. Lee AF, Yip S, Smith AC, et al. Low-grade fibromyxoid sarcoma of the perineum with heterotopic ossification: case report and review of the literature. Hum Pathol. 2011;42:1804–9.
20. Lane KL, Shannon RJ, Weiss SW. Hyalinizing spindle cell tumor with giant rosettes: a distinctive tumor closely resembling low-grade fibromyxoid sarcoma. Am J Surg Pathol. 1997;21:1481–8.
21. Reid R, de Silva MVC, Paterson L, et al. Low-grade fibromyxoid sarcoma and hyalinizing spindle cell tumor with giant rosettes share a common t(7;16)(q34; p11) translocation. Am J Surg Pathol. 2003;27:1229–36.
22. Zamenik M. Low-grade fibromyxoid sarcoma: a report of eight cases with histologic, immunohistochemical, and ultrastructural study. Ann Diagn Pathol. 2000;4:207–17.
23. Doyle LA, Wang W-L, Dal Cin P, et al. MUC4 is a sensitive and extremely useful marker for sclerosing epithelioid fibrosarcoma. Am J Surg Pathol. 2012;36:1444–51.
24. Storlazzi CT, Mertens F, Nascimento A, et al. Fusion of the FUS and BBF2H7 genes in low grade fibromyxoid sarcoma. Hum Mol Genet. 2003;12:2349–58.
25. Bartuma H, Möller E, Collin A, et al. Fusion of the FUS and CREB3L2 genes in a supernumerary ring chromosome in low-grade fibromyxoid sarcoma. Cancer Genet Cytogenet. 2010; 199:143–6.
26. Mezzelani A, Sozzi G, Nessling M, et al. Low grade fibromyxoid sarcoma. A further low-grade soft tissue malignancy characterized by a ring chromosome. Cancer Genet Cytogenet. 2000; 122:144–8.
27. Lau PPL, Lui PCW, Lau GTC, et al. EWSR1-CREB3L1 gene fusion. Am J Surg Pathol. 2013;37:734–8.
28. Rubinstein JC, Visa A, Zhang L, et al. Primary low-grade fibromyxoid sarcoma of the kidney in a child with the alternative EWSR1-CREB3L1 gene fusion. Pediatr Dev Pathol. 2014;17: 321–6.
29. Doyle LA, Wang W-L, Dal Cin P, et al. MUC4 is a sensitive and extremely useful marker for sclerosing epithelioid fibrosarcoma: association with FUS gene rearrangement. Am J Surg Pathol. 2012;36:1444–51.
30. Prieto-Granada C, Zhang L, Chen H-W, et al. A genetic dichotomy between pure sclerosing epithelioid fibrosarcoma (SEF) and hybrid SEF/low-grade fibromyxoid sarcoma: a pathologic and molecular study of 18 cases. Genes Chromosomes Cancer. 2015;54:28–38.
31. Arbajian E, Puls F, Magnusson L, et al. Recurrent EWSR1-CREB3L1 gene fusions in sclerosing epithelioid fibrosarcoma. Am J Surg Pathol. 2014;00:1–8.
32. Hwang S, Kelliher E, Hameed M. Imaging features of low-grade fibromyxoid sarcoma (Evans tumor). Skelet Radiol. 2012;41: 1263–72.
33. Merchant SH. Low grade fibromyxoid sarcoma: report of a case with epithelioid cell morphology, masquerading as a papillary thyroid carcinoma. Acta Cytol. 2009;53:689–92.
34. Viswanathan S, Rahman K, Pallavi S, et al. Sarcomatoid (spindle cell) carcinoma of the head and neck mucosal region: a clinicopathologic review of 103 cases from a tertiary referral cancer centre. Head Neck Pathol. 2010;4:265–75.
35. Lewis JS, Ritter JH, El-Mofty S. Alternative epithelial markers in sarcomatoid carcinomas of the head and neck, lung, and bladder-p63, MOC-31, and TTF-1. Mod Pathol. 2005;18:1471–81.
36. Thompson LDR, Wieneke JA, Miettinen M, et al. Spindle cell (sarcomatoid) carcinomas of the larynx: a clinicopathologic study of 187 cases. Am J Surg Pathol. 2002;26:153–70.
37. Anderson CE, Al-Nafussi A. Spindle cell lesions of the head and neck: an overview and diagnostic approach. Diagn Histopathol. 2009;15:264–72.
38. Olsen KD, Lewis JE, Suman VJ. Spindle cell carcinoma of the larynx and hypopharynx. Otolaryngol Head Neck Surg. 1997;116:47–52.
39. Ansari-Lari MA, Hoque MO, Califano J, et al. Immunohistochemical p53 expression patterns in sarcomatoid carcinomas of the upper respiratory tract. Am J Surg Pathol. 2002;26: 1024–31.
40. Bishop JA, Montgomery EA, Westra WH. Use of p40 and p63 immunohistochemistry and human papillomavirus testing as ancillary tools for the recognition of head and neck sarcomatoid carcinoma and its distinction from benign and malignant mesenchymal processes. Am J Surg Pathol. 2014;38:257–64.
41. Miettinen M, Mccue PA, Sarlomo-rikala M, et al. Sox10—a marker for not only schwannian and melanocytic neoplasms but also myoepithelial cell tumors of soft tissue. Am J Surg Pathol. 2015;39:1–10.