Original Article

A multicentric case study of fibroblastic and myofibroblastic oral spindle cell lesions

Kiran Jot, Vivek Nayyar, Varun Surya, Deepika Mishra, Sowmya SV[1], Dominic Augustine[1], Indu M[2], Vanishri C. Haragannavar[1]

Department of Oral Pathology and Microbiology, Fifth Floor, Centre for Dental Education and Research, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, [1]Department of Oral Pathology and Microbiology, Faculty of Dental Sciences, Ramaiah University of Applied Sciences, MSR Nagar, Bengaluru, Karnataka, [2]Department of Oral Pathology, Government Dental College, Kottayam, Kerala, India

Abstract

Context: Spindle cell lesions comprise a vast plethora of benign and malignant lesions with similar clinical and radiographic features. Their overlapping histopathologic features ensure a diagnostic dilemma.

Aim: The current multicentric study aims to delineate fibroblastic and myofibroblastic oral spindle cell lesions based on cytomorphology and comprehensive immunohistochemical analysis.

Settings and Design: The experimental study was conducted at MS Ramaiah University of Applied Sciences, Bangalore, and All India Institute of Applied Sciences, Delhi.

Methods and Material: A comprehensive histological scoring criteria and panel of immunohistochemical makers (STAT6, CD31, CD34, S100, SMA, vimentin, pan-CK, HHF-35, Ki67, ALK, desmin, HMB-45, SATB2, ERG, EMA and CD99) were employed concurrently for the first time for fibroblastic and myofibroblastic oral spindle cell lesions. The data obtained was tabulated and studied.

Statistical Analysis Used: NA. Results: Using cytological scoring criteria and panel of immunohistochemical makers, the cases analysed and characterized were desmoplastic fibroma, fibrosarcoma, leiomyosarcoma, nodular fasciitis, neurofibroma and epithelioid inflammatory myofibroblastic sarcoma (EIMS).

Conclusions: The diagnostic strategies need to be upgraded for the diagnosis of spindle cell lesions. Emphasis must be placed on cytomorphology, an immunohistochemistry (IHC) panel of markers is imperative for the accurate diagnosis of fibroblastic and myofibroblastic oral spindle cell lesions.

Keywords: Fibroblastic, immunohistochemistry, multicentric, myofibroblastic origin, spindle cell

Address for correspondence: Dr. Deepika Mishra, Additional Professor, Department of Oral Pathology and Microbiology, Fifth Floor, Centre for Dental Education and Research, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India.
E-mail: deepika1904@gmail.com
Submitted: 26-Jun-2023, **Revised:** 18-Nov-2023, **Accepted:** 20-Nov-2023, **Published:** 20-Dec-2023

INTRODUCTION

Spindle cell lesions of the oral cavity comprise a heterogeneous group of tumours, categorized under benign, borderline and malignant subtypes. They have a variety of appearances; therefore, most common issues that arise while making a diagnosis are distinguishing a non-mesenchymal spindle cell malignancy like spindle cell carcinoma from a true sarcoma, differentiating a benign and malignant spindle cell lesion, classifying and grading a spindle cell neoplasm.[1] Challenging cases can

Access this article online

Quick Response Code:

Website: https://journals.lww.com/JPAT/

DOI: 10.4103/jomfp.jomfp_282_23

How to cite this article: Jot K, Nayyar V, Surya V, Mishra D, Sowmya SV, Augustine D, *et al*. A multicentric case study of fibroblastic and myofibroblastic oral spindle cell lesions. J Oral Maxillofac Pathol 2023;27:629-41.

get valuable diagnostic clues through varied architectural patterns.[2] The diagnostic approach for these tumours is dependent on sound knowledge of tumour type frequencies, accurate interpretation of histopathologic features and an effective clinicopathologic correlation.[1] The lesions show considerable morphological overlap, and immunohistochemistry (IHC) acts as a useful aid in distinguishing between them. It confirms the histopathologic impression and supports the diagnosis of a rare tumour type, tumours of unusual anatomic location and affecting patients of uncharacteristic age.[3]

Fibroblasts are metabolically active spindle-shaped mesenchymal cells that can present as several phenotypes such as non-contractile fibroblasts, contractile myofibroblasts, and intermediate types (protomyofibroblast).[4] Myofibroblasts are spindle-shaped mesenchymal cells that resemble the ultrastructure of both fibroblasts and smooth muscle cells.[5] These cells were first described by Gabbiani, Ryan and Majne in 1971.[6] Prototypical myofibroblasts can be distinguished from the fibroblasts with the presence of alpha-smooth muscle actin (α-SMA) with stress fibres while the fibroblasts express vimentin in the absence of desmin and α-SMA.[4] Although specialized cells such as myofibroblasts share ultrastructural similarity to fibroblasts and smooth muscle cells, they are different from both types. Histologically, these are bipolar or stellate cells with elongated and tapered/wavy nuclei like fibroblasts with lightly eosinophilic, or amphophilic cytoplasm. The nuclei can be short, oval and pale stained, with distinct and punctate small nucleoli. The cells exhibit ill-defined cell boundaries.[7] The features under electron microscope are nuclear indentation, increased rough endoplasmic reticulum, microfilament bundles with stress fibres and attachment plaques at the plasmalemma, a discontinuous basal lamina, micropinocytic vesicles, well-developed fibronexus (attachment of cell to stroma) and intermediate and gap intercellular junctions.[8] There are a number of fibroblastic and myofibroblastic tumours occurring in the body.[9] But here we consider only the oral cavity and these lesions will include fibrous hyperplasia, peripheral ossifying fibroma, inflammatory myofibroblastic tumour (IMT), solitary fibrous tumour (SFT), desmoplastic fibroma, low-grade myofibroblastic sarcoma and fibrosarcoma not otherwise specified (NOS). We will be discussing the diagnostic approach used in the identification of the spindle cell lesions occurring in oral cavity, with special attention to the cytomorphology along with the role of IHC in order to highlight diagnostically relevant points.

SUBJECTS AND METHODS

This study includes all the fibroblastic and myofibroblastic lesions of the oral cavity, obtained from the archives of the Department of Oral Pathology and Microbiology of All India Institute of Medical Sciences, New Delhi, and Faculty of Dental Sciences, Ramaiah University of Applied Sciences, Bengaluru, from 2018 to 2022. All cases were re-evaluated, and IHC was performed in doubtful cases. The histopathological features were assessed based on the following parameters—capsule, overall cellularity, architectural (growth) pattern of the tumour, cellular and nuclear features, cytological atypia, mitoses (n/10HPF), myxoid areas, blood vessels (shape), inflammation, necrosis and haemorrhagic areas. These parameters were further divided into subcategories; capsule: well-capsulated, partial capsulated or non-capsulated; cellularity: loose, moderate or highly cellular; cytological atypia: mild, moderate or marked; myxoid areas: 0-absent, 1-<25%, 2-26-50%, 3->50% area; inflammation: mild, moderate or intense; necrosis: absent or present; haemorrhagic areas: absent or present. The proposed histological scoring criteria are shown in Table 1. Based on these histopathological parameters, differential diagnosis was made. IHC was done to reach the final diagnosis. Ethical approval was obtained from the Institutional Review Board IEC-720/04.10.2019, RP/2019 dated 30/10/2019.

RESULTS

The present study includes a total of eleven cases of spindle cell lesions of fibroblastic and myofibroblastic origin. Initially, a total of 177 cases of spindle cell lesions of fibroblastic and myofibroblastic origin were retrieved. These lesions comprised of fibrous hyperplasia (n = 117), peripheral ossifying fibroma (n = 40), desmoplastic fibroma (DF) (n = 8), fibrosarcoma (n = 4), leiomyosarcoma (n = 1), nodular fasciitis (n = 1), neurofibroma (n = 1), SFT (n = 2) and IMT (n = 1), low-grade myofibroblastic sarcoma (LGMS) (n = 1) and epithelioid inflammatory myofibroblastic sarcoma (EIMS) (n = 1). As fibrous hyperplasia and peripheral ossifying fibroma are the most common lesions reported routinely, therefore only twenty cases of uncommon lesions of the oral cavity are discussed in the current manuscript. The twenty cases comprised of DF (n = 8), fibrosarcoma (n = 4), leiomyosarcoma (n = 1), nodular fasciitis (n = 1), neurofibroma (n = 1), SFT (n = 2), IMT (n = 1), LGMS (n = 1) and EIMS (n = 1). Male predominance (14/20) was observed in the included cases with mean age of 40 years (ranges from 2.5 to 73 years). Out of these twenty cases, eleven cases were intraosseous while

Table 1: Proposed histological scoring criteria for fibroblastic and myofibroblastic oral spindle cell lesions

Capsule	Histological Pattern	Overall Cellularity	Cellular and Nuclear Features	Cytological Atypia	Mitoses (*n*/10HPF)	Collagen	Myxoid Areas	Vascularity	Inflammation	Necrosis	Haemorrhagic Areas
Well capsulated, Partial capsulated or non-capsulated	Short fascicles Herringbone Storiform Whorled Long fascicles Hypocellular and Hypercellular Interlacing short fascicles	3- High 2- Moderate 1-Mild	Monomorphic spindle-shaped Vesicular nuclei Fine dispersed chromatin Inconspicuous nucleoli Eosinophilic cytoplasm Indistinct cell borders Comma-shaped hyperchromatic nuclei Wavy hyperchromatic nuclei Epithelioid cells Prominent nucleoli Coarse chromatin Bland spindle-shaped cells Cigar-shaped nuclei Collagenous areas	3- High 2-Moderate 1-Mild 0-Absent	*n*=number of mitotic figures per 10 HPF	Fibrillary Wiry Keloid Ropey Focal	0-Absent 1-<25% 2-26-50% 3->50%	Variably shaped Staghorn Uniform Hemangiopericytoma-like	3- High 2-Moderate 1-Mild 0-Absent (0-3 further divided into focal and diffuse)	3- High 2-Moderate 1-Mild 0-Absent	3- High 2-Moderate 1-Mild 0-Absent

the rest were extraosseous. These intraosseous lesions were DF (n = 8), neurofibroma (n = 1), fibrosarcoma (n = 1) and EIMS (n = 1). Demographic data including radiographic findings are discussed in Table 2.

On histopathological examination, all cases of fibrosarcoma showed moderate to high cellularity, with fascicular pattern. Three cases displayed herringbone and storiform patterns while the other one showed whorled pattern. The tumour cells were pleomorphic, spindle-shaped with vesicular nuclei, fine dispersed chromatin, inconspicuous nucleoli, eosinophilic cytoplasm and indistinct cell borders. The maximum mitoses noted was 11 per 10 HPF. Mild inflammation with focal haemorrhagic areas was also seen.

Two cases of SFT showed moderate to high cellular stroma with spindle cells arranged in irregular patterns. One case was well-circumscribed and encapsulated while the other case was unencapsulated. The tumour cells were spindle-shaped with vesicular nuclei, inconspicuous nucleoli, eosinophilic cytoplasm and distinct cell borders with mild cytological atypia. Herringbone pattern vascularity was observed in both cases with moderate inflammation. The above features have been depicted in Figure 1 A1-F2. Both cases displayed STAT6 and CD34 positivity. [Figure 2a – 2c]

All the cases of DF showed fascicular arrangement of tumour cells with mild to moderate cellularity. Two cases displayed bland spindle-shaped cells with hyperchromatic nuclei, eosinophilic cytoplasm and indistinct cell borders merging into the fibrous stroma. Other cases showed spindle-shaped cells with vesicular nuclei, inconspicuous nucleoli, eosinophilic cytoplasm and distinct cell borders. Predominantly ropey type collagen was found in all the cases with one case showing myxoid areas. Predominantly mild inflammation and mild vascularity were noted. No cytological atypia, mitoses, necrosis and haemorrhagic areas were found. Immunopositivity for beta-catenin and vimentin and negative reaction for S100 concluded DF as the final diagnosis with one case that showed SMA immunopositivity [Figure 2d and 2e].

Leiomyosarcoma showed long fascicles, few whorled areas, spindle-shaped cells with vesicular nuclei, fine dispersed chromatin, inconspicuous nucleoli and few cigar-shaped nuclei. The high amount of vascularity, areas of haemorrhage and moderate inflammation were noticed. It was found to be positive for vimentin, Ki67: 15% and SMA. It was found negative for pan-CK and S100.

Table 2: Demographic data of patients

Case no.	Age/ sex	Duration	Site	Intraosseous/ Extraosseous	Radiographic Features	Diagnosis
1.	21/M	2.5 months	Left maxilla	EO	Erosion of bone	Fibrosarcoma
2.	5/M	3 months	Left Mandible	IO	Radiolucency i.r.t angle and ramus region of mandible extending upto sigmoid notch	Fibrosarcoma
3.	42/M	1 month	Anterior Mandible	EO	-	Fibrosarcoma
4.	68/M	2 months	Left Buccal Mucosa	EO	-	Inflammatory Myofibroblastic Tumour
5.	73/M	12 months	Right Maxillary Alveolus	EO	-	Low-Grade Myofibroblastic Sarcoma
6.	31/M	5 months	Right Anterior Maxilla	IO	Osteolytic lesion with soft tissue component reaching up to midline	Epithelioid Inflammatory Myofibroblastic Sarcoma
7.	61/M	24 months	Right Posterior Mandible	IO	OPG showed a multilocular osteolytic lesion with ill-defined border involving the left ramus and angle region of mandible. Buccal and lingual cortical perforation was evident on CECT	Desmoplastic Fibroma
8.	11/F	12 months	Chin	IO	OPG showed ill-defined radiolucent lesion w.r.t. the right mandibular lateral incisor and canine causing displacement of roots. CBCT showed buccal plate expansion with evidence of calcification at periphery. The inferior cortical margin also showed bony expansion with small radiating striae.	Desmoplastic Fibroma
9.	2.5/M	6 months	Right Posterior Mandible	IO	CECT revealed well-defined osteolytic lesion in right angle and ramus region of mandible with multiple areas of breach in the inner and outer cortex. No area of ossification and periosteal reaction seen. Lesion was eroding right-sided pterygoid process, pterygoid plates and involving the masticatory, submandibular and parapharyngeal spaces.	Desmoplastic Fibroma
10.	33/M	7 months	Left Buccal Mucosa	EO	-	Solitary Fibrous Tumour
11.	65/M	3 months	Floor of Mouth	EO	-	Solitary Fibrous Tumour
12.	37/F	3 months	Left GBS	EO	-	Fibrosarcoma
13	42/F	4 months	Right GBS	EO	-	Leiomyosarcoma
14.	41/M	6 months	Right Posterior Mandible	IO	OPG showed ill-defined radiolucent lesion involving the body of the mandible with intact cortical plates	Neurofibroma
15.	55/M	6 months	Left Buccal Mucosa	EO	-	Nodular Fasciitis
16.	70/M	9 months	Left Anterior Maxilla	IO	OPG showed ill-defined radiolucent lesion. No area of ossification and periosteal reaction seen	Desmoplastic Fibroma
17.	65/F	12 months	Left Posterior Mandible	IO	OPG showed osteolytic lesion with ill-defined border involving the left ramus	Desmoplastic Fibroma
18.	09/M	11 months	Right Posterior Mandible	IO	OPG showed ill-defined radiolucent lesion. CBCT showed buccal plate expansion	Desmoplastic Fibroma
19.	42/F	1 year	Right Posterior Maxilla	IO	OPG showed osteolytic lesion with ill-defined border involving the right maxilla	Desmoplastic Fibroma
20.	28/F	8 months	Left Posterior Maxilla	IO	OPG showed ill-defined radiolucent lesion. CBCT showed buccal plate expansion	Desmoplastic Fibroma

Nodular fasciitis displayed short fascicles, irregular focal storiform pattern and spindle-shaped cells with distinct nuclei with no pleomorphism. Collagenous areas were also noted with mild vascularity. Focal immunopositivity for vimentin, HHF-35 and SMA was observed with negative staining for desmin, CD34 and low Ki67=<1% score.

Neurofibroma exhibited long fascicles, focal storiform pattern and spindle-shaped cells with vesicular wavy nuclei, fine dispersed chromatin and inconspicuous nucleoli. Minimal inflammatory response and vascularity were noticed. The tumour was immunopositive for S100, and weakly positive for vimentin, while it was negative for pan-CK and SMA [Figure 2f and 2g].

The myofibroblastic cases showed spindle-shaped cells arranged predominantly in storiform pattern followed by short fascicles. All these cases displayed moderate cellularity with two cases that showed marked pleomorphism. The tumour cells were spindle in shape with vesicular nuclei exhibiting tapering ends, eosinophilic cytoplasm and distinct cell borders. Two cases showed prominent nucleoli in which one case showed epitheloid morphology along with areas of necrosis. The presence of myofibroblasts-like spindle cells along with prominent inflammatory component and immunopositivity of SMA and ALK (focal) diagnosis of IMT was given, [Figure 2h and 2i]. In the other case,

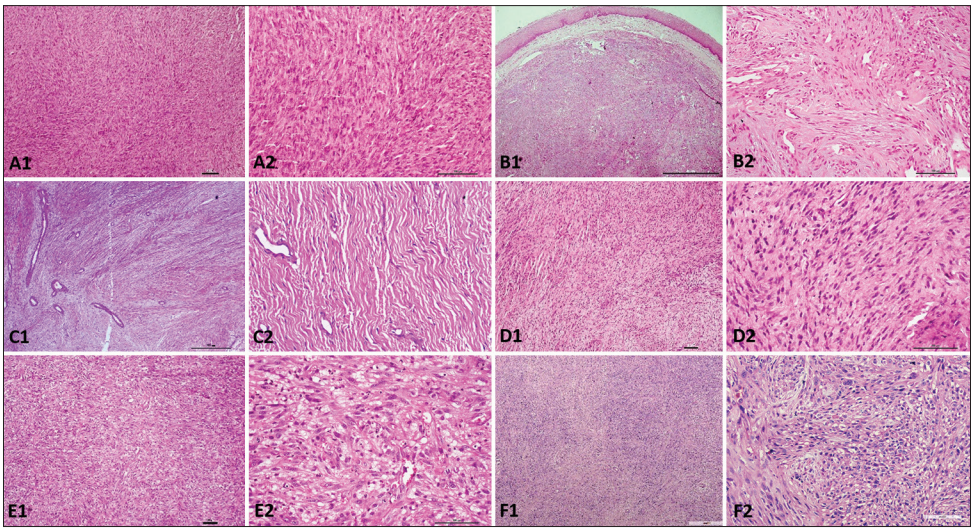

Figure 1: Histological features of Spindle Cell Lesions. (a) Fibrosarcoma displaying highly cellular stroma with monomorphic spindle cells in predominantly herringbone pattern (A1-H&E Stain 100x view). Monomorphic spindle-shaped cells with vesicular nuclei with finely dispersed chromatin, inconspicuous nucleoli, eosinophilic cytoplasm and indistinct cell borders (A2-H&E Stain 200x view). (b) Well-circumscribed tumour of SFT displaying highly cellular stroma showing irregular pattern of spindle cells (B1-H&E Stain 100x view). Spindle-shaped cells with vesicular nuclei, inconspicuous nucleoli, eosinophilic cytoplasm and distinct cell borders with stroma showing fibrillary collagen to keloid-like areas (B2-H&E Stain 200x view). (c) Case of DF showing long fascicles of bland spindle cells with mild to moderate cellularity and densely collagenized stroma (C1-H&E Stain 100x view). Spindle-shaped cells with vesicular to hyperchromatic nuclei, inconspicuous nucleoli, eosinophilic cytoplasm and distinct cell borders with stroma showing predominantly ropey type collagen (C2-H&E Stain 200x view). (d) Case of IMT showing moderately cellular stroma displaying spindle cell proliferation in a short fascicular and storiform patterns with inflammatory component (D1-H&E Stain 100x view). Spindle-shaped cells with tapering ends and cytoplasmic extensions. The cells exhibit vesicular nuclei with coarse chromatin and inconspicuous nuclei (D2-H&E Stain 200x view). (e) LGMS displaying storiform and whorled arrangement of spindle cells in a background of moderate cellular stroma (E1-H&E Stain 100x view). Pleomorphic spindle-shaped cells with vesicular nuclei, prominent nucleoli, coarse chromatin, eosinophilic cytoplasm with tapering ends and indistinct cell borders (E2-H&E Stain 200x view). (f) EIMS shows highly cellular stroma with spindle-shaped cells arranged in storiform pattern (F1-H&E Stain 100x view). Pleomorphic spindle to epithelioid cells with vesicular nuclei, coarse chromatin, prominent nuclei, tapering ends and eosinophilic cytoplasm. Aberrant mitotic figures were also seen (F2-H&E Stain 200x view)

tumour cells were immunopositive for vimentin and focally positive for calponin with 10% Ki67 proliferative index. The cytomorphological features of tumour cells predominantly resembled myofibroblastic cells and focal positivity for calponin favours the diagnosis of myofibroblastic sarcoma. Immunonegativity for desmin, SMA, HMB-45, S100, ALK, SATB2, ERG, CD34, CD31, EMA, Pan-CK, STAT6 and CD99 ruled out a broad differential, i.e. melanoma, muscle and vascular sarcomas, SFT, synovial sarcoma, and osteosarcoma (along with the absence of osteoid). In another case of myofibroblastic origin, unusual predominant epithelioid cell morphology along with marked atypical nuclear features led to a broad differential diagnosis, including rhabdomyosarcoma, Ewing's sarcoma, vascular sarcoma, undifferentiated sarcoma, myxofibrosarcoma and osteosarcoma. Immunonegativity for desmin, myogenin, EMA, CD99, CD34 and SATB2 along with the absence of osteoid ruled out all these differentials. Immunopositivity for SMA and ALK confirmed the myofibroblastic cell origin. With the presence of predominant pleomorphic epithelioid cells along with spindle-shaped cells, a final diagnosis of EIMS was given. The detailed histopathological features are described in Table 3.

DISCUSSION

In this study, we described eleven cases of fibroblastic and myofibroblastic origin. The amount of tissue showing normal architecture, lesional symmetry, zonation and nature of cellularity is helpful to differentiate benign from malignant tumours at scanner view. At higher magnification, the malignant features observed are abnormal mitoses and nuclear atypia. Pattern-based diagnostic approach facilitates the narrowing of differential diagnostic possibilities.[1] Further, IHC plays an important role in finalizing the expected differential diagnosis.

In the case of highly cellular stroma exhibiting cytological atypia, it is necessary to rule out epithelial malignancy (spindle cell carcinoma and melanoma) first. Spindle cell squamous cell carcinoma (SpSCC), was ruled out based on the absence of dysplasia in the overlying epithelium, the absence of carcinoma *in situ* component

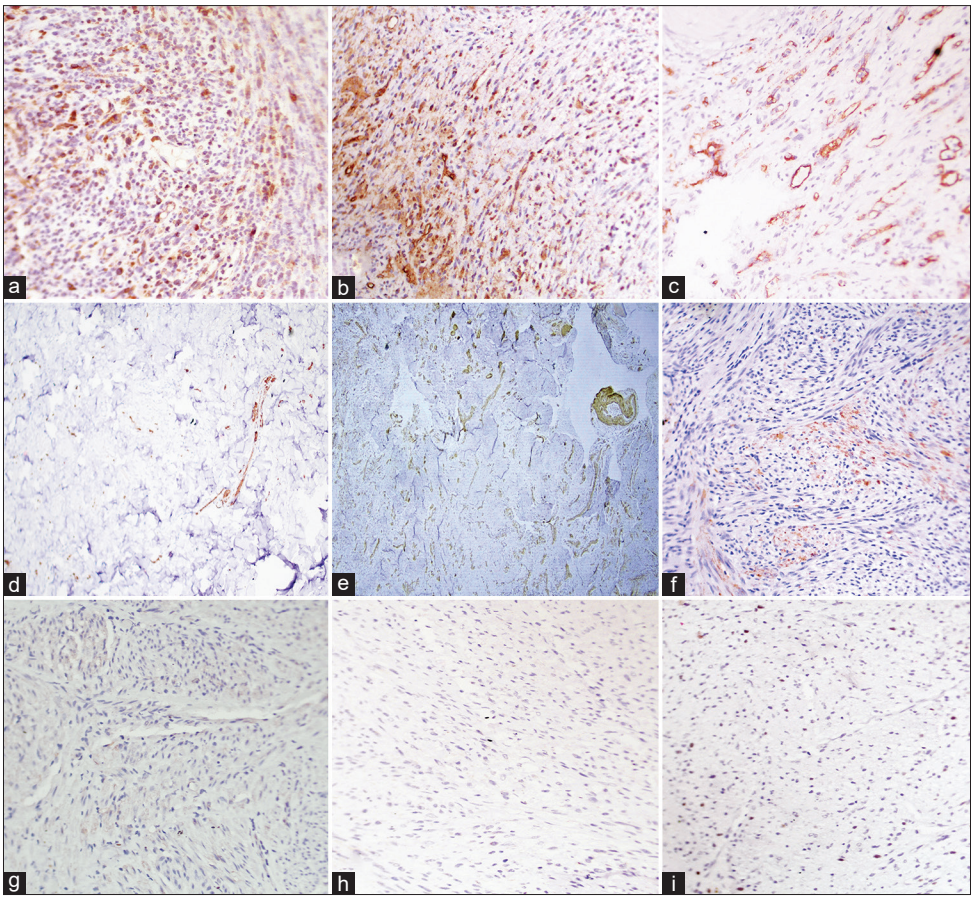

Figure 2: Immunohistochemistry Photomicrographs of Spindle Cell Lesions. (a) SFT stained with antibody to STAT-6 showing positivity (IHC, x100). (b) SFT stained with antibody to CD34 showing positivity (IHC, x100). (c) SFT stained with antibody to STAT-6 showing positivity (IHC, x200). (d) Desmoplastic fibroma stained negative with antibody to S100 (IHC, x100). (e) Desmoplastic fibroma stained with antibody to SMA showing positivity (IHC, x100). (f) Neurofibroma stained with antibody to S100 showing positivity (IHC, x100). (g) Neurofibroma stained with antibody to vimentin showing positivity (IHC, x100). (h) IMT stained with antibody to ALK showing mild positivity (IHC, x100). (i) IMT stained with antibody to SMA showing positivity (IHC, x100)

and the absence of better-differentiated epithelium-like areas. Melanoma was ruled out based on immunonegativity for S100 and HMB45.

Fibrosarcoma is a malignancy of mesenchymal tissue arising from fibroblasts showing no other line of differentiation. It occurs predominantly in the fifth and sixth decades of life but literature review shows that it can develop in children and adolescents too.[10] The prevalence of fibrosarcoma in the jaws of children is extremely rare.[11] Mandible is the most common site of intraosseous form of fibrosarcoma in the head and neck.[12] Similar to our case, the tumour affected the mandible in 5-year-old female. Approximately seven cases of intraosseous fibrosarcomas have been reported in the literature.[10] Histologically, tumour cells have a monomorphic arrangement in dense fascicles (predominantly herringbone pattern). The differential diagnoses comprise SFT, monophasic synovial sarcoma, malignant peripheral nerve sheath tumour (MPNST), myofibroblastic sarcoma and leiomyosarcoma.

The intermediate-grade fibroblastic neoplasm occurring most commonly in middle-aged adults as seen in our cases is solitary fibrous tumours (SFTs). They occur at different anatomic sites with 10–15% in the head and neck region, with increased frequency in the orbit, sinonasal tract, oral cavity and salivary glands.[13] Similar to our cases, Shmuly *et al.* reported cellular stroma, with uniform spindle cells and a disorganized pattern. The connective tissue matrix showed irregularly shaped vascular channels with a stag-horn appearance in the tumour mass. These cases were similar to our cases in terms of well-circumscription and non-infiltrative nature of the tumour.[14] STAT6 immunopositivity was found in our cases along with CD34. It is reported that STAT6 is a specific and sensitive marker for SFT.[15]

DF occurs most frequently in mandible, femur, pelvis, radius and tibia. Literature showed mandible predominance like our cases. In contrast to our cases, it showed a wide range of occurrences in the second or third decade

Table 3: Histopathological and immunohistochemical features of cases

Case No	Histopathological Features												IHC	Final diagnosis
	Capsule	Histological Pattern	Overall cellularity	Cellular and nuclear features	Cytological atypia	Mitoses (*n*/10HPF)	Collagen	Myxoid areas	Vascularity	Inflammation	Necrosis	Haemorrhagic Areas		
1.	Absent	Short fascicles, herringbone, storiform	3	Monomorphic spindle-shaped cells with vesicular nuclei, fine dispersed chromatin, inconspicuous nucleoli, eosinophilic cytoplasm and indistinct cell borders	2	11	Fibrillary	0	Variably shaped	Mild to moderate	0	1	Positive- S100, vimentin Ki67: >30% Negative- myogenin, pan-CK, CD99, desmin, HMB45 and SMA	Fibrosarcoma
2.	Absent	Short fascicles, whorled	2	Spindle to asymmetrical oval-shaped cells with vesicular nuclei, indistinct cell borders, few areas of comma-shaped hyperchromatic nuclei	2	4	Fibrillary	0	Few staghorn blood vessels	Mild	0	1	Positive- vimentin, mild positivity for NSE, SMA Ki67: Negative- pan-CK, S100, CD99 and HMB45, SATB2	Intraosseous Fibrosarcoma
3.	Absent	Long fascicles, herringbone, storiform. Hypocellular and hypercellular areas	2	Spindle-shaped cells with vesicular nuclei, fine dispersed chromatin, inconspicuous nucleoli, eosinophilic cytoplasm and indistinct cell borders. Spindle cells were intermingled with cells exhibiting wavy hyperchromatic nuclei. Aggregates of epithelioid cells with vesicular nuclei and abundant cytoplasm were also present.	2	5	Wiry	1	Variably shaped	Mild	0	1	Positive- Bcl2, vimentin, pan-CK Ki67: 15% Negative- S100, desmin, myogenin, SMA and CD99	Fibrosarcoma
4.	Absent	Short fascicles, storiform	2	Spindle-shaped cells with vesicular nuclei, coarse chromatin, inconspicuous nuclei, tapering ends and cytoplasmic extensions. Areas of hyperchromatic wavy nuclei were also present.	2	4	Fibrillary	0	Variably shaped	Scattered Mild to Moderate	0	0	Positive- vimentin, SMA, ALK mild positive Negative- S100	Inflammatory Myofibroblastic Tumour

Contd...

Table 3: Contd...

Case No	Histopathological Features												IHC	Final diagnosis
	Capsule	Histological Pattern	Overall cellularity	Cellular and nuclear features	Cytological atypia	Mitoses (*n*/10HPF)	Collagen	Myxoid areas	Vascularity	Inflammation	Necrosis	Haemorrhagic Areas		
5.	Absent	Storiform, whorled, short fascicles	2	Pleomorphic spindle-shaped cells with vesicular nuclei, prominent nucleoli, coarse chromatin, eosinophilic cytoplasm, tapering ends and indistinct cell borders.	3	6	Wiry	0	Variably shaped	Diffuse Scattered Moderate	0	1	Positive- vimentin, CD68, calponin (focal) Ki67: 10% Negative- desmin, SMA, HMB-45, S100, β-catenin, ALK, SATB2, ERG, CD34, CD31, EMA, pan-CK, STAT6 and CD99	Myofibroblastic Sarcoma (low to intermediate grade)
6.	Absent	Storiform, short fascicles	3	Pleomorphic spindle-shaped cells with vesicular nuclei, coarse chromatin, prominent nuclei, eosinophilic cytoplasm and tapering ends. Epithelioid cell morphology was also found.	3	7	Fibrillary	2	Variably shaped	Moderate	1	1	Positive- vimentin, pan-CK, β-catenin (cytoplasmic), S100 (focal), ALK and SMA. Negative- desmin, CD99, CD34, myogenin, EMA and SATB2.	Epithelioid Inflammatory Myofibroblastic Sarcoma
7.	Absent	Long fascicles	1	Bland spindle-shaped cells with hyperchromatic nuclei, eosinophilic cytoplasm and indistinct cell borders with areas showing hyperchromatic wavy nuclei.	1	0	Keloid Type, Ropey	0	Variably shaped	Mild	0	0	Positive- β-catenin (patchy nuclear), vimentin Negative- SMA, SATB2, S100 Ki67=1%	Desmoplastic Fibroma
8.	Absent	Long fascicles	2	Spindle-shaped cells with vesicular nuclei, inconspicuous nucleoli, eosinophilic cytoplasm and distinct cell borders.	0	0	Ropey	1	Variably shaped	Mild	0	0	Positive- β catenin (nuclear), vimentin, SMA Negative- desmin, SATB2, S100 Ki67=1%	Desmoplastic Fibroma

Contd...

Table 3: Contd...

Case No	Histopathological Features												IHC	Final diagnosis
	Capsule	Histological Pattern	Overall cellularity	Cellular and nuclear features	Cytological atypia	Mitoses (*n*/10HPF)	Collagen	Myxoid areas	Vascularity	Inflammation	Necrosis	Haemorrhagic Areas		
9.	Absent	Small fascicles	2	Bland spindle-shaped cells with hyperchromatic nuclei, eosinophilic cytoplasm and indistinct cell borders.	0	0	Ropey	2	Variably shaped	Moderate	0	0	Positive- β catenin, vimentin, SMA Negative- SATB2, S100 Ki67=<1%	Desmoplastic Fibroma
10.	Well encapsulated	Interlacing short fascicles, irregular pattern, focal storiform pattern	3	Spindle-shaped cells with vesicular nuclei, inconspicuous nucleoli, eosinophilic cytoplasm and distinct cell borders.	1	2	Fibrillary, focal keloid	1	Variably shaped, hemangiopericytoma-like	Mild to moderate	0	0	Positive- STAT6 (nuclear), CD34 Negative- SMA, NSE, CD56	Solitary Fibrous Tumour
11.	Absent	Irregular pattern	2	Spindle-shaped cells with vesicular nuclei, inconspicuous nucleoli, eosinophilic cytoplasm and distinct cell borders.	1	2	Fibrillary	1	Variably shaped, focal hemangiopericytoma pattern	Moderate	0	0	Positive- STAT6 (cytoplasmic to nuclear), CD34 Negative-SMA, S100.	Solitary Fibrous Tumour
12.	Absent	Short fascicles, herringbone, storiform	3	Monomorphic spindle-shaped cells with vesicular nuclei, fine dispersed chromatin, inconspicuous nucleoli, eosinophilic cytoplasm and indistinct cell borders	3	8	Fibrillary	1	Variably shaped	Diffuse Scattered Moderate	1	1	Positive- vimentin, Ki67: 10% Negative- pan-CK, S100	Fibrosarcoma
13.	Absent	Long fascicles, few whorled areas	3	Spindle-shaped cells with vesicular nuclei, fine dispersed chromatin, inconspicuous nucleoli, eosinophilic cytoplasm and indistinct cell borders. Few cigar-shaped nuclei were observed	3	10	Fibrillary	1	Variably shaped	Diffuse Scattered Moderate	2	2	Positive- vimentin, Ki67: 15%, SMA Negative- pan-CK, S100	Leiomyosarcoma

Contd...

Table 3: Contd...

Case No	Histopathological Features												IHC	Final diagnosis
	Capsule	Histological Pattern	Overall cellularity	Cellular and nuclear features	Cytological atypia	Mitoses (*n*/10HPF)	Collagen	Myxoid areas	Vascularity	Inflammation	Necrosis	Haemorrhagic Areas		
14.	Absent	Long fascicles, focal storiform pattern	2	Spindle-shaped cells with vesicular wavy nuclei, fine dispersed chromatin, inconspicuous nucleoli, eosinophilic cytoplasm. Collagenous areas were also noted	0	0	Wiry	3	Variably shaped	Mild	0	0	Positive- S100, Vimentin Negative- pan-CK, SMA	Neurofibroma
15.	Absent	Short fascicles, irregular pattern, focal storiform pattern	2	Spindle-shaped cells with distinct nuclei. No pleomorphism is present. Collagenous areas were also noted	0	0	Ropey	2	Variably shaped	Mild	0	0	Positive- Focal positivity for vimentin, HHF-35 & SMA Negative- Desmin, CD34, Ki67=<1%	Nodular Fasciitis
16.	Absent	Short fascicles, irregular pattern	2	Spindle-shaped cells with hyperchromatic nuclei, eosinophilic cytoplasm and indistinct cell borders with areas showing hyperchromatic wavy nuclei.	1	1	Ropey	1	Variably shaped	Diffuse Scattered Moderate	0	1	Positive- β catenin, vimentin, Negative- S100 Ki67=<1%	Desmoplastic Fibroma
17.	Absent	Short fascicles, irregular pattern	2	Spindle-shaped cells with hyperchromatic nuclei, eosinophilic cytoplasm and indistinct cell borders with areas showing hyperchromatic wavy nuclei.	0	0	Ropey	1	Variably shaped	Diffuse Scattered Moderate	0	0	Positive- β catenin, vimentin, Negative- S100 Ki67=<1%	Desmoplastic Fibroma
18.	Absent	Short fascicles, irregular pattern	2	Spindle-shaped cells with hyperchromatic nuclei, eosinophilic cytoplasm and indistinct cell borders with areas showing hyperchromatic wavy nuclei.	0	0	Ropey	1	Variably shaped	Diffuse Scattered Moderate	0	0	Positive- β catenin, vimentin, Negative- S100 Ki67=<1%	Desmoplastic Fibroma

Contd...

Table 3: Contd...

Case No	Capsule	Histopathological Features										IHC	Final diagnosis
		Histological Pattern	Overall cellularity	Cellular and nuclear features	Cytological atypia	Mitoses (*n*/10HPF)	Collagen	Myxoid areas	Vascularity	Inflammation	Necrosis	Haemorrhagic Areas	
19.	Absent	Long fascicles, irregular pattern	2	Spindle-shaped cells with hyperchromatic nuclei, eosinophilic cytoplasm and indistinct cell borders with areas showing hyperchromatic wavy nuclei.	0	0	Ropey	1	Variably shaped	Focal moderate	0	0	Positive- β catenin, vimentin, Negative- S100 Ki67=<2%	Desmoplastic Fibroma
20.	Absent	Short fascicles, irregular pattern	2	Spindle-shaped cells with hyperchromatic nuclei, eosinophilic cytoplasm and indistinct cell borders with areas showing hyperchromatic wavy nuclei.	1	0	Ropey	3	Variably shaped	Diffuse Scattered Moderate	0	0	Positive- β catenin, vimentin, Negative- S100 Ki67=<1%	Desmoplastic Fibroma

of life with female predilection.[16] We reported male predominance with ages ranging from 2.5 years to 61 years. Radiographically, multilocular radiolucent lesion with ill-defined border and cortical expansion or destruction is the most common presentation seen in the literature. All cases were associated with cortical perforation. Histological features were quite like our cases showing long fascicles of bland spindle cells with mild to moderate cellularity with densely collagenized stroma. Similar to our cases, Hauben *et al*., Taher LY *et al*. and Azola AM *et al*. have reported immunopositivity for beta-catenin in DF cases.[17–19] Similar to one of our cases, Hauben *et al*., Wood *et al*. and Kahraman *et al*. reported SMA positivity in DF cases.[16,17,20]

IMT and LGMS are significant intermediate- or low-grade malignancies.[21] IMT mainly affects the children and young adults and primarily occurs in abdominal cavity. However, up to 15% of IMTs originate from the head and neck region and are more common in adults[22] similar to our case. Microscopically, it exhibits spindle cell proliferation with inflammatory component and pseudo-sarcomatous appearance. It shows three histological patterns—1) loosely arranged tumour cells in an edematous, myxoid and vascular background, 2) compactly arranged tumour cells exhibiting fascicular arrangement and prominent inflammation and 3) less cellular pattern resembling scar or desmoid fibromatosis.[22] On IHC, tumour cells are immunopositive for SMA, MSA and desmin. Immunopositivity for ALK is usually cytoplasmic, nuclear or perinuclear. In the present case of IMT, there was focal positivity for ALK. It is reported that approximately half of IMTs harbour a rearrangement of the ALK gene.[21,23] Microscopically, there is an extensive differential diagnosis including myxoid and spindle cell sarcomas, MPNST and desmoid fibromatosis. A combination of histological, IHC and cytogenetic or molecular genetics findings helps to reach the final diagnosis. Coffin *et al*. reported that ALK-negative IMTs occurred in older patients with a mean age of 20.1 years and had increased nuclear atypia, pleomorphism and abnormal mitoses.[24]

LGMS has a predilection for head and neck region (30%) with oral cavity being more common (8.2%) site.[25] It mainly affects the middle-aged adults. Only 62 reported cases of primary LGMS of the head and neck region are available in the literature. The most common site is the tongue, followed by the paranasal cavity, mandible, neck and larynx.[26] In contrary to this, the present case was in elderly adult and in maxillary region. It has been described in soft tissues and bone as a fasciitis or fibrosarcoma-like spindle cell sarcoma that infiltrates locally but rarely metastasizes.[7] Our case showed marked pleomorphic

spindle cells with vesicular nuclei, prominent nucleoli with tapering ends and indistinct cell borders along with diffuse scattered inflammation throughout the lesional tissue. LGMS consists of long fascicles of spindle cells with abundant eosinophilic cytoplasm and ill-defined cell borders. On IHC, tumour cells are diffusely positive for SMA and desmin. It also shows positivity for calponin and h-caldesmon in some cases.[21,27,28] In our case of LGMS, tumour cells were immunopositive for calponin but immunonegative for SMA. The positive immunostaining for calponin, α-SMA and MSA at the periphery of myofibroblasts confirmed the presence of myofilaments in them.[21,28] Microscopically, it should be differentiated from desmoid tumour (less infiltrative, devoid of nuclear variability and atypia), leiomyosarcoma (shorter fascicles, tumour cells with broader blunt-ended nuclei and more distinct cell borders) and spindle cell rhabdomyosarcoma (exhibiting hypercellularity, rhabdomyoblasts with brightly eosinophilic cytoplasm, nuclear staining of MyoD1 and myogenin).

A small population of IMTs show histopathologic transformation to a highly proliferative tumour displaying atypical polygonal, round or spindle cells with vesicular nuclei, large nucleoli, and increased and atypical mitoses.[29] IMT with predominantly epithelioid morphology is considered as a variant of IMT and named as epithelioid inflammatory myofibroblastic sarcoma (EIMS). The malignant features in this tumour are similar comprised of round-to-epitheloid cells with nuclear membrane pattern or perinuclear immunostaining for ALK receptor tyrosine kinase.[29,30] EIMS mainly affects the young and adolescents and is found in the abdominal cavity. In contrary to this, our case occurred in oral cavity of an adult male, which defines its rarest occurrence site. Microscopic features of our case resembled EIMS, in terms of pleomorphic epitheloid cells with vesicular nuclei, coarse chromatin, prominent nuclei, tapering ends, eosinophilic cytoplasm with intermixed areas of spindle-shaped cells and immunopositivity for SMA and ALK (nuclear).

CONCLUSION

In the current study, we attempted to summarize the clinicopathologic features and differential diagnoses of oral spindle cell lesions (fibroblastic and myofibroblastic origin). In the diagnosis of spindle cell lesions, cytomorphology of cells and architectural patterns were key points to identify the cell of origin. In addition to it, ancillary studies with IHC and molecular testing aids provide the best path for accurate diagnosis. It is very important to first rule out the epithelial malignancies (spindle cell carcinoma and melanoma) when a spindle cell neoplasm of the oral cavity is observed.

Key messages

The diagnostic strategies need to be upgraded for the diagnosis of spindle cell lesions. Emphasis must be placed on cytomorphology, and an immunohistochemistry panel of markers is imperative for the accurate diagnosis of fibroblastic and myofibroblastic oral spindle cell lesions.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Choi JH, Ro JY. Cutaneous spindle cell neoplasms: Pattern-based diagnostic approach. Arch Pathol Lab Med 2018;142:958–72.
2. Anderson CE, Al-Nafussi A. Spindle cell lesions of the head and neck: An overview and diagnostic approach. Diagn Histopathol 2009;15:264–72.
3. Hornick JL. Novel uses of immunohistochemistry in the diagnosis and classification of soft tissue tumors. Mod Pathol 2014;27:S47–63.
4. McAnulty RJ. Fibroblasts and myofibroblasts: Their source, function, and role in disease. Int J Biochem Cell Biol 2007;39:666–71.
5. Pereira de Oliveira DHI, da Silveira ÉJD, de Souza LB, Caro-Sanchez CHS, Dominguez-Malagon H, Mosqueda Taylor A, *et al*. Myofibroblastic lesions in the oral cavity: Immunohistochemical and ultrastructural analysis. Oral Dis 2019;25:174–81.
6. Gabbiani G, Ryan GB, Majno G. Presence of modified fibroblasts in granulation tissue and their possible role in wound contraction. Experientia 1971;27:549–50.
7. Fisher C. Myofibroblastic malignancies. Adv Anat Pathol 2004;11:190–201.
8. Mentzel T. Myofibroblastic sarcomas: A brief review of sarcomas showing a myofibroblastic line of differentiation and discussion of the differential diagnosis. Curr Diagn Pathol 2001;7:17–24.
9. Sbaraglia M, Bellan E, Dei Tos AP. The 2020 WHO classification of soft tissue tumours: News and perspectives. Pathologica 2020;113:70–84.
10. Swain N, Kumar S, Dhariwal R, Routray S. Primary fibrosarcoma of maxilla in an 8-year-old child: A rare entity. J Oral Maxillofac Pathol 2013;17:478.
11. Gosau M, Draenert FG, Winter WA, Mueller-Hoecker J, Driemel O. Fibrosarcoma of the childhood mandible. Head Face Med 2008;4:21.
12. Pereira CM, Jorge J, Di Hipólito O, Kowalski LP, Lopes MA. Primary intraosseous fibrosarcoma of jaw. Int J Oral Maxillofac Surg 2005;34:579–81.
13. Smith SC, Gooding WE, Elkins M, Patel RM, Harms PW, McDaniel AS, *et al*. Solitary fibrous tumors of the head and neck: A multi-institutional clinicopathologic study. Am J Surg Pathol 2017;41:1642–56.
14. Shmuly T, Ben Zvi Y, Chaushu G, Kaplan I. Oral solitary fibrous tumor: A retrospective clinico-pathological study and long-term follow-up. Medicina 2021;57:152.
15. Kao Y-C, Lin P-C, Yen S-L, Huang S-C, Tsai J-W, Li C-F, *et al*. Clinicopathological and genetic heterogeneity of the head and neck solitary fibrous tumours: A comparative histological, immunohistochemical and molecular study of 36 cases. Histopathology 2016;68:492–501.
16. Woods TR, Cohen DM, Islam MN, Rawal Y, Bhattacharyya I. Desmoplastic fibroma of the mandible: A series of three cases and review of literature. Head Neck Pathol 2015;9:196–204.

17. Hauben E, Jundt G, Cletonjansen A, Yavas A, Kroon H, Vanmarck E, *et al*. Desmoplastic fibroma of bone: An immunohistochemical study including -catenin expression and mutational analysis for -catenin. Hum Pathol 2005;36:1025–30.
18. Taher LY, Saleem M, Velagapudi S, Dababo A. Fibromatosis arising in association with neuromuscular hamartoma of the mandible. Head Neck Pathol 2013;7:280–4.
19. Azola AM, Wartmann CT, Fischer MK, Ambro BT, Pereira KD. Desmoplastic fibroma arising from the anterior maxillary sinus in a child. Arch Otolaryngol Head Neck Surg 2012;138:859.
20. Kahraman D, Karakoyunlu B, Karagece U, Ertas U, Gunhan O. Desmoplastic fibroma of the jaw bones: A series of twenty-two cases. J Bone Oncol 2021;26:100333.
21. Qiu X, Montgomery E, Sun B. Inflammatory myofibroblastic tumor and low-grade myofibroblastic sarcoma: A comparative study of clinicopathologic features and further observations on the immunohistochemical profile of myofibroblasts. Hum Pathol 2008;39:846–56.
22. Baranov E, Hornick JL. Soft tissue special issue: Fibroblastic and myofibroblastic neoplasms of the head and neck. Head Neck Pathol 2020;14:43–58.
23. Tothova Z, Wagner AJ. Anaplastic lymphoma kinase-directed therapy in inflammatory myofibroblastic tumors. Curr Opin Oncol 2012;24:409–13.
24. Coffin CM, Hornick JL, Fletcher CDM. Inflammatory myofibroblastic tumor: Comparison of clinicopathologic, histologic, and immunohistochemical features including ALK expression in atypical and aggressive cases. Am J Surg Pathol 2007;31:509–20.
25. Chan JYK, Gooi Z, Wong EWY, Ng SK, Tong MCF, Vlantis AC. Low-grade myofibroblastic sarcoma: A population-based study: Low-grade myofibroblastic sarcoma. Laryngoscope 2017;127:116–21.
26. Kawaharada M, Katagiri W, Maruyama S, Nishiyama H, Hayashi T, Kobayashi T, *et al*. Low-grade myofibroblastic sarcoma of the tongue with difficulty of diagnosis: A case report and review of the literature. J Oral Maxillofacial Surg Med Pathol 2021;33:93–7.
27. Perez-Montiel MD, Plaza JA, Dominguez-Malagon H, Suster S. Differential expression of smooth muscle myosin, smooth muscle actin, h-caldesmon, and calponin in the diagnosis of myofibroblastic and smooth muscle lesions of skin and soft tissue. Am J Dermatopathol 2006;28:105–11.
28. Makuch R, Birukov K, Shirinsky V, Dabrowska R. Functional interrelationship between calponin and caldesmon. Biochem J 1991;280:33–8.
29. Mariño-Enríquez A, Wang W-L, Roy A, Lopez-Terrada D, Lazar AJF, Fletcher CDM, *et al*. Epithelioid inflammatory myofibroblastic sarcoma: An aggressive intra-abdominal variant of inflammatory myofibroblastic tumor with nuclear membrane or perinuclear ALK. Am J Surg Pathol 2011;35:135–44.
30. Du X, Gao Y, Zhao H, Li B, Xue W, Wang D. Clinicopathological analysis of epithelioid inflammatory myofibroblastic sarcoma. Oncol Lett 2018;15:9317-26.