



Desmoplastic fibroma of the jaw bones: A series of twenty-two cases

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ABSTRACT

Desmoplastic fibroma (DF) is an intraosseous counterpart of desmoid-type soft tissue fibromatosis. It is most frequently seen in the jawbones. The clinical and radiological features of the present cases were nonspecific. The accumulation of beta-catenin in the nuclei of neoplastic cells which is a diagnostic feature of desmoid-type soft tissue fibromatosis could not be detected in the present DF series. The aim of this study is to report a series of 22 cases of DF involving either mandible or maxilla. A retrospective evaluation of desmoplastic fibroma and beta-catenin, smooth muscle actin, nestin, cyclin D1 immunostaining's patterns.

Most of the DF cases expressed only cytoplasmic beta-catenin immunostainings. We suggest that nuclear beta-catenin staining may not be used as a corroborating the diagnosis of DF. Immunohistochemical staining difference of jaw bone desmoplastic fibromas from other soft tissue and bone lesions may be related to the origination of jaw bone from the neural crest. Strong nestin and cyclin D1 positivity in our series supported this. A combined clinical, radiological, and histopathological analysis of the DF cases is essential in the diagnosis and management.

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1. Introduction

The word “fibromatoses” is a generic term used to describe a group of reactive/neoplastic proliferation of fibroblastic/myofibroblastic cells with rather similar microscopic features but diverse biological behavior [1]. Although the term fibromatosis should preferably be applied to neoplastic ones, it is still in use for various reactive, neoplastic, developmental, and hereditary lesions [1].

Desmoid-type soft tissue fibromatosis, also called a desmoid tumor or aggressive fibromatosis, is neoplastic and it can arise from the soft tissues in almost all parts of the body. It is characterized by infiltrative growth and a tendency to recur locally. These can be divided into two major groups such as superficial (fascial) and deep (musculoaponeurotic) fibromatoses [1]. Some of these have been labeled according to their localizations such as mesenteric, palmar, and plantar fibromatosis. Fibromatosis occurs mostly sporadically. Multiple ones are usually accompanied by Gardner syndrome or Tuberous sclerosis [1,2].

Desmoplastic fibroma (DF) is considered as an intraosseous counterpart of desmoid-type soft tissue fibromatosis but is relatively rare. They are histologically almost identical to soft tissue fibromatoses. Although the DF can be seen in any bone, the posterior mandible is the most common location [3]. It is usually a slowly growing painless lesion. Extragnathic ones usually involve the metaphyseal region of the long bones [3,4]. Data on this lesion is limited to case reports and small series [2,3,5,6]. Radiographically the DF may be seen as a multilocular or unilocular ill-defined radiolucency without mineralization. Thinned and expanded cortex or destruction of the involved bone without a sclerotic border is a common feature [7–9]. There may be an extension into the surrounding soft tissues. Histologically, DF contains spindle-shaped fibroblastic and/or myofibroblastic cells without atypia within a collagenous background with focal myxoid changes.

2. Calculation

The spindle cells of DF do not show any specific diagnostic immunohistochemical staining. Loss of beta-catenin regulation and accumulation of beta-catenin in the nuclei of fibroblastic and/or myofibroblastic cells is a diagnostic feature of desmoid-

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type soft tissue fibromatosis. However, this immunohistochemical feature is less consistent in DF. It is suggested that, unlike desmoid-type soft tissue fibromatosis, the beta-catenin pathway may not have an essential role in the tumorigenesis of DF [8].

On the other hand, craniofacial bone development is different from long bones and that it develops from the neural crest [10–13]. Clinical and radiologic appearances of the jaw bone DF are nonspecific and they can mimic several other common lesions including odontogenic tumors. There is a need larger series for a better understanding of the pathogenesis, correct diagnosis, and treatment planning. In this retrospective study, we aimed to report a series of twenty-two cases of DF involving the jawbones. We have also focused on their immunohistology to assess their relationship with desmoid-type soft tissue fibromatosis.

3. Material and methods

Twenty-two desmoplastic fibroma cases involving the jawbones diagnosed between 2009 and 2018 were collected retrospectively from the archives of private Gören Pathology Laboratory, Ankara, Turkey. Oral and maxillofacial cases form a large part of the tissues evaluated in this laboratory. All hematoxylin and eosin-stained slides and paraffin blocks were retrieved from the files. Patient records were reviewed to extract the information on demographics. They were analyzed by age, gender, tumor location, size, and recurrences if any. The available clinical and radiographic findings were presented in Table 1. The follow-ups of the patients were made on the records of recurrences. The authors re-evaluated the histologic slides. Representative tissue blocks of twenty cases were selected for immunohistochemical studies.

Since nuclear immunostaining for beta-catenin constitutes a marker of the Wnt pathway and is used to diagnose desmoid-type soft tissue fibromatosis, two different monoclonal antibodies against beta-catenin (RB-9035, dilution 1/500, Thermo Fisher Scientific, Kalamazoo, MI, USA, and Beta-Catenin 14 mouse monoclonal antibody, 760-4242, Cell Marque, Sigma-Aldrich, USA) were used for immunostainings on our cases. Desmoid-type soft tissue fibromatosis was used as a positive control.

Table 1
Main clinicopathologic data of the present series.

Number	Age-gender	Location of tumor	Radiological description	Provisional clinical diagnosis
1	16F	Mandibula left corpus	Radiolucent lesion 1 cm in diameter	Radiolucent destructive lesion
2	66F	Mandibula anterior	Expansive radiolucent lesion	Asymptomatic swelling
3	50F	Mandibula corpus	Expansive radiolucent lesion, 2 cm in diameter	Ameloblastoma
4	17M	Maxilla, left lateral	Expansive well demarcated radiolucent lesion, 3 cm in diameter	Soft tissue lesion
5	-F	Mandibula, left corpus	Radiolucent lesion	Giant cell granuloma
6	32M	Mandibula corpus	Radiolucent lesion well demarcated 4 cm in diameter	Solid lesion
7	8F	Mandibula, bilateral, antero-lateral	Large, multilocular, expansive radiolucent lesion	Cherubism
8	46F	Mandibula right corpus	Multilocular, destructive 2 cm in diameter, radiolucent lesion	Ameloblastoma
9	22F	Mandibula left corpus	Radiolucent, lobular 2 cm in diameter lesion	-
10	65F	Mandibula left corpus	Radiolucent, 1 cm in diameter	Malignancy
11	42F	Maxilla, right posterior mandibula	-	Gardner syndrome
12	27M	Maxilla left lateral	Radiolucent, poorly demarcated 3 cm in diameter lesion with root resorption	-
13	12F	Mandibula anterior	Multilocular large radiolucent lesion with tooth luxation	-
14	52M	Maxilla, posterior	Asymptomatic radiolucent lesion	-
15	9M	Mandibula right corpus	Radiolucent lesion, 2 cm in diameter	Ameloblastoma myxoma
16	25F	Mandibula right posterior	Radiolucent solid lesion	Soft tissue lesion
17	-F	Mandibula right posterior	Radiolucent lesion 2 cm in diameter	Swelling
18	58F	Mandibula antero-lateral	Radiolucent lesion, 1 cm in diameter	-
19	25F	Mandibula	Radiolucent lesion, poorly demarcated 6 cm in diameter	Ossifying fibroma
20	50F	Mandibula lateral	Expansive lesion, 1,5 cm in diameter	-
21	4M	Mandibula anterior	Radiolucent destructive lesion	Swelling
22	F	Mandibula anterior	Large radiolucent lesion with cystic change	Asymptomatic swelling

Labeling with smooth muscle actin Ab-1 (MS-113, clone 1A4, dilution 1/800, Thermo Fisher Scientific, Fremont, CA, USA) was used for myofibroblastic differentiation. Vessels within the lesions were used as a positive control for smooth muscle actin stainings.

Nestin is a class VI intermediate filament protein; it is known as a specific marker of neural or neural crest stem cells [10,13,27–29]. Nestin, which tends to be more strongly expressed in mandibular bone morphogenetic stem cells (R). The presence of neural crest-associated nestin positivity in desmoplastic fibromas of the jaws was detected (Nestin, RMab, clone EP287, Bio SB, CA, USA). Glomerular nestin staining of kidney tissue was a positive control.

Cyclin D1 is a transcriptional target of β catenin and plays an essential role in the expansion of skeletal precursors [11,12]. Cyclin D1 positivity in the present series was also detected (Cyclin D1/Bcl-1(SP4) Thermo Scientific, CA, USA). Section of tonsillar tissue was taken as a positive control for cyclin D1.

Immunoreactivity for beta-catenin, smooth muscle actin, nestin, and cyclin D1 were graded semiquantitatively as negative (-), mild (+), and strong (++)

Ki-67 (RM-9106, clone SP6, dilution 1/200, Thermo Fisher Scientific, Fremont, CA, USA), a nuclear marker for determination of the growth fraction were analyzed immunohistochemically and positive cells were manually counted on the hot spots at the 400X magnification. The mean percentage of positive cells was recorded. The Ki-67 index of the cases was then labeled accordingly as low (<1%) and high (>=2%). Streptavidin-peroxidase technique was used for immunostainings. Immunohistological results are shown in Table 2.

4. Results

As seen in Table 1, the postero-lateral mandible (11 cases) was the most frequently affected site in this series. Others were found in the anterior mandible (7 cases) and the postero-lateral region of maxillae (4 cases). Most of the patients were female (15 female, 7 male) and the age range was between 4 and 66. The largest DF was six centimeters in diameter and it was located in the anterolateral area of the mandible. Asymptomatic swelling, ameloblastoma,

Table 2
Immunoreactivity for smooth muscle actin, beta-catenin and Ki-67.

	Patient	Smooth muscle actin-cytoplasmic	Beta-catenin-cytoplasmic	Beta-catenin-nuclear	Ki-67(%)	Nestin
1		++	–	–	<1	+
2		++	+	–	<1	
3		–	++	–	<1	+
4		++	++	–	<1	
5		++	++	–	<2	
6		++	–	–	<1	
7		–	+	–	<1	
8		++	–	–	<1	
9		++	++	–	<1	+
10		–	+	–	<1	
11		–	++	–	<1	+
12		++	–	–	<1	+
13		++	++	–	<2	
14		++	++	–	<2	+
15		–	++	–	<1	+
16		++	++	–	<1	
17		++	+	–	<1	+
18		–	–	–	<1	
19		–	++	–	<1	
20		–	–	–	<1	

– : negative, + : mild, ++ : strong

myxoma, giant cell granuloma, solid soft tissue lesion, malignant tumor, and ossifying fibroma were frequent provisional clinical diagnoses. A panoramic radiograph was available in some cases and it showed a destructive, ill-defined, unilocular, or multilocular radiolucent lesion (Figs. 1 and 2). There was no discernable periosteal reaction and/or thickening. Cortical expansion and some perforation were noted. In a single case (case 22) a cystic lesion was seen in the anterior mandible. Displacement of tooth and tooth germs were seen in one child (Fig. 2). The majority of patients suffered from local swelling. Four of them were asymptomatic. There was no pathologic fracture. There was no history of chemotherapy or radiotherapy in any of our cases. Complete surgical excision was the usual treatment. No recurrence was found in our files.

The histopathologic appearances in our series were quite similar. The unencapsulated, infiltrative tumors were composed of irregular fascicles of spindle, uniform fibroblastic/myofibroblastic cells with low to variable cellularity (Figs. 3 and 4). The cytoplasmic membrane of the cells was ill-defined and the surrounding matrix was collagenized, variably hyalinized, focally myxoid connective tissue (Fig. 4a,b,c). There were no hard tissue formations within the lesions. Mitosis is exceptional and none were atypical. There was no necrosis.

Table 2 shows the results of the immunohistochemical stainings of the present cases. Briefly, there was no nuclear reactivity with beta-catenin immunostaining in the present series. Four cases

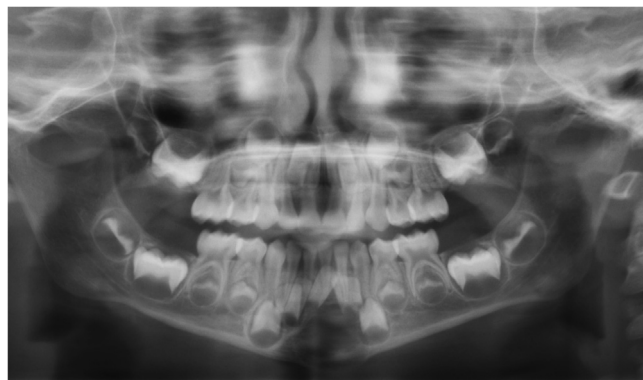


Fig. 2. The pre-operative panoramic radiograph of a desmoplastic fibroma of the mandible in a child (case 21) shows a radiolucent area in the anterior region causing teeth displacement.



Fig. 1. Large multilocular radiolucency and expansion in the left angulus mandible caused by desmoplastic fibroma (case 9).

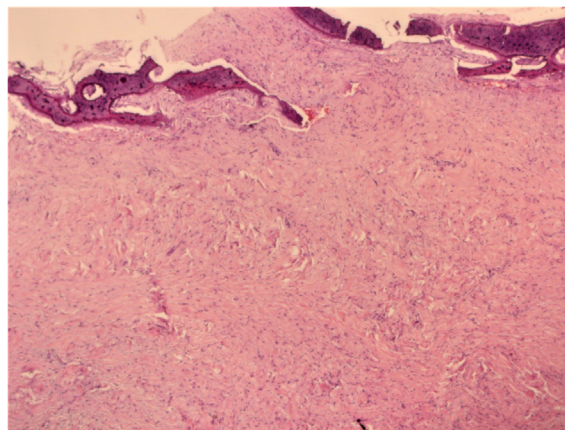


Fig. 3. Desmoplastic fibroma extending through cortical bone trabeculae (HEX100).

showed mild and ten cases showed strong cytoplasmic beta-catenin immunostainings (Fig. 5a). There was no staining in six cases. Control immuno stainings showed in Fig. 6 shown (Fig. 6a, b,c,d).

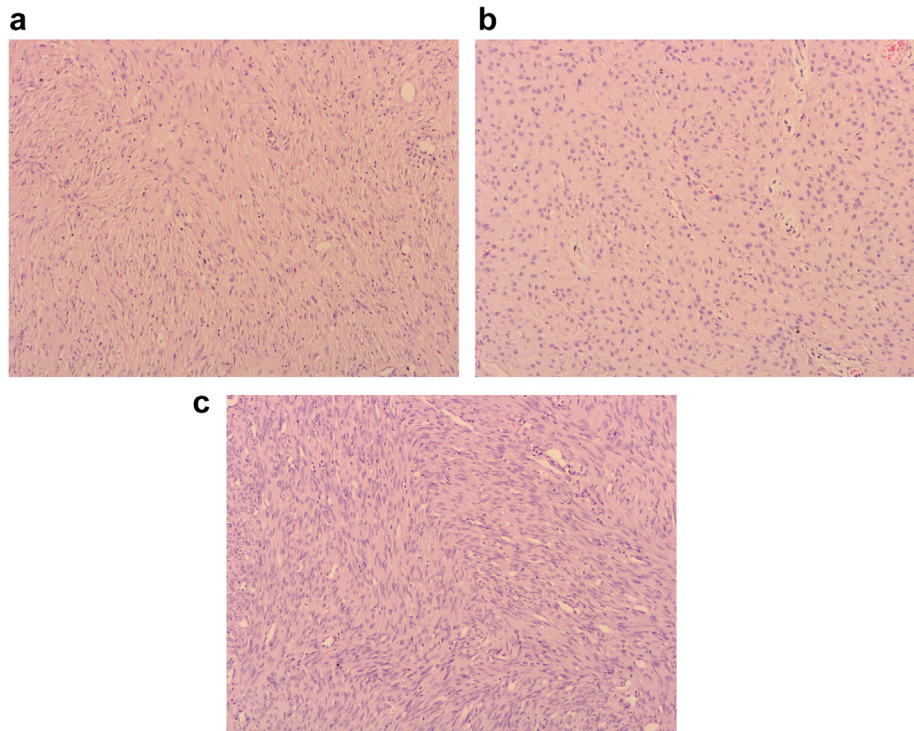


Fig. 4. Histologic appearance showing fascicles of spindle fibroblastic proliferation of desmoplastic fibroma (a). Some cases contained plump fibroblasts and more collagenized matrix (b) and others were more cellular (c). (HEX200).

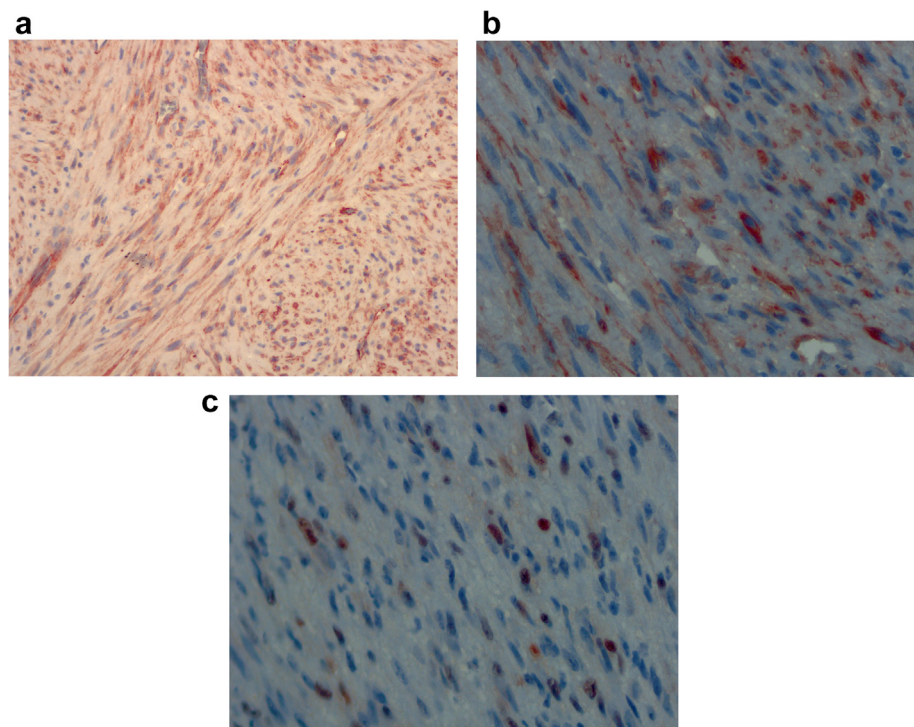


Fig. 5. The neoplastic spindle cells of desmoplastic fibromas showed cytoplasmic immunoreactivity for beta-catenin and nestin (a, b) without any nuclear staining. Some cases showed nuclear cyclin D1 reactivity (c), Streptavidin-peroxidase techniqueX400).

Most of the tumor cells (12/20) showed strong cytoplasmic reactivity for smooth muscle actin. There was no cytoplasmic smooth muscle actin reactivity in eight cases. Histologically, no difference was found between smooth muscle actin positive and negative cases.

There was diffuse, moderate cytoplasmic immunopositivity in neoplastic cells with nestin antibodies (Fig. 5b) in the present cases. Eight cases showed nuclear cyclin D1 positivity (Fig. 5c), others were negative. All control tissues showed positive immunostainings as expected.

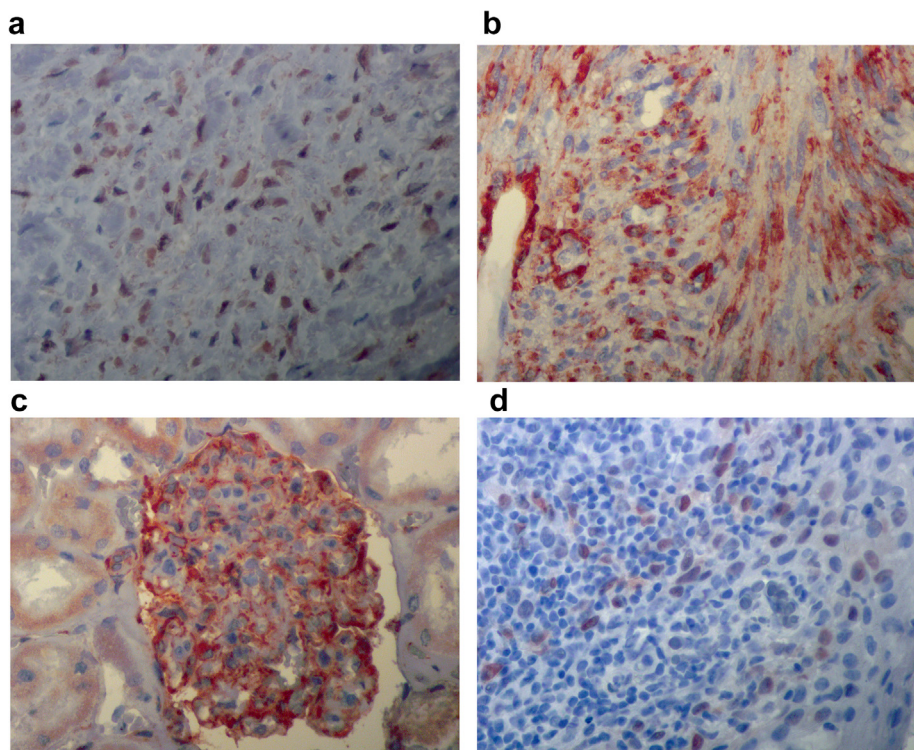


Fig. 6. Control immunostainings: Desmoid-type soft tissue fibromatosis used as control tissue and showed strong nuclear beta-catenin immunopositivity (a). There was strong cytoplasmic positivity for smooth muscle actin in a case of desmoplastic fibroma. Vessels within the lesion were positive control (b). Control positive nestin immunostaining of kidney section seen predominantly in glomeruli(c). Tonsil tissue served control tissue of cyclin D1 immunostaining. Suprabasal squamous epithelial cells, scattered lymphocytes, and endothelial cells showed strong nuclear immunostaining (d). (Streptavidin-peroxidase techniqueX400).

Ki-67 activity index was low (<1%) in most of the cases and reached to a high level (≥ 2) only in three cases. There was no significant clinical or histological difference between low and high Ki-67 activity cases.

5. Discussion

The first case of jaw bone DF was reported by Griffith and Irby in 1965 in the mandible of an 8-year-old girl [14]. In 2015, Woods et al reviewed 152 gnathic DFs which had been reported in the English language literature [2]. A female predilection of 56% was noted [2]. Most of the cases were below the age of 30. The mandibular (84%) posterior location was favored [2]. Gnathic lesions were usually painless, slow-growing, asymptomatic swellings [2,3]. Facial asymmetry, tooth displacement, root divergence, pain, trismus, and infections were the other symptoms [2,3,15]. Radiologic features of DF affecting the jaws were not unique and they overlapped with many other lesions [2]. Likewise, the age range, tumor location, and radiologic findings of our cases were not significantly different from those reported in earlier studies of DF of the jawbones. The wide range of provisional clinical diagnosis reflects the overall non-specific clinical and radiologic appearances of DF in this region.

The nuclear and cytoplasmic beta-catenin expression is a typical finding in nearly all of the desmoid-type soft tissue fibromatosis [16–18]. On the other hand, reports of such genomic alterations in DF are exceptional [8,19,20]. In 2005, Hauben et al suggested that in contrast to desmoid-type soft tissue fibromatosis, the beta-catenin mutation was not essential in diagnosis [8]. Genetically, there seems to be no evidence to consider DF as the intraosseous counterpart of desmoid-type soft tissue fibromatosis [8,19,20]. A literature review showed only eight gnathic intraosseous DFs with nuclear beta-catenin reactivity [2,8,9,21–23]. In

the present case series, we did not detect any cases with nuclear beta-catenin expression. On the other hand, cytoplasmic beta-catenin staining of varying intensity was found in most of all our cases (14/20).

Normally, beta-catenin is a cytoplasmic membraneous protein. Activated Wnt signaling causes accumulation of beta-catenin in the cytoplasm then translocates to the nucleus to regulate cell proliferation and differentiation. Neoplastic overexpression of Wnt signaling may contribute to an increased level of cytoplasmic and nuclear beta-catenin expression [24]. DF is composed of mature fibroblasts and myofibroblasts as in desmoid-type soft tissue fibromatosis. Fibroblasts are versatile cells and may show differentiation into the other connective tissue cells. Transitions of fibroblasts to myofibroblasts can occur along with the increased activity of beta-catenin [25]. Myofibroblastic differentiation in DF may be less prominent or lacking compared to that of the desmoid-type soft tissue fibromatosis. Our findings support the view that the cellular components of jaw bone lesions are immunologically different. We also believe that nuclear beta-catenin staining should not be a prerequisite for the definitive diagnosis of DF.

Hauben et al reported 7/13 cases of DF were immunoreactive for one or more muscle-specific markers in more than %10 of the cells [8]. In their literature review, Wood et al reported that 77% of the DF cases showed labeling with smooth muscle actin [2]. Similarly, most of our cases (12/20) expressed cytoplasmic SMA positivity in varying degrees.

Skeletal site-specific functional differences of cells may also affect the neoplasias. Therefore, bone lesions may display unique histological changes in the jawbones. Craniofacial bone development is different from long bones and that it develops from neural crest [27,13,10,28,29]. This difference may also be effective in immunostaining results. Absence of nuclear beta-catenin

immunoreactivity and the diffuse cytoplasmic positivity of neural crest-associated nestin and in some cases cyclin D1 stainings also may support this idea.

Proliferation markers such as Ki-67 are used as a surrogate marker for evaluating the tumor's aggressiveness. A low rate of cell turnover expected in DF as in desmoid-type soft tissue fibromatosis [2]. Our Ki-67 staining results are in agreement with those reported in earlier studies.

The clinical and radiologic appearance of DF may mimic many other jaw bone lesions including ameloblastoma, odontogenic fibroma, odontogenic cysts, aneurysmal bone cyst, chondromyxoid fibroma, central hemangioma, eosinophilic granuloma, osteomyelitis, cemento-ossifying fibroma, giant cell granuloma and rarely primary malignant lesions such as the low-grade fibrosarcoma and osteosarcoma. Averna et al suggested that the gold standard for the diagnosis of DF is the histologic appearance [26].

The histologic differential diagnosis of DF includes myofibroma, odontogenic fibroma, cemento-ossifying fibroma, and fibrous dysplasia. The absence of nuclear pleomorphism, very low mitotic activity, lack of traces of odontogenic epithelium, and lack of cementum or bone components should help differentiate DF from other jaw bone lesions histologically [26].

Myofibroma is a solitary circumscribed, unencapsulated nodular lesion of the soft tissues and bone of the head and neck area [1]. Myofibroma consists of short fascicles and whorls of spindle myofibroblastic cells with characterized haemangiopericytomatous pattern. These clinical and pathological features are not the expected findings of DF. The odontogenic fibroma is made up of plump, oval to spindle cells within a collagenous matrix with irregular strands of immature odontogenic epithelial cells. The odontogenic epithelium is not a component of DF. Cemento-ossifying fibroma presents with radiologically well-defined margins and is composed of vascularised fibro cellular connective tissue with cementoid and osseous components distributed throughout the lesion. Fibrous dysplasia is an ill-defined lesion that contains cellular fibrous connective tissue stroma with irregular trabeculae of woven bone blending into the surrounding normal bone. Hard tissue formations such as cementum and bone are findings that exclude the diagnosis of DF. However, peripheral parts of a DF may contain adjacent reactive bone which can lead to a misdiagnosis of the benign fibro-osseous lesion. Said-Al-Naief et al suggested that a generous diagnostic biopsy should be taken from the center of the lesion rather than the periphery in order to avoid misinterpreting the presence of reactive bone at the periphery as osteoid, which may, in turn, lead to a misdiagnosis of the benign fibro-osseous lesion or even osteosarcoma [3]. Khatib and Pogrel suggested that DFs need to be included in the differential diagnosis for aggressive, radiolucent mandibular lesions, particularly in children [6]. Immunohistochemical studies are of limited utility in the differentiation of DF from lesions with a morphologically similar fibroblastic/myofibroblastic component [3].

Neither the location nor histology of DFs permits accurate prediction of their potentially aggressive clinical course [6]. Optimum treatment strategies for DF of bone are total excision or resection to minimize the risk of recurrence [3]. Treatment with curettage should be avoided since the lack of sharp demarcation can make total removal impossible. Khatib and Pogrel reported that patients who were treated with resection or wide excision showed no recurrence [6]. In other series, the recurrence rate in those treated with simple excision or enucleation was 20% to 40%, as compared to 70% in those treated with curettage alone [3]. Malignant change is very uncommon in desmoplastic fibroma and it is usually in the form of fibrosarcoma characterized with a high rate of recurrence, hypercellularity, increased mitotic activity and, nuclear atypia [15]. In 2011 Min et al reported 20 cases of primary desmoid-type fibro-

matosis arising from the oral and maxillofacial region and three of them were intraosseous [15]. They found a malignant change in six cases, one of which was intraosseous [15]. The records of our patients did not reveal any recurrence or malignant transformations. Other therapeutic interventions like radiotherapy and chemotherapy were suggested in controlling recurrent and aggressive tumors especially when complete tumor resection is impossible or avoiding a mutilating operation is a concern [5,6,15]. Further series of DFs of the jawbones may improve our understanding of this lesion allowing us better treatment methods.

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CRedit authorship contribution statement

Devrim Kahraman: Investigation, Software, Visualization, Writing - original draft, Writing - review & editing. **Berkem Karakoyunlu:** Data curation. **Ulker Karagece:** Resources. **Umit Ertaş:** Data curation, Formal analysis. **Omer Gunhan:** Conceptualization, Methodology, Project administration, Supervision, Validation, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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