Desmoplastic fibroma associated with tuberous sclerosis: case report and literature review

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Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder that affects the skin, brain, kidneys, and other organ systems. It may exhibit a wide spectrum of clinical manifestations. Desmoplastic fibroma (DF) of the jaw is a rare benign myofibroblastic neoplasm. Less than 10 cases of DF associated with TSC have been published previously. We report a new case of a maxillary DF in a 12-year-old girl with TSC. The presentation, diagnostic process, and management of this case are discussed, and the literature is reviewed for the additional cases of DF associated with TSC; 7 previously reported cases are summarized. Small sample size limits conclusions, but there may be differences in the presentations of DF of the jaws in patients with TSC vs those in the general population. DF of the jaws may be a manifestation of TSC, and the authors propose surveillance panoramic radiographs every 2 to 3 years in patients with TSC. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:e92−e99)

Tuberous sclerosis complex (TSC) is an autosomal dominant disorder that was first characterized by von Recklinghausen in 1862[1] and named by Bourneville et al. in 1880.[2] The name refers to the numerous sclerotic masses that are scattered throughout the brain in affected individuals. Studies have estimated a population prevalence of 1 in 20,000.[3] Although TSC was classically described as a triad of facial angiofibromas, epilepsy, and cognitive delay, it is now recognized that patients with the condition can have abnormalities of the skin, brain, kidneys, heart, and lungs. TSC is diagnosed on the basis of the presence of 2 major features, or 1 major feature with 2 or more minor features (Table I). Features beyond the major and minor criteria have also been described and include aortic aneurysms and other cardiac malformations.[4-6] The diagnosis may also be established with genetic testing, although up to 25% of patients with TSC have no pathogenic mutations identified, so genetic testing with unremarkable results does not exclude a clinical diagnosis.[4]

Oral findings reported in patients with TSC include dental enamel pitting, gingival angiofibromas, and intrabony lesions.[7,8] Several of the previously reported cases of intrabony lesions were diagnosed as desmoplastic fibroma of bone (DF).[8-11]

DF is a rare benign myofibroblastic tumor, accepted as the osseous counterpart of soft tissue fibromatosis.[11] DF of bone has been described as an aggressive and infiltrating neoplasm that does not have the ability to metastasize. Although benign, DF has a high recurrence rate and requires careful follow-up even after complete resection.[11,12]

DF can occur in any bone in the body. In an early comprehensive literature review, the mandible was the most commonly affected skeletal site, representing 22% of all reviewed cases.[13] A more recent review of gnathic DFs demonstrated a strong predilection for the mandible (84%) over the maxilla (16%), with most lesions occurring in the posterior regions of the jaws.[12] DF presents in patients in a wide age range, with the majority (84%) occurring in individuals younger than age 30 years.[12] Gnathic DFs show a modest degree of female predilection.[12]

Interestingly, these 2 rare disorders (TSC and gnathic DF) have previously been described as occurring concomitantly.[8,9,11] We describe here a new case of DF occurring in a patient with TSC and present a review of the literature on this phenomenon. At our institution, institutional review board approval is not required for a case report involving a single case. The patient's mother gave written permission for publication of the case.

Statement of Clinical Relevance

This case report and literature review regarding desmoplastic fibroma of the jaws associated with tuberous sclerosis complex will provide a valuable resource for clinicians who may be encountering these rare entities concomitantly in their patients.

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Table I. Major and minor diagnostic criteria for tuberous sclerosis complex (TSC)[4,*]

Major features	*Minor features*
• Hypomelanotic macules (3+, >5 mm diameter)	• "Confetti" skin lesions
• Angiofibromas (3+)	• Dental enamel pits (3+)
• Shagreen patch	• Intraoral fibromas (2+)
• Ungual fibromas (2+)	• Retinal achromic patch
• Multiple retinal hamartomas	• Multiple renal cysts
• Cortical dysplasias	• Nonrenal hamartomas
• Subependymal nodules	
• Subependymal giant cell astrocytoma	
• Cardiac rhabdomyomas	
• Lymphangioleiomyomatosis (LAM)	
• Angiomyolipomas (2+)	

*Definitive diagnosis: Two major features or one major feature with 2 or more minor features.Possible diagnosis: Either 1 major feature or 2 or more minor features.Note that a combination of lymphangioleiomyomatosis and angiomyolipomas without other features does not meet the criteria for a definitive diagnosis of TSC.

CASE REPORT

A 12-year-old girl was referred to the Oral and Maxillofacial Surgery Clinic at the Medical College of Wisconsin by her orthodontist for exposure and bonding of tooth #9, which was completed successfully. The patient had been diagnosed with TSC with intractable epilepsy, cardiac rhabdomyomas, and cognitive delay. In addition, she had a history of asthma and attention deficit hyperactivity disorder. One year later, her orthodontist noted an asymptomatic, expansile lesion of the left palate; intraoral radiographs showed root resorption and crestal bone loss on tooth #9 (Figure 1). He referred her to Oral and Maxillofacial Surgery Clinic at the Medical College of Wisconsin for evaluation of this new problem. Upon examination, a nontender, firm expansion of the maxilla palatal to tooth #9, extending to the mid hard palate, was observed. The overlying palatal mucosa was normal appearing, although the gingiva adjacent to tooth #9 was edematous and erythematous, with significant plaque biofilm accumulation. Similar but smaller erythematous marginal gingiva lesions were noted in association with multiple other teeth. The differential diagnosis for these lesions included irritant-associated gingivitis, localized juvenile gingival hyperplasia, polyangiitis with vasculitis (Wegener granulomatosis), multiple pyogenic granulomas, and inflammatory fibrous hyperplasia associated with medications. In addition, there was a sessile, round, smooth-surfaced, erythematous nodule on the attached gingiva between teeth #28 and #29; the differential diagnosis for this lesion included pyogenic granuloma, peripheral ossifying fibroma, peripheral giant cell granuloma, irritation fibroma, and neurofibroma. Computed tomography (CT) of the face showed modest, primarily hyperdense bony expansion in the region of tooth #9, with a thin, irregular, well-circumscribed hypodense area around the tooth (Figure 2). We performed incisional biopsies of the maxillary lesion and the surrounding soft tissue adjacent to tooth #9 and excision of the gingival lesion between teeth #28 and #29.

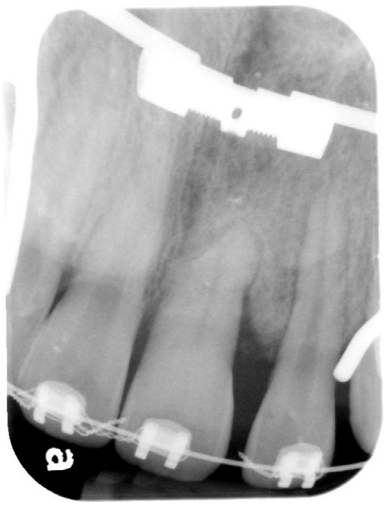

Fig. 1. Periapical radiograph demonstrating distal crestal bone loss and root resorption on tooth #9.

Histopathologic examination of the biopsy specimens of the soft tissue lesions associated with teeth #9 and #29 showed inflammatory fibrous hyperplasia with focal mild spongiosis of the surface epithelium, leading to a diagnosis of oral gingival fibromas (traumatic/irritation fibromas). The intrabony lesion showed a benign dense fibrous stroma with low- to mid-cellularity and bland ovoid to focally spindle-shaped nuclei exhibiting different cellular arrangements that varied from nodular to fascicular. The fibroblastic proliferation was seen infiltrating adjacent vital bone. The histologic differential diagnosis, based on hematoxylin and eosin−stained sections, included central odontogenic fibroma, myofibroma, DF of bone (intrabony fibromatosis), leiomyoma, solitary fibrous tumor, and low-grade fibrosarcoma. Immunohistochemical studies were performed despite their known limited use in benign spindle cell lesions of bone. Factor XIIIa was negative, and beta catenin was focally positive. The controls for immunohistochemistry (IHC) reacted appropriately. A final diagnosis of DF of bone was rendered. The patient was lost to follow-up for 6 months but returned to our service for enlargement of the palatal mass. Examination revealed erythematous gingival enlargement buccal to tooth #9 and also a firm, nontender bony mass with buccal expansion overlying teeth #9 and #10, and palatal expansion in the left maxilla from the middle of tooth #8 to the distal portion of tooth #1. The lesion narrowed as it extended posteriorly in the hard palate for a distance of approximately 2.5 cm (Figures 3A to 3C). No altered sensation was noted in the area. A sessile, ovoid, smooth-surfaced nodule with focal surface

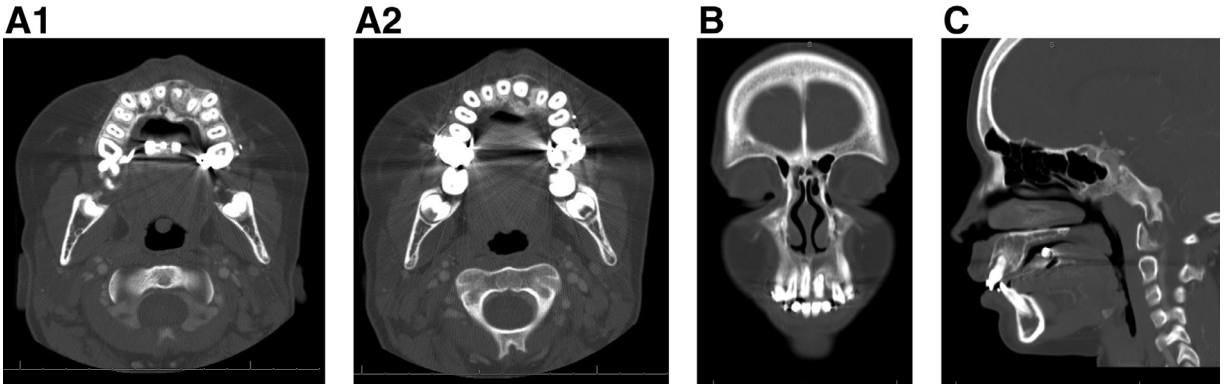

Fig. 2. Facial computed tomography (CT) scan obtained before initial biopsy. **(A)** Axial views. **(B)** Coronal view. **(C)** Sagittal view. Thin, irregularly shaped hypodensity surrounds resorbed root of tooth #9 with adjacent sclerosis as well as mild buccal and palatal expansion.

erythema on the attached gingiva between teeth #28 and #29 extended from the mucogingival junction to the occlusal surface of these teeth (Figure 3D).

A new CT scan taken 9.5 months after the initial scan showed increased facial and palatal expansion; the hypodensity adjacent to the resorbed root of tooth #9 had enlarged facially, where the cortex was perforated. Sclerotic bone was noted palatal and apical to tooth #9 (Figure 4). Because the lesion in the left anterior maxilla had enlarged and it was unclear from the prior operative note which portion of the lesion (hypodense, hyperdense, or both) had been subjected to biopsy, additional biopsies were performed to evaluate for DF in the sclerotic bone. The right mandibular gingival lesion was re-excised at the same time.

Histopathology confirmed oral gingival fibroma (traumatic/irritation fibroma) on the right mandibular gingiva and DF in both the soft tissue and bone specimens from the anterior maxilla. The histopathologic features were identical to those of the previous biopsy specimens, and DF was seen infiltrating the adjacent sclerotic bone. The treatment options for the DF were discussed with the family and included enucleation and curettage or resection of the tumor with 1-cm margins. A resection with 1-cm margins was performed, and clear margins were achieved (Figure 5). Final histopathology of the maxillary tumor specimen confirmed the diagnosis of DF. Representative images of the specimen's microscopic features are shown in Figure 6. Six months postoperatively, CT showed no signs of recurrence and only the expected postoperative changes. One year after resection, the patient remained clinically and radiographically free of recurrent tumor.

DISCUSSION

Jaw lesions associated with tuberous sclerosis have been reported rarely. To our knowledge, Miyamoto et al. were the first to discuss a case of DF of the mandible in TSC in an 8-year-old Caucasian female,[9] although Rushton had previously described fibrous osteitis in a patient with TSC.[14] The case reported by Rushton cannot be definitively identified as DF, but in our opinion,

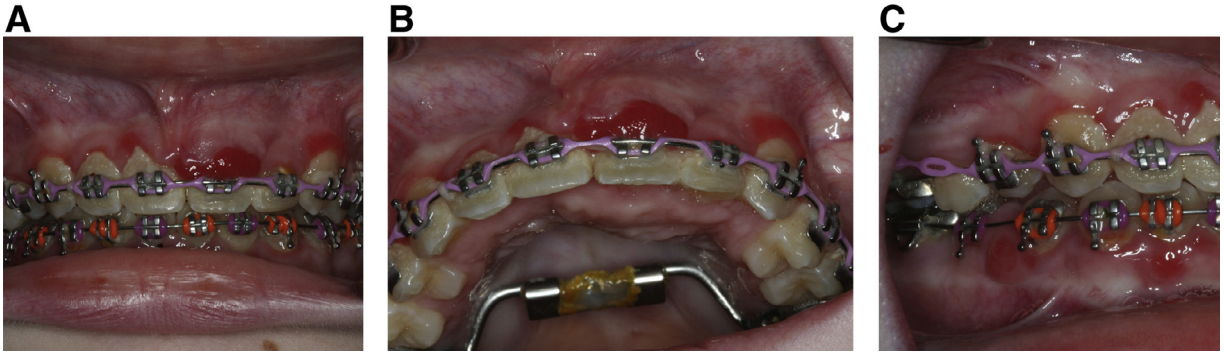

Fig. 3. Clinical photographs taken after patient presented again to clinic. **(A)** Erythematous marginal gingiva with gingival enlargement particularly at tooth #9; generalized poor oral hygiene. **(B)** Buccal and palatal expansion with normal appearing overlying palatal mucosa. **(C)** Sessile, ovoid, smooth-surfaced nodule with focal surface erythema on the attached gingiva between teeth #28 and #29.

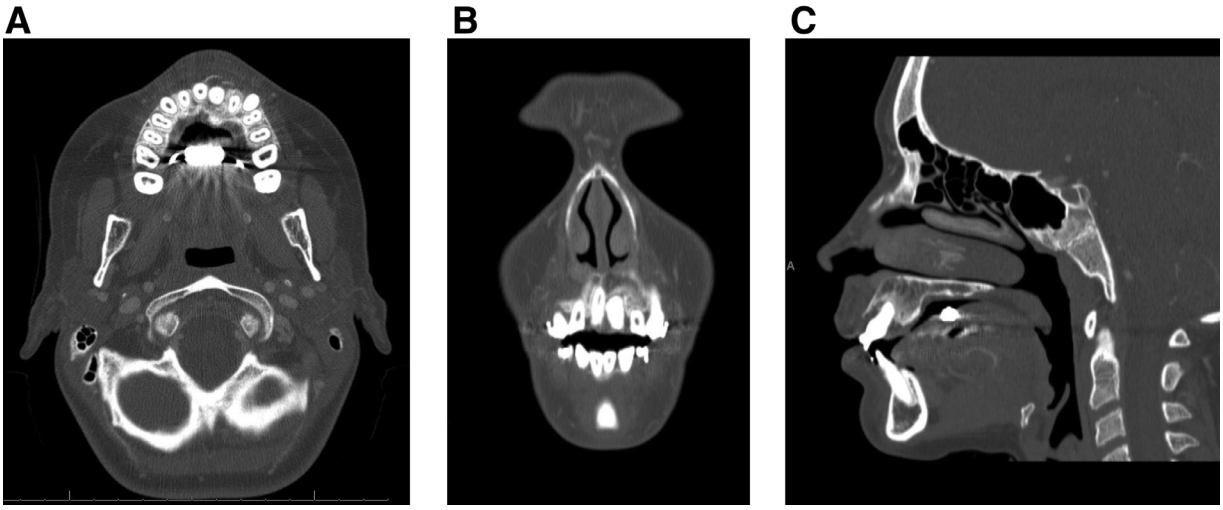

Fig. 4. Facial computed tomography (CT) scan obtained after patient presented again to clinic. **(A)** Axial view. **(B)** Coronal view. **(C)** Sagittal view. The irregularly shaped hypodensity surrounding the resorbed root of tooth #9 has enlarged. There is persistent surrounding sclerosis along with increased buccal and palatal expansion.

it may represent one. Other authors have subsequently published reports, for a total of 7 cases.[8-11] Table II summarizes cases of TSC-associated DF of the maxillofacial skeleton reported to date in the English language literature, including the present case.

DFs are benign, locally aggressive tumors.[12] Any bone may be involved in DF, but the mandible is the most common site.[13] Generally, the radiographic features of DF are nonspecific and may include a unilocular or multilocular, well-demarcated or irregular radiolucency; therefore, the differential diagnosis is broad, and biopsy is indicated for a definitive diagnosis. It is difficult to differentiate between DF and central odontogenic fibroma on the basis of histopathology alone.[15] However, The World Health Organization's definition of central odontogenic fibroma includes the occasional presence of odontogenic epithelium and/or calcifications and frequent association with impacted teeth, and all of these features were absent in our case. With collagenized lesions without odontogenic epithelium, DF should be strongly considered.[8] It is important to note that low-grade fibrosarcoma of bone must be entertained when DF is considered on the basis of histopathology results. In low-grade fibrosarcoma, the cells usually assume fascicular growth and focal mild atypical features, whereas in DF, they favor a single orientation and are typically arranged in bundles.[12] The IHC profile of DF is nonspecific, but IHC can be used to rule out other lesions in the differential diagnosis, such as myofibroma, leiomyoma, nonossifying fibroma, and other benign spindle-shaped mesenchymal neoplasms.[12]

Management of DF should consist of resection with wide margins, especially when there is aggressive destruction of the surrounding bone and soft tissue

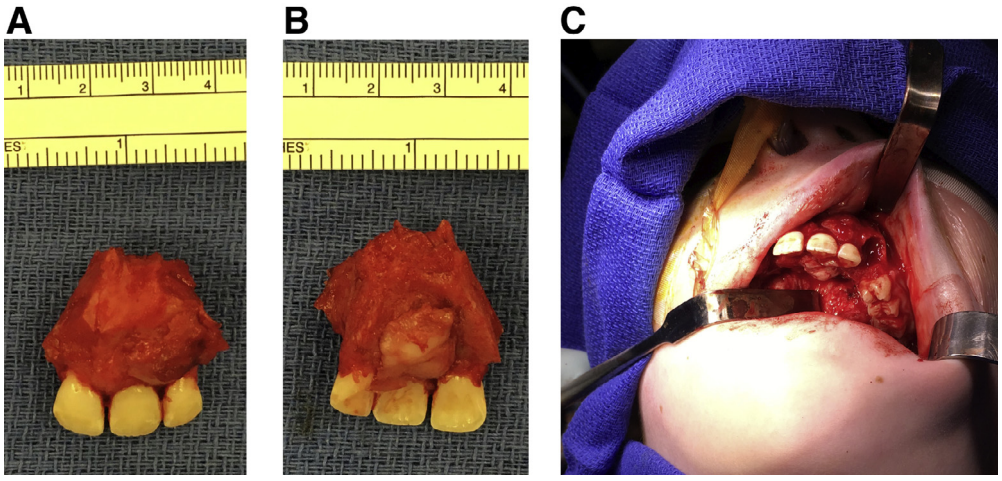

Fig. 5. Intraoperative photographs. **(A)** Resected segment, facial view. **(B)** Resected segment, palatal view. **(C)** Intraoperative view before bone cuts but after extraction of teeth at sites of planned osteotomies.

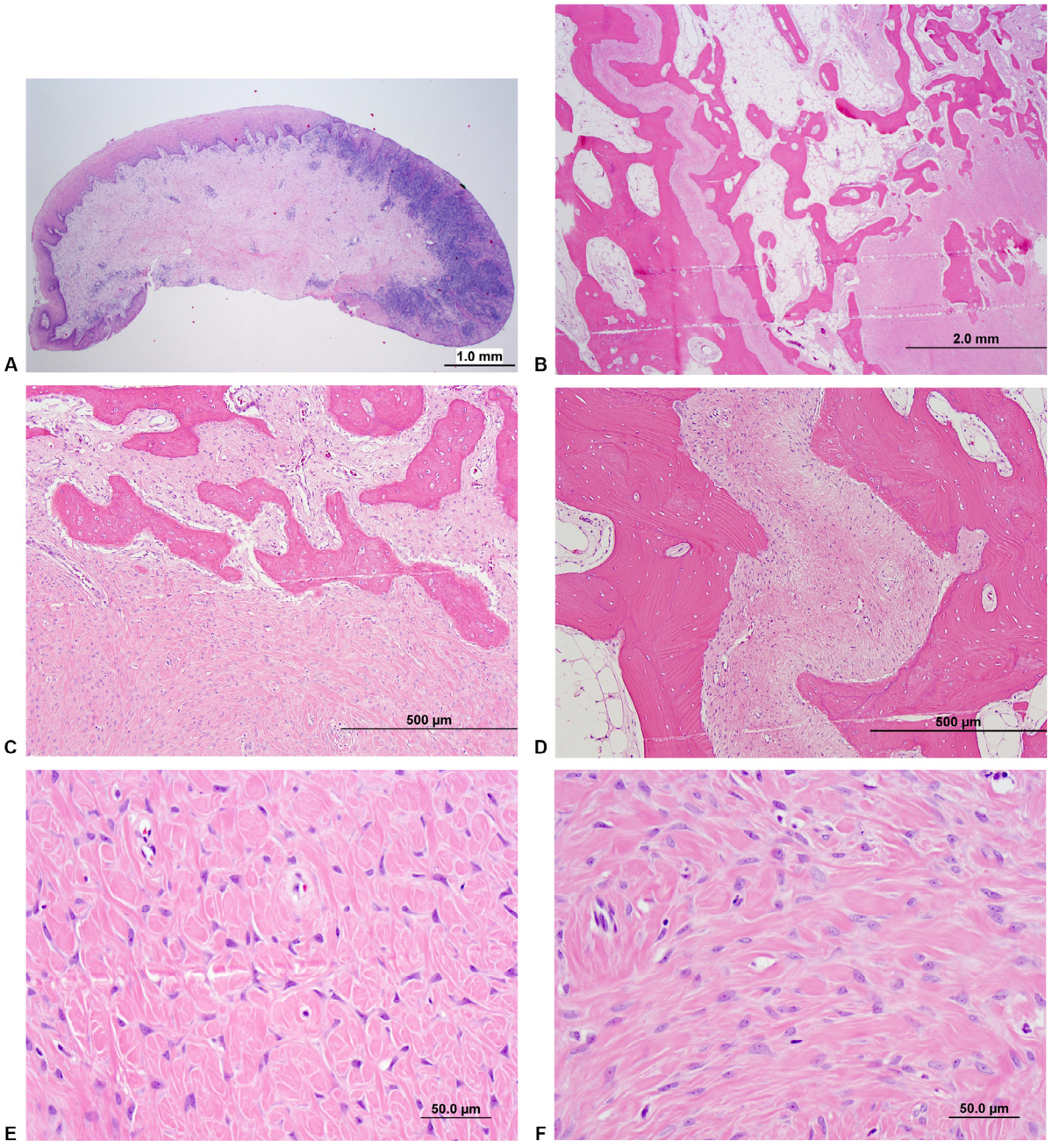

Fig. 6. **(A)** Whole-mount microphotograph of the gingival fibroma. Note the presence of inflammation on the right side of the specimen and the overlying focal epithelial spongiosis. Reference bar is 1 mm. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05380.* **(B)** Low-magnification hematoxylin and eosin (H&E)−stained section of the decalcified specimen showing vital bone and fatty marrow being infiltrated by the desmoplastic fibroma. Reference bar is 2 mm. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide: VM05381.* **C, D,** Medium-magnification H&E-stained section of desmoplasic fibroma (DF) infiltrating the adjacent bone and marrow spaces. Reference bar is 0.5 mm. *A high-resolution version of this slide for use with the Virtual Microscope is available as eSlide VM05382.* **E, F,** High-magnification H&E-stained section of DF showing the bland cytologic morphology varying from ovoid to spindle-shaped nuclei and dense fibrous stroma. Reference bar is 0.05 mm. **G,** Beta catenin immunohistochemical stain highlighting the most positive areas of the lesion. Some areas were weak-staining, and others were negative. The internal and external controls of the immunohistochemical stain reacted appropriately. Reference bar is 0.1 mm.

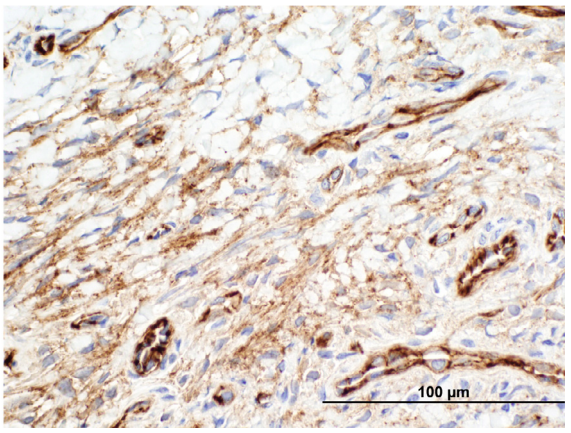

Fig. 6 Continued.

infiltration. Recurrence rates of up to 40% have been reported when DF is treated with simple excision or enucleation and up to 70% with curettage alone.[16] Recurrence rates with resection are lower at 4.3%.[12] Several alternative treatment modalities, including radiation and chemotherapy, have been proposed. However, it has been reported that radiation does not yield a better prognosis and may increase the risk of postradiation sarcoma.[17] Given the recurrence rate and aggressive nature of DF, the minimum recommended follow-up period is 3 years.[18]

The presentation of our case was somewhat unusual. The patient presented with a mixed density lesion of the maxilla. It has been previously reported that only 4% of gnathic DFs showed mixed radiodensity.[12] Whether DFs of mixed radiodensity are more common in TSC remains to be seen as more cases are

Table II. Reported cases of desmoplastic fibromas associated with tuberous sclerosis complex, including the present case

Authors (year)	*Patient age/ Sex*	*Clinical/Radiographic presentation*	*Histopathologic features*	*Site*
Damm et al. (1999)	10-year-old Caucasian male	Swelling of anterior mandible Multilocular radiolucency of anterior mandible	Basophilic and spindle shaped nuclei within a dense fibrous connective tissue; widely spaced fibroblastic cells	Anterior mandible
	9-year-old African American male	Clinical information absent Radiolucency of anterior maxilla, cortical expansion with perforation	Basophilic and spindle shaped nuclei within a dense fibrous connective tissue; widely spaced fibroblastic cells	Anterior maxilla
	14-year-old Caucasian female	Clinical information absent Radiolucency apical to retained tooth H	Basophilic and spindle shaped nuclei within a dense fibrous connective tissue; widely spaced fibroblastic cells	Anterior maxilla
	23-year-old Caucasian female	Clinical information absent Interradicular radiolucency between teeth #20 and #21	Basophilic and spindle shaped nuclei within a dense fibrous connective tissue; increased cellularity with fascicular arrangement	Posterior mandible
Miyamoto et al. (1995)	29-year-old Asian female	Firm buccal swelling of mandible between teeth #20 to #26 Well-defined radiolucency with expansion	Irregularly distributed fibroblasts and abundant plump collagen fibers, hyalinized stroma in areas	Anterior/posterior mandible
Vargas et al. (2004)	14-year-old Hispanic male	Slowly enlarging osseous mass involving left nasomaxillary/ orbital region Expansile trabeculated "soap bubble" lesion involving nasoorbitomaxillary region	Fibroblastic-like spindle cells proliferating in delicate mesenchymal stroma with intertwining collagen fascicles	Anterior/posterior maxilla (extension to orbit, nose)
Tandon & Garg (2012)	8-year-old Caucasian female	Slowly enlarging firm buccal mass extending from tooth #9 to deciduous molar region Radiolucency with expansion	Spindle-shaped cells (myofibroblastic differentiation), abundant collagen formation, areas of hyalinized stroma	Anterior/posterior maxilla
Fahmy et al. (2017) (present case)	12-year-old Caucasian female	Buccal and palatal enlargement of the left anterior maxilla Radiolucency surrounding root of tooth #9 with surrounding radiopacity and expansion	Fibrous spindle cell lesion of low to moderate cellularity involving soft tissue and bone. Spindle cells with small oval bland nuclei and collagenous matrix with an intersecting or vaguely nodular patter	Anterior maxilla

reported. In our case, the initial incisional biopsy demonstrated DF; a second incisional biopsy was performed to determine whether there was DF in the sclerotic bone before definitive management was initiated. The tumor was ultimately resected with 1-cm margins, and the patient has remained free of recurrence at 1 year. The patient also had a recurrent oral gingival fibroma (traumatic/irritation fibroma), which apparently was not associated with trauma, excised twice; this is consistent with TSC-associated gingival fibroma.

Only 7 cases with documented TSC and DF of the jaws have been previously reported in the literature.[8-11] Our case represents the 8th case of DF associated with TSC (see Table II). It is unknown whether other fibrous jaw lesions previously described in TSC may also represent DFs that were not accurately identified at the time.

Our review of TSC-related DF shows that all cases occurred in patients in the first 3 decades of life. Six of the 8 cases occurred in the first 2 decades. Five of the cases were in the maxilla, which is a less common site for DF compared with the mandible in the general population. Seven of the 8 cases involved the anterior maxilla or mandible, and 4 of the cases involved the posterior maxilla or mandible. Four of the 8 cases were isolated to the anterior maxilla, and one of the 8 cases was isolated to the posterior mandible. Five of the 8 patients were females, demonstrating a slight female predilection, in contrast to the reported trends in non−TSC-associated DF. The small number of reported cases limits generalizability and as more cases are reported, more reliable data will be generated.

In the 7 previous reports, no management was described beyond biopsy in 4 cases.[8] Curettage with no recurrence at the 3-year follow-up was reported by Miyamoto[9]; Tandon performed enucleation during excisional biopsy and reported only an uneventful postoperative course.[10] In another report, the tumor was treated with resection, but no follow-up information was reported.[11]

CONCLUSIONS

In summary, we presented a new case of DF of the jaws in a patient with TSC. Although the sample size of a single case limits the ability to draw definitive conclusions, our case report and review of the literature suggest that there may be differences in the presentations of DF of the jaws between patients with TSC and those in the general population. Our findings also add credence to the idea that DF of the jaws may be a manifestation of TSC in some patients. Finally, current recommendations for patients with TSC include dental examinations every 6 months and panoramic radiography at age 7 years[19]; we recommend that panoramic radiography be obtained every 2 to 3 years for ongoing surveillance in this population.

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