Comparing Clinical and Radiographic Characteristics of Chronic Diffuse Sclerosing Osteomyelitis and Craniofacial Fibrous Dysplasia in the Mandible

Kuankuan Jia, DDS, Xiaoli Li, DDS,† Jingang An, DDS, MD,‡ and Yi Zhang, PhD, MD, DDS§*

Purpose: Differential diagnosis of chronic diffuse sclerosing osteomyelitis of the mandible (DSOM) and craniofacial fibrous dysplasia (CFD) involving the mandible is challenging. The purpose of this study was to explore the differences of the clinical and radiographic characteristics between these 2 conditions.

Patients and Methods: In this retrospective cross-sectional, blinded, comparative study, clinical and imaging data of patients with DSOM and CFD at the Peking University Hospital of Stomatology from 2012 to 2018 were retrieved. Clinical characteristics, mainly pain, swelling, and trismus, and radiographic findings, including sclerosis, lysis, and subperiosteal bone formation, were evaluated. The *t* test, χ^2 test, and Fisher-Freeman-Halton test were used to determine differences.

Results: Thirty-seven patients with DSOM and 32 patients with CFD were included (mean ages, 24.2 and 28.4 years, respectively); both groups showed a female predilection. DSOM (91.9%) and CFD (84.4%) were mainly unilateral. Patients with DSOM mainly presented with pain (94.6%), soft-tissue swelling (100.0%), and trismus (54.1%), whereas those with CFD did not experience pain (90.6%) and showed bone enlargement (87.5%) without trismus (6.3%). Panoramic radiographs and computed tomography scans of patients with DSOM showed subperiosteal bone formation, cortex lysis, and poorly demarcated cortex, whereas those patients with CFD mainly showed moderate-to-severe bone expansion, well-demarcated cortex, and tooth and mandibular canal displacement.

Conclusions: These findings emphasize the importance of clinical and radiographic features in differentiating between DSOM and CFD. Pain, soft-tissue or bone-tissue swelling, subperiosteal bone formation, clarity of the boundary of the cortex and medulla, and continuity of the cortical bone are key points facilitating differentiation.

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Chronic diffuse sclerosing osteomyelitis of the mandible (DSOM) is rare chronic nonsuppurative osteomyelitis of the mandible.[1] The pathogenesis of DSOM is not well understood. Some scholars have claimed that DSOM might be caused by an infection; however, an underlying infectious process has not

Received from Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, Beijing, China.

*Resident.

†Resident.

‡Associate Professor.

§Professor.

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Address correspondence and reprint requests to Dr An: Department of Oral and Maxillofacial Surgery, Peking University School and Hospital of Stomatology, 22 Zhongguancun South Avenue, Haidian District, Beijing 100081, PR China; e-mail: anjingang@126.com

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been identified.[2,3] It has also been claimed that DSOM might be caused by muscle hyperactivity[4] or could be a localized type of the synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome.[5-7] Patients with DSOM experience cyclic episodes of pain and swelling in the mandible. Some patients also present with trismus and progressive bone deformity. The radiographic features of these patients include intermingled osteosclerosis and osteolysis in the mandibular bone and subperiosteal bone formation.[1]

The clinical and radiographic features of DSOM are similar to those of craniofacial fibrous dysplasia (CFD),[1,8,9] especially CFD that only affects the mandible.[10] CFD is characterized by a progressive and painless bone deformity[11,12]; however, a few patients present with pain and nerve entrapment.[13] Three radiographic patterns have been described in CFD: osteosclerotic, osteolytic or cyst-like, and mixed pattern.[14,15] In most cases, CFD presents as the mixed type (osteosclerosis with osteolysis).

Identifying DSOM and CFD of the mandible can be challenging because the clinical and radiographic characteristics of the 2 diseases are similar.[1,9] Furthermore, a considerable difficulty may be encountered in differentiating between the 2 diseases by using microscopy.[16-19] Clinically, DSOM is often misdiagnosed as CFD or CFD with infection; however, the pathophysiology of the 2 diseases and their treatment strategies differ. No previous study has compared the clinical and radiographic characteristics of these 2 diseases. Comparing the clinical and radiographic characteristics of these 2 diseases, especially radiographic characteristics, is helpful for a differential diagnosis.

The purpose of this study was to explore the key points for differential diagnosis between the 2 diseases. We hypothesized that the clinical and radiological features of the 2 diseases are different. The specific aims of the study were to summarize the age- and sex-related findings and clinical courses associated with the 2 diseases and to compare their clinical and radiographic characteristics.

Patients and Methods

STUDY DESIGN AND SAMPLE

To address the research purpose, the investigators designed and implemented a retrospective cross-sectional study that included consecutive inpatients diagnosed with DSOM or CFD involving the mandible from 2012 to 2018 at the Department of Oral and Maxillofacial Surgery, Peking University Hospital of Stomatology (Beijing, China). These patients were rediagnosed based on clinical signs and symptoms, radiography findings, and histologic findings of biopsy and surgery material by 2 experienced clinicians from the Department of Oral and Maxillofacial Surgery. Pathology reports of all these cases were rereviewed. When the patient's reports did not match the clinical and radiological findings, we consulted a senior pathologist of our hospital and obtained new diagnosis by combining clinical and radiographic findings. The study protocol was in accordance with the Declaration of Helsinki, and the regional Ethical Review Board of Peking University School and Hospital of Stomatology approved this study.

Using medical records, we analyzed patients' age, sex and course of the disease and evaluated the clinical characteristics of the 2 diseases. Panoramic radiographs and computed tomography (CT) were available. Two observers from the Department of Oral and Maxillofacial Surgery of our institution jointly evaluated all images for each patient. The observers were blinded to the clinical information and diagnoses of the patients. The observers determined whether the lesions were unilateral or bilateral and evaluated the lesion sites in the mandible, including the body, angle, ramus, and condyle, and chin.

VARIABLES

The predictor variables studied were clinical characteristics and radiographic characteristics. Clinical characteristics inclued pain, soft-tissue swelling, bone enlargement, trismus, numb lips, fistula, abscess, and cutaneous temperature elevation of lesions. Radiographic characteristics, including the cortex, medulla, and condylar process of the mandible for features including sclerosis, lysis, subperiosteal bone formation, bone expansion, the boundary of cortex with the medulla, condylar process deformation, tooth displacement, mandibular canal displacement, and the boundary of the lesion, were assessed by the observers using panoramic radiographs and CT scans separately. The other variables included patient demographics (ie age, sex, and course of the disease). The outcome variables measured were the 2 groups of patients rediagnosed as DSOM and CFD. The patients with CFD included those with the polyostotic forms and monostotic forms involving the mandible.

DATA COLLECTION METHODS AND DATA ANALYSES

We retrospectively reviewed the medical records, radiological images, and histologic characteristics of all patients. Patients with incomplete data were excluded. Data were analyzed using SPSS v24.0 (IBM, Armonk, NY). The χ^2 test and Fisher-Freeman-Halton test were used to determine differences in sex, the clinical and radiographic characteristics of DSOM and CFD in 2×2 and 2×4 tables. Continuous variables (age and course of the diseases) were

summarized as the means ± standard deviation and compared between groups using the *t* test. $P < .05$ was considered significant.

Results

In this study, 69 inpatients were evaluated. Among them, 37 were diagnosed with DSOM and 32 with CFD. Six patients with DSOM were misdiagnosed previously. Of these 6 patients, 2 were misdiagnosed with CFD and 4 were misdiagnosed as CFD with infection (Table 1).

DSOM and CFD both showed a female predilection. The demographic information of the 2 diseases is shown in Table 2. In the 32 patients with CFD, the lesion developed only in the mandible in 10 patients; in the remaining 22 patients, lesions were present in other maxillofacial bones besides the mandible, with 1 patient showing café-au-lait spots on the facial skin.

DSOM and CFD were mainly unilateral (occasionally bilateral) in the mandible. The former was localized mainly in the body, angle, and ramus of the mandible, followed by the chin and condylar process. CFD was localized mainly in the body, chin, and angle of the mandible, followed by the ramus and condyle (Table 2).

CLINICAL CHARACTERISTICS

Pain, soft-tissue swelling and trismus were more common in patients with DSOM than in those with CFD ($P < .001$). Bone swelling was more common in patients with CFD than in those with DSOM ($P < .001$). Very few patients with DSOM or CFD exhibited numb lips, and there were no significant differences ($P = .809 > 0.05$). No patient with DSOM and CFD showed fistula, abscess, or cutaneous temperature elevation. The clinical characteristics of the mandible did not significantly differ between monostotic and polyostotic CFD. Table 2 shows the clinical features evaluated in patients with DSOM and CFD.

RADIOGRAPHIC CHARACTERISTICS

Panoramic radiographs were available for all 37 patients with DSOM, while CT scans of the mandible were available for 36 patients. For the 32 patients with CFD, panoramic radiographs were available for 24 patients, while CT scans were available for 31 patients.

Panoramic Radiographs

Patients with DSOM exhibited intermingled sclerosis and lysis in the medulla; these findings were not significantly different from those patients with CFD. Cortical lysis and poorly demarcated cortex and medulla were more common in the patients with DSOM compared with those patients with CFD ($P = .014 < 0.05$, $P < .001$, respectively). Patients with DSOM showed subperiosteal bone formation, which was not observed in patients with CFD. Condylar process deformation was more common

Table 1. INFORMATION OF MISDIAGNOSED PATIENTS WITH DSOM

Patient	Age (yr)	Sex	Diagnosis in the Hospital	Lesion Site	Clinical Features
1	22	M	CFD with infection	Entire mandible	Pain, swelling, trismus, and nonsuppurative osteomyelitis
2	7	F	CFD	Right condylar process, ramus, angle of the mandible	Pain, swelling, and nonsuppurative osteomyelitis
3	18	F	CFD with infection	Entire mandible	Pain, swelling, trismus, and nonsuppurative osteomyelitis
4	15	F	CFD	Right condylar process, ramus, angle of the mandible	Pain, swelling, trismus, and nonsuppurative osteomyelitis
5	18	F	CFD with infection	Left ramus and angle of the mandible	Pain, swelling, and nonsuppurative osteomyelitis
6	24	F	CFD with infection	Left body and angle of the mandible	Pain, swelling, and nonsuppurative osteomyelitis

Abbreviations: CFD, craniofacial fibrous dysplasia; DSOM, diffuse sclerosing osteomyelitis of the mandible.

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Table 2. DEMOGRAPHIC AND CLINICAL VARIABLES OF THE PATIENTS WITH DSOM AND CFD

Variables	DSOM (n = 37)	CFD (n = 32)	*P*
Sex			0.765
Male	14	11	
Female	23	21	
Mean age (yr) (mean ± SD)	24.2 ± 16.2	28.4 ± 9.2	0.185
Age range (yr)	5 to 65	17 to 49	-
Mean course (yr)	2.1 ± 2.2	9.1 ± 9.0	<0.001
Lesion sides			0.551
Unilateral	34 (91.9%)	27 (84.4%)	
Bilateral	3 (8.1%)	5 (15.6%)	
Lesion sites			
Chin	15 (40.5%)	24 (75.0%)	0.004
Body	31 (83.8%)	30 (93.8%)	0.362
Angle	30 (81.1%)	22 (68.8%)	0.236
Ramus	31 (83.8%)	19 (59.4%)	0.024
Condyle	12 (32.4%)	14 (43.8%)	0.333
Clinical features			
Pain	35 (94.6%)	3 (9.4%)	<0.001
Soft-tissue swelling	37 (100.0%)	1 (3.1%)	<0.001
Bone swelling	2 (5.4%)	28 (87.5%)	<0.001
Trismus	20 (54.1%)	2 (6.3%)	<0.001
Numb lips	4 (10.8%)	2 (6.3%)	0.809

The lesion sites and clinical features were scored as "present" or "absent." This table represents the number of patients (% of patients) exhibiting clinical features. *P* represents the *P*-value of DSOM and CFD.

Abbreviations: CFD, craniofacial fibrous dysplasia; DSOM, diffuse sclerosing osteomyelitis of the mandible.

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in the patients with CFD, this finding differed significantly from the patients with DSOM ($P = .001 < 0.05$). Bone expansion was more common in the CFD group than in the DSOM group ($P < .001$). Tooth and mandibular canal displacement were also more common in the CFD group than in the DSOM group (both $P = .000 < 0.05$). Both groups presented with poorly defined boundaries of the lesion and a normal bone (Table 3; Fig 1).

CT Images

Patients with DSOM and CFD both showed intermingled sclerosis and lysis in the medulla on CT scans ($P = 1.00 > 0.05$, $P = .534 > 0.05$). Cortical lysis was more common in patients with DSOM than in those with CFD ($P < .001$). The patients with DSOM showed subperiosteal bone formation and poorly demarcated cortex, which were not observed in patients with CFD. The DSOM and CFD groups showed no significant difference in condylar process deformation on CT scans ($P = .282 > 0.05$). Bone expansion was more common in the CFD group ($P < .001$). Tooth and mandibular canal displacement and poorly defined boundaries of the lesion with normal bone were consistent with the results of panoramic radiography (Table 3; Fig 2).

Discussion

This study aimed to investigate and compare the clinical and radiographic characteristics of DSOM and CFD in the mandible to exploring the key points for differential diagnosis. The findings emphasized the importance of clinical and radiographic features in differentiating between the 2 diseases. Among clinical characteristics, pain, soft tissue swelling or bone enlargement, and trismus are the key points for differentiation. With regard to the radiographic characteristics, the 2 diseases both showed intermingled sclerosis and lysis in the medulla, condylar process deformation, and poorly defined boundaries of the lesion and normal bone. However, they also showed some differences. Cortical lysis, subperiosteal bone formation, and a poorly demarcated cortex were more common in DSOM, while a continuous cortex, bone expansion, and tooth and mandibular canal displacement were more common in CFD.

The presence of pain is an important factor in the diagnosis of the 2 diseases. Pain is 1 of the main symptoms of DSOM, and it is characterized by recurrence every few weeks or months. In general, there are no symptoms of pain in CFD. Very few patients with CFD present with pain, which may be secondary to

Table 3. RADIOGRAPHIC FINDINGS FOR EVALUATED MANDIBULAR BONE STRUCTURES IN PATIENTS WITH DSOM AND CFD

	Panoramic Radiographs			CT		
Radiographic Findings	DSOM (n = 37)	CFD (n = 24)	*P*	DSOM (n = 36)	CFD (n = 31)	*P*
Cortical lysis	15 (40.5%)	2 (8.3%)	0.014	35 (97.2%)	2 (6.5%)	<0.001
Medullary sclerosis	35 (94.6%)	24 (100%)	0.515	36 (100%)	31 (100%)	1.000
Medullary lysis	30 (81.1%)	19 (79.2%)	0.854	34 (94.4%)	27 (87.1%)	0.534
Subperiosteal bone formation	14 (37.8%)	0 (0)	<0.001	24 (66.7%)	0 (0)	<0.001
Condylar process deformation	5 (13.5%)	13 (54.2%)	0.001	15 (41.6%)	17 (54.8%)	0.282
Bone expansion			<0.001*			<0.001*
Mild	4 (10.8%)	6 (25.0%)	0.009	7 (19.4%)	10 (32.3%)	<0.001
Moderate	0 (0)	5 (20.8%)	<0.001	0 (0)	8 (25.8%)	<0.001
Severe	1 (2.7%)	7 (29.2%)	<0.001	1 (2.8%)	11 (35.5%)	<0.001
Poorly demarcated cortex	32 (86.5%)	3 (12.5%)	<0.001	32 (88.9%)	0 (0)	<0.001
Tooth displacement	0 (0)	8 (33.3%)	<0.001	0 (0)	14 (45.2%)	<0.001
Mandibular canal displacement	1 (2.7%)	16 (66.7%)	<0.001	1 (2.8%)	21 (67.7%)	<0.001
Poorly defined lesion boundaries	36 (97.3%)	24 (100%)	1.000	36 (100%)	31 (100%)	1.000

Radiographic findings were scored as "present" or "absent." This table represents the number of patients (% of patients) with clinical radiographic findings. *P* represents the *P*-value of DSOM and CFD.

Abbreviations: CFD, craniofacial fibrous dysplasia; CT, computed tomography; DSOM, diffuse sclerosing osteomyelitis of the mandible.

* The Fisher-Freeman-Halton test was used to determine differences in 2 × 4 tables.

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nerve compression or local infection.[20,21] The swelling observed in DSOM is a combination of soft-tissue swelling and mild bone enlargement. Bone enlargement in DSOM is mainly caused by subperiosteal bone formation. However, the enlargement observed in patients with CFD is caused by bone expansion rather than soft-tissue swelling. Moreover, the swelling in DSOM is mostly recurrent, while the bone expansion in CFD is often progressive. Soft-tissue swelling in DSOM is caused by hypertrophic and edematous changes in masticatory muscles,[3] which may be one of the reasons for trismus. Trismus also may be caused by deformation of the condylar process in DSOM.[1] In the present study, we found that 35.1% presented with both trismus and condylar process deformation. However, 18.9% of the patients with DSOM presented with trismus without condylar process deformation, and 5.4% of the patients presented with condylar process deformation without trismus. These data suggest that condylar process deformation is not the main reason for trismus in DSOM.

In imaging examinations, medullary lysis presents as a small area of scattered lesions in the patients with DSOM, whereas it often appears as a large area of well-defined cyst-like lesions in patients with CFD. Medullary sclerosis resulted in a similar density to the cortex and an unclear boundary with the cortex in patients with DSOM. However, medullary sclerosis and expansion compressed the cortex, so the cortex was continuous, albeit thin, in patients with CFD. In addition, rapid expansion of the alveolar bone or mandible caused teeth displacement or displacement of the mandibular canal. The findings for condylar process deformation are different in panoramic radiographs and CT, and we think this is because small deformations are difficult to observe in panoramic radiographs, while CT shows more details.

DSOM is an autoinflammatory disease,[22] but CFD is a developmental and self-limiting disease. Fibrous dysplasia results from postzygotic activating mutations in GNAS.[23-25] Mutations occur at 1 of 2 positions: Arg201 (>95% of reported cases)[26] or Gln227 (<5%).[27] However, the etiology of DSOM remains unclear. Multiple theories have been proposed regarding the etiology of DSOM. There is debate whether DSOM has an infectious etiology or not. Some authors report that bacterial cultures of bone specimens produce positive results.[2,18,28] However, bacterial cultures of bone specimens cannot exclude specimen contamination, and the culture often produces negative results.[2,3,28,29] van Merkesteyn et al[3] proposed that chronic tendoperiostitis from muscle overuse may be the etiology of DSOM, which is reactive hyperplasia of bone from overuse of the masseter or the digastric muscle. However, Matharu et al[30] thought that with myofascial pain from parafunctional habits being a common condition, the rarity of DSOM does not

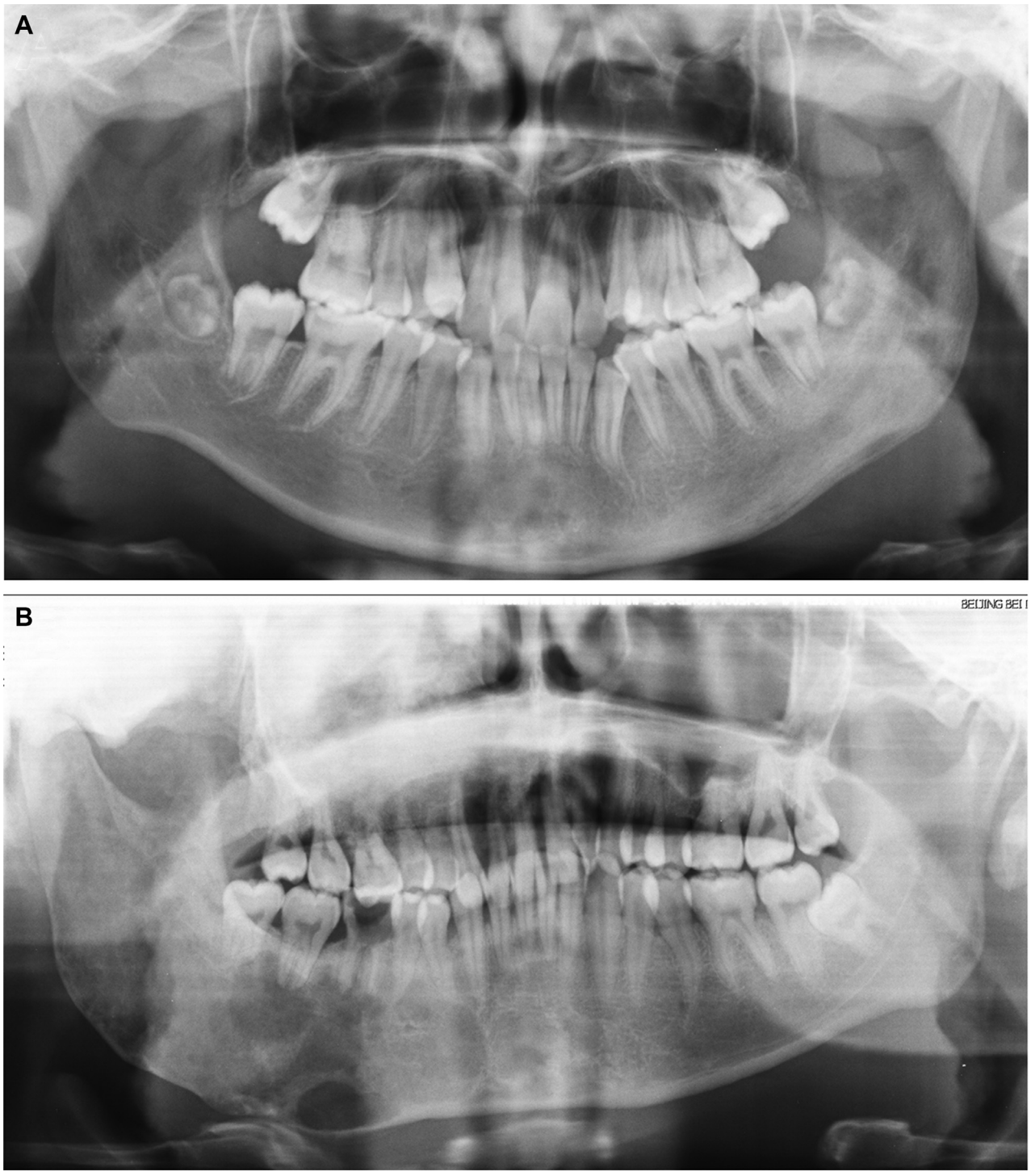

FIGURE 1. Representative panoramic radiographs of DSOM and CFD. *A,* Radiograph of a patient with DSOM involving the left side of the mandible, which shows subperiosteal bone formation and intermingled osteosclerotic and osteolytic patterns of the ramus, angle, and body. *B,* Radiograph of a patient with CFD involving the right side of the mandible, which shows asymmetry, bone swelling, and a cyst-like pattern. Abbreviations: CFD, craniofacial fibrous dysplasia; DSOM, diffuse sclerosing osteomyelitis of the mandible.

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appear to correlate with this. Recently, autoinflammatory disorder[22] with a genetic component also was considered to be an etiology of DSOM. Determining the etiology of DSOM is of great significance for the diagnosis and treatment, so we expect further progress in etiology research.

Identification of a somatic GNAS mutation has been used to improve the diagnostic accuracy of fibrous

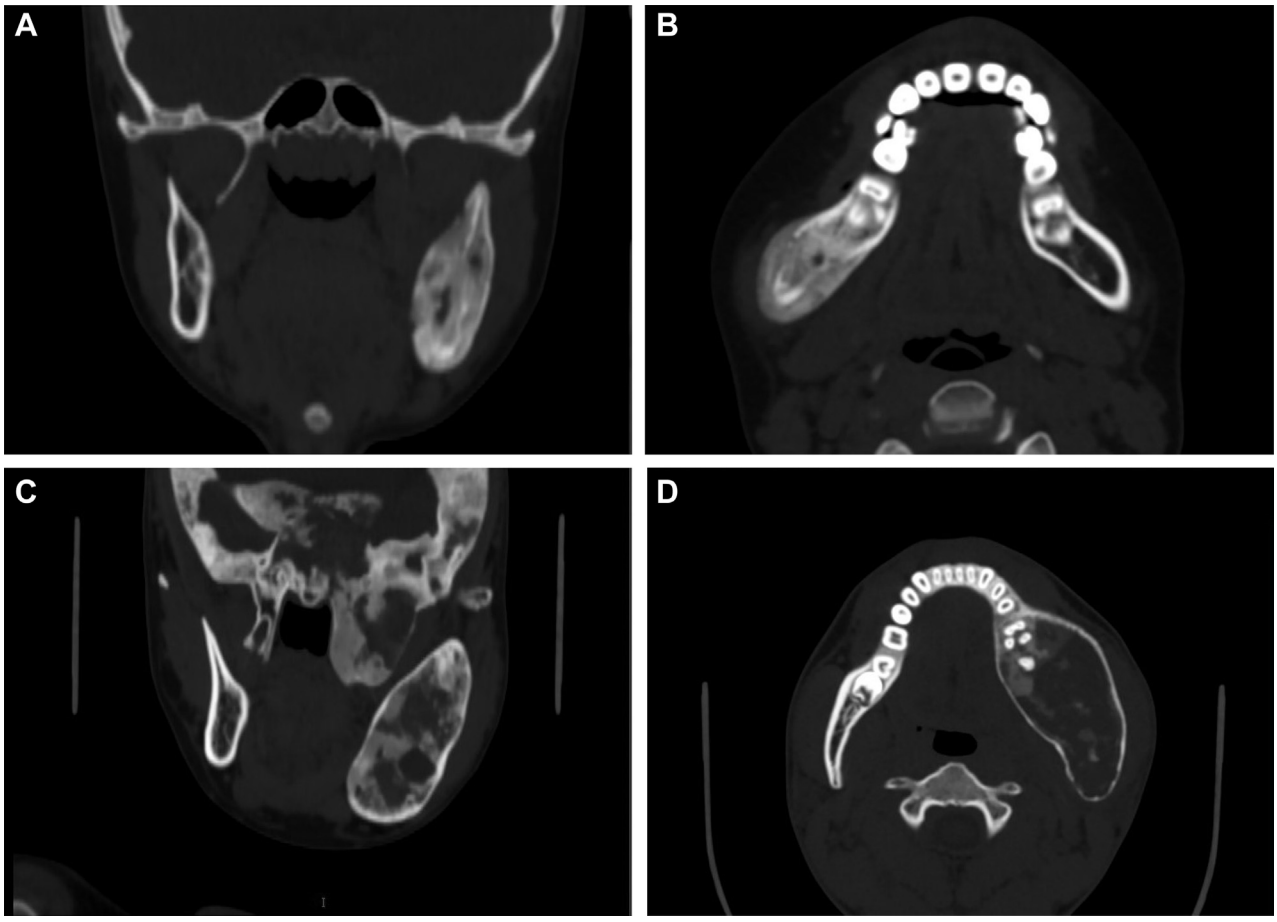

FIGURE 2. Representative computed tomography images of DSOM and CFD in the mandible. *A* and *B*, Radiograph of a patient with DSOM showing excessive subperiosteal bone formation, an intermingled osteosclerotic and osteolytic pattern, poor cortical continuity, and a poorly demarcated cortex. *C* and *D*, Radiograph of a patient with CFD showing a ground-glass change, a cyst-like pattern of the medulla, swelling, thin cortex, as well as a continuous and clearly demarcated cortex. Abbreviations: CFD, craniofacial fibrous dysplasia; DSOM, diffuse sclerosing osteomyelitis of the mandible.

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dysplasia.[20] Especially in individuals whose only clinical finding is monostotic fibrous dysplasia, identification of a somatic-activating GNAS pathogenic variant is required to confirm the diagnosis.[17,31] DSOM is agnogenic and poorly understood by clinicians owing to its rarity and the lack of clear diagnostic criteria. Moreover, it is often confused with suppurative osteomyelitis, fibroosseous lesions, and sarcomas of the mandible.[32] DSOM is most easily misdiagnosed as CFD or CFD with infection. CFD is easily diagnosed when the lesions occur in maxillofacial bone other than the mandible. Patients with CFD secondary to an infection may present with suppurative lesions, such as fistula, abscess, and cutaneous temperature elevation.[16] Moreover, their imaging findings may show the symptoms of suppurative osteomyelitis, such as sequestrum and pathological fracture.

The management of the 2 diseases is different. Surgery is the mainstay of treatment in CFD. In many cases, the dysplastic bone can be successfully contoured by conservative surgical measures to approximate facial symmetry and/or prophylactically decompress the optic nerve without attempting complete resection in the jaws after puberty.[31,33] However, there is no standard management for DSOM. Surgical treatments such as curettage and decortication have been used to treat DSOM, but the disease tends to recur after surgery.[34,35] Drug therapy with agents such as antibiotics, nonsteroidal anti-inflammatory drugs, glucocorticoids, and disease-modifying antirheumatic drugs have also been used to treat DSOM. Recently, bisphosphonates[36,37] and denosumab[38,39] showed good results in the treatment of DSOM. Successful clinical management begins with accurate diagnosis, so the differential diagnosis of the 2 diseases is of critical importance. Patients with DSOM who receive treatment with bisphosphonates tend to have longer pain-free periods and a lower maximum-pain level.[36] Bisphosphonates act by binding the mineral component of bone and interfere with the action of

osteoclasts,[40] so osteoclast activity may play an important part in the development of concomitant pain.[36]

The limitation of this study is that a retrospective study limits the kind of information that can be obtained, and the information in the charts may be inaccurate. Moreover, the number of monostotic CFD of the mandible is limited, so more samples are needed to improve the credibility of the study. Another limitation is that because of the lack of magnetic resonance imaging, it is impossible to perform an evaluation of the soft tissue in the mandible.

In conclusion, the findings of this study emphasize the importance of clinical and radiographic features in differentiating the diagnosis of the 2 diseases. The difference in the clinical characteristics between the 2 diseases is that DSOM presents with pain, swelling, and trismus, while CFD presents with bone enlargement. The difference in the radiographic characteristics is that DSOM presents with cortical lysis, subperiosteal bone formation, and poorly demarcated cortex, while CFD presents with moderate and severe bone expansion, well-demarcated cortex, and tooth and mandibular canal displacement. Further studies on the histopathological characteristics of the 2 diseases are expected in the future.

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