

Case Report

Surgical treatment of polyostotic craniomaxillofacial fibrous dysplasia in adult: a case report and review of the literature

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Abstract: The lesions of fibrous dysplasia usually stabilize after adolescence, and the surgical treatment of adult patient remains the mainstay. However, the surgical treatment alone may be not enough for patient with polyostotic fibrous dysplasia. We present the case of a surgically treated 36-year-old man with a diagnosis of progressive polyostotic fibrous dysplasia in the craniomaxillofacial region. The patients presented the swelling symptoms originally in the parietal bone at the age of 8 years, and extended gradually to almost all of the craniomaxillofacial bones during the following 28 years without specific treatment for socio-economic reasons. The symptom impelled the patient visit our department in 2009 was the rapidly progressive swelling in the chin during the last 3 years, which severely impacted his speech and feeding. The radiographs showed the typical intramedullary located and ill-defined lesions. The patient was treated with segmental mandibulectomy and reconstruction with vascularized fibular myocutaneous flap; the deformities in other craniomaxillofacial bones were not treated simultaneously. The local recurrence was not present in the chin. The visual acuity of right eye severely deteriorated and the left mandibular ramus continued expanding gradually when the patient was followed up through telephone 5 years later. A combination of surgical and medical treatment may be considered for patients with polyostotic craniomaxillofacial fibrous dysplasia.

Keywords: Fibrous dysplasia, craniomaxillofacial surgery, reconstructive surgery, bisphosphonates

Introduction

Fibrous dysplasia (FD) is a developmental dysplastic disorder of bone in which the normal bone matrix is replaced by fibroblastic proliferation. Although the first case may be described as far back as 1931 by Telford, the term of fibrous dysplasia of bone was first used by Lichtenstein in 1938 [1]. The proximal part of the femur and craniomaxillofacial bones are the two most commonly affected sites.

Craniofacial FD typically presents at around 10 years of age and then progresses throughout adolescence. Dysplastic bone lesions seem to stabilize after puberty, but their disabling consequences (pain, fractures, etc.) may continue into adulthood [2]. It was seen more frequently in females, the ratio arising in females was

reported to be 1.5 to 3.0 times higher than in males [1, 3]. FD of bone accounts for 7% of benign bone tumors [4] and 10% of them in oral area [3].

FD is a genetic, non-inheritable disease, caused by mis-sense mutations in the gene coding for the α -subunit of the stimulatory G-protein in the guanine nucleotide binding, alpha stimulating (GNAS) complex locus in chromosome 20q13.2-13.3 during embryogenesis [5]. The mutation was first identified in patients with McCune-Albright syndrome (MAS) but was later demonstrated in the lesions of patients suffering from either monostotic or polyostotic FD. The protein product of the GNAS gene has a pleiotropic effect depending on its time and location of action. The earlier the mutation, the more widespread the organ involvement, with the severity

of the disease being proportional to the number of mutated cells. Thus, FD is an embryonic stem cell and osteoblastic lineage disease, leading to various clinical manifestations related to the individual's organ involvement. MAS is characterized by the clinical triad of polyostotic fibrous dysplasia, café-au-lait pigmented skin lesions and precocious puberty. Jaffe-Lichtenstein type present as polyostotic FD with café-au-lait spots but without precocious puberty. When the mutation involves only one or multiple bones, it results in monostotic form or polyostotic form of FD. FD presents usually in the monostotic form, but rarely in the polyostotic form or MAS.

Diagnosis of FD is based generally on the clinical ground and typical radiographic findings. Bone biopsy is typically reserved for cases suspicious of malignant change. Diagnosis is usually easy in polyostotic FD and MAS because of the gross distribution of typical bone lesions, while may be difficult in monostotic forms. One must consider clinical, radiographic or histological factors together to diagnose correctly. The typical plain radiological appearance is that of radiolucent lytic lesions with a homogeneous ground-glass appearance and ill defined borders [6]. The most important roles of computed tomography (CT) are to give information on the size of the bone lesion and on cortical erosions that may not be visible on plain radiographs [6]. Bone biopsy is necessary whenever there is a sizeable doubt on the diagnosis with imaging. The histological hallmark of the disease is the extensive proliferation of fibrous tissue within the bone marrow, involving immature spindle fibroblast-like cells, and expanding from the medullary cavity to the cortical bone. These fusiform fibroblast-like cells, corresponding to poorly differentiated osteoblasts, arranged in parallel arrays or in whirls, are embedded in poorly mineralized collagen fibrils [7].

Since it was described in the 1930s, the only therapeutic possibility was surgical management until the 1990s [8]. Important insights into the pathophysiology of the disease have been gained over the last two decades, with description of the mutated gene and the main abnormal biological pathways. Also, medical therapy with bisphosphonates has been developed.

The prognosis generally is good, although poor outcomes are more frequent in younger patients and in those with polyostotic forms of the disease [4]. The risk of malignant transformation is a rare but established complication. It should be considered when recurrent or stable fibrous dysplasia produces pain or soft tissue extension or neurologic deficits. The most common malignant transformation reveals osteosarcoma, followed by fibrosarcoma and chondrosarcoma, giant cell sarcoma [9].

This report demonstrates radical surgical treatment to an adult patient with severe polyostotic craniomaxillofacial FD characterized with rapidly progressive swelling in the chin, and the outcome of the follow-up 5 years later.

Case presentation

In March 2009, a 36-year-old man with craniofacial asymmetry for 28 years was referred to the Department of Oral and Maxillofacial-Head and Neck Surgery (Capital Medical University, Beijing Stomatological Hospital), who complained a rapidly progressive swelling in the chin for 3 years. The patient presented a swelling in hair-bearing cranium at the age of 8 years, which was diagnosed as FD of parietal bones 2 years later at a local hospital. Owing to socio-economic reasons, no specific treatment was performed on this patient. The swelling gradually extended to the other craniomaxillofacial bones since then. The progressive swelling appeared slow down during the patient's 3rd decade, however, the bilateral hearing and the visual acuity have been gradually decreasing since the age of 32 years. The patient presented a rapidly progressive swelling in the chin 3 years before the visiting, the swelling tissue protruded from inside of the lower lip and the overlying mucosa bled several times during the last 2 years. The voice of the patient was hoarse and diagnosed as paralysis of right vocal cord at a local hospital. It was the increasing weight of the tumor in the chin made the patient decided to seek medical treatment, which impacted speech and feeding severely.

Physical examination showed the extensive and severe deformity of the craniomaxillofacial bones (**Figure 1**), which involved bilateral parietal bones and temporal bones, the mandible, the frontal and occipital bone, and the right

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Figure 1. The craniomaxillofacial appearance of the patient. A. The left view of the patient. B. The front view of the patient. The right eye was higher than the left horizontally, and the right zygoma and maxilla was disfigured. C. The right view of the patient.



Figure 2. The superior view of the disfigured chin.

zygoma and maxilla. The tumor in the mental region was 15 cm × 15 cm × 14 cm in size, protruded from inside of the lower lip (**Figure 2**). On palpation, the swelling was non-tender, hard, with no local rise of temperature. The lower lip was prolonged and the skin overlying mental region expanded. There was numbness in the right lower lip. The mandibular incisors and canines were loose and displaced, while the other teeth was healthy and functioned normally. The right eye was higher than the left horizontally. The right pupil size was smaller in diameter than that of the left, the right pupillary light reflex delayed. The detailed visual acuity was not tested. There was no “café-au-lait

spots” with irregular borders over the skin of the body.

CT and X-ray showed the extensive changes in craniomaxillofacial bones (**Figures 3 and 4**), and clavicle was also involved (**Figure 5**). The involved lesions presented with ground glass like changes with ill-defined borders. The affected bones expanded irregularly, and appeared sclerotic, lytic or mixed on radiographic examination. The lesion in the chin showed cystic changes in X-ray and CT (**Figures 3 and 4**). There was no periosteal reaction or soft tissue involvement. Both side of the mandibular ramus became thicker, expanded and deformity. The cortex of the mental region of the mandible was eroded (**Figure 3**). The diagnosis of polyostotic fibrous dysplasia was established.

Given the chief complaint of the patient was the progressively swelling in the chin which impact speech and feeding severely, and the rapid progressive swelling may suggest malignant transformation, the primary treatment plan was radical resection of the lesion in the chin and reconstruction with vascularized fibular myocutaneous flap, and mandibular contouring if possible. The bilateral fibular bones were X-rayed before the operation to exclude the possibility of involvement of FD (**Figure 6**). The bilateral facial arteries were ligated to reduce the blood lost as far as possible. The designed bilateral residual mandibular ends were fixation with a reconstruction titanium plate to keep the original dental occlusion. Then, the segmental mandibulectomy between the bilateral bicuspid regions where the lesion involved was per-

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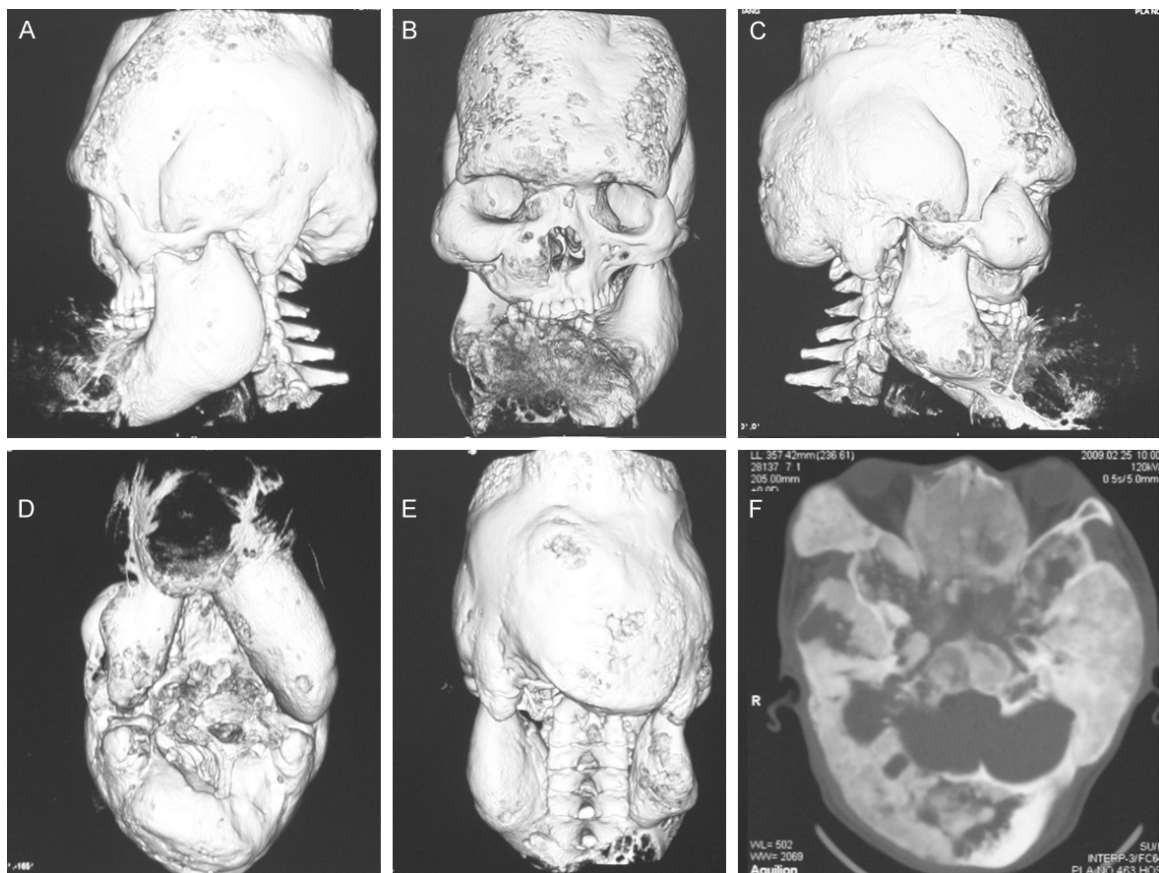


Figure 3. The CT scan of the craniomaxillofacial region. A. The left view of the craniomaxillofacial bones showed the disfigured parietal, occipital, temporal, mandibular bones. B. The front view of the craniomaxillofacial bones showed the disfigured right zygoma, maxilla and the orbital cavity. C. The right view. D. The inferior view of the skull base and the mandible showed the erosion of the cortex of the mental region. E. The posterior view showed the disfigured occipital bone and bilateral mandibular ramus. F. The horizontal view showed the involvement of ethmoid, sphenoid, temporal bones and the right zygoma.

formed. Lesions of the other part of mandible had been planned to contoured, while the diffuse blood oozing made this impossible. The left facial artery, the common facial vein and the external jugular vein were prepared as the recipient vessels, and anastomosed with the fibular artery and the two accompanied veins, respectively. The fibular bone was remodeled and fixed with reconstruction titanium plate in the defect of the chin; the accompanied skin flap supplied by the perforating vessels was inserted in mucosal defect as a “monitor” for the viability of fibular bone. The total blood lost reached up to 2000 mL and the blood transfusion was performed. The “tumor” in the chin weighed 4.5 Kg (**Figure 7**) and was examined histopathologically. The diagnosis of FD was confirmed and no evidence of malignant transformation was found (**Figure 8**).

The patient was satisfied with the postoperative facial appearance and the recovery of the easiness of speech and feeding (**Figure 9**). Owing to socio-economic reasons, the patient never revisited our department again. In October 2014, the patient was followed up through telephone, and the picture of the patient were taken and emailed back. The lesion in the chin has not been recurrent since the operation. The hearing impairment seemed stabilized. However, the left mandibular ramus continued expanded gradually (**Figure 10**), and the visual acuity of right eye deteriorated significantly.

Discussion

Several breakthroughs in the understanding of the pathophysiology have been made in the past two decades. The mutation of GNAS gene

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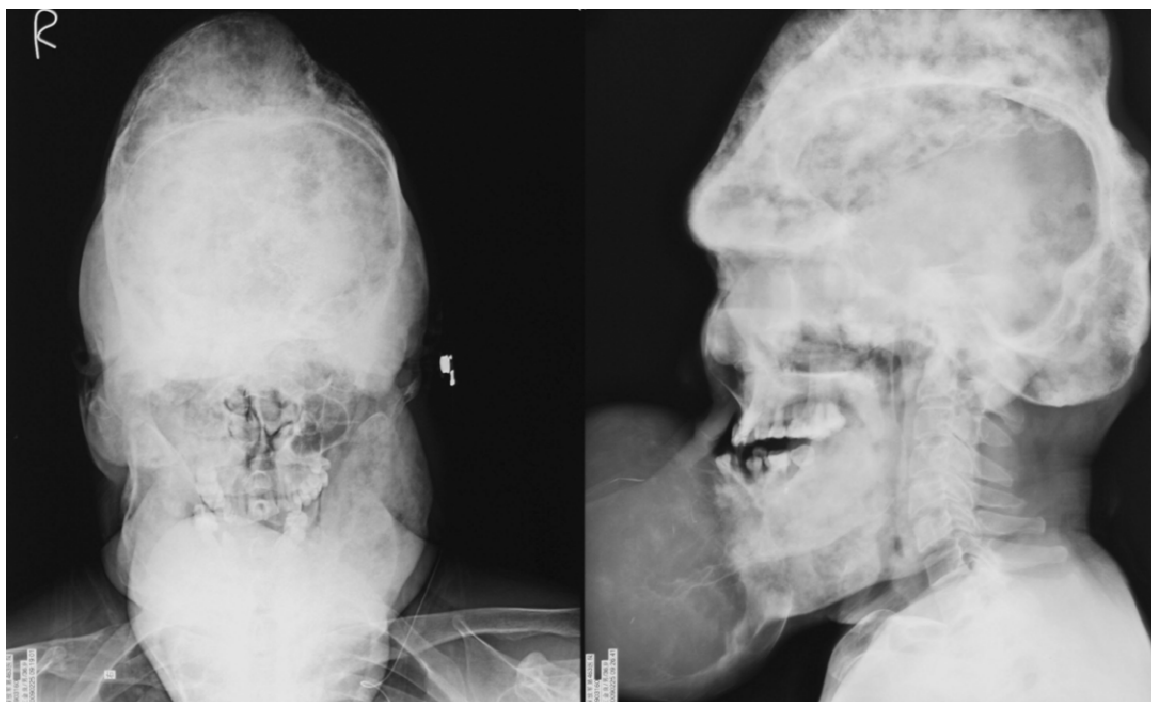


Figure 4. The posteroanterior and lateral radiographs of the craniomaxillofacial region. The lateral radiograph showed the cystic appearance of the lesion in the chin.

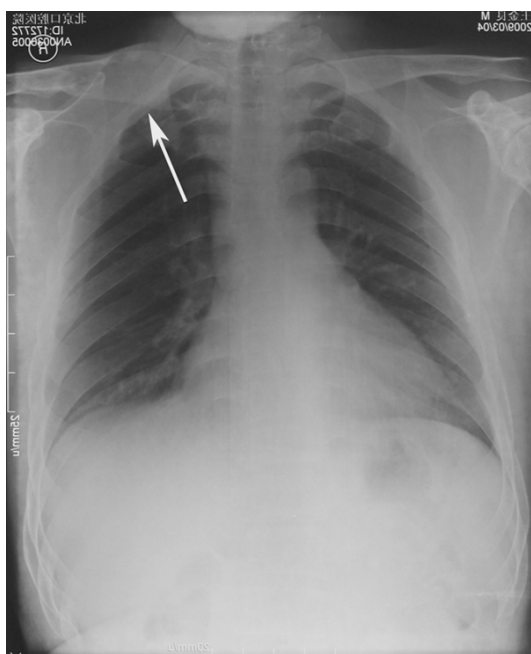


Figure 5. The posteroanterior chest radiograph. The right clavicle was involved with FD.



Figure 6. The posteroanterior radiograph of the legs. Both tibia and fibula were not involved with FD.

reduces GTPase activity, with increased adenylyl cyclase activation as a consequence [2]. Therefore, the mutated cells constitutively gen-

erate high levels of cAMP and have a high rate of proliferation. It has been suggested that increased cAMP may downregulate the osteo-

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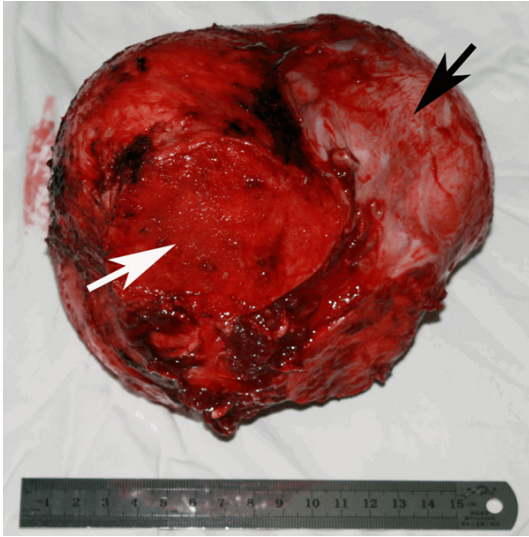


Figure 7. The specimen of the lesion in the mental region. White arrow showed the section of the mandibular body, and black arrow showed the mucosa inside the lower lip.

blastic transcription factor Runx2, thus contributing to abnormal osteoblastic differentiation [10]. In these osteoblastic cells, the secretion of interleukin-6 is increased as a result of Gs activation, with consequent activation of surrounding osteoclasts, allowing the FD lesion to expand and create osteolytic lesions [11]. Minor factors have also been considered, such as raised platelet-derived growth factor- β contributing to osteoclastic activation, and elevation of sex steroid receptors in mutated cells explaining impaired symptoms during pregnancy or oral contraceptive use [12, 13].

The clinical presentation of craniofacial FD depends on the site, duration, extent and nature of the lesion. In the craniofacial region, the ethmoid bones were most commonly involved (71%), followed by the sphenoid (43%), frontal (33%), maxilla (29%), temporal (24%), parietal (14%), and occipital (5%) bones [14]. The clinical manifestations range from disfigurement, proptosis, to atypical facial pain and numbness, headache, diplopia, and hearing loss. Blindness may present as a sudden complication of lesions involving the skull base. Some complications, such as nerve compression and malignant transformation, are uncommon. Many patients can, however, be asymptomatic [15]. In this case, the patient presented as severe disfigurement, lip numbness, hearing and visual acuity decrease, while complained

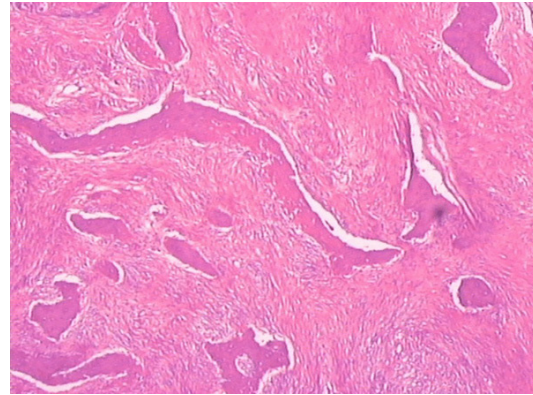


Figure 8. Low-power histopathological view of the fibrous dysplasia in mental region. Fibro-osseous lesion with curvilinear branching appearance of bony trabeculae surrounded with spindle fibroblast-like cells, arranged in whorls. Haematoxylin-eosin staining, original magnification $\times 10$.

no pain. The rapid swelling in the mental region suggested malignant transformation, but was not validated by the histopathological examination.

FD has characteristic appearances on CT and consists of three varieties: ground-glass pattern (56%), homogeneously dense pattern (23%) and cystic variety (21%) [7]. In this case, all the three varieties of CT appearances presented. The rapid enlargement of mental region presented a cystic appearance in CT, while the extensive craniomaxillofacial bones showed ground glass changes and homogeneously dense pattern (ethmoid bones).

The treatment aim of craniofacial FD is to relieve cosmetic or functional problems, and it can range from observation, medical treatment with bisphosphonates, to extensive surgery. Regular follow-up is required for early detection of disease progression or malignant transformation.

Surgery is indicated for confirmatory biopsy, correction of deformity, prevention of pathologic fracture, and/or eradication of symptomatic lesions [16]. Because of the benign nature of the condition, the surgery itself should be relatively conservative, with the primary goal being preservation of existing function [14]. The choice of surgical option depends on several factors: site of involvement, rate of growth, aesthetic disturbance, functional disruption, patient's preference, general health of the patient,

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Figure 9. The facial appearance of patient 10 days after operation.



Figure 10. The facial appearance of the patient 5 years after operation.

surgeon's experience and the availability of a multi-disciplinary team [6]. The craniofacial skeleton can be classified into 4 major zones in the surgical treatment of FD [17]. Zone 1 includes the fronto-orbital, zygomatic and upper maxillary regions; zone 2 represents the hair-bearing cranium; zone 3 is the central cranial base; and zone 4 includes the teeth-bearing regions of the maxillary alveolus and mandible. For lesions in zone 1, radical resection of the dysplastic bone was recommended, while for lesions in other zones, conservative excision or shaving were proposed [6]. The effect of further growth on the reconstructions and the deformities change and recur must be considered. There were controversies in the bone grafting and the use of common internal fixation devices (plates and screws), some argued they were almost always doomed to early failure [18], some thought reconstruction after excision was important in the management of craniofacial FD, and recommended grafts of calvarial bone and rib [6], some suggested the use of cortical grafts rather than cancellous grafts or bone-graft substitutes because of the superior physical qualities of remodeled cortical bone [5]. In this present case, the patient underwent reconstructive operation with vascularized fibular myocutaneous flap and rigid internal fixation, and acquired satisfactory outcome in the control of local recurrence and the mandibular function rehabilitation. The patient also presented radiographic optic nerve com-

pression, which suggested potential risk for visual deterioration. However, most patients with such signs were asymptomatic and would remain that way. Expectant management, repeated ophthalmologic exams, and long-term radiologic follow-up were indicated in asymptomatic FD patients who have optic nerve encasement [19]. Unfortunately, this patient could not afford to such follow-up owing to socio-economic reasons and the visual acuity of right eye deteriorated significantly 5 years later.

FD usually stop progressing after adolescence, the patient in this case was 36 years old when visited our department in 2009 and the disfiguration seemed to be stabilized. However, the rapid swelling in the chin within 3 years suggested the lesions may be progressive locally, and the deterioration of the visual acuity of the right eye also indicated the progressiveness of lesions in related bones. Medical treatment may have been suitable accompanied with surgical resection of the tumor in the chin. In the past 10 years, the bisphosphonate has been used for FD with good results [7]. The gene mutation stimulates release of several cytokines (mainly interleukin-6) which cause normal osteoclasts to congregate and increase bone resorption [20]. This is the rationale for treating these patients with bisphosphonate [15]. It has been used for the treatment of

patients with osteolytic bone metastases and tumor induced hypercalcaemia [21, 22]. Bisphosphonate therapy may help to improve function, decrease pain, and lower fracture risk in appropriately selected patients with fibrous dysplasia, but they are still under clinical evaluation. Patients with polyostotic fibrous dysplasia often have renal phosphate wasting. Calcium, vitamin D and phosphorus supplements may be useful in some patients [7].

There were several parameters to assess or predict the outcome of medical treatment. Subjective criteria have been suggested, such as rapid pain relief and cosmetic improvement [23]. Serum alkaline phosphatase (ALP) as a marker for bone turnover was also a good monitor of response to medical treatment [24], although there was controversy on the reliability of preoperative serum ALP as a prognostic marker of craniomaxillofacial FD [25]. The use of urinary hydroxyproline as a marker has also been suggested, which along with ALP indicated bone metabolic activity [16, 26]. Serial radiographs and local bone mineral density were both important to assess the outcome of medical treatment.

We demonstrated the radical resection of an abnormal rapidly progressive craniomaxillofacial FD lesion in the mental region of a patient with polyostotic FD and the follow-up findings 5 years later. In our case there was no malignant transformation, as well as no recurrence of the FD in the mental region after 5 years. However, the lesion was still progressive locally and the visual acuity of right eye deteriorated significantly.

Conclusions

FD is often found in childhood and usually stabilizes in adulthood, but can still be progressive locally after puberty in rare case. The diagnosis is based on the results of radiographic investigations, and histopathological evaluation. Surgical treatment of fibrous tissue is indicated in the symptomatic cases, and reconstruction with vascularized fibular flap can be considered in cases underwent radical resection. Given the potential progressiveness of polyostotic FD, rigorous follow-ups is still recommended in adult patients. A combination of surgical and medical treatment with bisphosphonate for polyostotic craniomaxillofacial FD may be considered.

Disclosure of conflict of interest

None.

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