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CASE REPORT

Successive generations with inherited craniofacial fibrous dysplasia

Pornkawee Charoenlarp · Wichitsak Cholitgul · Phonkit Sinpitaksakul · Kittipong Dhanuthai · Somchai Sessirisombat

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Abstract Craniofacial fibrous dysplasia is a benign fibro-osseous lesion of bone that only affects the bones of the craniofacial complex. Here, we report a case of craniofacial fibrous dysplasia in a 16-year-old Thai male who presented with mild swelling and tenderness at the mandibular right first molar area and ipsilateral nasal congestion. Conventional and cone-beam CT radiographic examinations were performed. The radiographs revealed multiple mixed radiolucent and radiopaque lesions involving most of the craniofacial bones. The first biopsy from the right mandibular area was diagnosed as juvenile ossifying fibroma, whereas a biopsy from the right maxillary area was diagnosed as fibrous dysplasia. The defects appeared to have a genetic basis, because his mother and younger brother had the same clinical and radiological findings. Furthermore, the family history given by his mother revealed that several other members of her family had similar clinical signs and symptoms. We diagnosed this case as inherited craniofacial fibrous dysplasia on the basis of previously reported clinical, radiographic and histologic findings as well as family history.

Keywords Monostotic fibrous dysplasia · Polyostotic fibrous dysplasia · Craniofacial fibrous dysplasia · $G_s\alpha$ gene

P. Charoenlarp (✉) · W. Cholitgul · P. Sinpitaksakul
Department of Radiology, Faculty of Dentistry, Chulalongkorn University, Henry Dunant Road, Pathumwan District, Bangkok 10330, Thailand
e-mail: kiwi_dent@hotmail.com

K. Dhanuthai
Department of Oral Pathology, Faculty of Dentistry, Chulalongkorn University, Henry Dunant Road, Pathumwan District, Bangkok 10330, Thailand

S. Sessirisombat
Department of Oral and Maxillofacial Surgery, Faculty of Dentistry, Chulalongkorn University, Henry Dunant Road, Pathumwan District, Bangkok 10330, Thailand

Introduction

Fibrous dysplasia is a congenital nonhereditary pathologic condition of bone characterized by replacement of normal bone with fibrous connective tissue, followed by the development of multiple mineralized masses in this tissue. Most previous reports have indicated that the etiology of fibrous dysplasia is linked to a mutation in the $G_s\alpha$ gene located at chromosome 20q13.2-13.3 [1, 2]. The extent of fibrous dysplasia is believed to be related to the point during embryonic or postnatal development when the postzygotic mutation in $G_s\alpha$ occurs [3, 4]. The severity and extent of $G_s\alpha$ mutation-associated diseases are also related to the degree of proliferation of the mutated cells within the clone during migration, growth, and differentiation as well as the ratio of mutated to normal cells at the affected anatomical sites [3, 5].

Fibrous dysplasia may affect single (monostotic) or multiple (polyostotic) bones. The monostotic form is more common, occurring in 75–80% of fibrous dysplasia cases [6]. The polyostotic form is divided into three types: (1) craniofacial fibrous dysplasia, in which only the bones of the craniofacial complex, including the mandible and maxilla, are affected; (2) Lichtenstein–Jaffe type, in which multiple bones of the skeleton are involved, with instances of café-au-lait pigmentation of the skin and rare endocrinopathies; and (3) Albright's syndrome, characterized by a triad of severe polyostotic fibrous dysplasia (mostly

unilateral), café-au-lait pigmentation of the skin, and various endocrinopathies, most notably precocious puberty in girls [7]. The monostotic form generally exhibits an equal gender distribution and affects the 20- to 30-year age group. The polyostotic form occurs more commonly in females and mainly has its onset in children under 10 years of age.

In most craniofacial fibrous dysplasia cases, the lesions grow slowly and cause expansion of the jaw, resulting in facial asymmetry. The lesions usually stabilize after puberty, although postpubertal enlargement has been reported in some cases [8]. Craniofacial involvement occurs more frequently in polyostotic cases than in monostotic cases [9, 10]. Any cranial or facial bones can be affected by fibrous dysplasia, and the clinical features depend on the specific bones affected. The signs and symptoms include facial pain, headache, cranial asymmetry, facial deformity, tooth displacement, and visual or auditory impairment [9, 11]. The base of the skull, especially the sphenoid bone, is the most common site of involvement in craniofacial fibrous dysplasia [12].

Leontiasis ossea is a rare form of craniofacial involvement that exhibits extensive bilateral maxillary enlargement, leading to encroachment on the orbital cavities, mouth, and paranasal sinuses and producing a wide facial appearance similar to a lion's face [13].

The radiographic features of fibrous dysplasia are diverse and depend on the proportion of mineralized bone to fibrous tissue in the lesion [14]. Early fibrous dysplasia lesions of the craniofacial bones appear radiolucent and can have either an ill-defined border or a well-defined border. As the lesions mature, the bony defects acquire a mixed radiolucent and radiopaque appearance, and established fibrous dysplasia exhibits a mottled radiopaque pattern often described as resembling ground glass, orange peel, or fingerprints, with ill-defined borders blending into the normal adjacent bones [10, 15, 16].

Microscopically, fibrous dysplasia consists of irregularly shaped trabeculae of immature bone in a loosely arranged fibrous stroma. The bony trabeculae are not connected to one another and have been likened to Chinese script writing in appearance. The trabeculae are not lined by plump osteoblasts. The affected bone blends into the normal bone at the periphery of the lesion. Jaw and skull lesions tend to be more ossified than their counterparts in the rest of the skeleton [15].

Fibrous dysplasia usually occurs with no family history, although craniofacial fibrous dysplasia has been shown to be inherited in an autosomal dominant fashion [17, 18]. This form does not result from mutations in the $G_s\alpha$ gene [19]. Some previous reports showed that fibrous dysplasia was associated with familial occurrence [17, 18, 20]. The purposes of this article are to report a rare case of a young Thai male with inherited craniofacial fibrous dysplasia, which was described as being present in five consecutive generations, and to emphasize that comprehensive patient information, especially the radiographic features and family background, are very important in reaching an accurate diagnosis.

Case report

A 16-year-old Thai male patient attended the Faculty of Dentistry, Chulalongkorn University, Bangkok, presenting with mild swelling and tenderness at the right lower first molar area. There was no history of trauma, loosening of teeth, paresthesia of the lower lip or trismus. The mandibular swelling was first noticed by the patient's mother at 1 month before he saw a dentist. An intraoral examination revealed a slight buccal expansion extending from the right mandibular first premolar to the first molar. This expansion was hard, smooth and slightly tender to palpation. The overlying mucosa and teeth in this area appeared normal. An associated symptom of this patient was ipsilateral nasal congestion.

A subsequent clinical examination revealed that the area of the right maxillary first premolar to the first molar also exhibited a slightly bony expansion, similar to the mandible. Several other similar bony hard swellings varying in size were found in various areas of the skull, especially in the forehead area. Neither swelling in other parts of the body nor café-au-lait skin pigmentation was observed. Conventional radiographs revealed a unilocular relative radiolucency (hazy appearance) with a well-defined and corticated border of approximately 2.5 cm in diameter, extending from the distal aspect of the right lower first premolar to the distal aspect of the right lower first molar. A relatively dome-shaped radiopaque lesion was located between the right upper first molar to the right upper third molar, and extended to the maxillary sinus (Fig. 1a). Slight buccal expansion could be seen in these areas. The lateral (Fig. 1b) and posteroanterior (Fig. 1c) skull radiographs showed numerous mixed radiolucent and radiopaque lesions scattered throughout the skull. Chest and radius–ulna radiographs revealed normal radiographic appearances.

Cone-beam CT (CBCT) images showed multiple mixed radiolucent and radiopaque lesions, involving craniofacial structures such as the cranial vault, zygoma, all paranasal sinuses, sella turcica, maxilla, and mandible (Fig. 2). Microscopic examination of a bone biopsy from the mandibular area revealed several trabeculae of immature bone, some of which were rimmed by osteoblasts, in a loose and vascularized stroma (Fig. 3a). Focal aggregates of multinucleated giant cells and areas of hemorrhage were also seen (Fig. 3b). Based on the microscopic examination of

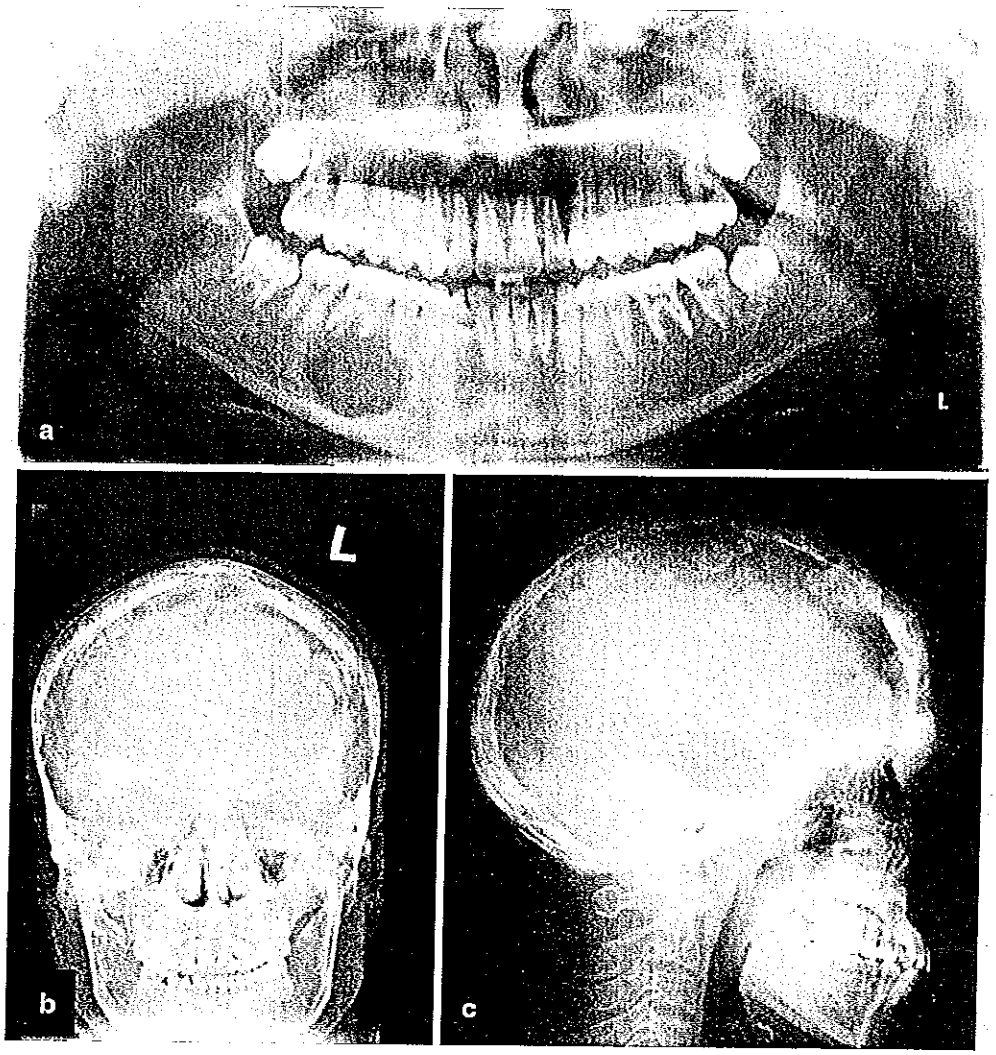

Fig. 1 a Panoramic, b lateral skull, and c posteroanterior skull radiographs of the patient. Note the numerous radiopaque lesions scattered throughout the calvaria

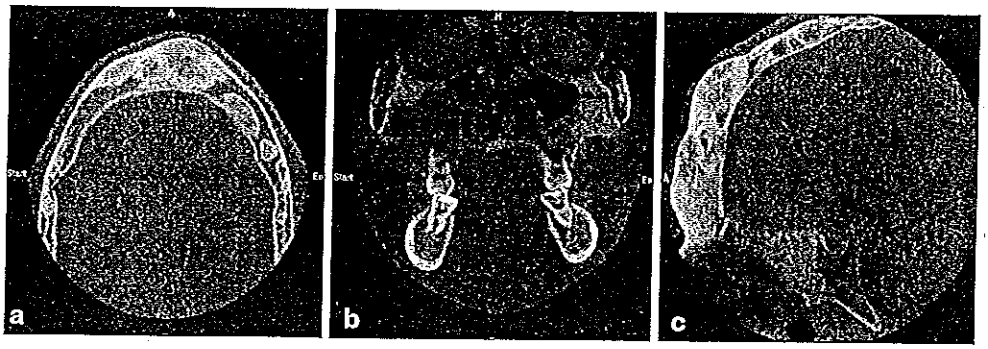

Fig. 2 a Axial, b coronal, and c sagittal CBCT images showing numerous radiopaque lesions that involve craniofacial structures such as the cranial vault, maxillary bone, zygoma, paranasal sinuses, sella turcica, and jaws

this area, the diagnosis for this patient was suggestive of juvenile ossifying fibroma.

At 1 month after the mandibular lesion was diagnosed, the patient underwent excision of the lesion located in the right maxillary area. The microscopic findings revealed irregular trabeculae of immature bone without osteoblastic rimming in the fibrous connective tissue (Fig. 4). The diagnosis was suggestive of fibrous dysplasia.

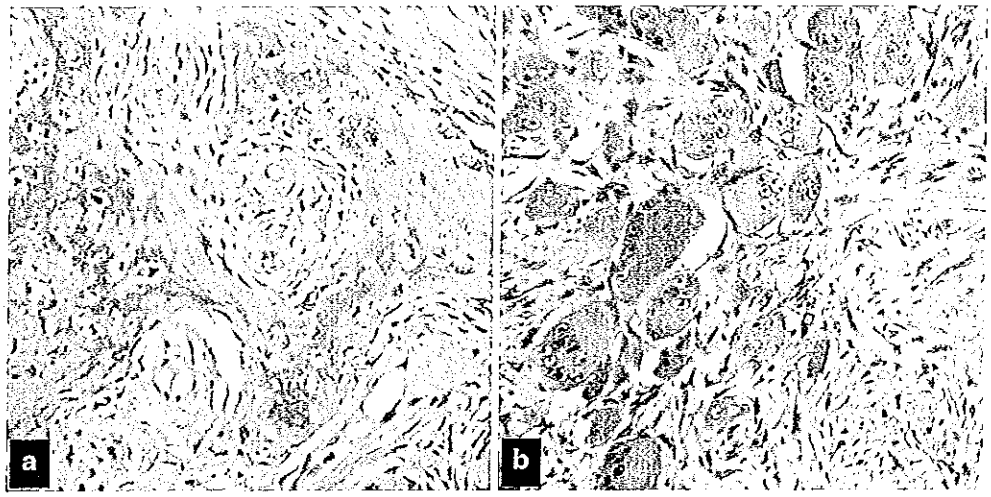

Fig. 3 Microscopic examination of a biopsy from the mandibular area. a Irregular trabeculae of woven bone and b aggregation of multinucleated giant cells in the fibrous connective tissue are seen (H&E, ×100)

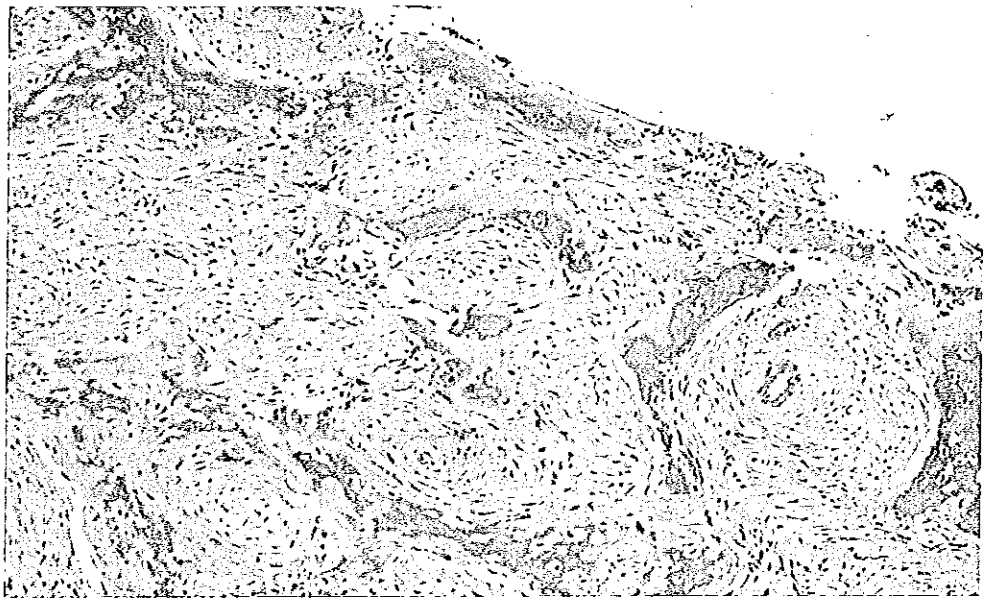

Fig. 4 Microscopic examination of a biopsy from the maxillary area. Irregular trabeculae of immature bone without osteoblastic rimming are present in the fibrous connective tissue (H&E, ×100)

Regarding the patient's family history, similar clinical and radiological findings were encountered for relatives from his mother's side (Figs. 5, 6). The establishment of a family tree revealed that successive generations of the family were affected (Fig. 7), indicating that the condition was genetically inherited.

Based on the above information and a review of the literature for this disease, the final diagnosis of the lesion was inherited craniofacial fibrous dysplasia.

Discussion

Fibrous dysplasia is one of the fibro-osseous lesion types that can affect the craniofacial bones. In most reports on fibrous dysplasia, no evidence of a familial basis has been identified. Craniofacial involvement occurs more commonly in polyostotic cases than in monostotic cases [21, 22]. Oral and maxillofacial radiographs play an important role in the diagnosis of these defects. CBCT is the method of choice for evaluating suspected bony lesions in the craniofacial area, because it provides better characterization and localization of the lesion [23, 24]. In the present case, CBCT provided valuable information regarding lesions at several anatomical locations in the craniofacial complex.

Craniofacial fibrous dysplasia is a polyostotic type of fibrous dysplasia, in which only the bones of the craniofacial complex are affected with no other abnormalities. This type has been reported to be associated with familial occurrence [17, 18, 20]. To date, it has remained controversial whether craniofacial fibrous dysplasia is a disease associated with familial occurrence and develops from an unknown gene mutation.

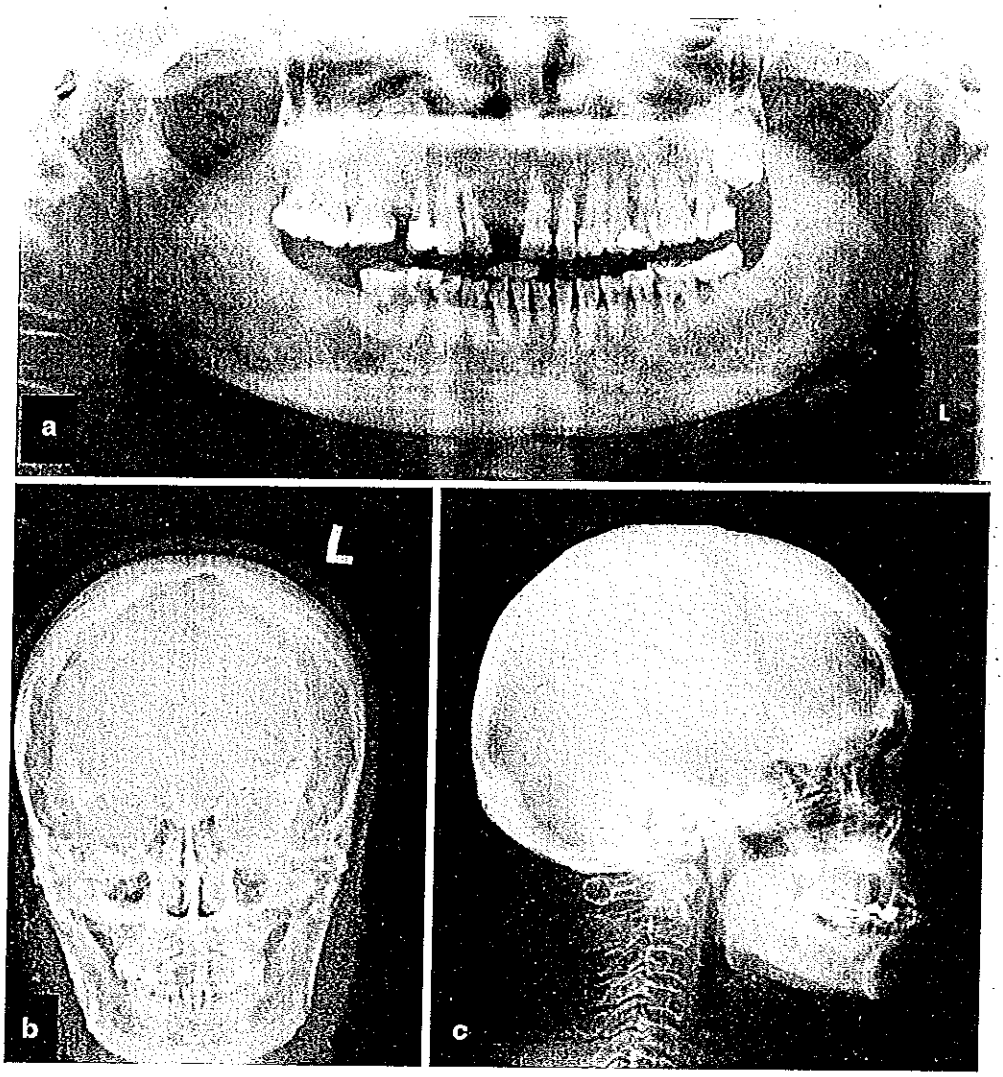

Fig. 5 **a** Panoramic, **b** lateral skull, and **c** posteroanterior skull radiographs of the patient's mother. The involved bones show sclerosis and mixed radiolucent and radiopaque patterns

In the present case, the clinical appearance and symptoms were mild bony expansion and nasal congestion resulting from the presence of the lesion on the affected side. Several bony hard swellings were detected on the craniofacial complex with no other symptoms. There was no evidence of premature puberty, swelling, or café-au-lait spots in other parts of the body. The radiographic findings regarding the craniofacial complex were related to the clinical appearance, whereas the chest and radius–ulnar radiographs revealed normal radiographic features. Therefore, only the bones of the craniofacial complex were affected. The biopsy specimen from the right mandible was diagnosed as suggestive of juvenile ossifying fibroma. However, the diagnosis for the lesion located in the maxilla was suggestive of fibrous dysplasia. The different diagnoses for the two lesions could be explained by the fact that the pathologist initially only received information on the lesion in the right mandibular area which exhibited clinical symptoms, and radiographic and histological findings were compatible with juvenile ossifying fibroma.

If the lesion had been juvenile ossifying fibroma, it would have shown more aggressive behavior and better demarcation from the surrounding bone. In addition, the patient would have had more symptoms and obvious bony expansions in other craniofacial bones.

Florid cemento-osseous dysplasia (FCOD) was another fibro-osseous lesion included in the differential diagnosis, but was excluded because it appeared as multifocal lesions in the tooth-bearing or edentulous areas of the jaws. The epidemiology of FCOD was also exclusionary, because it more commonly occurs in middle-aged females [25].

With the above information in hand, the present case was diagnosed as craniofacial fibrous dysplasia. After thorough history-taking, several relatives with similar

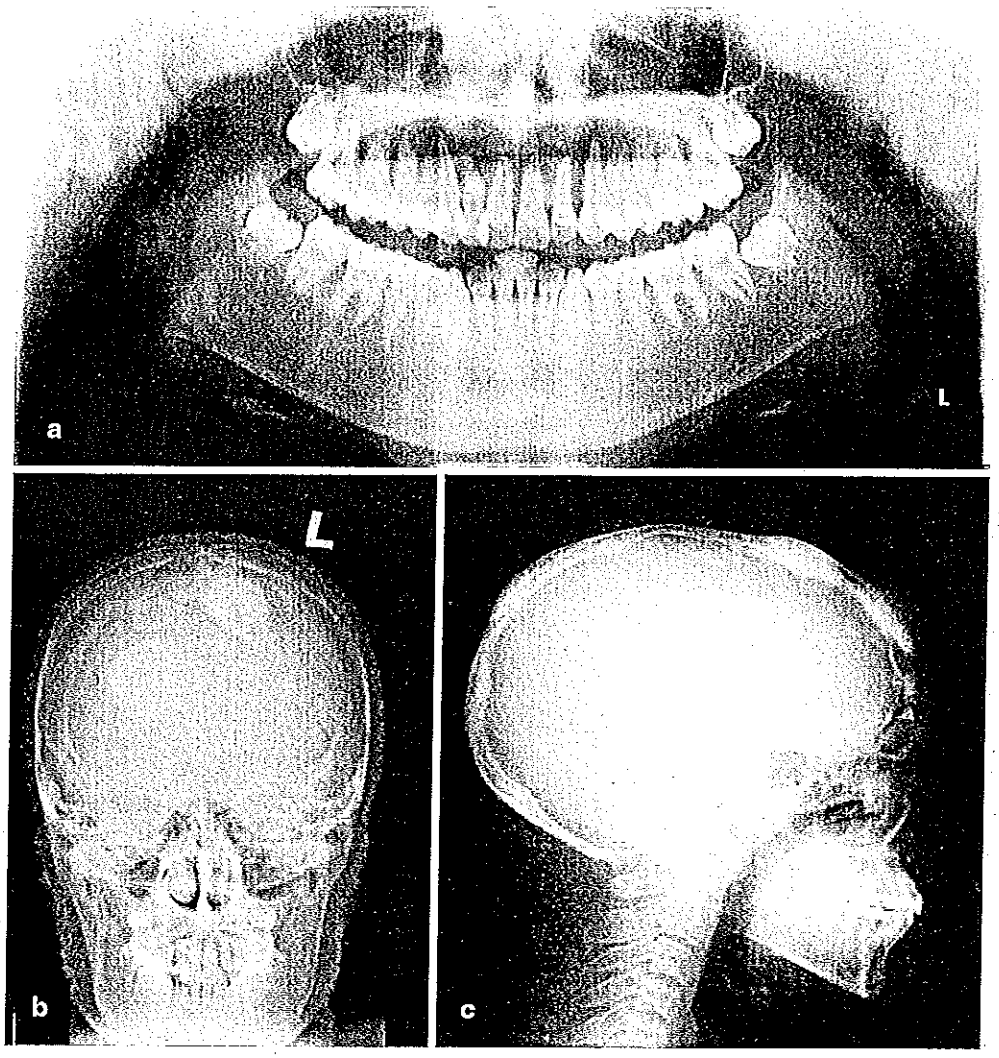

Fig. 6 a Panoramic, b lateral skull, and c posteroanterior skull radiographs of the patient's younger brother. Numerous mixed radiolucent and radiopaque lesions are scattered throughout the skull, similar to the findings for the patient

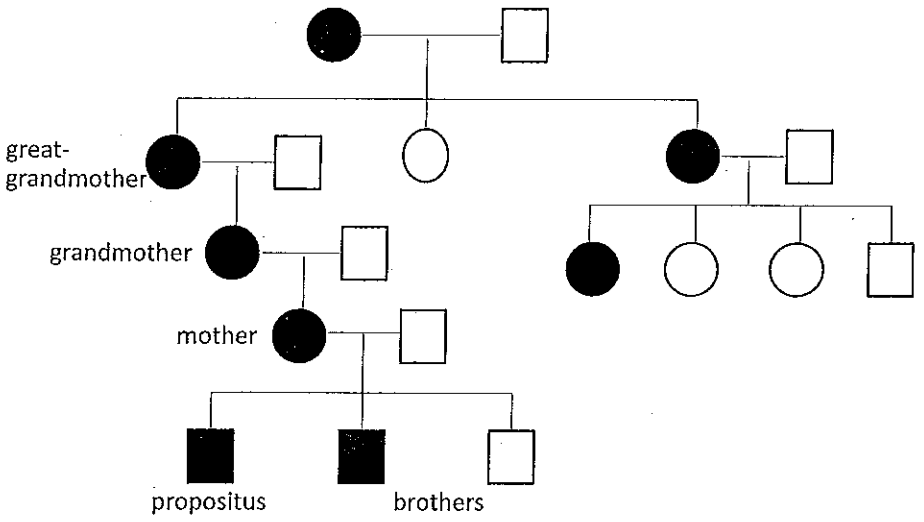

Fig. 7 Family tree of five consecutive generations. Note that every generation in the family is affected. *Black squares* affected males; *black circles* affected females; *white squares* unaffected males; and *white circles* unaffected females

defects were found on the patient's mother's side. On the basis of the family history, our case is likely to be inherited craniofacial fibrous dysplasia.

From a review of the literature on familial craniofacial fibrous dysplasia, the radiographic findings and familial pattern of occurrence in every generation seen in the present family are similar to those in a previous report [17]. In our case, the lesion at the right mandible was a well-defined unilocular radiolucency, which rarely occurs in the mature stage of fibrous dysplasia. The presence of osteoblastic rimming is a diagnostic dilemma in discriminating between fibrous dysplasia and ossifying fibroma. However, some studies have shown that craniofacial lesions tend to have greater osteoblastic activity than lesions in other bones [26]. In our case, the observation of minimal osteoblastic rimming is similar to another published case [18].

The focal aggregates of multinucleated giant cells seen in the present case are not commonly found in fibrous dysplasia. These may occur through secondary changes in older lesions. However, a prior case reported to show numerous multinucleated giant cells was consistent with fibrous dysplasia [27].

The common fibro-osseous lesions of the jaws include fibrous dysplasia, ossifying fibroma and cemento-osseous dysplasia. The pathologic features of biopsy specimens can be similar for each of these lesions. Therefore, correlation of the microscopic findings, clinical features, and radiographic appearance is important for the proper diagnosis of craniofacial fibrous dysplasia [15, 28, 29].

Furthermore, the surgeon should carefully examine the patient history, clinical signs, symptoms, and radiographs and consult with a radiologist and pathologist to establish a definitive diagnosis of the lesion to avoid overtreatment of the patient.

In conclusion, we propose that the present case is an example of inherited craniofacial fibrous dysplasia, which has rarely been reported in the literature to date. It is very important to carefully examine other abnormalities in addition to the chief complaint of the patient. In some conditions, occult disease can be diagnosed by integrating other patient information, as occurred in the present case. Additional laboratory tests to identify the genetic mutation linked to the etiology of the disease and examination of consecutive generations from this patient may be performed to establish the definite diagnosis and confirm a genetic basis.

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