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Up-to Date Review And Case Report

Oral management of two sisters with pycnodysostosis

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Abstract – Introduction: Pycnodysostosis, or Toulouse Lautrec's disease, is a rare lysosomal genetic disease with an autosomal recessive transmission, and it is classified as one of the osteo-chondro-dysplasias (ICD-10). Patients with pycnodysostosis manifest with several clinical features, including osteosclerosis, bone fragility, short stature and acro-osteolysis of the distal phalanges. Maxillofacial symptoms mainly associate a lack of maxillary and mandibular growth, open mandibular angle, and significant dental crowding. **Observations:** This work presents the case of two sisters suffering from pycnodysostosis as part of a family affected by it (mother and maternal aunt also affected). The first patient has received regular monitoring and oral care. The second one suffered from spontaneous mandibular osteomyelitis, which was difficult to treat and cure. **Discussion:** Oral symptoms of this disease make maintaining oral hygiene difficult and predispose to tooth decay and periodontal disease. The most common complications are mandibular osteomyelitis and pathological fractures. Pycnodysostosis must be differentiated from osteopetrosis and cleidocranial dysplasia. **Conclusion:** These cases illustrate the difficulty of managing the patients suffering from pycnodysostosis, whose treatment may be difficult.

Introduction

Pycnodysostosis, or Toulouse–Lautrec disease, is named like this in reference to a 19th-century French painter who presented the disease characteristics. He had typical findings of the disease such as a small stature, parental consanguinity, facial dysmorphosis, frequent long-bone fractures, and enlarged fontanelles [1]. It is a rare lysosomal genetic disease with autosomal recessive transmission, and it is classified among the osteo-chondro-dysplasias (ICD-10). Its prevalence is estimated between 1 and 1.7 per million inhabitants, with a male:female ratio of 1:1 [1]. The diagnosis is most often made during childhood. Parental consanguinity is found in 30% cases [2,3]. This disease originates from a mutation of the gene located on human chromosome 1q21, which encodes cathepsin K (CTSK), a lysosomal enzyme member of the papain–cysteine protease family [3]. CTSK is strongly expressed in osteoclasts, and it is involved in the degradation of bone matrix proteins, such as type-I and type-II collagen, osteopontin, and osteonectin [1]. Its deficiency thus leads to the formation of thick, fragile bones [4].

Pycnodysostosis was first described by Maroteaux and Lamy in 1962, and it is characterized by osteosclerosis, bone fragility, short stature, acro-osteolysis of the distal phalanges, dysplasia of the clavicles and a delay in the closure of cranial sutures and fontanelles [5]. Maxillofacial symptoms characteristically include a short maxilla and mandibule, an open mandibular angle, a deep and narrow palate, enamel hypoplasia, multiple impacted or retained teeth, and significant dental crowding [6]. Such oral abnormalities, which result in difficulties in maintaining oral hygiene, facilitate tooth decay and periodontal disease [7,8]. The most common complications are mandibular osteomyelitis [9,10] and pathological fractures of the jaws [7,11]. Differential diagnoses of this condition include osteopetrosis and cleidocranial dysplasia [8,12,13].

The purpose of this work is to present the case of two sisters affected by pycnodysostosis in the context of a familial pycnodysostosis (mother and maternal aunt affected in a similar manner) to discuss the histological, clinical, radiological, and therapeutic aspects of this rare disease.

Observations

Case 1

A 24-year-old patient consulted the Department of Odontology in November 2013. She wanted an oral assessment for fear of a "serious dental problem" in the context of pycnodysostosis diagnosed during childhood. An examination

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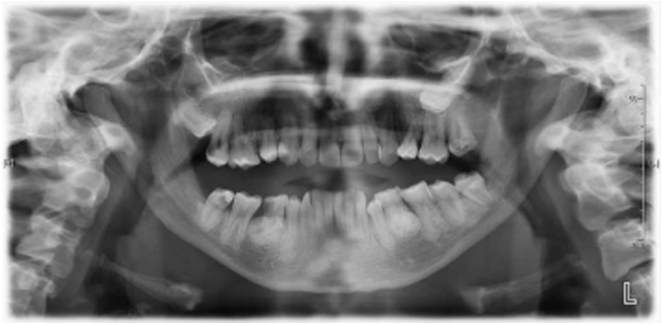

Fig. 1. Case 1. Preoperative orthopantomogram demonstrating several decayed teeth, decidual teeth, and hypercementosis.

revealed a history of multiple lower-limb fractures, sleep apnea syndrome, atrial septal defect, and a gastrectomy performed on the previous year. Clinical and radiographic examinations demonstrated a characteristic facies (maxillary and mandibular hypoplasia, open mandibular angle), front crossbite, dental crowding with persistance of lacteal tooth, as well as many decays. Cemento-osseous lesions were also noted at the apices of teeth 36, 75, and 85 (Fig. 1). Therapy consisted of conservative care and three tooth extractions, which were performed under general anesthesia because the patient was extremely anxious. The patient has come for checkup visits every 6 months and so far has presented no complications despite persisting inadequate dental hygiene (Fig. 2).

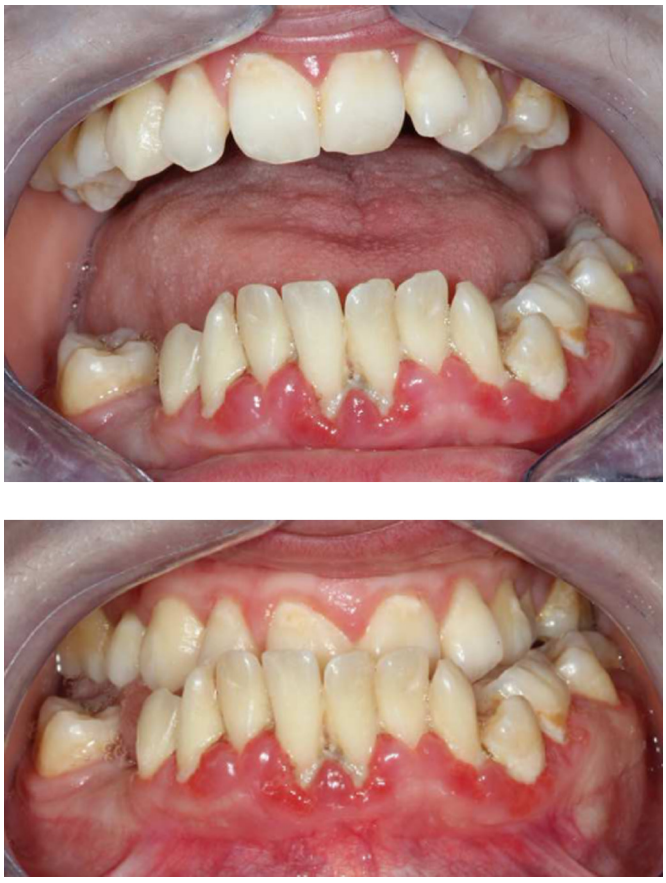

Fig. 2. Case 1. Open (2a) and closed mouth (2b) intraoral views, showing poor hygiene and cross bite.

Case 2

The 27-year-old sister of the above discussed case consulted the Department of Odontology in June 2015. She was diagnosed with pycnodysostosis at age 9 months, and she complained of right mandibular swelling. In her medical backround, she had many bone fractures (especially implicating long bone), a malformative syndrome of the nasal pyramid operated several times, a sleep apnea syndrome, and an aspirin intolerance.The patient also reported the occurrence of low-grade cellulitis of the right side of the face the previous year, which led to the endodontic treatment of tooth no. 45. Extraoral examination revealed hyperdivergence with maxillary and mandibular hypoplasia. Intraoral examination revealed a left-side anterolateral gap tending to class III skeletal pattern, major dental obstruction,and the presence of vestibular and lingual fistulas on the free gum of tooth 46 which was moving (Fig. 3a, b). In front of the infectious picture, the patient received oral antibiotic treatment with a combination of amoxicillin and clavulanic acid for 7 days. Maxillofacial computed tomography (CT) performed on the following days revealed an osteolysis area in sector 4, spanning 3 cm along the basilar, vestibular, and lingual cortices (Fig. 4a, b). Mandibular osteitis was diagnosed. Piezosurgery-assisted multilevel bone biopsies were performed at three levels (superficial, intermediate, and deep) under general anesthesia, while avoiding salivary contamination as much as possible. The excised superficial sample consisted of a bone block (Figs. 5–8) including teeth 45 and 46. Afterward, two intermediate and deep samples were collected. All excised tissues were sent to histopathological and bacteriological analysis. After the intervention, the patient received antibiotic treatment with a combination of amoxicillin and clavulanic acid for 15 days. She also received paracetamol and tramadol for pain relief, as well as chlorhexidine digluconate mouthwash. Mucous membrane detachment occurred 3 days after the surgery. Regular follow-up and multiple daily irrigations with an iodine solution resulted in the partial closure of the surgical site. Histological findings were compatible with mandibular osteitis: empty, necrotic bone was found on superficial bone biopsy samples, along with fibro-inflammatory remodeling rich in plasmocytes in the deepest samples. Bacteriological cultures of the superficial sample (bone block) revealed an abundant growth of *Actinomyces oris*, with some growth of *Streptococcus gordonii* and scanty growth of *Rothia aeria*. Bacteriological cultures of the intermediate samples revealed scanty growth of *A. oris*, whereas the deepest samples were sterile. On the recommendation of the Department of Infectious and Tropical Diseases (DITD), the antibiotic treatment was revised to oral clindamycin (1.8 g/day for 30 days) to encourage healing. Thus, postoperative antibiotherapy lasted 6 weeks. Three months later, the patient reported bone pain on the left mandibular sector, without other clinical or radiographic signs. These pains

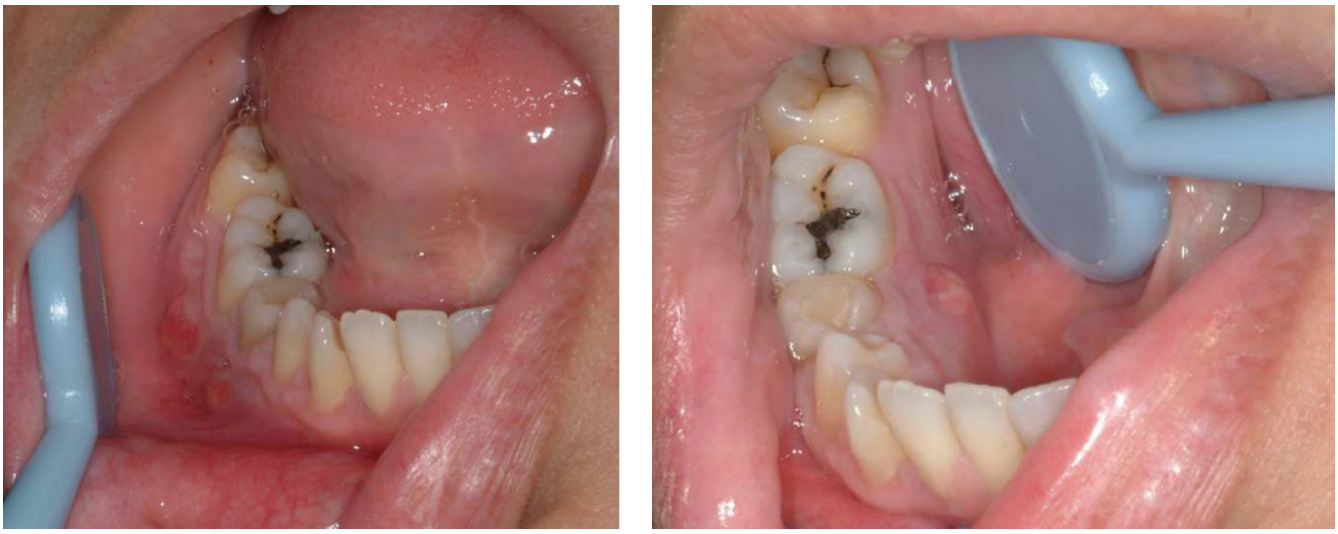

Fig. 3. Case 2. Buccal (3a) and lingual (3b) fistulas, close to tooth no. 46.

regressed spontaneously thereafter. Only a mucosal bud persisted on the right side 6 months after the procedure (Fig. 9).

Discussion

The two cases presented above showed the characteristic symptoms of pycnodysostosis, particularly the small stature (1.50 m for both patients) and long-bone fractures. Regarding the maxillofacial sphere, the characteristic features of the disease are also present in these two cases: open mandibular angle; large skull with frontal, parietal, and occipital bossing; narrow, deep palate; maxillary and mandibular hypoplasia; hypopneumatization of the maxillary sinuses; impacted or unerupted teeth; and enamel hypoplasia. Among the rarer morphological characteristics of the disease, Alves and Cantin [6] similarly note the presence of a class-III skeletal pattern, elongated coronoid processes and condyles, the persistence of primary teeth, dental deformities, and hypodontia or a hypercementosis in some teeth, all of which were present in both cases reported above. The multiple carious lesions, found in both cases, are frequently and often associated with periodontal disease. They are similarly related to dental obstruction [14,15] that hinders brushing.

All these characteristics suggested a clinical diagnosis of pycnodysostosis, but the differential diagnoses such as osteopetrosis and cleidocranial dysostosis needed to be ruled out [8,12,13]. In fact the following characteristics are common to pycnodysostosis and cleidocranial dysostosis as well: clavicular hypoplasia; delayed closure of the sutures; frontal, occipital and/or parietal bossing; hypopneumatization of the maxillary sinus; and a narrow, deep palate [16,17]. Clinical differentiation may be achieved, among other factors, by the more frequent presence of supernumerary teeth in cleidocranial dysostosis than in pycnodysostosis [6,17]. The small size, as well as increased density and bone fragility is common to pycnodysostosis and osteopetrosis [6,11,18,19]. Differential diagnosis between these two diseases is made by the absence of frontal and parietal bossing [6], and acro-osteolysis of the distal phalanges in osteopetrosis [16]. Maxilla and mandible size, maxillary sinus volume, cranial sutures, and mandibular angle are also normal in osteopetrosis [6,14]. All of these elements thus allow the definitive diagnosis of pycnodysostosis in these two patients.

The dense, fragile bones found in patients affected by pycnodysostosis result in maxillofacial complications, especially the occurrence of maxillary or mandibular osteomyelitis [8,10,20], as well as pathological mandibular fractures [7,11,20]. Osteomyelitis may result from an infection [21–23], as in the second case, either spontaneously [6,14] or after surgery/extraction [6,9,23]. They can also be complicated by and/or follow iatrogenic fractures [6,11,24]. They are more frequent in adulthood. These complications are explained by deficient bone resorption by CTSK. This lack of remodeling leads to the development of an osteosclerotic phenotype, characterized by increased bone density, because of ongoing endosteal apposition and trabeculation of the medullary space [12,20]. This reduction in medullary space, and therefore in blood supply, leads to a decline in local immune defenses, with a bone tissue that is more susceptible to attacks of oral pathogens [20,25]. Moreover, the highly disturbed collagen network reflects the lack of adaptation to mechanical constraints and contributes to bone fragility [12]. These elements contribute to awareness regarding difficulty in correcting facial dysmorphia, which is sometimes severe in these patients, by treatments that combine orthodontics and orthognathic surgery. Several techniques have been reported, including conventional osteotomies and external distractions [26–30]. No recommendation exists regarding the effectiveness or safety of orthodontic treatment in these patients [7,27]. The same is true for orthognathic surgery. In fact, the success reported in the literature is isolated cases, and the authors are aware of the relevant risks of osteomyelitis, fractures, and fracture nonunion [26–30]. The decision to

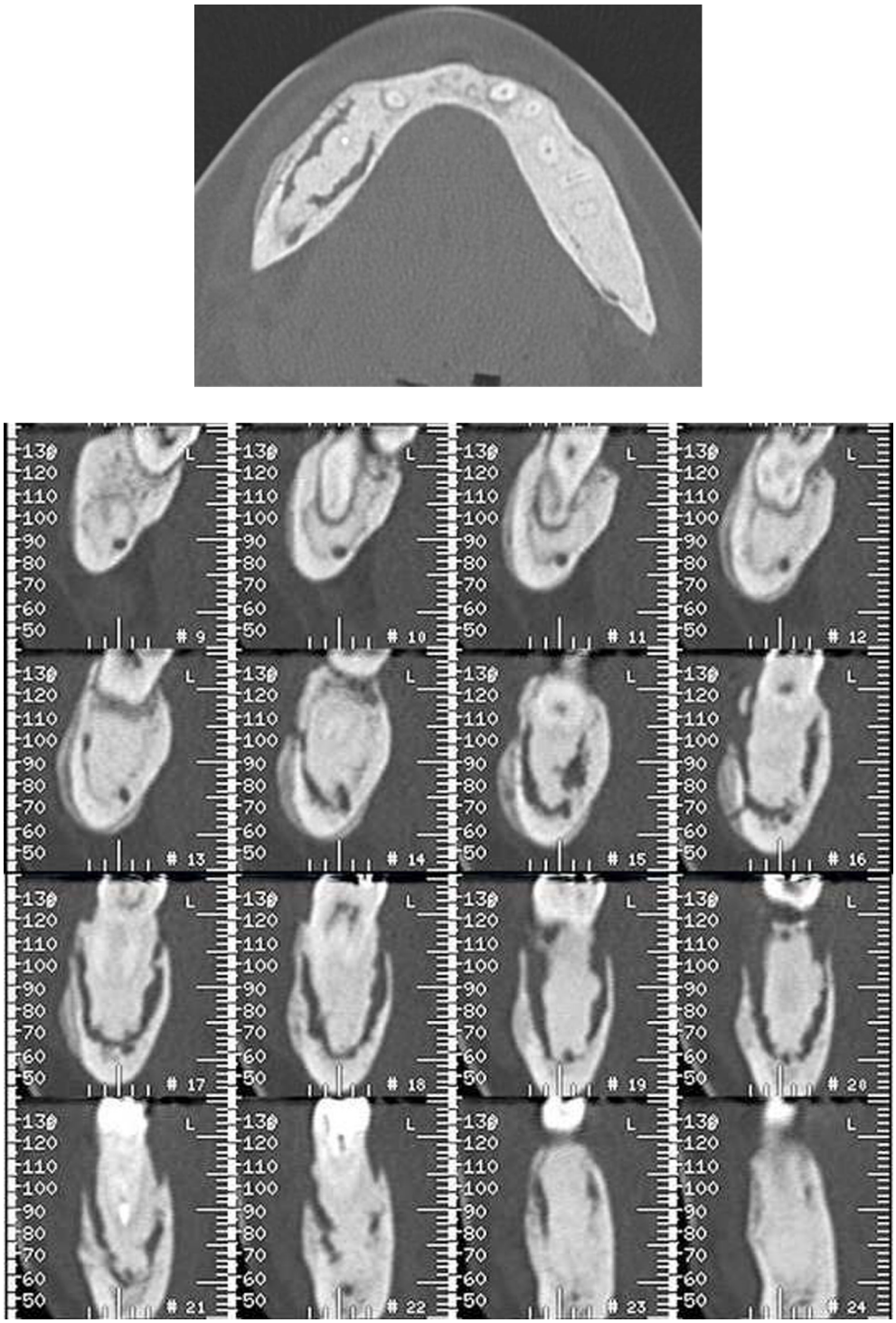

Fig. 4. Case 2. Preoperative maxillofacial CT, with sagittal (4a) and frontal (4b) views, demonstrating a right mandibular osteolysis.

undertake such treatments must consider the risk–benefit analysis of the degree of esthetic and functional improvement for these patients. That is why no treatment was undertaken for patient no. 2, who nevertheless wanted to undergo corrective surgery for her dysmorphia and malocclusion. However, it is clear that if a dysmorphia correction is decided, it must be attempted when the patient is young, as the risk factors for occurrence of osteomyelitis are lower [7].

Management of complications is complex [20,25,31], which is well highlighted in second case, in which partial, delayed, and difficult healing was observed. Although this is possible, a conservative approach should be preferred, similar to the strategy in the second patient. The treatment of choice is the association of decortication or sequestrectomy to systemic antibiotic therapy [22,32–34]. Hyperbaric oxygen therapy can be used in addition, but its contribution in the

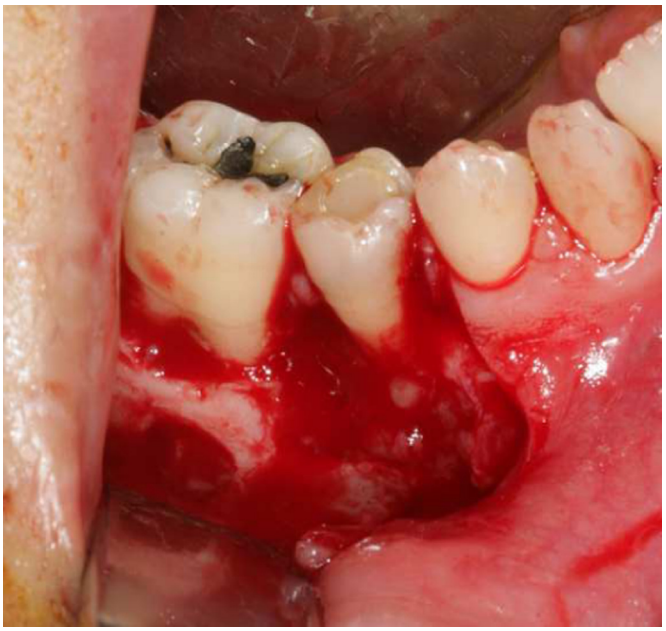

Fig. 5. Case 2. Surgical site before bone resection.

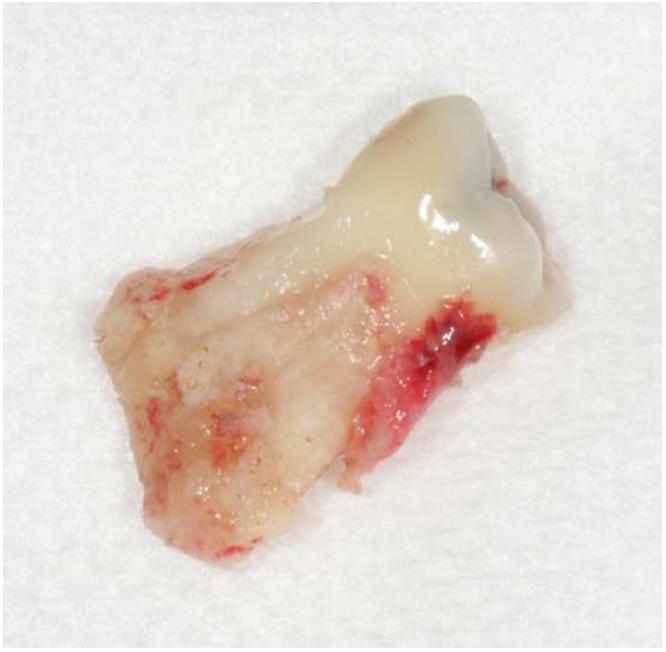

Fig. 6. Case 2. Resected bone block with teeth.

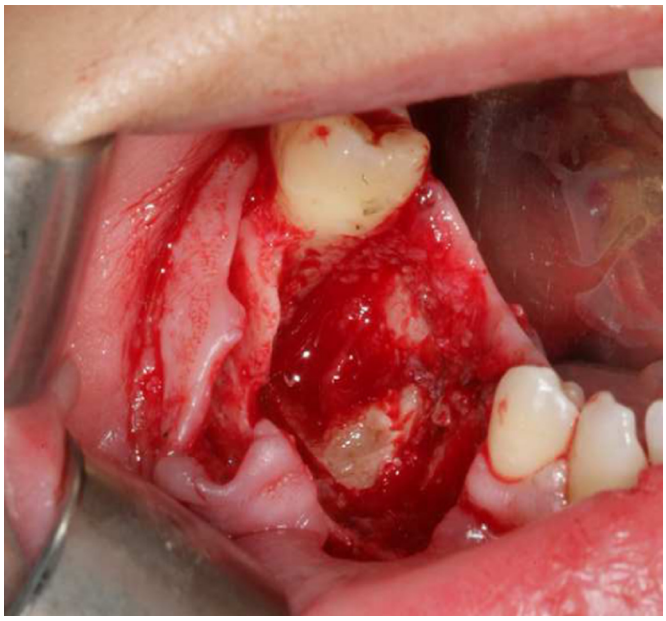

Fig. 7. Case 2. Surgical site after bone resection.

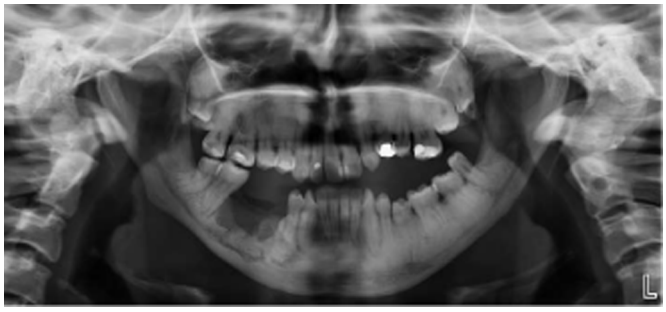

Fig. 8. Case 2. 6 months postoperative orthopantomogram showing bone defect.

improvement of the results has not been proven [10,20,25]. The elimination of infected or necrotic tissue is a mandatory prerequisite [22,33–35]. In fact, antibiotics have a low ability to penetrate such ischemic or avascular tissues [23,35]. The second case illustrates the prevalence of mandibular osteomyelitis, as compared to maxillary osteomyelitis. The higher bone density and relatively deficient blood supply to the maxilla are risk factors [24]. For these reasons, complications are more difficult to treat in these cases [15]. Decortication thus allows increased blood supply of the affected area, by placing the periosteum and the surrounding tissue in close contact with spongy bone and promoting greater vascular contribution [36]. Antibiotic treatment is usually broad spectrum and takes 4–8 weeks [22,23]. However, intraoperative samples must be taken for bacteriological and mycological examinations so as to adjust antimicrobial therapy in order to achieve better efficiency [22,35,37]. There currently is no consensus on bacteriological sampling protocols. That is why a protocol implemented by CHU's DITD was used in the second case, which seemingly yielded good results. It consists of the performance of multiple, layered bone biopsies, free from saliva and using piezosurgery. The goal is to avoid salivary contamination, which would distort the results. The floras usually found are polymicrobial, with aerobic and anaerobic microorganisms [23]. The species most often found are *Staphylococcus aureus*, *Streptococcus pyogenes*, *Streptococcus pneumoniae*, *Pseudomonas aeruginosa*, *Actinomyces spp.*, *Bacteroides spp.*, and *Klebsiella spp.* [22,23,34]. In the second case, most detected species were *Streptococcus* and *Actinomyces spp*. Intravenous antibiotic therapy is more effective in the treatment of osteitis than oral therapy. Oral clindamycin was used (1.8 g/

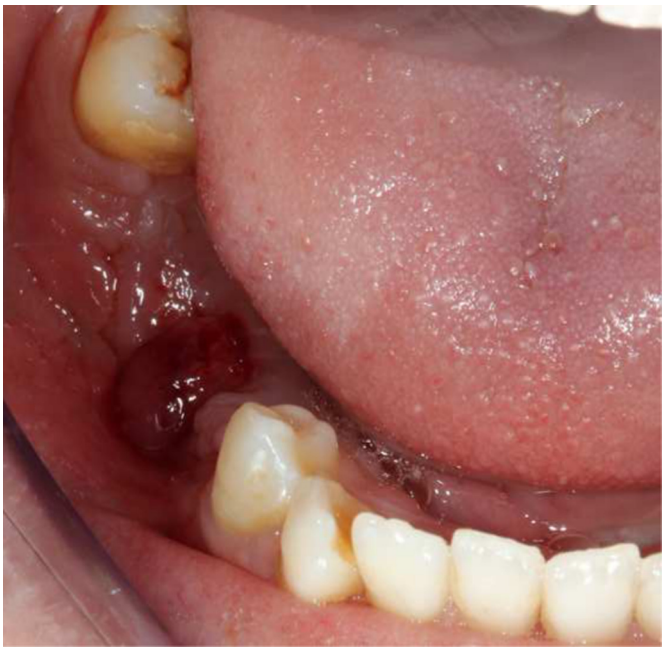

Fig. 9. Case 2. Partial closing of the surgical site with presence of a mucosal bud.

day for 30 days) because this antibiotic has a good bone permeability and its bioavailability is equivalent in intravenous or oral administration [35]. These treatments may be enough to achieve remissions of osteomyelitis, including that of the maxilla [9,20,38]. Nevertheless, they are to be implemented as early as possible [20,25]. In fact, it is not uncommon to find recurrence of osteomyelitis, notably in the mandible [14,25,39]. In addition, the occurrence of a pathological fractures may complicate the clinical picture [6,9,11,20,31,40].

Our experience with the first case may imply that regular follow-up by the dental surgeon and early management of care could help prevent complications, the treatment of which can be complex. In fact, as problems of bone remodeling render healing difficult, management of mandibular fractures and conservative treatment of osteomyelitis are rarely successful [20,24,25,39], and the decision to perform a disruptive resection of the mandible may be justified. The mandible is then restored by a reconstruction plate, with or without a bone graft, which is often of iliac origin [20,25]. This treatment most often ends in failure [20,25,39], and complications include nonunion of the bone, plate fracture, superinfection. Some authors therefore propose a free flap reconstruction, either peroneal [25] or iliac [39], relying on the fact that only a vascularized bone graft would enable full bone healing [24,41,42].

Conclusion

These cases illustrate the difficulty of managing patients suffering from pycnodysostosis, particularly those with difficult bone healing. The role of the dental surgeon is therefore critical to detect dental problems and their management as early as possible.

Conflicts of interests: The authors declare that they have no conflicts of interest in relation to this article.

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