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Case Report

Histological examination and clinical evaluation of the jawbone of an adult patient with cleidocranial dysplasia: a case report

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Abstract: Objectives: Cleidocranial dysplasia (CCD) is a rare congenital malformation syndrome, inherited autosomal-dominantly. During a course of treatment including surgical, implantological and restorative procedures, an opportunity arose to histologically examine biopsies of the maxilla and mandible of a CCD patient 47 years of age. Case report: The aim of this case report is to present the results of the histological evaluation of the alveolar bone and the surgical pretreatment for and placement of six implants each in the maxilla and the mandible. The implants were inserted in a minimally invasive procedure using 3D template guidance. Following uneventful healing of the implants, ceramically veneered bridges were cemented on individual titanium abutments. Since the patient had not received orthodontic treatment in childhood-which would have been the treatment modality of choice-this implantological and prosthodontic approach was necessary. Biopsies were taken from the maxilla and the mandible before placing the implants. Histological evaluation showed bone with strong, coarsely interconnecting trabeculae, especially in the maxilla. Both the bone and the gingiva otherwise exhibited a normal structure without pathological features or anomalies. Conclusion: The clinical parameters and histological evaluation of this one clinical case suggest that the concepts familiar from general oral implantology in terms of surgical and prosthetic procedures can be adopted for older patients with CCD.

Keywords: Cleidocranial dysplasia, dental implants, osseointegration, histology, computer-assisted surgery

Introduction

Cleidocranial dysplasia (CCD) is a rare congenital malformation syndrome, inherited autosomal-dominantly. CCD was first described in 1897 by Pierre Marie and Paul Sainton [1]. The prevalence is 1 in 1,000,000 and shows no dependence on gender or ethnic origin [2]. Mutations in CBFA1/RUNX2, a transcription factor on chromosome 6p21, have been identified as the cause [3-5]. This transcription factor is responsible for the differentiation of precursor cells into osteoblasts and also regulates function in the differentiation of chondrocytes of the growth plate [6]. Symptoms include hypoplastic or congenitally missing clavicles and cranial changes (brachycephaly, depressed nasal bridge, open or delayed closure of fontanelles) [7, 8]. Additional changes may be present in the thorax, spine, pelvis and extremities [9]. The general health of patients with CCD is usually good and there is no intellectual impairment [10].

Another main manifestation of CCD are dental anomalies [11, 12]. These regularly include supernumerary teeth (hyperdontia), late eruption of teeth of the deciduous and permanent dentitions or the impaction of teeth [13, 14]. This will be accompanied by malpositioned teeth as well as crowding and resulting malocclusions. Other possible skeletal symptoms include a hypoplastic maxilla [15] and associated pseudoprognathism [16, 17]. The maxilla may be characterized by reduced anterior and posterior height; in addition, the zygomatic bone will in most cases be hypoplastic. The palate has in many cases been described as high, narrow and strongly arched [18]. In the mandible, parallel mandibular rami, slender, distally

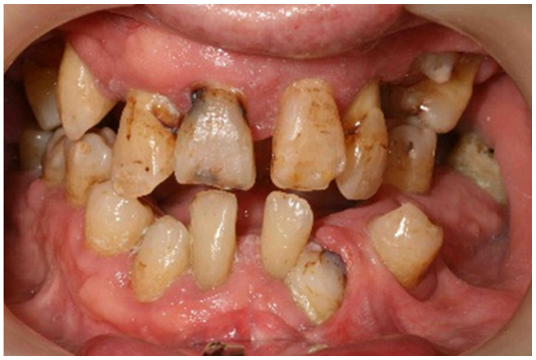

Figure 1. Baseline situation of the 43-year-old patient with CCD.

rounded coronoid processes and condylar changes have been described [8, 19, 20]. These structural anomalies also explain that the masseteric muscle is less voluminous in patients with CCD [21]. Radiographic and histological examinations of the alveolar bone show a dense and compact structure [19]. The jawbone is histologically represented as woven bone or lamellar bone with coarse and poorly aligned trabeculae [22, 23]. The morphological shape of the clinical tooth crowns is often anomalous, with the enamel presenting with hypoplasia. Histologically, the lack of a cement layer on the roots of unerupted teeth is a salient finding [24, 25].

Owing to usually complete irregular tooth positions and shapes, functional disturbances of masticatory function and a psychologically aggravating oral appearance are at the core of patient complaints [26]. Thus, the treatment of CCD patients will focus on establishing optimal masticatory function and improving the aesthetic appearance in early adulthood [27]. The treatment strategy for such patients will usually be multidisciplinary in nature due to the complexity of the condition. This multidisciplinary team approach will often benefit from the inclusion of a psychologist, because CCD patients often have to endure severe disfigurement in a world that places great store in physical appearances. In addition, it is not always easy to improve the patient's self-image through treatment options available to the dentist, even if they objectively result in changes for the better.

Malocclusion is corrected by interacting surgical, orthodontic and possibly prosthodontic measures [28]. Supernumerary and impacted teeth will often require extraction [29, 30]. Surgical tooth exposure for subsequent orthodontic or surgical repositioning as well as autologous transplants have been described as alternatives [31-34]. Anomalously shaped permanent teeth can be used as prosthetic abutments [35] or must be removed [36]. Various concepts have been described whose objectives were to restore normal masticatory function and normal aesthetics [37].

The common consensus behind all these treatment strategies has been that early diagnosis is necessary and that treatment should be initiated in childhood or early adolescence [26, 38, 39]. For example, the Toronto-Melbourne protocol attempts to start with extractions of deciduous teeth at age 5 and orthodontic therapy at age 9-12 [40, 41]. An alternative approach, the Jerusalem protocol, removes remaining deciduous teeth no later than at age 13; impacted teeth are exposed surgically and the necessary surgical orthodontic treatment is performed [27, 31].

If the orthodontic therapy is not successfully completed or if the patient does not seek dental treatment until adulthood, a prosthetic treatment approach is required. Here, teeth that show a favourable prognosis and are in a prosthetically useful position are used as abutment teeth for fixed or removable dentures [42-45]. Alternatively, complete dentures can be inserted as a lower-cost solution. Various case reports have demonstrated the successful use of dental implants to support removable or fixed dentures in CCD patients [29, 45-49].

The patient presented here had all the clinical symptoms of CCD. The aim of this case report is to present a procedure for treating CCD with an implant-supported fixed prosthesis later in life and to describe the treatment concept in histological and clinical terms.

Case report

The patient, a man, was 43 years old at the time of initial presentation in our practice. He exhibited pronounced symptoms of CCD, which had been clearly diagnosed and documented in the pre-treating orthodontic clinic based on the existing symptoms. His reason for seeking treatment was his desire for normal masticatory function, but especially a natural aesthetic appearance. The appearance of his teeth both-

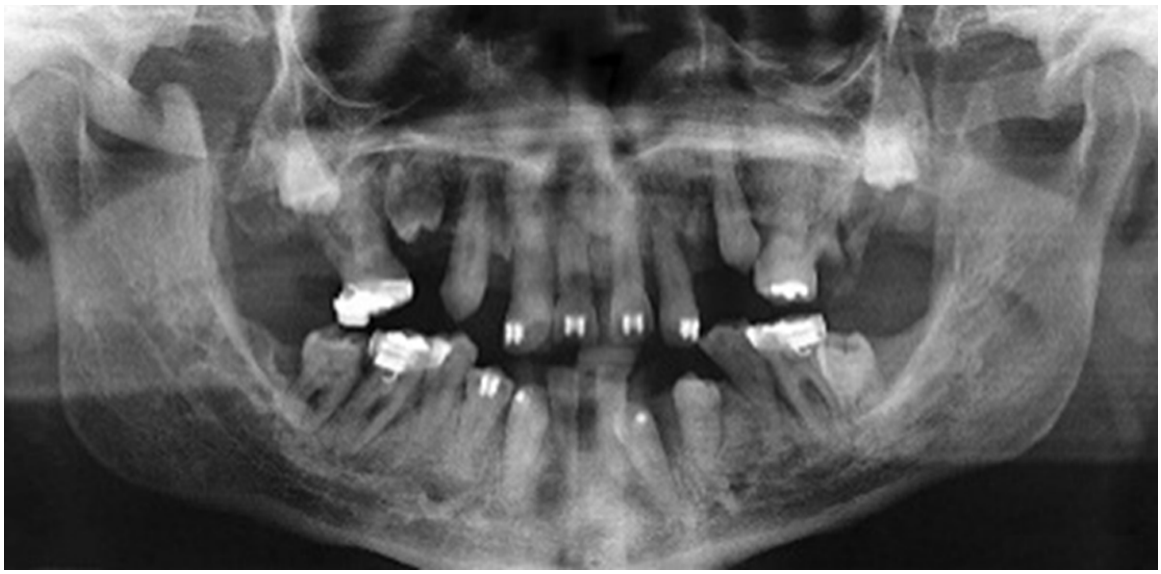

Figure 2. Panoramic radiograph showing findings typical of CCD: impacted and malpositioned teeth and variant bone structures.

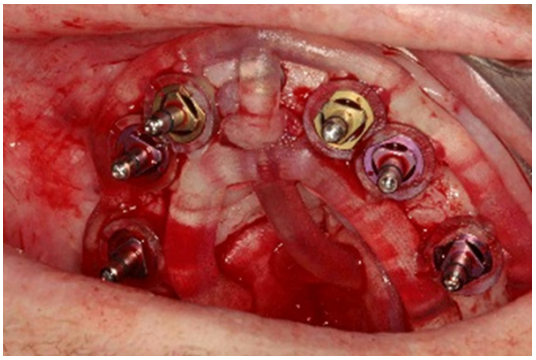

Figure 3. All implants were inserted in a minimally invasive procedure using a drilling and insertion stent.

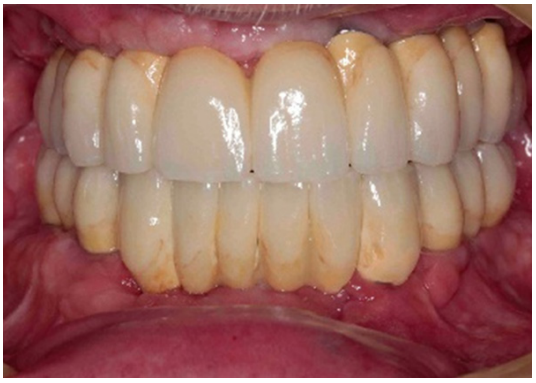

Figure 4. The fixed metal-ceramic bridges on custom titanium abutments.

Table 1. Measurement of implant stability using resonance frequency analysis (Osstell) given as ISQ values at the time of insertion or after three months (at the beginning of the restorative phase)

	Time: Day 1		Time: Day 91	
	ISQ mean	ISQ range	ISQ mean	ISQ range
Maxilla	64.3	57-69	67.3	58-71
Mandible	69.8	52-74	72.7	67-78

ered him greatly, so much that he avoided smiling altogether, showing a "frozen" facial expression. His general medical history was without contributory findings. No conditions were present that would have precluded a comprehensive dental rehabilitation. The patient was a moderate smoker (< 10 cigs/d). The patient reported that his son exhibited the same general and dental symptoms of CCD.

As far as the specific case history, the patient reported has had orthodontic treatment initiated only as an adult. By way of run-up to this treatment, several teeth had been extracted and a fixed orthodontic appliance had been provided. As this treatment had shown no improvement after several months, the patient discontinued the treatment and had the orthodontic wires removed. His brackets and bands had remained in situ and were still in place at the time of his initial visit to our practice.

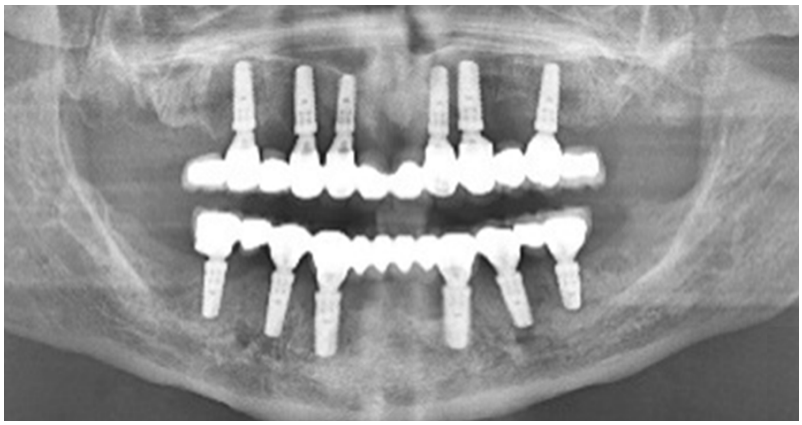

Figure 5. Control radiograph after insertion of the abutments and restorations.

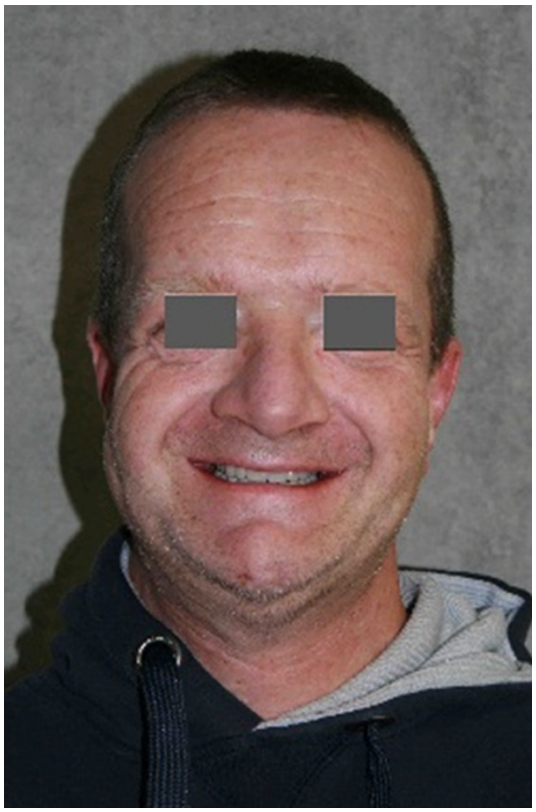

Figure 6. Post-treatment frontal view.

After a thorough professional tooth cleaning and removal of the brackets, a complete dental status was obtained (**Figure 1**). Teeth 16, 24, 25, 38, 31, 41 and 48 were missing. Teeth 18, 15, 23, 28, 37, 34, 33 were impacted and displaced. Only root fragments were left of tooth 27, while tooth 36 presented with acute periodontitis with pus discharge and pain on palpation. The first treatment step was therefore to extract tooth 36. Teeth 16, 12, 11, 21, 22, 35, 36, 46 and 47 showed class III mobility. Additional findings included enamel hypoplasia, unerupted teeth of abnormal size and shape and a high-arched palate with a deep furrow in its midline. The exploratory periodontal examination revealed advanced periodontitis with pocket depths of > 6 mm in all quadrants. There was a significant malfunction with an anterior open bite, where only the antagonist pairs 16/46 and 26/36 exhibited any static and dynamic contacts. The baseline radiograph (**Figure 2**) showed the typical signs of CCD: parallel orientation of the mandibular rami and slender and pointed coronoid processes. In addition, the maxillary sinuses was severely underdeveloped bilaterally.

The available treatment alternatives were discussed with the patient in detail. He was presented with three possibilities: (a) extraction of all teeth and insertion of complete dentures; (b) preservation of a few strategic abutment teeth and insertion of prostheses with by telescopic crowns as anchoring elements; (c) implant-supported restorations, fixed or removable, following extraction of all teeth. The patient desired the removal of all teeth and a set of complete dentures as long-term provisional. He had the surgical treatment performed after an additional year.

The patient was very satisfied with the dentures and initially postponed further treatment, not least for financial reasons. He presented again after three years, because the retention of the dentures had deteriorated. The patient, now 47 years old, now desired an implant-supported rehabilitation. Because he had developed a strong vomiting reflex, he preferred fixed restorations.

Using a minimally invasive, template-guided method, the maxillary and mandibular mucosa was punched and six implants were placed in each jaw (CONELOG: Camlog, Wimsheim, Germany). The virtual three-dimensional planning was carried out after scanning a wax-up

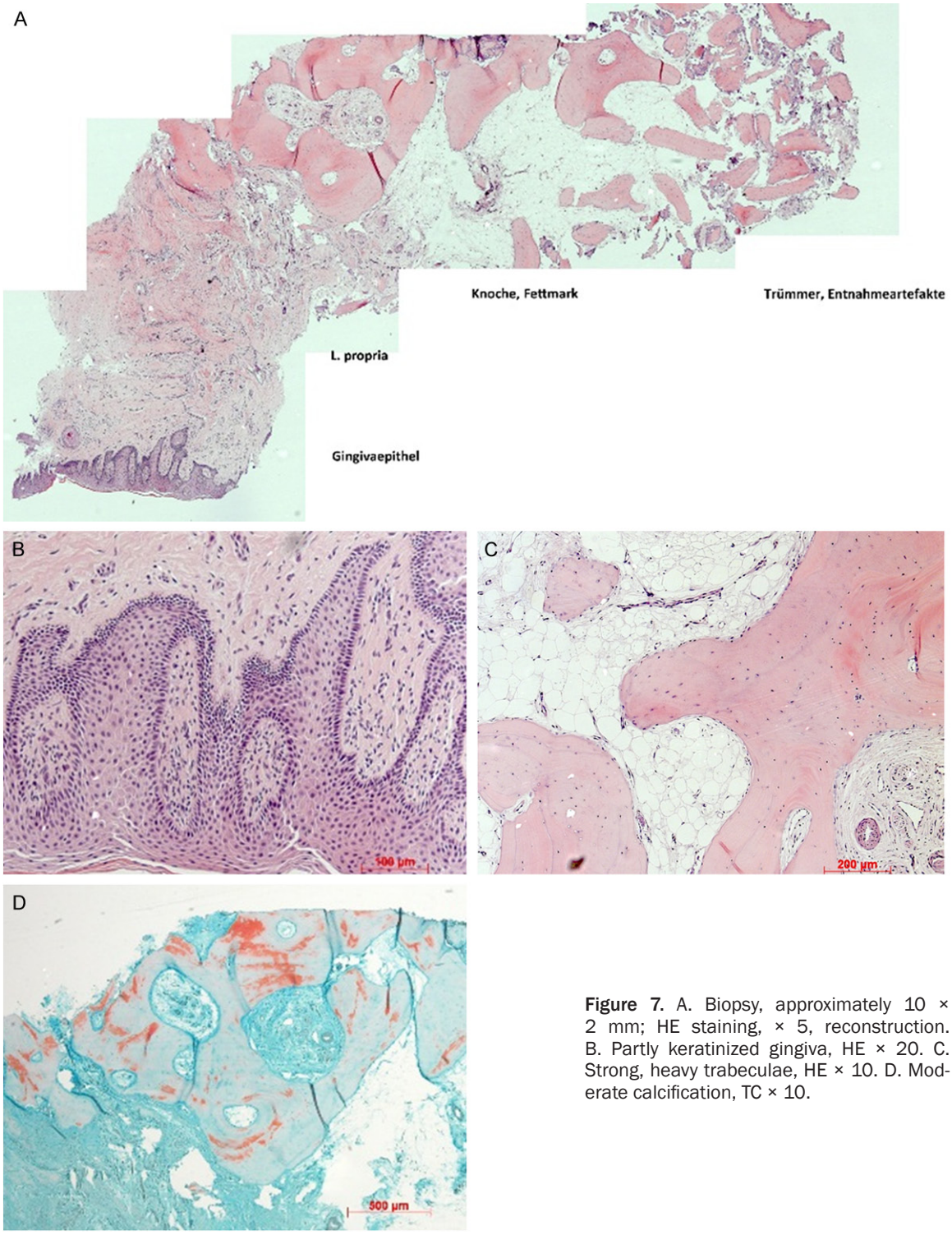

Figure 7. A. Biopsy, approximately 10 × 2 mm; HE staining, × 5, reconstruction. B. Partly keratinized gingiva, HE × 20. C. Strong, heavy trabeculae, HE × 10. D. Moderate calcification, TC × 10.

and importing the data of a CBCT into an implant-planning program (SMOP; Swissmeda, Zürich, Switzerland). Using a drilling and insertion stent produced by a 3D printer, the implants were inserted in local anaesthesia in a single session (**Figure 3**). All implants achieved primary stability (insertion torque: > 25 Ncm). Stability measurement was performed by resonance frequency analysis (Osstell AB, Göteborg, Sweden). All implants exhibited high ISQ values (**Table 1**). The implants were closed with healing abutments and the dentures relieved at the

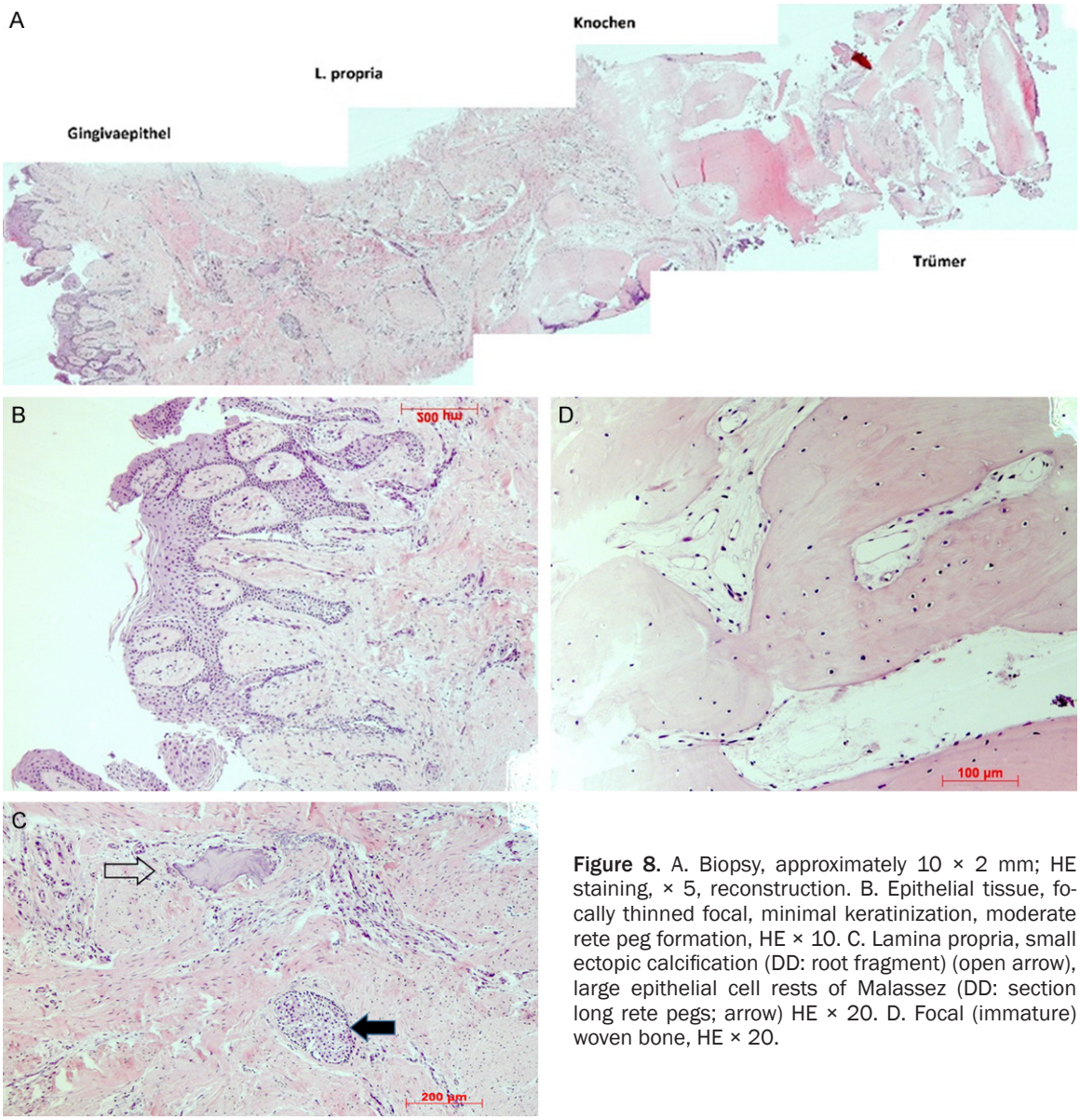

Figure 8. A. Biopsy, approximately 10 × 2 mm; HE staining, × 5, reconstruction. B. Epithelial tissue, focally thinned focal, minimal keratinization, moderate rete peg formation, HE × 10. C. Lamina propria, small ectopic calcification (DD: root fragment) (open arrow), large epithelial cell rests of Malassez (DD: section long rete pegs; arrow) HE × 20. D. Focal (immature) woven bone, HE × 20.

implant positions. The patient was instructed not to wear his denture for one week and to keep to a soft diet during the following six weeks. He was prescribed an analgesic (ibuprofen 500 mg), to be taken at the patient's discretion within the prescribed maximum dose.

The healing time of the implants, three months, followed the implant manufacturer's protocol and were uneventful, so that the prosthetic treatment could be carried out. Again, the stability of the implants was determined by resonance frequency analysis (**Table 1**).

Custom abutments were designed and milled in titanium (Dedicam; Camlog, Wimsheim, Germany). Milled frameworks made of a non-precious metal were milled and veneered with ceramics. Five months after implant placement, the restoration was delivered (**Figure 4**), and the patient was placed on a tight recall schedule.

The control radiograph (**Figure 5**) showed stable osseous conditions around the implants.

A satisfactory facial profile was achieved thanks to the increase in vertical dimension. A prosthetic compensation of the maxillary micrognathism and the pseudoprognathism was also achieved by the restorations. The patient was very satisfied with the functional and aesthetic result of the prosthetic treatment (**Figure 6**).

Histological examination

Accompanying the clinical treatment and the clinical measurements, a histological examination of the gingiva and the maxillary and mandibular bone was performed. Instead of the primary drilling hole using the implant drills, one sample each was taken at sites 13 and 43 through the template using a trephine drill (227A. 204032; Gebr. Brasseler, Lemgo, Germany). The two oblong biopsies of approximately 10 × 2 mm both included gingiva and bone.

Histology and histochemistry

Each biopsy was fixed by immersion in 4% buffered formaldehyde and subsequently decalcified for about 3 weeks in 4.1% disodium ethylene-diamino-tetraacetic acid (EDTA)-solution. After hydration, tissues were dehydrated in an ascending series of ethanol and embedded in paraffin. Serial sagittal sections of 2-3 µm were cut and representative slides were stained with haematoxylin-eosin (HE), Masson-Goldner trichrome and periodic acid Schiff (PAS) staining for overview. In order to identify osteoclasts, selected tissue sections were stained to demonstrate tartrate-resistant acid phosphatase (TRAP).

Histology of the maxillary biopsy (site 13)

The biopsy from site 13 was inconspicuously with regular cancellous, lamellar bone, with no signs of inflammation (**Figure 7A**). The gingival epithelium presented slightly keratinized with moderate rete peg formation (**Figure 7B**). The lamina propria was well capillarized and permeated by strong collagen fibre bundles. The bone showed sections of strong, sometimes gross, interconnecting trabeculae of mature lamellar bone (**Figure 7C**), with few osteons and cement lines. More pronounced mineralization was present focally (**Figure 7D**). Furthermore, there was a normal layer of lining cells, but no osteoblasts; some small focal, especially crestal, resorption lacunae without osteoclasts were also present. The intertrabecular spaces contained normal fatty tissue or vascularized connective tissue. No signs of inflammation were found.

Histology of the mandibular biopsy (site 43)

The overview of the biopsy of site 43 shows generally unremarkable, regular, strong cancellous, lamellar bone. Apical, a larger debris zone constitutes a sampling artifact. No inflammation was present (**Figure 8A**).

The gingival epithelium was barely keratinized, at times thin with moderate rete peg formation (**Figure 8B**). The lamina propria exhibited strong collagen fibre bundles with moderate capillary density. Small ectopic calcifications and extensive epithelial cell rests of Malassez were evident (**Figure 8C**). The bone showed sections of very strong, at times gross, interconnecting trabeculae. The apical sections exhibited mature lamellar bone, with few osteons and cement lines and generally strong mineralization, with crestally and focally hardly calcified fibrous bone (**Figure 8D**). The bone showed a normal layer of lining cells; no osteoblasts were detected. Minor bone apposition was observed in some areas. There were focal, especially crestal, small resorption lacunae with no osteoclasts. The intertrabecular spaces contained richly vascularized, loose connective tissue and normal fatty tissue. There were no signs of inflammation.

Discussion

The treatment of patients with CCD should begin in early childhood and adolescence. An early diagnosis is therefore crucial. If this phase could not be utilized for treatment, a prosthetic rehabilitation can be a successful treatment mode. It is possible to perform this treatment with complete dentures [50], which provide adequate function and an improved aesthetic appearance by simple means at limited cost. Beyond this approach, however, an implant-supported rehabilitation is also possible. The advantages of implant therapy compared to conventional complete dentures include the prevention of jaw resorption and the possibility to deliver fixed or dentist-removable restorations or to stabilize a removable denture.

The decision whether fixed or removable implant-supported restorations are to be provided must be discussed in advance with the patient. Advantages and disadvantages, such as chewing comfort, phonetic issues, cleanability, psychological acceptance and aesthetics should be mentioned [51]. Variations in cost between the various types of care resulting from different implant number and different levels of complexity of the dental services

should also be discussed with the patient [52]. Thus, on the one hand, CCD patients can be treated with removable dentures supported by implants. Relevant case reports have been published that describe a stable implant situation over the years [46, 48, 53]. Alternatively, fixed prostheses on implants can be provided [49]. The procedures and underlying concepts mentioned in the present case report were adopted for the CCD case following the rules of general oral implantology. The number of implants, especially the maxillary six implants, was selected following currently accepted findings [54].

The case presented showed a favourable baseline situation for implant therapy. The high values for primary and secondary stability as determined by resonance frequency analysis indicated the suitability of the bone for implant treatment [55, 56]. Despite the high ISQ values at the time of inserting the implants, a conventional loading protocol was chosen with a healing period of three months in order not to increase the risk of extraneous factors compromising treatment success [57, 58]. The histological examination of the biopsy from the maxillary showed strong, thick trabeculae of lamellar bone, compared to healthy bone in patients of the same age.

The histological studies presented so far relate to adolescent patients [41, 59]. The maxilla consisted otherwise of soft, trabecular bone with distinct woven bone remnants, hence the bone quality was inferior [60, 61]. However, the bone was not consistently mineralized; it showed no signs of remodelling and only minor resorption. The biopsy from the mandible showed a bone structure similar to the maxilla. However, areas of woven bone were found here as well.

In this way, the histological findings in this case are similar to those described by Fleischer-Peters, Luckinmaa and Dard [23, 59, 62]. In these and other publications [41, 59], the histological studies relate to the bone structure of juvenile patients. Data on the structure of the jawbones of adult CCD patients were not found in the recent literature. No negative effects of bone quality on osseointegration can be derived from the clinical and histological findings.

Because of the wide zone of keratinized gingiva and the voluminous available bone, a minimally invasive surgical approach was selected. Less pain, swelling and patient discomfort have been described for this “flapless surgery” [63]. The flapless approach yielded similar results compared to the conventional flap with regard to the remodelling of the crestal bone around the implant [64]. Possible disadvantages included the fact that the insertion depth (vertical endpoint) of the implant cannot be visually checked and that no corrective manipulation of the soft tissue around the implant is possible. Punching results in a loss of keratinized gingiva, with possible aesthetic and functional disadvantages [65].

Conclusion

The implant-supported rehabilitation of a patient with CCD was described in a case report. Since the 47-year-old patient had not received orthodontic treatment in childhood-which would have been the treatment modality of choice-six implants each were inserted in each jaw and restored with fixed ceramically veneered bridges. The clinical parameters and histological evaluation of this one clinical case suggest that the concepts familiar from general oral implantology in terms of surgical and prosthetic procedures can be adopted for older patients with CCD.

Disclosure of conflict of interest

None.

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