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Up-to Date Review And Case Report

Dental implant placement in a patient with cystinosis. A case report

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Abstract – Introduction: Cystinosis is a rare genetic disease due to a defective transport of cystine out of the lysosomes, caused by a mutation of the gene encoding for the lysosomal carrier protein, the cystinosin. Cystine accumulation results in the formation of intracellular cystine cristals, that causes tissular and multi-organic lesions (kidney, eyes, endocrine glands). **Observation:** We report a rare case of a patient affected by infantile nephropathic cystinosis, who consulted for an implant placement in a single-tooth gap. **Discussion:** Accumulation of cystine leads to tissue damage, primarily in the kidney, the liver and the cornea, but other organs, such as the mouth, teeth and jaws may be also involved. The article aimed to present oral manifestations associated with this storage disease and to discuss how oral surgeon can evaluate and manage these patients despite the lack of a standardized protocol.

Introduction

Cystinosis [OMIM 219800] is a genetic systemic disease caused by mutations of the *cystin transport nephrotic syndrome* gene, located on the 17p13 chromosome, encoding for cystinosin. Cystinosin is a lysosomal transmembrane protein exporting cystine, the dimer form of the aminoacid cysteine, to the cytoplasm. Cystinosis is an orphan incurable metabolic disease affecting about 2,000 people worldwide. In France, the prevalence is estimated to 1 per 200 000 inhabitants [1,2]. Cystinosis affects many organs and tissues, especially kidneys causing a chronic renal impairment, cornea and endocrine glands (with hypothyroidism, diabetes mellitus and hypogonadism). In kidneys, cystine accumulation provokes apoptosis of proximal tubular cells resulting in Fanconi syndrom. Extrarenal manifestations are due to intracellular cystine crystallization. Three clinical forms are described: (1) the infantile nephropathic form (>95% of cystinosis patients) is the most severe one with a Fanconi syndrom emerging during the first years of life, complicated by growth impairment by the age of 6 months and chronic renal insufficiency by the age of 6 years old; (2) the juvenile nephropathic form with a late onset during late childhood or adolescence and with mild manifestations; (3) the adult non-nephropathic form affecting only the cornea and rarely appearing before adulthood. Diagnosis of cystinosis is confirmed by increased levels of cystine leukocyte content and can also be reached by demonstration of cystine crystals in tissues [3].

The main treatments aim to take care of the chronic renal insufficiency with hemodialysis or renal transplantation, and of other complications. Since 1994, cysteamine, a cystine-depleting treatment is available, reducing intralysosomal cystine concentration (Fig. 1), thus preventing crystallization [4]. Two main forms exist: the oral form (cysteamine bitartrate) and the topical one by eye drops (cysteamine hydrochloride) that dissolves corneal crystals [5]. If those specific treatments are started early in life, the evolution of the disease is favorable with a reduction of mortality and morbidity [6].

This report, associated with a literature review, describes the case of a patient suffering from cystinosis, the clinical oro-maxillofacial manifestations of the disease observed and the precautions required for oral surgery.

Observation

A 34-year-old male patient was referred to the Department of Oral Surgery of the University Hospital of Reims for the replacement of the upper left first molar by a dental implant. The tooth had been removed because of an advanced dental decay. His medical history revealed an infantile nephropathic cystinosis, resulting in a terminal renal insufficiency treated

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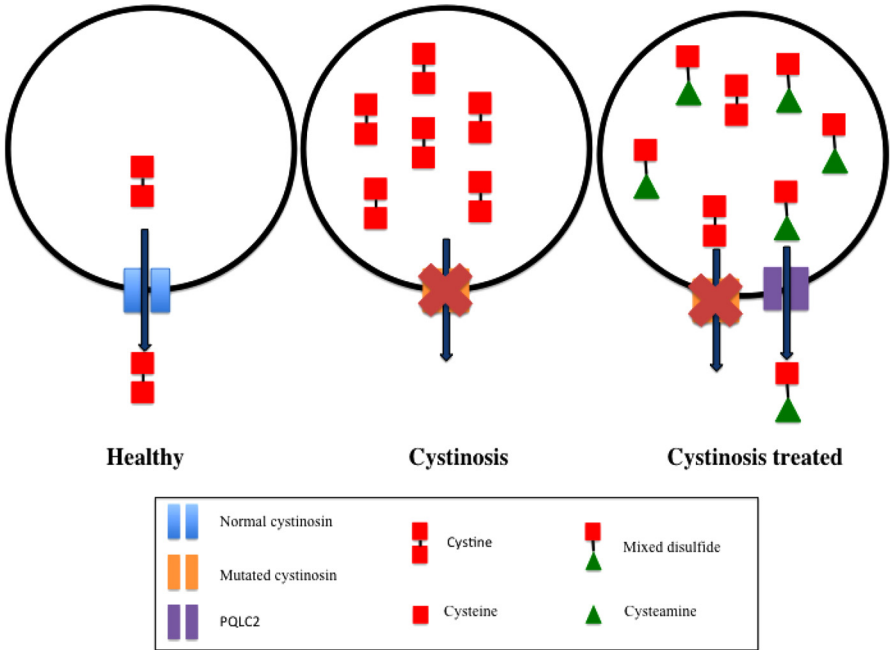

Fig. 1. Cysteamine prevents cystine accumulation in lysosomes (C. Brétaudeau). In healthy patients, cystine is exported from lysosomes by a specific protein, cystinosin. In cystinotic cells, cystinosin is inefficient and cystine accumulates into cells. The specific treatment, cysteamine replaces one cysteine creating a mixed disulfide molecule, and allowing it to exit the lysosome by an other transmembrane protein, PQLC2.

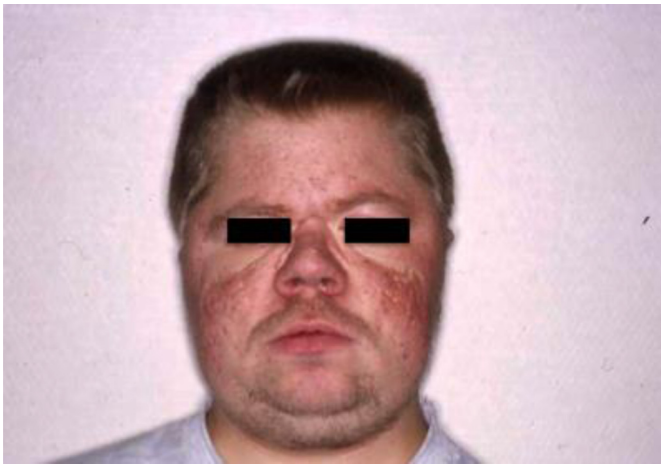

Fig. 2. Extraoral examination. The facial examination presents a severe acne with papulo-pustular lesions and comedons, a mesiofacial typology and a class III profile. The central third of the face appears smaller than the frontal and lower thirds.

with renal transplantation at the age of 10 (1993). The immunosuppressive treatment consisted in prednisone (15 mg/24 h), mycophenolate mofetil (1000 mg/24 h) and ciclosporine (100 mg/24 h). The specific treatment consisted in cysteamine bitartrate (750 mg 4 times each 24 h) and cysteamine hydrochloride 0.55% (2 drops 3 times a day). His medication included darbepoetine alfa (20 μm IV monthly), iron supplementation (66 mg twice a day), and folic acid (5 mg daily) against anemia, enalapril (5 mg daily) for renovascular arterial hypertension, calcium and vitamin D supplementations for osteoporosis, isotretinoin, spiramycine and protective cream for acne. Corticosteroid-induced diabetes was diagnosed in 2004 and was normalized with a balanced diet. The patient was non-smoker. He was 1 m 43 tall, weighted 42 kg, and his body mass index was 20.5 $kg \cdot m^{-2}$. His surgical background reported an arteriovenous fistula in 1991, an appendicectomy in 2005, and the removal of his 4 third molars and of the first left maxillary molar in 2006 in the same Department. The biology report found a stable kidney function 23 years after transplantation and a well-tolerated immunosuppressive treatment.

Facial examination (Fig. 2) highlighted a mesiofacial typology with hyperdivergence and skeletal class I with class III tendency, and severe acne. Intra-oral examination showed that the edentulous span was acceptable in size for the replacement of upper first molar (Fig. 3A). It also revealed bone deformities (Fig. 3B), dental malpositions (Fig. 3), soft tissue lesions, such as benign migratory glossitis (Fig. 4A) and gingival plaques mimicking hyperkeratosis (Fig. 4B); dental abnormalities with enamel defects, enamel hypoplasia and exogenous discolorations (Fig. 3). The panoramic radiograph (Fig. 5) showed complete bone healing of surgical sites. The Cone Beam Computed Tomography (Fig. 6) revealed the detailed planning of implant placement. The mesiodistal gap, the bone height and the crest width permitted the placement of a 6 × 10 mm implant. The bone quality was low with thin cortical bone surrounding a loose trabecular bone (Class IV according to Lekholm and Zarb, 1985). There were no medical conditions or obstacles to implant therapy. The decision was made to use the Zimmer Dental® Trabecular Metal implant (Fig. 7A) and a conventional loading protocol. No biological analysis was realized prior to the surgery. Dental

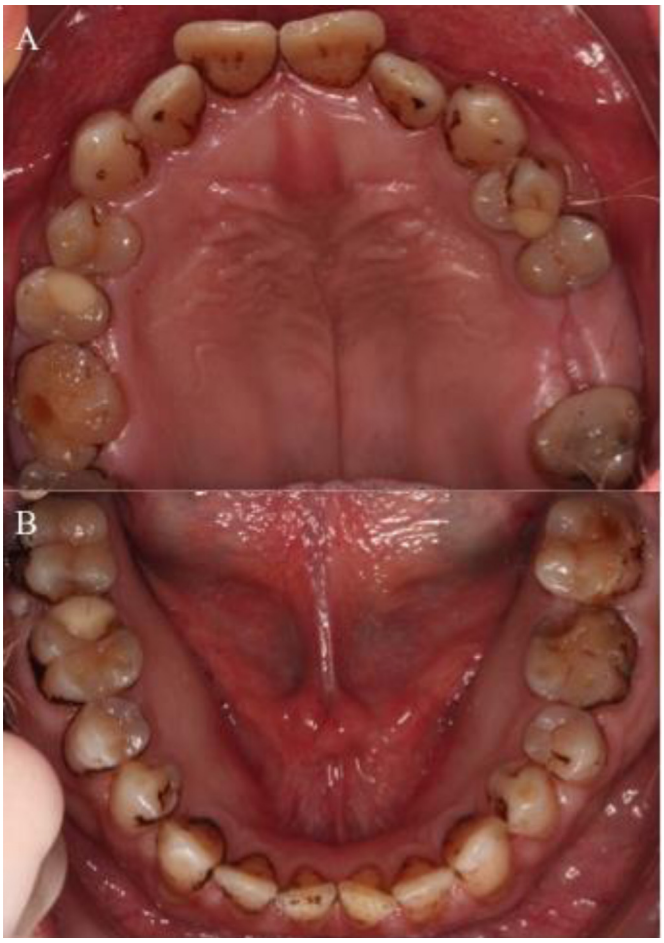

Fig. 3. Dental examination. Figure shows many dental abnormalities: enamel defects and enamel striations as clinical signs of enamel hypoplasia, cervical exogenous discolorations on all teeth, and dental malpositions.

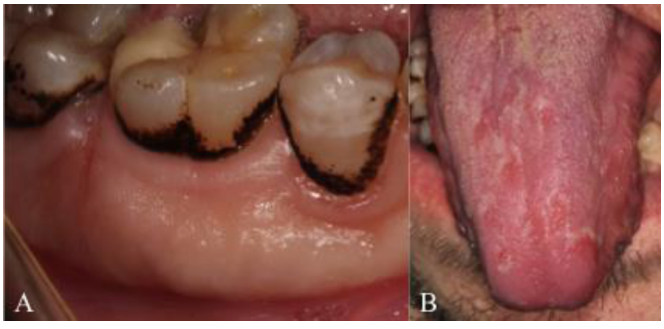

Fig. 4. Oral mucous examination. Figure presents mucous membrane abnormalities, (A) on the gingiva and (B) on the tongue. (A) shows gingival hyperkeratosic lesions. (B) shows benign migratory glossitis.

implant surgery was performed under prophylactic antibiotics (amoxicilline 1000 mg 3 times a day, started 48 h before surgery). Despite a low-density bone protocol (slight sub-drilling [diameter: 5.1 mm], no thread and slow speed drilling [800 rpm] for the final implant bed preparation), the implant was seated at approximately 20 $N \cdot cm^{-1}$ of insertion torque. The

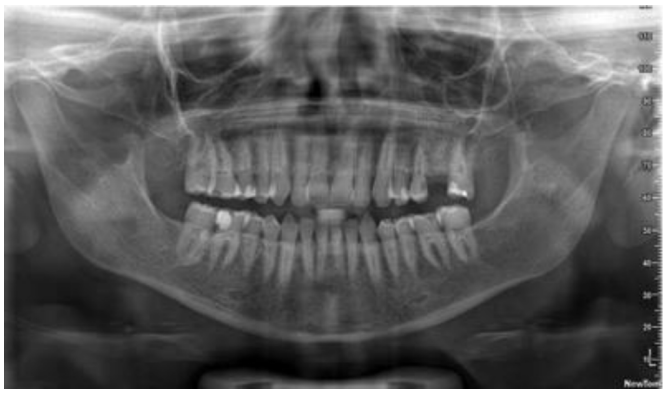

Fig. 5. Orthopantomogram. The panoramic radiograph shows the absence of the wisdom tooth and the first left upper molar. The bone volume is sufficient in the gap between 25 and 27 for an implant placement.

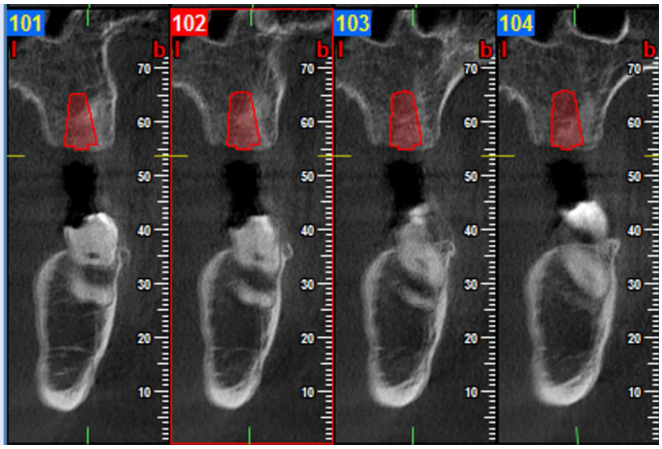

Fig. 6. Pre-implant CBCT examination. NNT Viewer software (NewTom, Verona, Italy) allowed to visualize implant in the alveolar ridge and to determine orientation, diameter and length of the proposed implant. A 6 × 10 mm implant (Zimmer Dental Trabecular Metal®) was chosen. Trabecular bone appeared loose. Bone hypertrophic abnormalities were notable on the lingual side of the mandibule.

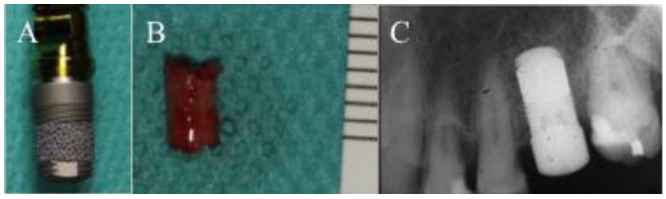

Fig. 7. Trabecular Metal Implant placement (Zimmer Dental®). A poor-bone quality implant, with large diameter was chosen to replace the upper left first molar. (A) The implant presents a structure with interconnected-porosity made of tantalum. (B) The drilling bone was harvested to be analyzed. (C) The 3 months postoperative radiograph shows a good osseointegration.

drilling bone was harvested (Fig. 7B). A biopsy of the gingival hyperkeratosis was performed. Both microscopic analyses found no histological abnormality. After a 4-month period, the healing cap was placed (Fig. 7C) and the implant

osseointegration was manually confirmed. Then, the patient was referred to the Prosthodontic Department for the fabrication of a prosthetic restoration.

Discussion

Cystinotic patients have no specific oral manifestation and jawbones disorder. They present osteodystrophy caused by metabolic acidosis, hypophosphatemia, reduced synthesis of calcitriol and reduction of differentiation of osteoblasts precursors into mature cells [7]. Some authors have found polygonal crystals inside macrophages from bone marrow aspirate [8,9]. These crystals, which are pathognomonic for cystinosis, appear birefringent under polarized light. Furthermore, cystinosic patients may present rickets caused by the chronic renal insufficiency [10]. In addition, transplanted patients may develop glucocorticoid-induced osteoporosis [11]. In the present case, the low trabecular density was confirmed on ConeBeam CT scan and during the surgical implant placement. No cysteine crystal was found in bone drilling. The low-bone quality exhibits a higher rate of dental implant failure. Trabecular Metal Implant may be indicated. Porous implant, tantalum surface and large diameters are used to improve the contact between osseous structure and dental implant. Tantalum has been used in orthopedic surgery since 1940s and a porous structure mimicking the bone one was developed in the 1990s. It presents a high biocompatibility [12,13]. The porosity of the tantalum structure promotes the ingrowth of bone within the implant core. However, this design structure raises the question of its use in a septic environment. Orthopedic clinical studies have shown that the main cause of implant failure in low-quality bone is the infectious complication [14]. Further studies will be needed to evaluate the real advantages of Trabecular Metal Implant in comparison with conventional titanium dental implant.

Soft-tissue lesions have also been described, especially benign migratory glossitis appearing more frequent in cystinotic patients [15]. A gingival hyperplasia including cystine crystals on biopsy was also reported in a patient with kidney transplant treated by cyclosporin [16]. In the case reported, geographic tongue was present but no crystal was found in the attached gingiva. Lack of cystine crystal in alveolar bone and in gums can be explained by its histological absence or by technical difficulties. Indeed, the visualization of cystine crystals requires many precautions, including an analysis on frozen sections (no fixation technique). The absence of cystine crystal can be related to the cystine-depleting therapy. Here, the treatment seemed rather efficient since the patient doesn't present major non-renal complication, like hypothyroidism, that generally occurs in the second decade of life [4].

Craniofacial anomalies are also described. Indeed, Bassim *et al.* [15] found a tendency to reduced body length, increased gonial angle associated with reduced mandibular ramus height, increased lower anterior facial height and increased vertical growth with retropositionning of both maxilla and mandible. These abnormalities are associated to growth retardation and muscular dysfunctions, caused by crystals accumulation in myocytes, inducing reduced activity of masticator muscles and a low tongue position. In the case presented, the hyperdivergence and class III tendency follow those features. The patient presented no muscular abnormality.

Some studies have also reported dental abnormalities, such as taurodontism, absence of lamina dura, enlarged pulp, delayed dental development and enamel defects, mostly in children with chronic renal failure [15,17,18]. In this case, the patient presents enamel hypoplasia but no taurodontism nor pulp calcification.

The caries status was similar to general population and usual direct restorations were used. The involvement of salivary changes is hypothesized as protective, mainly because of higher salivary concentrations of urea, potassium, sodium, creatinin and proteins, that increase its pH and its buffering capacity and reduce dental demineralization [15,18,19]. Thus, salivary samples could be harvested and analyzed to compare to general population.

All these oral manifestations described will be less frequently observed because there is now a specific treatment. Cysteamine (Cystagon®) was allowed on the market in the US and in France respectively in 1994 and 1997. This drug decreases toxic levels of cystine in cells that can lead to irreversible organ damage by cystine crystal formation. A new extended release form of cysteamine (Procysbi®) provides a continuous control cystine and may delay the progression of cystinosis and its complications in multiple organs, in particular in bone tissue.

Patients suffering from cystinosis require specific precautions because of kidney failure and immunosuppressive drugs, that expose them to a high infectious risk. Antibiotic prophylaxis is systematically required before dental care and oral surgery [20].

Conflict of interest

The team declares a conflict of interest with the Zimmer Company that offered the Trabecular Metal Implant.

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