Severe Periodontitis in a Patient With Hyperoxaluria and Oxalosis. A Case Report and Review of the Literature

Vasilios Panis, DDS, DrOdont, Associate Professor, National and Kapodestrian University of Athens,* Athens, Greece, Konstantinos I. Tosios, DDS, DrOdont, Lecturer, National and Kapodestrian University of Athens ,† Athens, Greece, Eleni Gagari, DMD, DMSc, Assistant Professor, National and Kapodestrian University of Athens ,‡ Athens, Greece, Terrence J. Griffin, DMD, Associate Professor, Tufts University,# Boston, Massachusetts, USA, Petros D. Damoulis, DMD, DMSc, Private Practice, Athens, Greece

* Department of Periodontology, National and Kapodestrian University of Athens School of Dentistry

† Department of Oral Pathology, National and Kapodestrian University of Athens School of Dentistry

‡ Department of Dermatology, National and Kapodestrian University of Athens School of Medicine

Department of Periodontology, Tufts University School of Dental Medicine

Background: Hyperoxaluria is a metabolic disease with excessive urinary oxalate excretion, which can be primary or secondary. Hyperoxaluria can result in chronic renal disease and renal failure. Calcium oxalate crystals can be deposited in oral tissues and the disease can be associated with severe periodontitis and tooth loss.

Methods: The periodontal condition of a 38-year-old patient with a diagnosis of hyperoxaluria and end-stage renal disease is presented. The patient's periodontal status was monitored over a period of several weeks and extracted teeth were submitted for histopathologic evaluation.

Results: The patient was diagnosed with generalized severe periodontitis and external root resorption. Initial periodontal treatment consisting of oral hygiene instructions and scaling and root planing was performed. However, despite an initial decrease of soft tissue inflammation, the patient's periodontal condition deteriorated and eventually all the teeth had to be extracted. Deposition of calcium oxalate crystals in the periodontal tissues was confirmed histologically.

Conclusions: Long-standing hyperoxaluria can be associated with severe periodontitis and external root resorption, resulting in tooth loss. The pathogenetic mechanisms of hard tissue destruction are still unclear.

Key Words: hyperoxaluria; calcium oxalate; inflammation; periodontal diseases; tooth loss.

Hyperoxaluria is a metabolic disease characterized by excessive (>45 mg / day) urinary oxalate excretion.[1] It is classified as primary or endogenous, resulting from overproduction of oxalic acid, and secondary that is attributed to increased intestinal absorption (enteric hyperoxaluria) or increased dietary uptake (dietary hyperoxaluria) of oxalate.[1,2] Primary hyperoxaluria (PH) is inherited as an autosomal recessive trait and is characterized by a defect in glyoxylate metabolism due to lack or deficiency of the peroxisomal, liver-specific alanine glyoxylate aminotransferase (AGT) (PH type 1, PH-1) or, very rarely, a cytosolic enzyme with glyoxylate reductase, hydroxypyruvate reductase, and D- glycerate dehydrogenase activities (PH type 2, PH-2).[2] Dietary hyperoxaluria on the other hand, can be caused by malabsorption of diverse origin (Crohn's diseases, ileal bypass, short bowel syndrome, low calcium intake, *Oxalobacter formingenes* decolonisation of the gut etc), while increased concentration of urinary oxalate may result from the consumption of different foods, such as spinach, peanut oil, beetroots, nuts, tea, ethylic glucose, etc.[1]

The relative insoluble calcium oxalate concentrates in body fluids and tissues exerting various pathologic effects.[3] In particular, in PH-1, calcium oxalate precipitation in the supersaturated urine forms crystals and stones in the upper urinary tract, resulting in nephrocalcinosis and recurrent

urolithiasis.[2] The diagnosis of PH-1 is usually made during the first or second decade of life, although it may remain unrecognized in some patients until the third or fourth decade of life.[1] As PH-1 progresses, it adversely affects renal function, resulting in chronic renal disease (CRD) and possibly end-stage renal disease (ESRD). In the latter case, the patient most likely will require renal replacement therapy with hemodialysis, peritoneal dialysis, or kidney / liver transplantation.[2]

When deposition of calcium oxalate crystals in hyperoxaluria involves extrarenal tissues it is termed systemic oxalosis.[2] The bones are usually affected, followed by the retina, arterial walls, peripheral nervous system, myocardium, the thyroid gland, and the skin.[1,2] Oxalosis of the oral tissues and the jaws is an uncommon late onset manifestation of ESRD.[4-6] To the best of our knowledge only eight patients with oral manifestations of oxalosis have been reported in the English-language literature (table 1).[4-10] Most of these case reports include generic periodontal findings, however the periodontal condition of patients with hyperoxaluria has never been examined or discussed in detail.

In the present report, we present a patient with primary hyperoxaluria and ESRD, where oxalosis was accompanied by severe periodontitis. Furthermore, the patient's periodontal condition was monitored for 24 months, including an attempt to delay periodontal disease progression through scaling and root planning.

Case description and results

A 38-year-old male presented in November 2005 at the private dental office with recent gingival bleeding of the upper central incisors and significant mobility that caused difficulty in mastication. He reported that he had never undergone any kind of periodontal treatment. His medical record included primary hyperoxaluria, CRD and ESRD. The disease manifested with nephrolithiasis of the left kidney at the age of 3 years and extensive hematuria at the age of 4 years that was managed with surgical removal of the stone from the ureter. The operation was repeated twice at the ages of 16 and 26 years respectively, and was followed by lithotripsy. ESRD was diagnosed at the age of 36 years. The patient also developed secondary hyperparathyroidism (parathyroid hormone-PTH 105.20pg/ml, normal limits 16-65pg/ml; alkaline phosphatase-ALP 433U/L, normal limits 80-270U/L; phosphorus 5.5mg/dl, normal limits 2.5-4.8mg/dl; total calcium 8.7mg/dl, normal limits 8.8-10.8mg/dl). His CBC and differential was within normal limits. Finally, the patient was placed in renal replacement therapy with peritoneal dialysis, was medicated with ferric sulphide, folic acid and the calcium-free, aluminum-free phosphate binder sevelamer hydrochloride. He was scheduled for renal transplantation.

The patient brought with him a panoramic radiograph taken in July 2005 (Fig. 1A) and a full mouth series taken in October 2005 (Fig. 1B). Examination of the radiographs showed severe loss of alveolar bone (70-75%), loss of lamina dura and thickening of the periodontal ligament. Upon clinical examination, severe generalized periodontitis was evident (Fig. 2A), whereas some teeth presented light grayish discoloration and cervical root resorption (Fig. 2A, Fig. 2B). Periodontal examination included measurement of clinical probing depth and loss of clinical attachment in six sites of each tooth (mesial-mid-distal/bucal and lingual), plaque index,[11] gingival index,[12] and tooth mobility. Detailed occlusal analysis was not performed. A comprehensive description of the periodontal findings is presented in Table 2. The rest of the oral mucosa was within normal limits. Several teeth presented with pronounced external root resorption (Fig. 3A, 3B, 3C). There was no bone lesion suggestive of renal osteodystrophy.

Short and long term prognosis for most teeth was considered as poor or worse according to the criteria of McGuire and Nunn (table 2).[13] Since the patient was on a waiting list for renal transplantation, the treatment plan included immediate extraction of all teeth with questionable or hopeless prognosis, i.e., teeth with severe periodontal lesions (involvement of root bifurcation,

bone lesions demanding complex surgical procedures with questionable success), and teeth with periapical lesions or extensive caries. After consulting with the attending physician, antibiotic prophylaxis was administered during all phases of treatment. Due to the frequency of the dental appointments amoxicillin, clindamycin, and clarythromycin were interchangeably used, in accordance to the AHA protocol.

During the first session, the upper central incisors were extracted and a Maryland-type fixed prosthetic restoration was placed. Clinical photographs were taken after the placement of the prosthetic restoration at the patient's request and after signing an informed consent. The rest of the extractions were postponed, as the patient was uncomfortable with the idea of using a full or partial denture and he agreed to undergo initial periodontal therapy. This initial phase of the periodontal treatment included oral health instructions, as well as scaling and root planning (SRP). During SRP, it was noticed that the granulation tissue removed from the periodontal pockets contained large amounts of an unusual, psammomatous material, not consistent with tartar. The patient returned for re-evaluation in February 2006. Clinical examination revealed a remarkable decrease of plaque index (PI 20% vs. 36%), reduction of gingival inflammation (GI 20% vs. 32%), and decrease in the periodontal pocket depths (table 2). However, tooth mobility overall increased, a finding inconsistent with the apparent improvement of soft tissue findings. Teeth #23, 26, 28, 30, 31 were extracted shortly after the re-evaluation appointment. During the next few weeks, tooth mobility continued to increase, causing discomfort to the patient during mastication. Prognosis was reassessed and was determined that all the remaining teeth had questionable or hopeless prognosis. The patient stated that his renal transplantation was scheduled and after consultation with his attending physician, it was decided that the remaining teeth had to be extracted. Several of the extracted teeth and their surrounding tissues were fixed in 10% neutral buffered formalin and submitted for pathologic examination.

Pathologic examination

Soft tissues, totaling 1.3 × 1.0 × 0.4 cm, two premolar and two molar teeth were ultimately processed. The soft tissues were gray-white, with a grisly consistency, and on closer examination showed small, yellow-white granules. The teeth were decalcified. Five-micron thick hematoxylin and eosin stained sections showed granulation tissue partially covered by stratified squamous epithelium, focally covered by colonies of micro-organisms. The granulation tissue was occupied by circular crystalline aggregates focally surrounded by giant cells (Fig. 4). Individual crystals were light green, needle-shaped and, occasionally, radiated from the center of the deposits forming rosettes. They were refractile and birefringent on polarized light examination (Fig. 5), and stained positive with Pizzolato's silver method for calcium oxalate, but not with Alizarin red for phosphate oxalate. Spaces presumably occupied by crystalline deposits were seen in the predentin and odontoblastic layer of decalcified teeth, and some of them were embedded in pulp stones (Fig. 6). The microscopic findings were consistent with calcium oxalate crystals deposition and oxalosis.

Discussion

The presenting signs in our patient with hyperoxaluria, CRD, and ESRD were recent gingival bleeding and tooth mobility that caused difficulty in mastication. Although oral hygiene is reported as poor in individuals with ESRD, an increased risk of periodontitis has not been established.[14,15] However, periodontitis with tooth pain and mobility,[4-6,8-10] and grayish intrinsic discoloration of teeth,[7,10] as seen in our case, have been reported in oxalosis. Since the first report of oral manifestations in oxalosis by Glass in 1973,[7] seven additional cases have been reported in the English language.[4-6,8-10] The major oral findings in previously reported cases and the present one are summarized in Table 1. Six patients had primary and one secondary hyperoxaluria. In two patients the diagnosis of primary hyperoxaluria could neither be confirmed nor be excluded,[5] and in

one oxalosis was considered as a complication of hemodialysis due to chronic glomerulonephritis and ESRD.[4] Five patients were male and three female, and the age at diagnosis ranged from 7 to 55 years. A family history of renal disease was provided in three cases.[6,9,10]

Common oral radiographic findings in patients with oxalosis include alveolar bone loss[4,9] and loss of lamina dura,[5,8,10] thickening of the periodontal ligament,[9] and root resorption[4-6,8-10] that may be external or/and internal and result in pulp exposure.[9] In addition, radiolucencies of the body of the mandible[8] and a finely granular and homogenous trabecular pattern[4] have been described. Bone lesions in CRD patients may be manifestations of renal osteodystrophy.[16,17] In fact, the patient reported by Wysocki et al.[8] had developed osteomalacia, a type of renal osteodystrophy, but the jaw lesions were found to contain tophi of oxalate crystals, while in the case of Fantasia et al.[4] no pathologic diagnosis was provided. Aluminum-related osteomalacia, another type of renal osteodystrophy, was present in both cases of Boyce at al,[5] but no bone lesions were described in the jaws. Our patient was diagnosed with secondary hyperparathyroidism that is associated with osteitis fibrosa, the most common type renal osteodystrophy that may manifest in the jaws with lesions resembling fibrous dysplasia, enlargement of the mandible, and malocclusion.[16] The rather recent onset of secondary hyperparathyroidism may account for the lack of signs of osteitis fibrosa in the present case.

Oxalate crystals have been found in every anatomical location of the oral cavity subjected to microscopic study, including the oral mucosa,[6] gingival tissues,[4,5,8,10] alveolar bone[5,8,9] and the bone surrounding tooth germs,[7] periodontal ligament,[4,5,8,9] odontogenic epithelium,[7,9] cementum,[5,8,9] dentin,[7-9] dental pulp and pulp stones,[5-9] the odontoblastic layer,[7] as well as the submandibular gland.[7] The widespread presence of calcium oxalate crystals in the gingival tissues of patients with oxalosis prompted some authors to propose gingival biopsy as an easy and reliable procedure for the documentation of the diagnosis.[4] It should be noted that the presence of calcium oxalate on the root surfaces of teeth is not diagnostic of oxalosis, as has been found in primary teeth from four systemically healthy children with localized or generalized juvenile periodontitis.[18] Formation of those crystals in those cases were attributed either to the protracted fixation in acidic formalin or to the rapid root resorption.

Tooth mobility in the reported cases of oxalosis was very severe and one patient stated that “he had extracted several of his own teeth with his fingers”.[8] Fantasia et al.[4] associated tooth mobility to the extensive destruction of the periodontal ligament due to the deposition of calcium oxalate crystals. They hypothesized that circulating calcium oxalate crystals are preferentially deposited in the inflamed periodontium, as is usual in tissues with an increased vascular permeability, invoking an intense foreign body granulomatous reaction that progressively results into massive local tissue destruction. Oxalate extravasation may, also, be facilitated by fenestrated capillaries that are present in non-inflamed oral tissues, such as the odontoblastic layer of the pulp.[4] Boyce et al.[5] considered that this mechanism alone cannot account for the severe tooth mobility and suggested that it is exaggerated by the presence of aluminum-related osteomalacia in oxalosis patients. High levels of aluminum in the serum of patients undergoing hemodialysis can be attributed to contamination of dialysis water and/or use of aluminum salts per os to reduce absorption of dietary phosphate. According to their view, alveolar bone destroyed by the granulomatous reaction to oxalate crystals as well as secondary hyperparathyroidism, is replaced by osteoid that remains uncalcified due to the toxic effect of aluminum. This increases tooth mobility, propagates the deposition of new oxalate crystals, and enhances the granulomatous reaction.

The pathogenetic mechanisms that may be responsible for the pronounced alveolar bone loss in patients with oxalosis are unclear. It has been demonstrated that high concentrations of oxalate may promote free radical production in renal epithelial cells possibly by directly affecting mitochondrial metabolism and/or inhibition of the enzymes responsible for free radical degradation. These

reactive oxygen species, which include superoxide, peroxide and hydroxyl radicals, exert a direct toxic effect on these cells.[19] Furthermore, excessive IL-1 mRNA transcription has been demonstrated in hypercalciuric patients, as well as the presence of a polymorphism in the IL-1 receptor antagonist gene in patients with calcium oxalate stones.[20] Phagocytes also seem to play a role in tissue destruction associated with presence of crystals in various tissues. Oxalate crystals exocytosed to the interstitial tissues are destroyed through a local inflammatory response involving macrophages,[2] whereas monosodium urate crystals can activate neutophils via stimulation of tyrosine kinase activity.[21] Activated neutrophils in turn produce proinflammatory cytokines and free radicals, which are considered to play an important role in acute episodes of inflammatory diseases such as gouty arthritis.[21] It can be postulated that similar events take place in the periodontal tissues, initiated by the presence of oxalate crystals, thus accelerating periodontal tissue destruction.

There is no report in the literature regarding response to periodontal therapy in patients with hyperoxaluria. A common finding was that several teeth had to be extracted in a relatively short period of time. The same trend was evident with our patient, even though initial periodontal therapy was performed. During follow up it became apparent that control of soft tissue inflammation was not accompanied by arrest of periodontal disease progression. The increase in mobility was the most striking finding, which most likely was a result of inflammatory changes exacerbated by oxalate crystals. In that light, traditional mechanical periodontal therapy in our patient was probably of limited use. Given that the prognosis for most teeth at reevaluation was questionable to hopeless, no improvement was expected even after renal transplantation, therefore extraction of all teeth was recommended. Although we cannot attempt treatment recommendations based on case reports, it appears that long term periodontal prognosis in patients with long-standing hyperoxaluria is poor.

The number of patients with hyperoxaluria that require dental treatment is expected to be rising, as modern life-sustaining methods prolong survival of those individuals. Early periodontal diagnosis may be a critical factor in prolonging tooth survival, but this hypothesis has yet to be tested. Furthermore, it would be interesting to investigate the presence of calcium oxalate crystals in gingival biopsies from patients with laboratory findings consistent with oxalosis but no periodontal disease, in order to evaluate to role of gingival biopsy as a mean for establishing the diagnosis.[4]

Acknowledgments

N/A

Conflicts of Interest

None

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Address for correspondence: Vasilios Panis, Department of Periodontology, National and Kapodestrian University of Athens School of Dentistry, 2 Thivon Street, 11527 Athens, Greece. e-mail: vpanis@dent.uoa.gr fax: + 30 210 746 1202 (email and fax may be published).

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Figure 1. Radiographs demonstrating generalized severe alveolar bone resorption. A: panoramic (July 2005). B: full mouth series (October 2005)

Figure 2. Clinical manifestations of hyperoxaluria on the gingival tissues and teeth. Evidence of severe periodontitis and cervical root resorption. A: frontal view. B: right side view.

Figure 3. Severe external root resorption of teeth. A, B: radiographic evidence C: extracted lower incisor

Figure 4. Granulation tissue occupied by circular crystalline aggregates, focally surrounded by giant cells (hematoxylin and eosin stain, original magnification ×400).

Figure 5. Crystals' birefringence on polarized light (original magnification ×200).

Figure 6. Spaces presumably occupied by crystalline deposits embedded in pulp stones (hematoxylin and eosin stain, original magnification ×400).

Table 1. Major oral findings in 9 patients with hyperoxaluria and oxalosis

Reference	Diagnosis / Condition	Age	Gender	Clinical and radiographic findings	Anatomic location of depositions
Glass[7]	primary hyperoxaluria	7	F	• intrinsic discoloration of deciduous and permanent teeth	bony crypt of the developing tooth, odontogenic epithelium, dental pulp, odontoblastic layer, dentinal tubules, submandibular gland
Wysocki et al.[8]	primary hyperoxaluria	21	M	• tooth pain and mobility • loss of lamina dura, external and internal tooth resorption, radiolucencies of the mandibular body	gingival tissues, bone, periodontal ligament, cementum, dentin, dental pulp
Fantasia et al.[4]	chronic glomerulo-nephritis, ESRD, hemodialysis	55	F	• tooth mobility, periodontitis • alveolar bone loss, external root resorption, altered trabecular pattern	gingival tissues, periodontal ligament
Boyce et al.[5]	idiopathic hypercalcinosis, hemodialysis idiopathic renal calcuci, CRD, hemodialysis	22 14	M M	• tooth pain and mobility, periodontitis • loss of lamina dura, external and internal tooth resorption	gingival tissues, bone marrow, periodontal ligament, cementum, dental pulp and pulp stones
Moskow[9]	primary hyperoxaluria	29	M	• tooth pain and mobility, teeth loss, periodontitis • alveolar bone loss, periodontal ligament thickening, root resorption, pulp exposure	alveolar bone (haversian systems, marrow spaces), periodontal ligament, odontogenic epithelium (debris of Malassez), cementum, dentin, dental pulp, osteodentine
Hedemark et al.[6]	primary hyperoxaluria	25	M	• tooth mobility, periodontitis • root resorption	oral mucosa, periodontal membrane, dental pulp
Rahima and DiMauro[10]	primary hyperoxaluria	14	F	• tooth mobility and discoloration • loss of lamina dura, external root resorption	gingival tissues

F: Female, M: Male.

Table 2. Periodontal status of the patient

	Initial Visit	Re-evaluation
Probing Depth (No of sites)		
<4 mm	6	18
4-6 mm	22	25
7-9 mm	20	39
≥10 mm	72	22
Clinical attachment level (No of sites)		
<4 mm	4	NA
4-6 mm	16	NA
7-9 mm	20	NA
≥10 mm	80	NA
Plaque Index[11]		
	36%	20%
Gingival Index[12]		
	32%	20%
Furcation Involvement (teeth)		
II	19	NA
III	2, 3, 15, 30, 31	NA
Mobility (teeth)		
+	2, 3, 14, 15, 19, 21, 22, 27	NA
I / I+	4, 12, 13, 18, 19, 23, 29, 31	NA
II	26	NA
III	8, 9, 24, 25	NA
Prognosis (teeth)[13]		
Good	1, 16	NA
Fair	6, 11, 22	NA
Poor	21, 27	NA
Questionable	4, 5, 7, 10, 12, 13, 20, 29	NA
Hopeless	2, 3, 8, 9, 14, 15, 18, 19, 23, 24, 25, 26, 28, 30, 31	NA

NA: Not available

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Figure 1

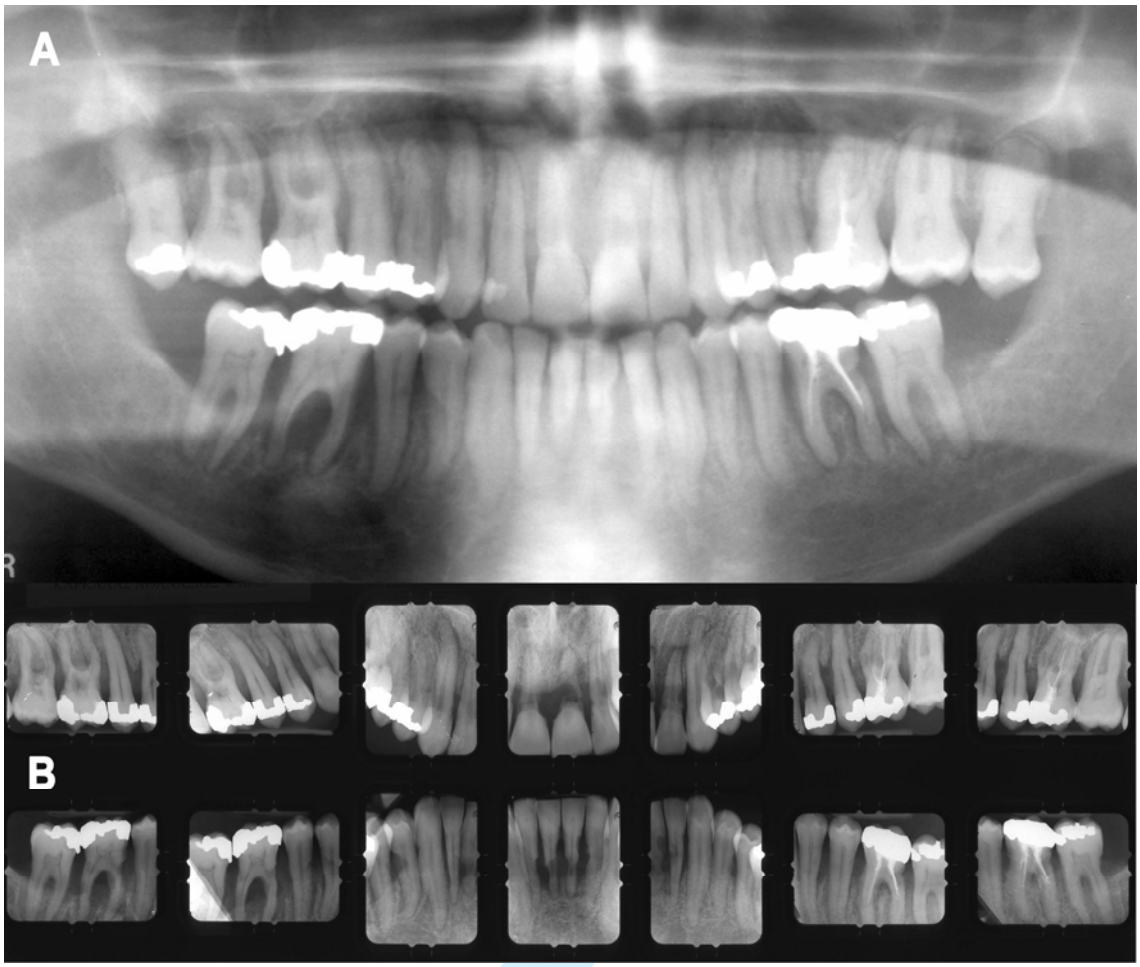

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Figure 2

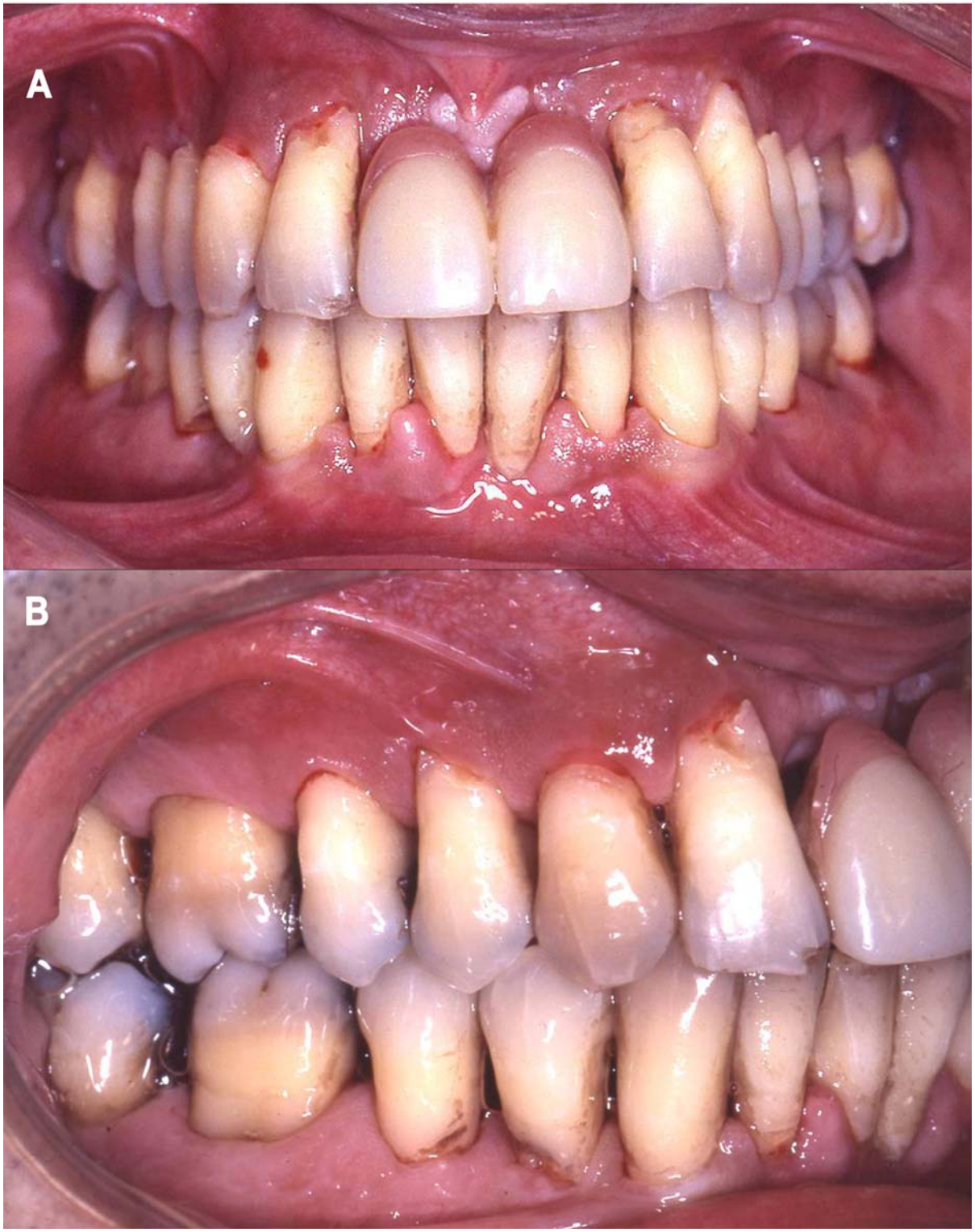

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Figure 3

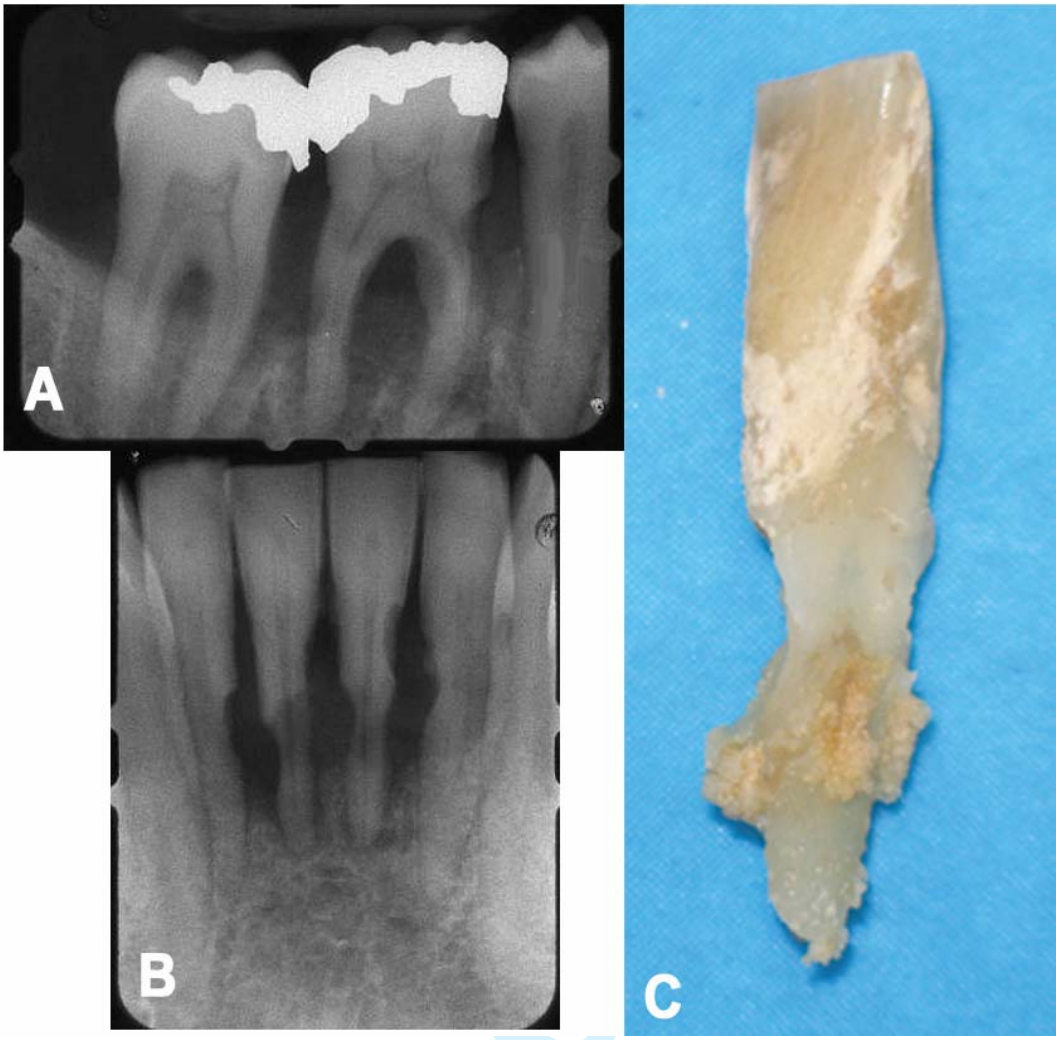

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Figure 4

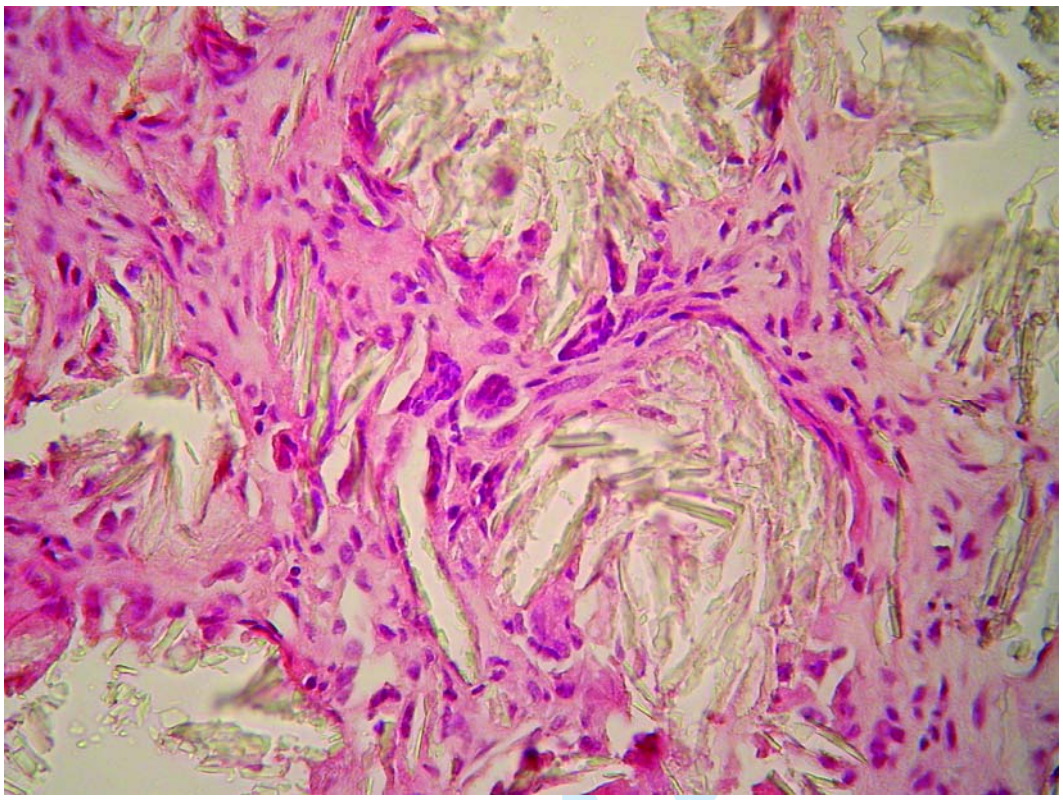

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Figure 5

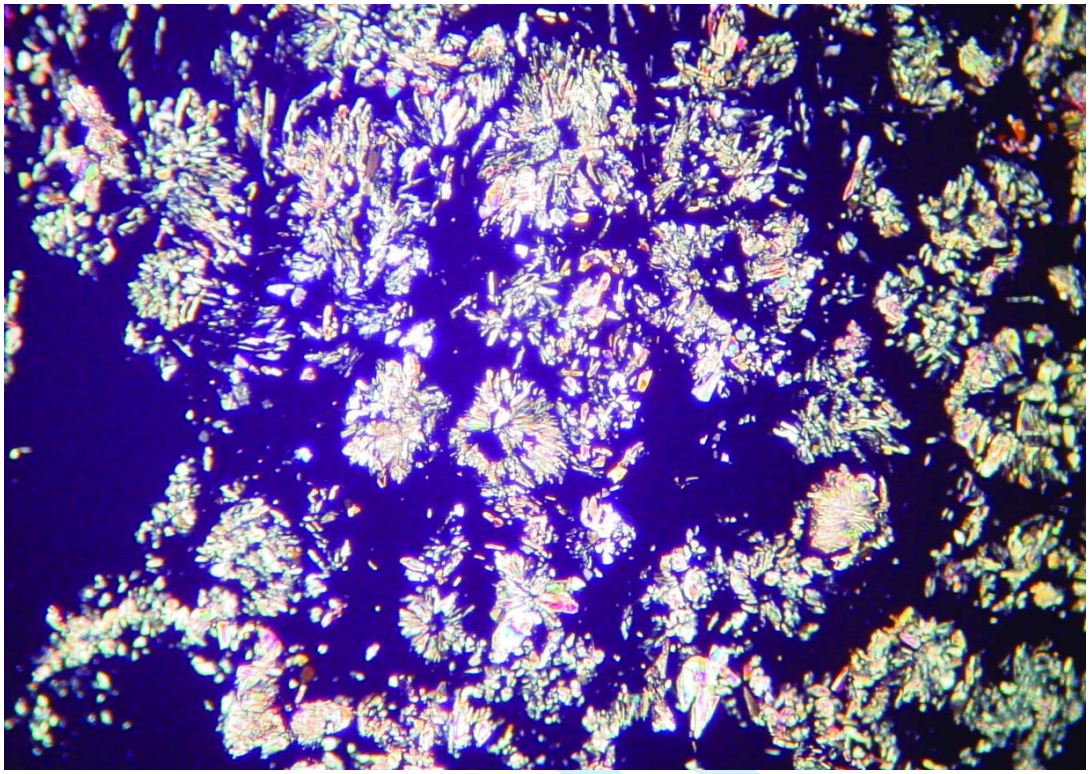

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Figure 6