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CASE REPORT

Dentoalveolar Abscesses Not Associated with Caries or Trauma: A Diagnostic Hallmark of Hypophosphatemic Rickets Initially Misdiagnosed as Hypochondroplasia

Silvia Elena Yacarini Paredes[1] · Raquel Assed Bezerra Segato[1] · Leila Daher Moreira[2] · Alcides Moreira[2] · Kranya Victoria Díaz Serrano[1] · Clarissa Teles Rodrigues[3] · Luciana Yamamoto Almeida[4] · Jorge Esquiche León[5]

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Abstract
Hypophosphatemic rickets is a rare genetic disorder involving the regulation of fibroblast growth factor 23 (FGF23), a phosphaturic agent, clinically showing bowing of the legs, short stature and dentoalveolar abscesses. A 7-year-old boy, with previous hypochondroplasia diagnosis, was referred to our pediatric dentistry clinic presenting short stature, bone deformities and sinus tracts at deciduous teeth apex levels not related with trauma, restorations or dental caries. After deciduous teeth extraction, due to root resorption and mobility, light microscopy exhibited typical hypophosphatemic dentin, and micro-computed tomography revealed tubular clefts and porosities throughout the teeth. Laboratory tests confirmed the HR diagnosis, after which the treatment was initiated.

Keywords Dentoalveolar abscesses · Oral manifestations · Hypophosphatemic rickets · Pediatric patient · Oral histopathology · μ-CT

Introduction

Rickets is a metabolic disorder frequently affecting children, which presents alteration of calcium and phosphate blood levels, disturbance of bone ossification, defective bone growth and neurological alterations such as tetany. The treatment includes administration of vitamin D and/or sufficient sunlight. Besides the classic rickets, there are also hereditary hypophosphatemic rickets (HR) which can be divided into autosomal dominant (ADHR), autosomal recessive (ARHR) and X-linked dominant (XLHR). Among them, the XLHR is the most common form of inherited metabolic rickets. The therapy of rickets-like disorders, different from classic rickets, is more difficult due to their genetic origins [1–4]. Thus, HR is a hereditary disease presenting hypophosphatemia due to renal tubular loss of phosphate into urine, which causes a decrease in the calcium and potassium ion product [5–7]. The systemic findings in HR include bowed legs, spinal curvature deformities, short stature and beading of the ribs. Typical oral findings include the presence of poorly mineralized dentin in both primary and permanent teeth. Because the teeth of HR patients are often associated with high pulp horns, large pulp chambers and dentinal clefts, it is believed that pulpal infection is caused by bacterial invasion through enamel cracks and dentinal clefts. This latter could be explained by the presence of large areas of poorly mineralized dentine, which consists of calcospherites, significantly affecting its integrity. Notably, dentoalveolar or periapical abscesses are also often observed

✉ Jorge Esquiche León
jleon@forp.usp.br

1 Department of Pediatric Dentistry, School of Dentistry of Ribeirão Preto, University of Sao Paulo, São Paulo, SP, Brazil

2 Diagnóstico Bucal do Centro Universitário da Grande Dourados (UNIGRAN-MS), Dourados, Brazil

3 Department of Dentistry, Endodontics and Dental Materials, School of Dentistry of Bauru, University of São Paulo, São Paulo, SP, Brazil

4 Hematology Division, Department of Clinical Medicine, Ribeirão Preto Medical School (FMRP/USP), University of São Paulo, São Paulo, SP, Brazil

5 Oral Pathology, Department of Stomatology, Public Oral Health, and Forensic Dentistry, School of Dentistry of Ribeirão Preto, University of São Paulo, São Paulo, SP, Brazil

in close association with teeth without dental caries, restorations, traumatic injury or periodontal lesion [2, 8–10].

Case Report

Medical history indicates a 5-year-old boy, which presented short stature, bone deformities in the lower limbs and skull, as well as "frequent oral sinus tracts with discharge of pus and necrosis of several teeth". The familiar history was noncontributory. He was born without intercurrences in the neonatal and natal period, and presented a prominent forehead, increased anteroposterior diameter of the skull, teeth with poor conservation status and genu varum. The venous gasometry and computed tomography (CT) scan of the skull show did not alterations. The X-ray examinations of the skull and face showed increased anteroposterior diameter of the skull and hypoplasia of the nasal bone; on the thoracic and lumbar spine, discrete scoliosis; on the upper limbs, a slight bilateral deformity of the radio; and on the lower limbs, a mild deformity of the tibia and fibula with anterior shortening and osteofibrous dysplasia-like features. The karyotype was 46 XY. After evaluation by pediatric geneticist and orthopedist, including the laboratory test results aged 5 years (Table 1), an initial diagnosis of hypochondroplasia was made.

After 2 years, the patient was referred to our pediatric dentistry clinic of the School of Dentistry of Ribeirão Preto, University of Sao Paulo (FORP/USP), and presenting facial asymmetry on the right side of probable inflammatory odontogenic origin. The physical examination showed a short stature and bone deformities (lower limbs and skull). The intraoral examination revealed multiple fistulas and abscesses in the apical region of the upper and lower deciduous teeth, in the absence of dental caries, restorations or history of trauma. The pulp vitality test was negative (Fig. 1). The periapical radiographs of the deciduous dentition showed an enlargement of pulp cavities and irregular circumpulpar dentine, high pulp horns, radicular resorptions, radiolucent images compatible with periapical lesions and apparently normal permanent tooth germs (Fig. 2). After deciduous teeth extraction, due to root resorption and mobility (Fig. 3a), the same were assessing by micro-computed tomography (μ-CT) and light microscopy.

For μ-CT analysis, the teeth were scanned with a μ-CT system (SkyScan 1174v2; Bruker- μ-CT, Kontich, Belgium) using 50 kV, 800 mA, an isotropic resolution of 19.6 μm, a rotation step of 1.0 degrees and projections from 360-degree acquisition rotation. The system included a charge-coupled device camera (1304 × 1024 pixels). The images of each specimen were reconstructed with dedicated software (NRecon v.1.6.3; Bruker-μ-CT) providing axial cross sections of the inner structures of the teeth in the bitmap (BMP) format. DataViewer and CTVol softwares (Bruker-μ-CT) were used for visualization and evaluation of the specimens. Thus, dentin showed clefts and areas with porosities mainly next to the pulp chamber. Moreover, pulp space and enamel did not appear to show alterations

Table 1 Biochemical tests, hemogram, weight and height at the 5- and 7-year-old

Biochemical tests	Results aged 5 years	Results aged 7 years	Reference values
Glucose (mg/dl)	–	83	60–99
Parathyroid hormone (PTH) (pg/ml)	20	22.8	15–65
Alkaline phosphatase (U/l)	–	1251	< 644
Phosphorus (mg/dl)	2.2	2.5	3–7
24-h phosphaturia (mg/kg)		18.7	< 13
Tubular phosphate reabsorption rate (%)	–	32	80–100
Magnesium (mg/dl)	1.9	1.2	1.9–2.5
25-hydroxy vitamin D (ng/ml)	–	41.5	> 30
Calcium (mg/dl)	10.1	10	8.5–10.5
24-h urine calcium (mg/kg)	–	3.3	< 4
Thyroid stimulating hormone (TSH) (uU/ml)	–	3.17	0.5–6
Free thyroxine (T4) (ng/dl)	–	1.1	0.7–1.9
Hemoglobin	14.2	14.7	12.5 g/dl
Hematocrit (%)	41.3	43.3	33–43
Mean corpuscular volume (fL)	81.3	82.0	74–89
White cell count (/l)	10×10^9	12×10^9	$4.0–12.0 \times 10^9$
Platelets (/l)	380×10^9	280×10^9	$150–450 \times 10^9$
Weight (kg)	19.4	24.5	18.3–22
Height (cm)	105.0	117.0	106.40–118.50

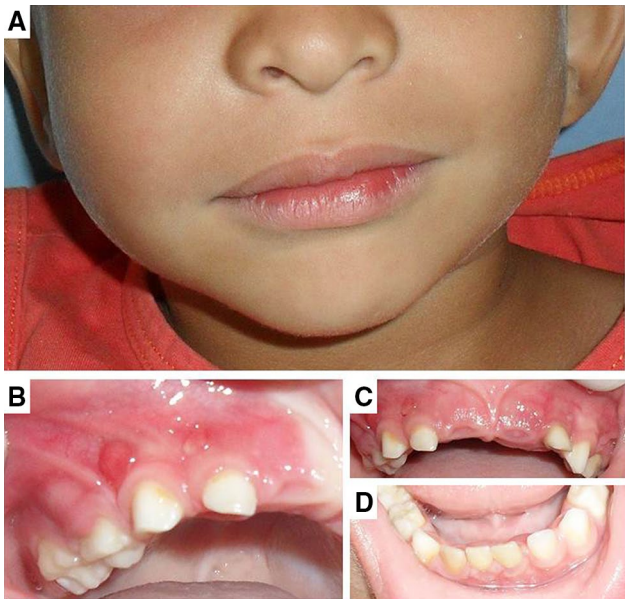

Fig. 1 **a** Clinical features of the 7-year-old boy, when referred to our service and diagnosed with HR. Note the facial asymmetry. **b, c, d** Multiple fistulas in the apical region of the upper and lower deciduous teeth free of dental caries

(Fig. 3b). The histopathological examination revealed large interglobular spaces and dentinal fracture lines, characterizing the hypophosphatemic dentin (Fig. 3c). Furthermore, in the pulp cavity, numerous bacterial colonies were observed (Fig. 4a), which on consecutive serial sections with Periodic acid–Schiff–diastase and Brown–Brenn stains revealed filamentous bacteria (Fig. 4b, c). Notably, bacterial colonies passing along the amelodentinal junction and spreading towards the pulp cavity were visualized with Grocott-Gomori stain (Fig. 4d).

Laboratory test results (remarkably, phosphorus, alkaline phosphatase, phosphaturia and tubular phosphate reabsorption rate) confirmed the diagnosis of HR (Table 1, results aged 7 years). Medical treatment recommended the replacement of phosphate (oral phosphate salts, 60mg/kg per day) and calcitriol (30mg/kg per day). Almost all deciduous teeth showed loss of pulp vitality, therefore, some of them (with high mobility due to root resorption) were extracted, whereas others received endodontic treatment (pulpectomy) with coronal restoration. Rarely, whether the tooth showed a positive responsiveness in thermal and electric pulp tests, topical fluoride varnish and sealing of pits and fissures were topically applied.

Discussion

HR, firstly reported by Albright et al. [11], is a syndrome showing marked hypophosphatemia, short stature and abnormal bone mineralization. It is considered a congenital impairment causing decreased phosphate reabsorption at the level of the proximal renal tubule and intestine.

In the current study, we report a HR case affecting a child, whose correct diagnosis began after microscopical

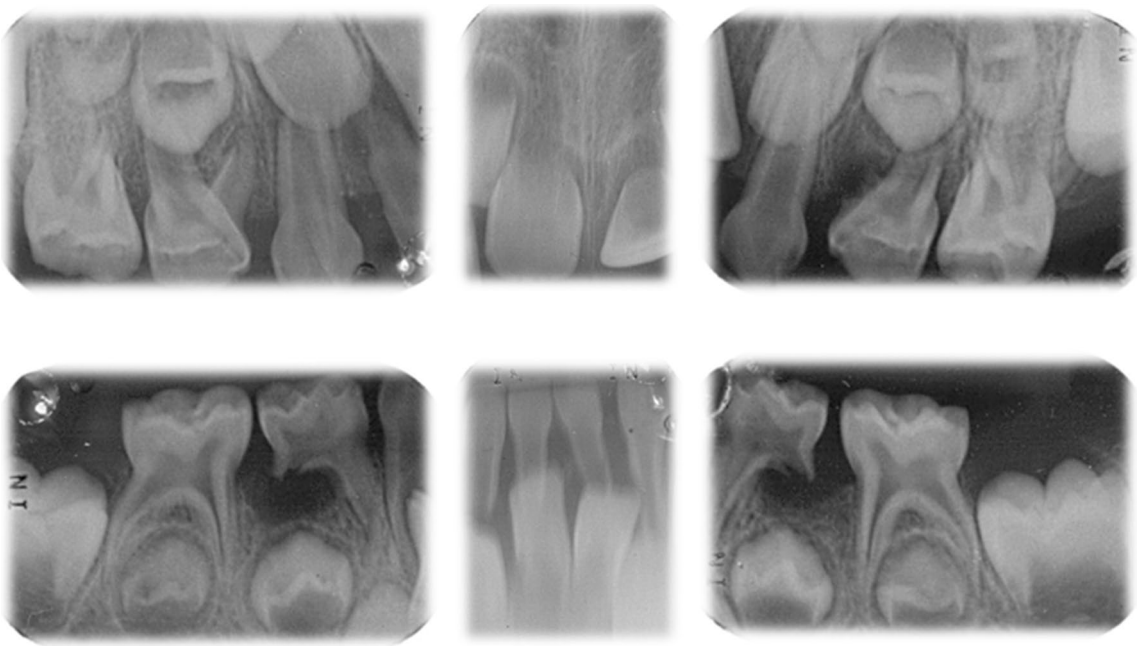

Fig. 2 The periapical radiographs showed a primary dentition with broader pulp cavity and irregular circumpulpar dentine, high pulp horns, radicular resorptions and radiolucent images compatible with periapical lesions

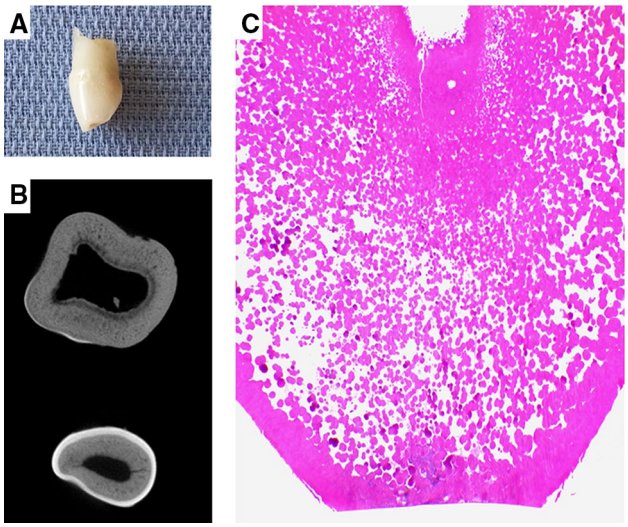

Fig. 3 **a** Macroscopy after deciduous tooth extraction. **b** The µ-CT analysis evidenced dentin with clefts and areas with porosities. **c** The histopathology showed lack of fusion of numerous calcospherites and large interglobular spaces, characterizing the hypophosphatemic dentin (H&E stain, ×4). Notice that the mantle dentin is preserved

examination of the extracted teeth, which showed the typical hypophosphatemic dentin, being supported by biochemical tests (Table 1, see laboratory test results aged 7 years). However, it is interesting to note that even the initial biochemical tests (Table 1, see laboratory test results aged 5 years) indicating hypophosphatemia and normocalcemia, besides the clinical findings and oral manifestations, the patient was diagnosed with hypochondroplasia. Thus, noteworthy, our findings highlight the importance of knowledge of the systemic disorders affecting the formation of dental tissues. Different from HR, hypochondroplasia is a skeletal dysplasia characterized by short stature, asymmetrically short limbs, broad and short hands and feet, lumbar lordosis and macrocephaly. Maxillary hypoplasia, relative mandibular prognathism and severe malocclusion are often observed, whereas anatomical and histological characteristics of the teeth do not show alterations. Several studies indicate that hypochondroplasia is caused by mutation in the gene for FGF receptor 3 (FGFR3) [12].

Since the early case reports of HR, and similar with our case, dentoalveolar fistulas or gingival abscess in close association with clinically normal-appearing teeth have been often described [13, 14]. Histopathological findings of teeth with HR include enlarged pulp chambers, thick predentin layer, prominent globular dentin and dentinal clefts. Interestingly, the mantle dentin is unaffected in RH (see the Fig. 3c of the current case), because its mineralization is independent of non collagenous protein phosphorylation [15]. In these patients, clinical findings such as dental caries, evident tooth fractures, periodontal lesions and traumatic injuries are not detected. However, the pulp vitally test is negative and the microscopical analysis shows numerous bacterial colonies into the dentin and pulp tissue and whose invasion is believed to be caused by microscopic cleavage of the enamel.

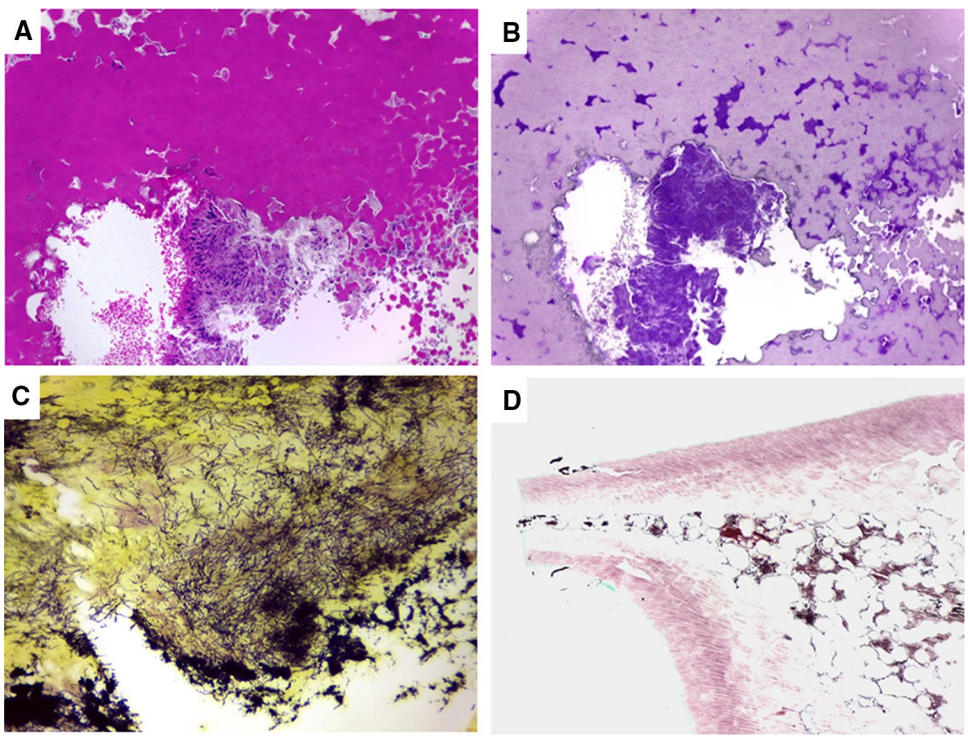

Fig. 4 **a** Numerous bacterial colonies in the pulp cavity were observed (H&E stain, ×10). **b** Bacterial colonies on consecutive serial sections were positive for Periodic acid–Schiff–diastase (×10). **c** Also positive for Brown–Brenn (×40), this latter highlighting filamentous bacteria. **d** Bacterial colonies along the amelodentinal junction and spreading towards the pulp cavity were visualized with Grocott-Gomori stain (×10)

X-ray μ-CT analysis is a high-resolution, nondestructive radiographic method, which has been progressively used in studies of dental anatomy. This technique permits microstructural analysis of small structures, such as mineral density, volume and mineralization pattern [16]. Similar with Ribeiro et al. [16] findings, the current case showed hypomineralization defects in dentin, including clefts and areas with porosities, this latter representing the close relationship between calcospherites and interglobular dentin.

The differential diagnosis of HR includes ARHR, ADHR, XLHR and Debré-de-Toni-Fanconi syndrome [1–3, 5, 17]. The ARHR is clinically similar with the other HR types. It manifests during childhood with clinical features such as short stature, bone pain and skeletal deformities; and during adulthood, with bone pain, fatigue, muscle weakness and bone fractures. The ARHR is caused by inactivation mutations in the gene encoding the dentin matrix protein 1 (DMP1). These mutations increase the production of FGF23, decreasing the renal tubular reabsorption of phosphate. The ADHR was mapped on chromosome 12p13.3 and it is associated with a mutation of the gene encoding FGF23. The XLHR is considered the most common cause of hereditary HR. It is a dominant X-linked disease caused by mutations in the PHEX gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome), located in Xp22.1. The FGF23 protein participates in the pathogenesis as it inhibits tubular phosphorous reabsorption and is controlled by PHEX-dependent proteolysis. In addition, FGF23 is produced by osteoprogenitor cells and bone tissue cells. The Debré-de-Toni-Fanconi syndrome differs from XLHR due to renal tubular acidosis that leads, in addition to reducing phosphate reabsorption, to increased urinary excretion of bicarbonate, glycosuria and aminoaciduria. Moreover, hereditary HR with hypercalciuria is clinically differentiated from XLHR due to muscular weakness, hypercalciuria, high plasma concentration of calcitriol and reduction of serum parathyroid hormone (PTH). Noteworthy, the muscle weakness, which is minimal or absent in XLHR, may aid in differentiation from other HR types. The present case appears to be transmitted in a sporadic manner. To date, about 84 patients with sporadic HR and presenting mutations on the PHEX gene have been reported [1].

To prevent multiple dentoalveolar fistulas or gingival abscesses, such as observed in our patient, both preventive care and early treatment for dental caries and attrition are recommended. Professional dental care consisting of periodical examinations, topical fluoride application and sealing of pits and fissures to prevent pulpitis and endodontic complications, as well as maintenance of good oral hygiene, should be rigorously performed in both primary and permanent dentitions. Placement of stainless steel crowns for primary dentition is recommended for prevention of attrition and enamel microfracture. Furthermore, for endodontic treatment in permanent dentition, the use of thermoplasticized gutta percha obturation techniques using a virtually insoluble sealer is advisable [2]. Moreover, dentists should be able to provide information about the dental characteristics of HR to the pediatrician, to prevent subsequent serious dental infections.

Conclusion

This case highlights the importance of early diagnosis of HR and knowledge of their dental implications to provide the best possible treatment options. This disease affects ossification causing disturbances in the growth and normal development of children, as well as frequent dental anomalies. Notably, the oral examination reveals dentoalveolar abscesses that occur in the absence of trauma, restorations or dental caries. The detection of hypophosphatemic dentin on histopathological and μ-CT analyses may help to establish the early diagnosis of HR.

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Compliance with Ethical Standards

Conflict of interest The authors have no conflict of interest in the present manuscript.

Ethical Approval According to Brazilian law, case reports do not need ethical approval by a committee.

Informed Consent The patient's parents authorized the publication of the clinical photographs.

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