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A clinical and histological study of dental defects in a 10-year-old girl with pseudoxanthoma elasticum and amelogenesis imperfecta

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Background. The prominent dental feature of a 10-year-old girl was severely hypoplastic enamel in permanent teeth.

Case report. Severe dental defects were detected in a 10-year-old female patient affected by pseudoxanthoma elasticum and amelogenesis imperfecta. An orthopantomographic examination revealed a reduction of enamel thickness on the crown of all erupted and unerupted teeth, agenesis of the maxillary right second premolar, delayed eruption of mandibular first premolars, and the presence of large calcifications in all tooth pulp chambers. A detailed histological analysis of permanent mandibular first molars showed that pulp calcifications presented a concentric laminate organization and merged to almost completely obliterate the pulp chamber. Osteodentine was visible all along the pulpal surface of the radicular dentine. Broad resorption areas were present in the outermost dentine at both coronal and radicular levels. Radicular resorption areas presented a typical rectangular form and were filled with acellular cementum. Cementum thickness was highly increased on the root surface. Apposition of cellular cementum-like tissue was also observed on the coronal dentine surface.

Conclusion. Before treating patients affected by amelogenesis imperfecta and/or pseudoxanthoma elasticum, paediatric dentists should be aware of the presence of pulp calcifications that add to the complexity of endodontic procedures.

Introduction

Amelogenesis imperfecta (AI) encompasses a group of hereditary diseases that involve the defective formation and/or calcification of enamel. Hypoplastic, hypomature, or hypocalcified enamel occurring in various inheritance patterns defines the different subtypes. The biologic potential of AI is not limited to defective enamel, and local stigmata often include unerupted teeth, anterior open bite, pulpal calcifications, interradicular dentine dysplasia, root and crown resorption, cementum deposition, truncated roots, or taurodontism[1–3].

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Pseudoxanthoma elasticum (PXE) (OMIM#-264800) is an inherited pleiotropic multisystem disorder of the connective tissue characterized by progressive dystrophic mineralization of elastic fibres[4–6]. The disease is progressive and as yet incurable. Its estimated prevalence is 1 in 25 000–100 000 with an almost 2 : 1 female preponderance[6]. A more common autosomal recessive and a less common autosomal dominant pattern of inheritance, with high penetrance, have been clinically described. The clinical manifestations of PXE show extensive inter- and intrafamilial variability, but typically involve the skin, eye, and cardiovascular system. The skin changes are generally diagnosed from 10 to 15 years, and consist of skin papules and cutaneous laxity mainly on the neck, axillae, groin, and flexural area. The characteristic eye signs of PXE are angioid streaks and recurrent

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haemorrhages in the retina which can lead to the loss of central vision. Cardiovascular manifestations are mainly intermittent claudication because of atherosclerosis, early coronary artery disease, and renovascular hypertension which can result in angina pectoris, myocardial infarction, congestive cardiac failure, renal failure, or stroke. Calcification of the atrial and ventricular endocardium valves can result in mitral valve prolapse and stenosis requiring antibiotic prophylaxis. PXE patients can also experience bleeding complications, especially gastrointestinal haemorrhages, because of fragility of calcified submucosal vessels. To reduce this risk, platelet inhibitors, such as aspirin and non-steroidal anti-inflammatory drugs, should be avoided[6].

We report in this article a unique case of severe dental defects in a young patient affected by both AI and PXE, characterized by severe alterations of dental tissues including enamel thinning, dentine resorption and replacement by cementum, intrapulpal osteodentine deposition, and formation of large calcifications in the pulp chamber of all permanent teeth.

Clinical features

A 10-year-old Caucasian female patient affected by AI was referred in January 2004 to the department of paediatric dentistry for treatment. Her major complaints were unaesthetic teeth, pain, and difficulties for eating. Several family members, including her father, were also affected by AI. The family pedigree, illustrated in Fig. 1, indicates an autosomal dominant inheritance. The medical history revealed that the patient was also affected by PXE, an inherited pleiotropic disorder of the connective tissue (OMIM#264800) characterized by progressive dystrophic mineralization of elastic fibres[5,6]. The patient presented various symptoms of the disease including numerous erythematous skin papules in antecubital fossae, ocular angioid streaks, and a mitral valve stenosis.

On extra-oral examination, the patient had a skeletal open occlusal relationship and an anterior open bite, but average facial proportions and normal temporomandibular joint function. Intra-orally, the patient had only permanent teeth except the primary maxillary right second molar.

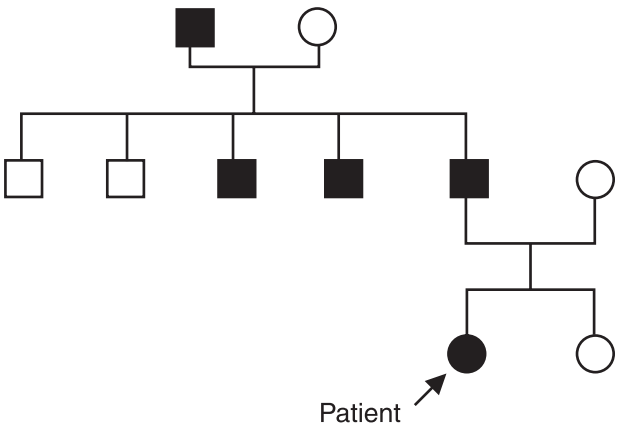

Fig. 1. Pedigree of the family affected by amelogenesis imperfecta that suggests an autosomal dominant inheritance. ○, unaffected female; □, unaffected male; ●, affected female; ■, affected male.

Fig. 2. Clinical view of the anterior teeth of the patient showing alterations in the tooth shape, reduction of the enamel thickness, and yellow/brown discolouration. Note the inflammation and hypertrophy of the marginal gingiva.

Intra-oral examination confirmed that the patient was affected by AI (Fig. 2). Teeth were discoloured yellow/brown, spaced, and exhibited simplified coronal morphology reflecting decreased enamel thickness. Residual enamel was hard and rough. In some areas, tooth crown surfaces were free of enamel, and dentine was visible. These anomalies suggested a rough hypoplastic type of AI[1]. The exposed dentine was extremely sensitive and rendered toothbrushing difficult to perform. Oral hygiene was consequently not well-maintained. Dental plaque

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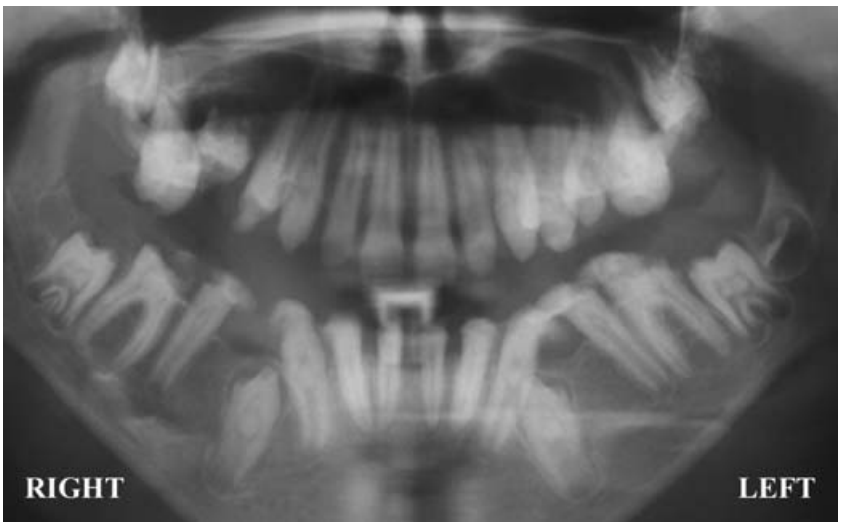

Fig. 3. Panoramic radiography of the patient at the age of 10 years, 5 months showing all erupted and unerupted teeth with intrapulpal calcifications. Note the agenesis of the maxillary right second premolar. Well-defined pericoronal radiolucencies were observed around the unerupted permanent mandibular second molars.

and calculus accumulation were observed on all teeth, mainly at the cervical level. Localized inflammation and hypertrophy of the marginal gingiva were present around all teeth. Other oral mucosae were normal. The permanent mandibular first molars were almost completely covered by an inflammatory fibrous gingiva.

A panoramic radiography showed a reduced enamel layer on the crown of the posterior teeth (Fig. 3). Radiopaque areas that usually reflect the presence of enamel were not visible on anterior teeth, confirming either the absence of enamel or the presence of a thin residual hypomineralized enamel layer observed intraorally. Agenesis of the maxillary right second premolar and delayed eruption of the mandibular first premolars were also observed. Tooth root size and radicular dentine appeared normal. The periodontal ligament space and surrounding bone had a normal radiographic appearance. No periapical pathology was discernible. Dental follicles surrounding permanent mandibular second molar crowns were enlarged. Large calcifications were detected in the pulp chamber of all permanent teeth, including unerupted ones. In some canines and premolars, calcifications were also present in the coronal third of the root canal.

A histological examination was performed on both permanent mandibular first molars removed under local anaesthesia. Teeth were extracted because the extensive intrapulpal calcifications precluded the endodontic treatment required to adequately reconstitute the crown.

Teeth were removed under antibiotic prophylaxis because of the mitral valvular stenosis. No carious lesion was detected. Teeth were collected with informed consent of the girl's parents, in accordance with the French Public Health Code and following a protocol approved by the local ethics committee. They were fixed in Bouin's solution for 2 months, demineralized with 10% nitric acid for 10 days, rinsed, dehydrated, and included in paraffin according to routine histological procedures. Teeth were then longitudinally cut, and 5-μm-thick sections were stained with Masson's trichrome. Tissue alterations were similar for both teeth, and only pictures of the permanent mandibular right first molar are presented here. Extended resorption areas were detected in the peripheral dentine at both crown and root levels (Fig. 4). Dentine structure appeared normal. Large rounded calcified structures were visible into the pulp chamber and a smaller one was detected at the entrance to a root canal. A thick layer of mineralized tissue was deposited along the periodontal and pulp surfaces of the radicular dentine. Intrapulpal calcifications had developed in a concentric and laminate way, most of them having merged into the pulp chamber to almost completely obliterate it (Fig. 5). A cellular tissue was detected in the central part of the calcification localized at the entrance to a root canal. Dentine resorption was observed close to the inflamed gingival connective tissue. In some places, collagenous fibres directly anchored to the dentine surface. In others, a mineralized

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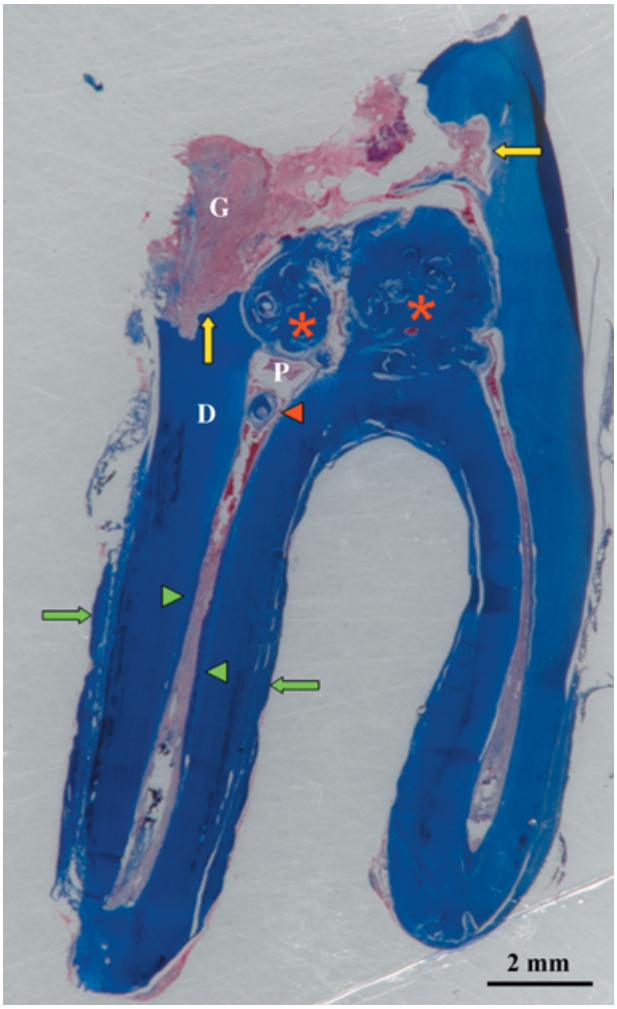

Fig. 4. Histological view of a longitudinal section of the permanent mandibular right first molar. Resorption areas were localized at the dentine surface in contact to the gingival tissue (yellow arrows). Large calcifications were visible into the pulp chamber (red asterisks), whereas a smaller one was detected at the entrance to a root canal (red arrowhead). Acellular cementum-like tissue and osteodentine had been deposited on the periodontal surface of the radicular dentine (green arrows) and on the pulpal surface of the radicular dentine (green arrowheads), respectively. Masson's trichrome staining. D, dentine; G, gingiva; P, pulp.

tissue similar to cellular cementum had been deposited by gingival cells, some of them having been finally entrapped in the calcified matrix. On the outer (periodontal) root surface, a thick acellular mineralized tissue filled rectangular dentine resorption areas (Fig. 6). The absence of vascularization in this newly formed tissue suggested a hypercementosis. A thick layer of mineralized tissue had also been deposited at the dentine–pulp interface. This tissue was similar to osteodentine, as it included pulp cells and was devoid of dentine tubules. Typical odontoblasts were not present between osteodentine and the pulp parenchyma. Many highly dilated blood vessels were present within the pulp tissue.

Treatment strategy first consisted of instructing the patient in oral hygiene and dietary control and of performing preventive interventions to achieve healthy soft tissue prior to and after restorative care. These interventions included professional cleaning and the use of antimicrobial oral rinses (chlorhexidine gluconate). Stainless steel preformed, and polycarbonate crowns (3M ESPE dental products, St Paul, MN, USA) were then fitted (Ketac-Cem, 3M ESPE) on the permanent maxillary first molars, and on maxillary and mandibular permanent incisors, premolars, and canines, respectively. This immediate temporary treatment of AI was previously designed to reduce teeth sensitivity; preserve pulp vitality in immature teeth; prevent attrition of erupting teeth; and restore appearance, masticatory function, and good oral hygiene until the end of maxillary and mandibular growth[7]. In addition to permanent mandibular first molars, the primary maxillary right second molar was extracted because of caries and reinclusion.

Discussion

AI encompasses a diverse group of hereditary conditions that primarily affect the quality and/or the quantity of dental enamel. It has also been associated with non-enamel anomalies, including taurodontism, congenitally missing teeth, dental follicle enlargement, delayed eruption, anterior open bite, crown resorption, and intrapulpal calcifications in unerupted and erupted teeth[8–12]. Review of the literature revealed reports of cases displaying several of these anomalies, but none associated so many defects or was as severe as the case described here. Several of the alterations we observed in this study have already been described in association with enamel defects in AI-affected patients. These include anterior open bite, congenitally missing teeth, dental follicle enlargement, and delayed eruption. These will not be further considered here. As enamel alterations

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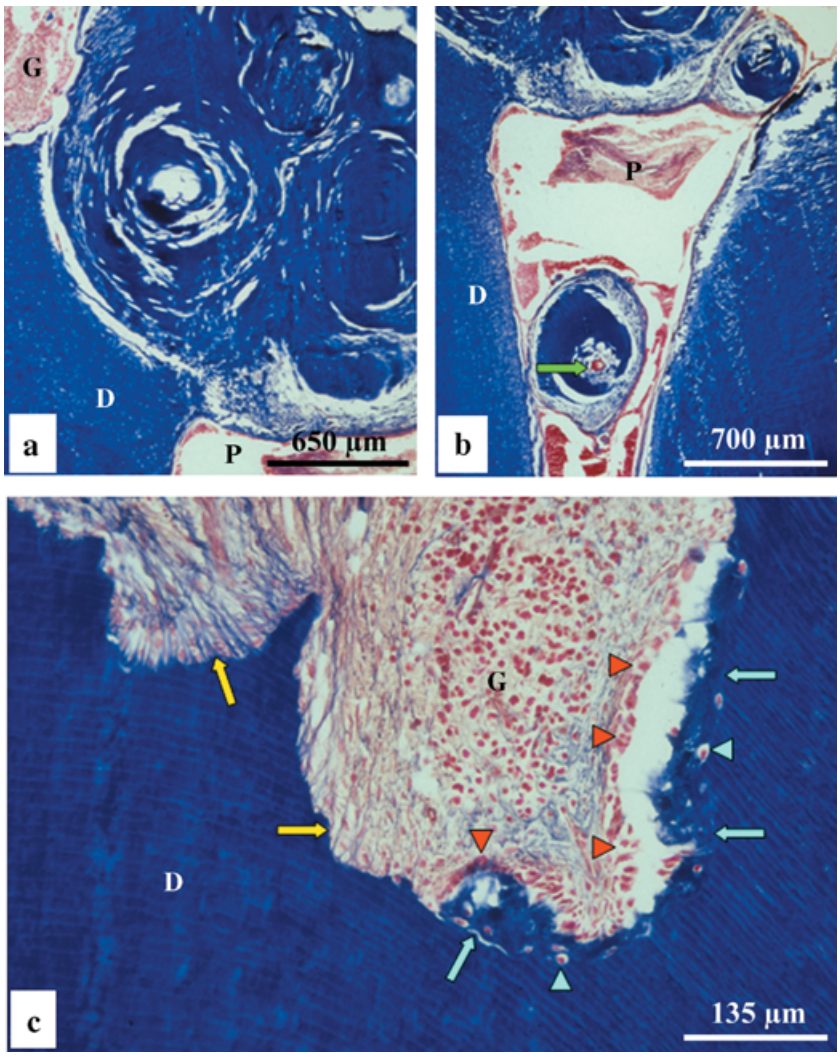

Fig. 5. Mineralized tissue deposition at the crown level. (a) Intrapulpal calcifications with a concentric and laminate organization. Most have merged into the pulp chamber. (b) A cellular tissue (green arrow) was observed in the central part of a small calcification localized at the entrance to a root canal. (c) Area of dentine resorption and cellular cementum-like tissue apposition were present close to the inflamed gingiva. In some places, gingival collagenous fibres anchored to the dentine surface (yellow arrows). Elsewhere, cellular cementum-like tissue (blue arrows) had been deposited by cells present in the inflammatory gingival connective tissue (red arrowheads), some of them being finally included into the mineralized matrix (blue arrowheads). Masson's trichrome staining. D, dentine; G, gingiva; P, pulp.

have largely been described in patients affected by AI, we focused our investigation on the histological modifications of dentine, pulp, and cementum tissues. Interestingly, large intrapulpal calcifications were detected in all permanent teeth. These generalized calcifications were seen in erupted and unerupted teeth, which implies that they were a primary defect and not a consequence of enamel wear after eruption, as suggested by Seow[13]. They appeared as the result of the merging of several large and well-formed concentric lamellate calcified units similar to pulp stones. Concentric calcifications have already been observed in the pulp of teeth affected by rough hypoplastic AI, but they were much more smaller, irregular, and disorganized[2]. Pulp stones have been associated with carious lesions, tooth operation, local pathological changes of the pulp tissue, dentine or enamel hereditary conditions such as dentine dysplasia and AI, and pulp ageing[14]. Some of them might be idiopathic. Most investigators consider that they may result from the initial calcification of tissue components, including collagen fibrils, non-collagenous glycoproteins, or necrotic cell remnants[15]. Others have suggested that vascular damage following trauma or a 'local metabolic dysfunction' was the precipitating factor for the development of calcification foci, because there is frequently a close spatial relationship between calcified structures and blood vessels and/or nerves in the pulp[14]. In our case, the presence of cellular tissue in the centre of the pulp stone localized at the entrance of a root

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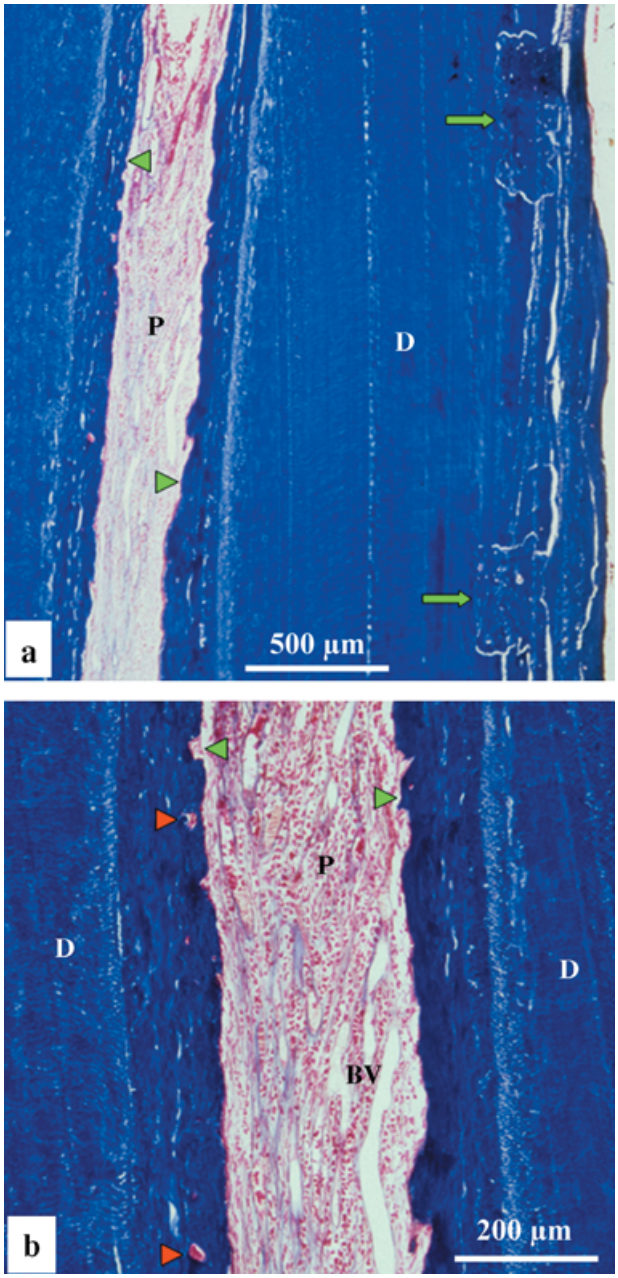

Fig. 6. Mineralized tissue deposition at the root level. (a) On the periodontal surface of root, dentine had been resorbed (green arrows), then resorption areas, that were more or less rectangular, had been filled by acellular cementum-like tissue. Osteodentine had been deposited at the dentine–pulp interface (green arrowheads). (b) Irregular surface of the pulp–osteodentine interface (green arrowheads). Odontoblasts were absent and some pulp cells had been included within the mineralized tissue (red arrowheads). Many highly dilated blood vessels (BV) were present within the pulpal connective tissue. Masson's trichrome staining. D, dentine; P, pulp.

canal suggests that pulp cells might be involved, at least in some cases, in the initiation of the calcification process.

DNA studies of families affected by PXE suggested that PXE is caused by mutations in the ATP-binding cassette (ABC) transporter C6 gene (*ABCC6*), a gene that encodes multidrug-resistance-associated protein 6 (MRP6), which belongs to the ABC transmembrane transporter family. The *ABCC6* gene is expressed at high levels in the liver (which is unaffected by PXE), to a lesser extent in kidneys, but only at a very low level in the main tissues affected by PXE (skin, eyes, and blood vessels)[6,16]. The ABCC6/MRP6 protein was localized to the basolateral membranes of hepatocytes and the basal membranes of kidney proximal tubules, but not at pathogenic sites[17]. The high expression of ABCC6/MRP6 in liver and kidney, its putative function as a transporter, and its localization to basolateral membranes of hepatocytes suggest a systemic origin of PXE related to changes in blood composition[18]. These changes might concern still unknown circulating ABCC6/MRP6 substrates interacting with the synthesis, turnover, and/or maintenance of an extracellular matrix. Indeed, various glycoproteins and proteoglycan/glycosaminoglycan macromolecules accumulated, and abnormal collagen fibrils mineralized, in the lesional skin areas associated with elastic fibres[19]. Ultrastructural analysis revealed that alterations were not restricted to skin or blood vessels, but were detected in many organs. Their severity was much more pronounced in the organs affected by the clinical manifestations of PXE. Unfortunately, dental tissues were not examined in this study. As lesions affected all soft connective tissues, even in the absence of specific clinical manifestations, it was speculated that PXE was a complex disorder of the fibroblast synthetic control[20,21]. Elastic fibre mineralization was thus considered a secondary event, which could depend on the abnormal synthesis and accumulation within the elastic fibres of proteins that are normally involved in mineralization processes (bone sialoprotein, osteonectin, alkaline phosphatase, and/or vitronectin). Such an accumulation might be the result of mild chronic generalized oxidative stress in fibroblasts[22]. Together, these data suggest that PXE might have influenced the

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occurrence of pulp calcifications in our patient via an alteration of pulp fibroblast metabolism. Ultrastructural studies of novel tooth specimen from patients affected by both AI and PXE are necessary to analyse mineralization foci responsible for dental pulp stone development and thus confirm this hypothesis.

What this case report adds

- Clinical complications usually associated with AI are tooth attrition, unaesthetic aspect and sensitivity, and pulp necrosis. We report here the presence of generalized large pulp calcifications that might be caused by PXE.
- For the first time, a detailed histological analysis of these pulp calcifications is provided.
- Further studies are needed to clarify the role of PXE in the initiation of the calcification process.

Why this paper is important to paediatric dentists

- This paper reveals the presence of generalized large pulp calcifications in one case of hypoplastic AI co-existing with PXE. Before treating patients affected by AI and/or PXE, paediatric dentists should seek for such calcifications that add to the complexity of endodontic procedures.

References

1 Witkop CJ, Jr. Amelogenesis imperfecta, dentinogenesis imperfecta and dentin dysplasia revisited, problems in classification. *J Oral Pathol* 1989; **17**: 547–553.

2 Peters E, Cohen M, Altini M. Rough hypoplastic amelogenesis imperfecta with follicular dysplasia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1992; **74**: 87–92.

3 Wright JT. The molecular etiologies and associated phenotypes of amelogenesis imperfecta. *Am J Med Genet A* 2006; **140**: 2547–2555.

4 Struk B, Neldner KH, Rao VS, St Jean P, Lindpainter K. Mapping of both autosomal recessive and dominant variants of pseudoxanthoma elasticum to chromosome 16p13.1. *Hum Mol Genet* 1997; **6**: 1823–1828.

5 Uitto J. Pseudoxanthoma elasticum – a connective tissue disease or a metabolic disorder at the genome/environment interface? *J Invest Dermatol* 2004; **122**: ix–x.

6 Laube S, Moss C. Pseudoxanthoma elasticum. *Arch Dis Child* 2006; **90**: 754–756.

7 Bouvier D, Duprez JP, Bois D. Rehabilitation of young patients with amelogenesis imperfecta: a report of two cases. *ASDC J Dent Child* 1996; **63**: 443–447.

8 Rosenberg Gertzmann GB, Gaston G, Quinn I. Amelogenesis imperfecta: local hypoplastic type with pulpal calcification. *JADA* 1979; **99**: 637–639.

9 Chosack A, Eidelman E, Wisotski I, Cohen T. Amelogenesis imperfecta among Israeli Jews and the description of a new type of local hypoplastic autosomal recessive amelogenesis imperfecta. *Oral Surg Oral Med Oral Pathol* 1979; **47**: 148–156.

10 Williams SA, Ogden AR. Failure of eruption associated with anomalies of the dentition in siblings. *Pediatr Dent* 1988; **10**: 130–136.

11 Collins MA, Mauriello SM, Tyndall DA, Wright JT. Dental anomalies associated with amelogenesis imperfecta. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1999; **88**: 358–364.

12 Lykogeorgos T, Duncan K, Crawford PJM, Aldred MJ. Unusual manifestations in X-linked amelogenesis imperfecta. *Int J Paediatr Dent* 2003; **13**: 356–361.

13 Seow WK. Clinical diagnosis and management strategies of amelogenesis imperfecta variants. *Pediatr Dent* 1993; **15**: 384–393.

14 Moss-Salentijn L, Hendricks-Klyvert M. Calcified structures in human dental pulps. *J Endod* 1988; **14**: 184–189.

15 Holan G. Tube-like mineralization in the dental pulp of traumatized primary incisors. *Endod Dent Traumatol* 1998; **14**: 279–284.

16 Kool M, van der Linden M, de Haas M, Baas F, Borst P. Expression of human MRP6, a homologue of the multidrug resistance protein gene *MRP1*, in tissues and cancer cells. *Cancer Res* 1999; **59**: 175–182.

17 Scheffer GL, Hu X, Pijnenborg AC, Wijnholds J, Bergen AA, Scheper RJ. MRP6 (ABCC6) detection in normal human tissues and tumors. *Lab Invest* 2002; **82**: 515–518.

18 Ringpfeil F, Pulkkinen L, Uitto J. Molecular genetics of pseudoxanthoma elasticum. *Exp Dermatol* 2001; **10**: 221–228.

19 Gheduzzi D, Sammarco R, Quaglino D, *et al*. Extracutaneous ultrastructural alterations in pseudoxanthoma elasticum. *Ultrastruct Pathol* 2003; **27**: 375–384.

20 Uitto J, Pulkkinen L, Ringpfeil F. Molecular genetics of pseudoxanthoma elasticum: a metabolic disorder at the environment–genome interface? *Trends Mol Med* 2001; **7**: 13–17.

21 Le Saux O, Bunda S, VanWart CM, *et al*. Serum factors from pseudoxanthoma elasticum patients alter elastic fiber formation *in vitro*. *J Invest Dermatol* 2006; **126**: 1497–1505.

22 Pasquali-Ronchetti IP, Garcia-Fernandez MI, Boraldi F, *et al*. Oxidative stress in fibroblasts from patients with pseudoxanthoma elasticum: possible role in the pathogenesis of clinical manifestations. *J Pathol* 2006; **208**: 54–61.

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