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Ossifying epulis in pseudohypo-parathyroidism: a case-based therapeutic approach

ABSTRACT

Background *The term Pseudohypoparathiroidism indicates a group of rare conditions characterised by end-organ resistance to the action of parathyroid hormone (PTH). Ossifying epulis (OE) is a exophytic gingival lesion characterised by spontaneous bone formation beneath the mucosa, which may affect children and adults: the exophytic, calcified outgrowths can occur in any bone and generally have favorable prognosis. Drug therapy may normalise calcium serum levels, but not completely avoid the occurrence of peripheral ossifying epulis.*

Case report *We report a representative case of a peripheral ossifying epulis in the mouth of a patient following a drug treatment protocol for her pseudohypoparathyroidism and to optimise serum markers. An 11-year-old girl was referred to our department, showing a bulky neoformation on the gingival margin of 0.6 mm diameter with sharp margins. The mass was completely excised. Histological analysis revealed distinctive features of a chronic and acute inflammatory microenvironment with plasma cells (positivity for CD38, MUM1, Lambda and Kappa chains) and bone tissue fragments with remodeling aspects referable to flogistic osteolysis. The biopsy result leads to hypothese a change in the patient's drug therapy. Multidisciplinary screening and individualised pharmacological treatment are strongly recommended in the clinical practice in order to improve the therapeutic results.*

Keywords *Biopsy, Bone diseases (metabolic), Gingival abnormalities, Oral diseases, Pseudohypoparathyroidism.*

Introduction

Pseudohypoparathyroidism is a sporadic or inherited genetic condition characterised by spontaneous bone formation beneath the skin [Scaramuzzo et al., 2009]; it may affect both children and adults [Sethuraman et al., 2006]. Epulis is a general term used to describe a number of reactive gingival lesions with vascular, fibroblastic, and granulation tissue proliferation [Cohen, 2013]. Primary ossifying epulis (OE) is exceedingly rare, whereas the secondary type most often develops in association with local tissue alteration (inflammatory, traumatic conditions) or pre-existing calcification disorders, such as Albright's hereditary osteodystrophy (AHO) [Ward et al., 2011].

Disorders caused by impairments in the parathyroid hormone (PTH) signaling pathway are historically classified under the term pseudohypoparathyroidism (PHP), which encompasses rare, related and highly heterogeneous diseases with demonstrated (epi)genetic causes [Thiele et al., 2016]. The aetiopathogenesis of pseudohypoparathyroidism underlies a metabolic disease caused by a receptor disturbance in the peripheral action of parathormone. From a clinical perspective, the disease is similar to idiopathic hypoparathyroidism.

We describe a case of surgical excision of an intraoral miliary ossifying epulis in an 11-year-old girl who had cutaneous, biochemical and phenotypic features of pseudohypoparathyroidism. This is a clinical case reported according to the CARE (CAse REport) guidelines [Gagnier, 2013].

Materials and methods

Patient information

An 11-year-old girl was referred to the Operative and Paediatric Dentistry Unit of the Department of Surgical Sciences for Head and Neck Diseases, hospital "A. Gemelli, Università Cattolica del Sacro Cuore" of Rome (Italy).

Medical, family and psychosocial history including relevant genetic information

Medical history of the patient revealed that she was diagnosed pseudohypoparathyroidism and Albright's hereditary osteodystrophy at the age of 5 years, caused by a frameshift GNAS mutation.

The girl reported to be followed by a dermatologist for the presence of other benign bone neoformations - located in the parasternal and in the right popliteal region - which had been surgically removed at the age of 5 years and 7 years. There was no family history of

FIG. 1, 2 Preoperative intraoral aspect of the epulis.

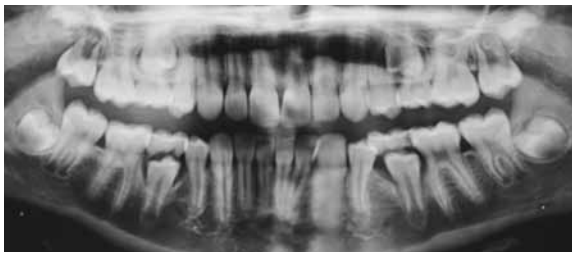

FIG. 3 Preoperative orthopantomograph.

FIG. 4 Intra-operative intraoral image: excision done.

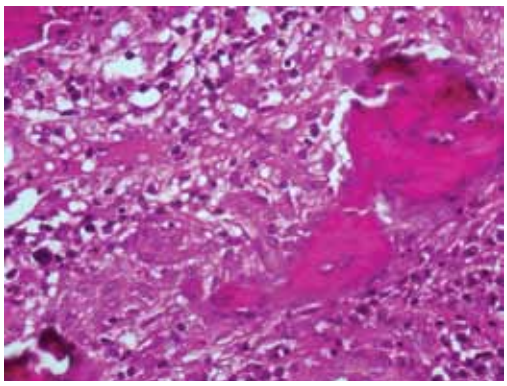

FIG. 5 Plasma cells and bone tissue fragments with remodeling aspects referable to flogistic osteolysis.

FIG. 6 Post-operative intraoral image.

heterotopic ossification or inherited diseases.

Chief complaint

She complained a single subgingival bulky neoformation [Biria et al., 2015] of 0,6 cm in diameter and hard-wooden consistency, well-defined margins and sessile-based attachment to the underlying bone, covered by non-keratinised ulcerated epithelium, at the level of tooth 2.1; moreover, a moderate gingival inflammation was noticed, with no bleeding, pain or tenderness. The extraoral examination revealed a moderately built girl with no evidence of facial or skeletal abnormalities. The clinical examination showed a round face with saddle nose and hypertelorism [Mariani et al., 2015]. Medical records were matched with clinical features, radiological and pathological findings for a definitive diagnosis.

Surgical treatment and diagnostic methods

The clinical features of the lesion resemble an osteoma or a central giant cell lesion: the term "giant-cell" refers to a group of benign granulomas, which were surgically treated by diagnostic biopsy only and then followed radiographically, and the majority of them did indeed appear to spontaneously resolve over a period of time [Ficarra et al., 1987]. With the approval of the girl's mother, it was decided to keep the lesion under control and to re-evaluate it monthly. During the first observation, intraoral photographs (Fig. 1, 2) were taken together with an orthopantomograph (Fig. 3) to evaluate the general oral status. After four months, the lesion did not show any signs of spontaneous regression; therefore, clinicians decided to perform a surgical enucleation and a biopsy.

The informed consent was obtained, even if the surgical procedure had a minimal risk for the patient [Ercoli et al., 2015].

Topical antiseptic (chlorhexidine gel 1%) was applied to the surgical area. Anesthesia was performed with local infiltration of 2% mepivacain with epinephrine at the lateral edge of the ossifying epulis and inside the lesion. The ossifying epulis was easily enucleated using appropriate forceps (Fig. 4). After peripheral courettage of the wound, a pressure bandage dressing was applied, and the lesion was left to heal by secondary intention.

Histological characterisation

The specimen was subjected to decalcification before fixation and embedding. Histological analysis revealed some typical features of chronic and acute inflammatory microenvironment with plasma cells (positivity for CD38, MUM1, Lambda and Kappa chains) and bone tissue fragments with remodeling aspects referable to flogistic osteolysis (Fig. 5). To select the most representative tissues for molecular studies, samples were analysed by immunohistochemical methods and reviewed by a cancer pathologist.

Results

Clinical and radiological follow-ups were scheduled every 6 and 12 months, respectively. Two years after excision, no signs of scar or recurrence were noticed (Fig. 6). Histological analysis revealed distinctive features of a chronic and acute inflammatory microenvironment with

plasma cells (positivity for CD38, MUM1, Lambda and Kappa chains) and bone tissue fragments with rehashing aspects referable to flogistic osteolysis. The biopsy results suggest a change in the patient's drug therapy.

Discussion

We have reported a patient with OE associated with POH, in whom an autoimmune thyroiditis has furthermore developed. According to the available literature [Ritchie, 1965; Mantovani, 2011; Altman et al., 2001], the evidence-based gold standard approach for this multisystemic disorder is still controversial. There is a strong evidence supporting the link between thyroid hypofunction and the development of benign calcified lesions. In accordance with the previously described cases of the literature, the drug therapy often failed to halt the progression of the disease and to obtain any improvement. Although hormonal drug therapy (Dibase® 25.000 I.U. /2,5 ml oral solution once a month) yielded a normalisation of serum calcium levels (Table 1), the appearance of a *de novo* calcified formation may suggest the clinicians either to change the drug regimen or to explore alternative pharmacologic therapies [Pippi et al., 2016]. In a minority of cases, clinical features are independent from laboratory parameters. If serum markers offer any additional useful information, it is worthy to adopt a case-based approach as a challenging model for a clinical routine workflow in rare or unfrequent syndromic disorders.

Conclusion

The aim of this study is to review and update the knowledge regarding the remarkable occurrence of drug-resistant GNAS mutations [Shin et al., 2017]. This case represents a clinical practice guideline, worthy of further studies to explore whether there are successful customised treatment modalities for this systemic condition. Considering that peripherical ossifying epulis can occur in any part of the body, all clinicians should focus their efforts to an early diagnosic assessment and, when possible, a multidisciplinary referral of the patients for a specialist examination [Patini et al., 2016].

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Exams	Results	UOM	Reference values
Potassium	4.4	mEq/l	3.5 - 5.1
Sodium	140	mEq/l	136 - 145
Phosphorus	4.8	mEq/dl	4.0 -7.0
Glycemia	87	mEq/dl	70 – 100 Normal 100 – 125 Altered > 125 Diabetes
Serum-calcium	9.4	mEq/dl	8.8 – 10.6
Lactate de-hydrogenase	241	U/l	120 - 245
Gamma GT	33	U/l	0 – 32
GOT	35	U/l	0 – 31
GPT	36	U/l	0 – 34
Cholesterol	209	mg/dl	<200 200 – 249 slight 250 – 299 moderate > 300 serious
Triglycerides	154	mg/dl	Deficient <10.0 slightly lacking 10 – 30 Normal 30 – 100 Toxicity > 100
Urine calcium	120	mg/24h	100 - 300
Vitamin D	15.2	ng/ml	
Total bilirubin	0.53	mg/dl	0.3 – 1.1
FT3	2.65	pg/ml	1.88 – 3.18
FT4	11.76	pmol/l	9.01 – 19.05
TSH	1.05	mUI/l	0.35 - 4.94
Thyroid anti-peroxidase	0.29	UI/ml	0.0 – 5.61
Anti-tyroglobulin antibodies	2.29	UI/ml	0.0 – 4.11
Parathyroid hormone	32.3	pg/ml	12 – 57

TABLE 1 Blood analysis of the surgery's day.

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