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ORIGINAL ARTICLE

Clinical, radiographic, pathological and inherited characteristics of odontogenic keratocyst in nevoid basal cell carcinoma syndrome: a study in three Chilean families

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Abstract

Introduction Nevoid basal cell carcinoma syndrome (NBCCS) is an autosomal dominant condition characterized by the development of odontogenic keratocyst (OKC), basal cell carcinomas and palmar–plantar pits among other conditions. Reports about Latin American population are scarce.

Objective To analyze the clinical, radiographic, histopathologic and inherited features of odontogenic keratocyst and palmar pits in three Chilean families with nevoid basal cell carcinoma syndrome.

Material and methods After histopathologic diagnosis of OKC, notified consent was requested and evaluation of the affected patients and their families was done.

Results Two families appeared to have only one affected adolescent, and both of them were considered de novo cases. In the third family, three affected members participated in this study, with an autosomal dominant presentation. All affected patients had OKC and palmar pits. Basal cell carcinomas were present only among adult patients. All examined patients were from Latin American ethnic groups.

Conclusions Patients with NBCCS had single or multiple OKCs that were located more frequently in the mandibular area. One family had autosomal dominant inheritance and the other two families were de novo cases. None of the three teenage patients had basal cell carcinomas.

Keywords Basal cell carcinoma · Keratocyst · Nevoid basal cell carcinoma syndrome

Introduction

The nevoid basal cell carcinoma syndrome (NBCCS) or Gorlin–Goltz syndrome is a dominant autosomal condition with high penetrance and variable expressivity, in which odontogenic keratocysts (OKCs) develop in the jawbone in the first decades of life [1, 2]. Other described lesions are palmar or plantar pits, skeletal abnormalities, medulloblastoma, and basal cell carcinomas (BCC) [2, 3]. A mutation in the tumor suppressor gene PTCH1, which encodes a receptor for Sonic hedgehog (SHH), has been described in this syndrome [4].

Basal cell carcinomas are the most common skin malignancy reported in Chile [5]. Sporadic cases are usually observed among individuals who are older than 40 years and have had prolonged sun exposure. However, the cases associated with NBCCS usually occur starting from adolescence, so the identification of early manifestations of the

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syndrome as OKC to protect these patients from the sun and periodic monitoring are vital. It has been found that patients with NBCCS appear to have these jaw lesions at an early age, on average at the age of 12 years [6] or multiple OKCs in the jawbone, while cases of OKC not associated with the syndrome are usually unique and are present among slightly older individuals [6, 7].

The OKC previously called keratocyst odontogenic tumor are generally intraosseous benign lesions of odontogenic origin, which have a specific squamous stratified parakeratinized epithelium and locally aggressive behavior [1]. The discovery of mutations in the PTCH gene and the more aggressive behavior of OKC compared to other maxillary cysts were some of the factors that led to the consideration of this lesion as a tumor. For this reason, it was classified by the WHO in 2005 as a keratocyst odontogenic tumor [8]. The WHO in its 2017 classification, due to the non-neoplastic behavior of OKC and the finding of PTCH1 mutations in non-neoplastic lesions such as dentigerous cysts, included this entity again in the group of odontogenic cysts [9, 10].

The OKC usually develop before BCC, so the dentist can play a key role in the evaluation of these lesions for early referral of patients. Most of the reported NBCCS series come from Europe or the USA, and Latin America has very few reports, which come from Brazil [11]. Considering that the development of BCC can be influenced by the degree of skin pigmentation [3, 12], it is important to study this syndrome among populations of different ethnic origins.

This study aims to analyze the clinical, radiographic, histopathologic and inherited characteristics of odontogenic keratocyst in three Chilean families with nevoid basal cell carcinoma syndrome.

Materials and methods

This descriptive study is part of the research project FIO-UChile 09-11 for which we invited potentially NBCCS patients and their families to the School of Dentistry at the University of Chile. Each patient and their guardians were asked to give notified consent or assent and the work was approved by the Ethics Committee of the Faculty of Dentistry, Universidad de Chile. All patients in the study were from Latin American ethnic groups.

A history of macrocephaly, ovarian fibroma and development of malignancies was considered among other records. The imaging characteristics of OKC were evaluated in panoramic radiographs taken at the Imaging Department of the Faculty of Dentistry at the University of Chile or in images that had already been taken in other enclosures. The number and location of OKCs, supernumerary teeth, impacted teeth, agenesis, taurodontism, dislacerations and hyperplasia of the coronoid process were analyzed using panoramic radiographs. Moreover, a study on magnetic resonance imaging (MRI) of facial bones was used in one case. Additionally, a dermatological examination for the possibility of developing basal cell carcinomas and preventive measures was indicated. For the evaluation of the palmar pits, the palms of hands were stained with toluidine blue 0.5% [13] and a digital photograph was taken. The genealogies were prepared on the basis of performed examinations, tests and the story told by an adult member of each family. The histopathologic diagnosis of OKC was verified on slides according to the WHO 2017 criteria. For the NBCCS diagnosis, the criteria of Kimonis 1997 were used [12].

Results

The sample consisted of three Chilean families, with a total of 12 examined members. Five of them had NBCCS, including three children under 20 years of age and two adults over 40 years of age. At the time of diagnosis the ages of patients ranged from 11 to 52 years (Table 1).

Family 1

The proband of this family aged 11 was diagnosed histopathologically with one OKC located in the right upper jaw and at that time it was suggested to exclude an NBCCS. When this patient was 13 years old, he appeared to have an infection in the left upper jaw and by taking panoramic radiography, four radiolucent areas were observed and histopathologically diagnosed as OKC (Fig. 1A and C). In the interview, parents reported that the affected child had macrocephaly in the first year of life. During the extraoral physical examination, palmar pits were identified (Fig. 1B). On the

Table 1 Clinical features of three Chilean families with NBCCS

Clinical features	Family 1	Family 2	Family 3		
	III.3	III.2	III.10	II.3	II.1
Age	13	11	16	47	52
Gender	M	F	M	F	F
Macrocephaly	+	N.D	N.D	N.D	N.D
Palmar pits	+	+	+	+	+
Basocellular carcinomas	–	-	-	+	+
Ovary fibroma	N.A	+	N.A	+	+
Fissured palate	–	–	–	–	–
Bifid uvula	–	–	–	–	–
Labial pits	–	–	–	–	–
Number affected	1	1		12	
Total family members	17	16		37	

N.D not determined, *N.A* not applicable, because of gender of patients

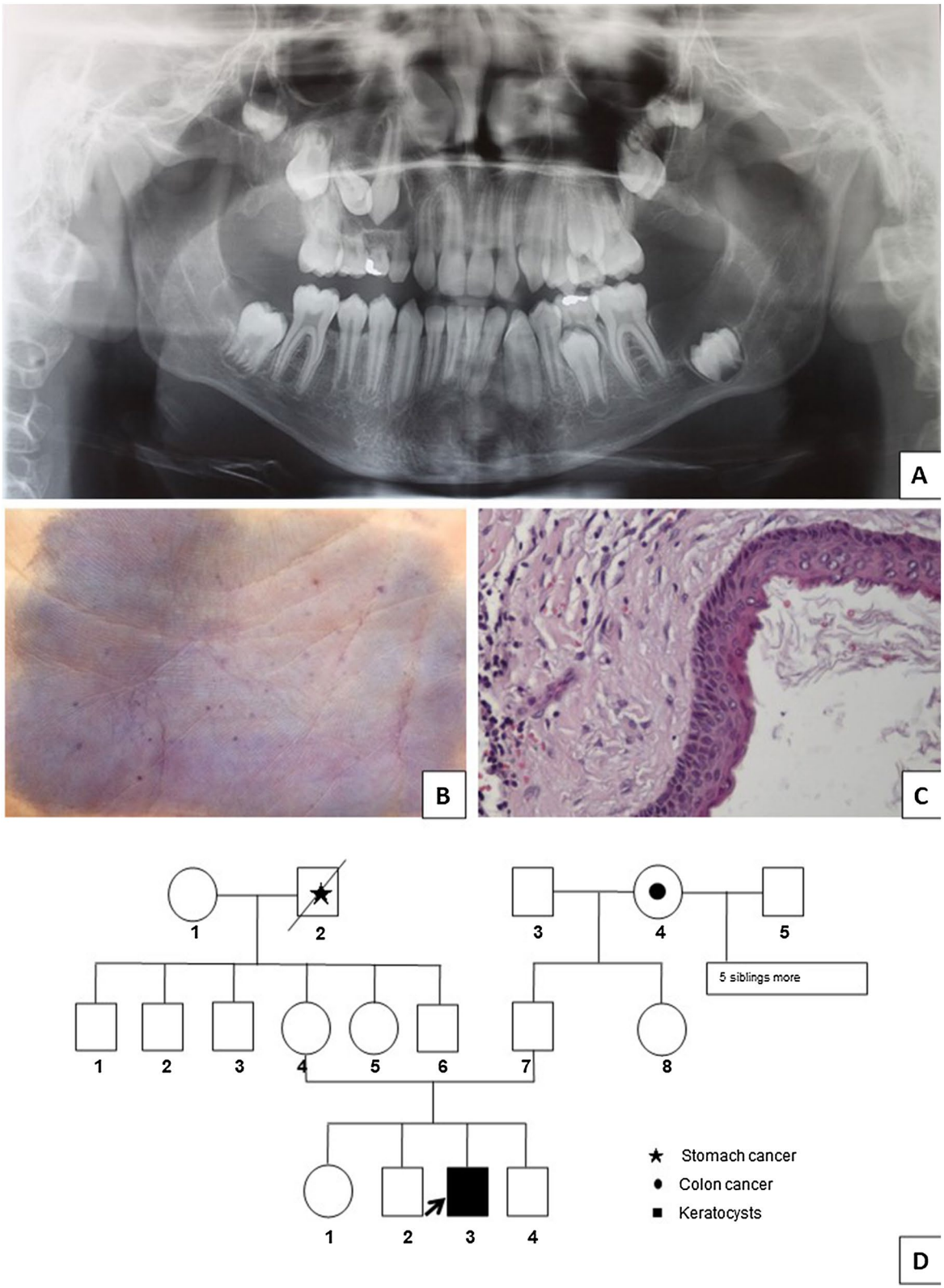

Fig. 1 Radiographs, palmar pits, histopathology and pedigree of the family. (**A**) Panoramic radiographs of the proband, patient FAM.1. III.3. (**B**) Palmar pits of proband. (**C**) Histopathology of one of the OKC. (**D**) Pedigree of family 1, FAM1

basis of this information, the patient was diagnosed with nevoid basal cell carcinoma syndrome.

The 17 members of this family were invited to participate in this study, of which only the parents and siblings of the proband signed informed consents or assents. A clinical and radiographic examination with orthopantomographies was performed on the mother and father (Individuals II.4 and II.7) and the other three children aged 16, 14 and 9 years (Individuals III.1, III.2 and III.4). Among them, only the 13-year-old child (patient III.3) was affected. (Table 2). The parents reported stomach cancer of the maternal grandfather, who died of the disease, and colon cancer of the paternal grandmother, who was alive at the time of recording the data. With this background, the genealogy (Fig. 1D) was compiled. As seen in Fig. 1, subject III.3 was the only one affected by NBCCS in the family, suggesting that it could be a de novo case. In the dermatological controls, BCC were not detected.

Family 2

We proceeded to the clinical examination of the patient, an 11-year-old girl, who presented with radiolucent lesions in her jawbones, which were diagnosed radiographically and histopathologically as two OKCs: one maxillary and another mandibular (Fig. 2A and C). The family was invited to participate in the evaluation and to sign a notified consent or assent. During anamnesis, the mother reported that her daughter had been surgically intervened because of ovarian fibroma at the age of 10. The extraoral examination showed hypertelorism and palmar pits (Fig. 2B). In the radiographic examination, multiple cystic lesions were observed in both jaws (Fig. 2A) (Table 2). Of the 16 members of the family shown in the pedigree (Fig. 2D), the mother, the sister of the proband and the proband signed informed consents or assents. A clinical and radiographic examination with orthopantomograpy was performed on the mother and sister aged 6 years (Fig. 2D, individuals II.7 and III.3). Only the 11-year-old girl had NBCCS (Fig. 2D). BCC was not detected on dermatologic examination.

Table 2 Radiographic and MRI features of the jaws of three Chilean families with NBCCS

	Family 1	Family 2	Family 3		
	III.3	III.2	III.10	II.3	II.1
Total number of OKCs[a]	4	3	3	1	1
Maxillary distribution	C/M	C/M			
Mandibular distribution	M/M-R	I/M	C-PM	R	PM-M
Supernumerary tooth	–	–	–	N.A	N.A
Impacted tooth	+	+	+	N.A	N.A
Tooth agenesis	+	–	+	N.A	N.A
Taurodontism	–	–	–	N.A	N.A
Root dislaceration	+	–	–	N.A	N.A
Hyperplasic coronoid process	–	–	–	–	–

I incisive, *C* canine, *PM* premolar, *M* molar, *R* ramus, *N.A* not applicable because of multiple extractions

[a]Number of OKCs detected at the time the imaging study was performed

Family 3

This family was made up of 37 members, of which 12 were affected, 8 women and 4 men. Several members of this family previously diagnosed with nevoid basal cell carcinoma syndrome were invited to participate in this study; three of them agreed to participate and signed a notified consent or assent. Orthopantomography images from the three participants of this family (Fig. 3A, E and F), computed tomography (CT) and magnetic resonance (MRI) from patient III.10 are presented (Fig. 3B–D). In the case of patient III.10, with panoramic radiograph one OKC was detected (Fig. 3A). However, with CT and MRI two other OKCs were detected (Figs. 3 B–D) (Table 2).

The two sisters, 47 and 52 years old, subjects II.1 and II.3 in pedigree, respectively (Fig. 4E), have been surgically intervened due to numerous BCCs that were principally located on the face and due to OKC in the jaws. The 16-year-old patient identified as III.10 in the pedigree recently underwent surgery to treat an OKC. No BCC was observed in dermatological controls. The rest of the affected patients in the family did not attend the examination, so that the genealogy was compiled with information provided by the two sisters (Fig. 4E).

The three participants of this family had palmar pits (Fig. 4A and B). The specific histopathologic image of an OKC from patient FAM.II.3 is shown (Fig. 4C and D).

The main clinical and radiographic findings of the five patients examined are summarized in Tables 1 and 2.

Discussion

The clinical and radiographic characteristics of five Chilean patients with NBCCS were analyzed; all of these patients had both OKC and palmar pits. This study, like those made by Shimada [14], Titinchi [3], Rosón-Gomez [15] and Habibi [16], was conducted at a School of Dentistry. Therefore, patients were evaluated for a possible NBCCS due to the presence of OKC, and in these studies all patients with the syndrome had OKC [3, 14–16]. In contrast to the above-mentioned reports, in the investigations by Shanley, Kimonis and Larsen [2, 17, 18], which were performed in hospitals, OKCs were found in 75%,

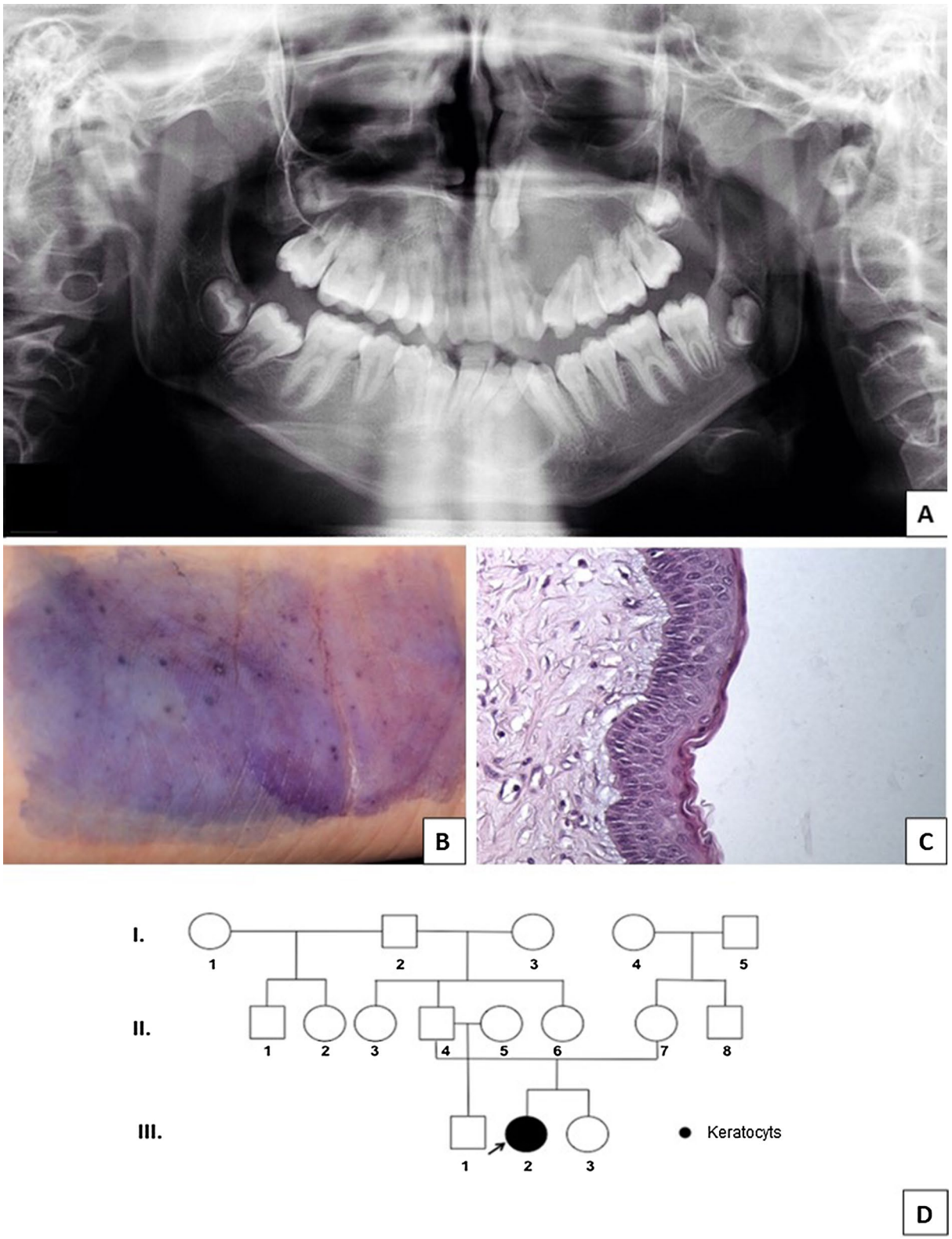

Fig. 2 Radiographs, pits, histopathology and pedigree of family 2. (**A**) Panoramic radiograph of the proband, patient FAM.2. III.2. (**B**) Palmar pits of proband. (**C**) Histopathology of one of the OKC. (**D**) Pedigree of family 2, FAM2

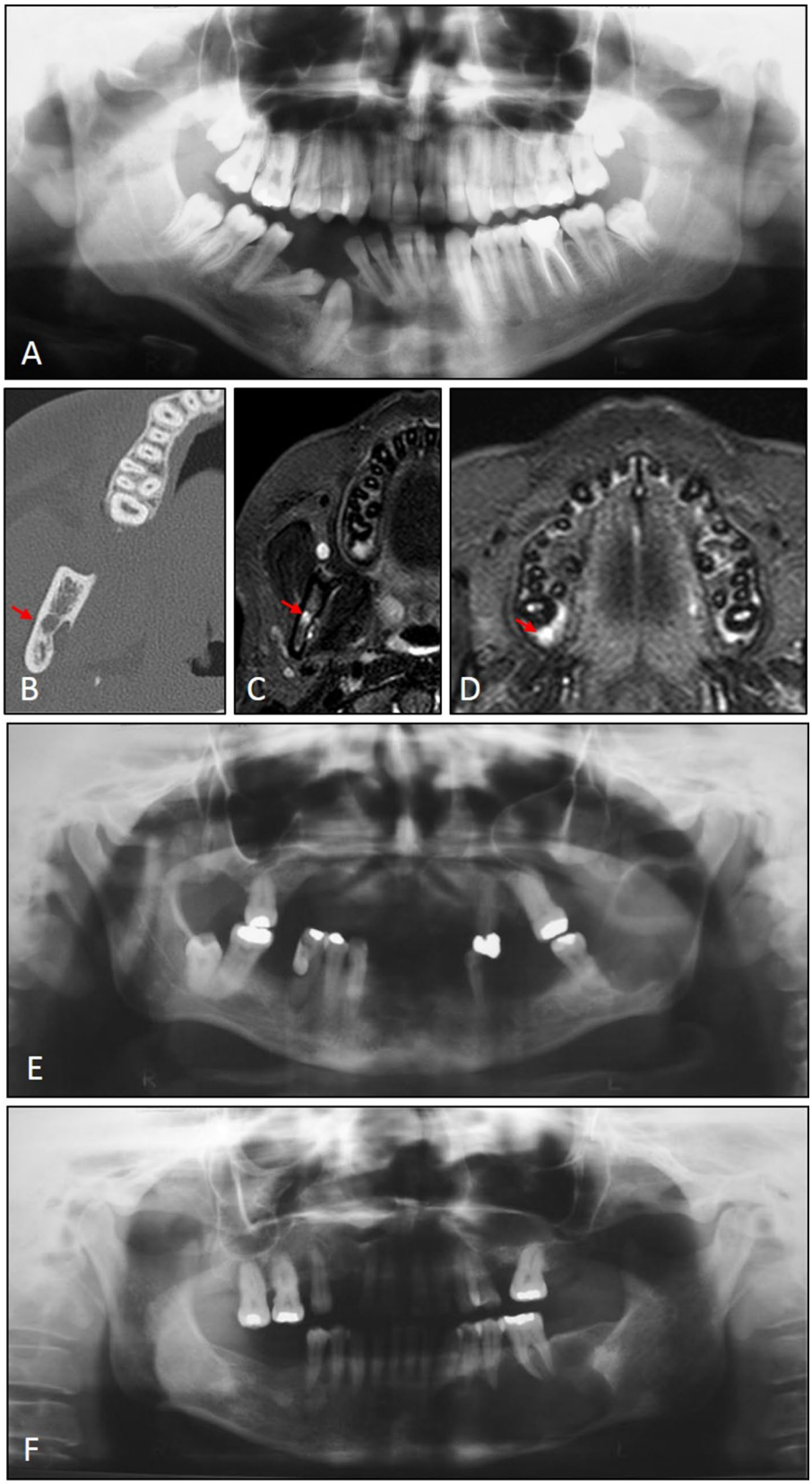

Fig. 3 Panoramic radiograph, CT and MRI of the patient of family 3. (**A**) The panoramic radiograph of patient III.10 shows an OKC on the right side of the mandible. In the CT of the same patient, a second osteolytic lesion (red arrow) in the right mandibular ramus (**B**) was seen, suggesting a cyst, especially when the lesion was examined by MRI STIR sequence (red arrow) (**C**). Another incidental finding was seen with an MRI STIR sequence in a patient of family 3 with the aspect of a cyst, related to the pericoronal space of the upper right third molar (red arrow) (**D**). Panoramic radiograph of patient II.3. with an extensive lesion on the left ramus. (**E**) Panoramic radiograph of patient II.1. with extensive lesion in the mandibular body (**F**)

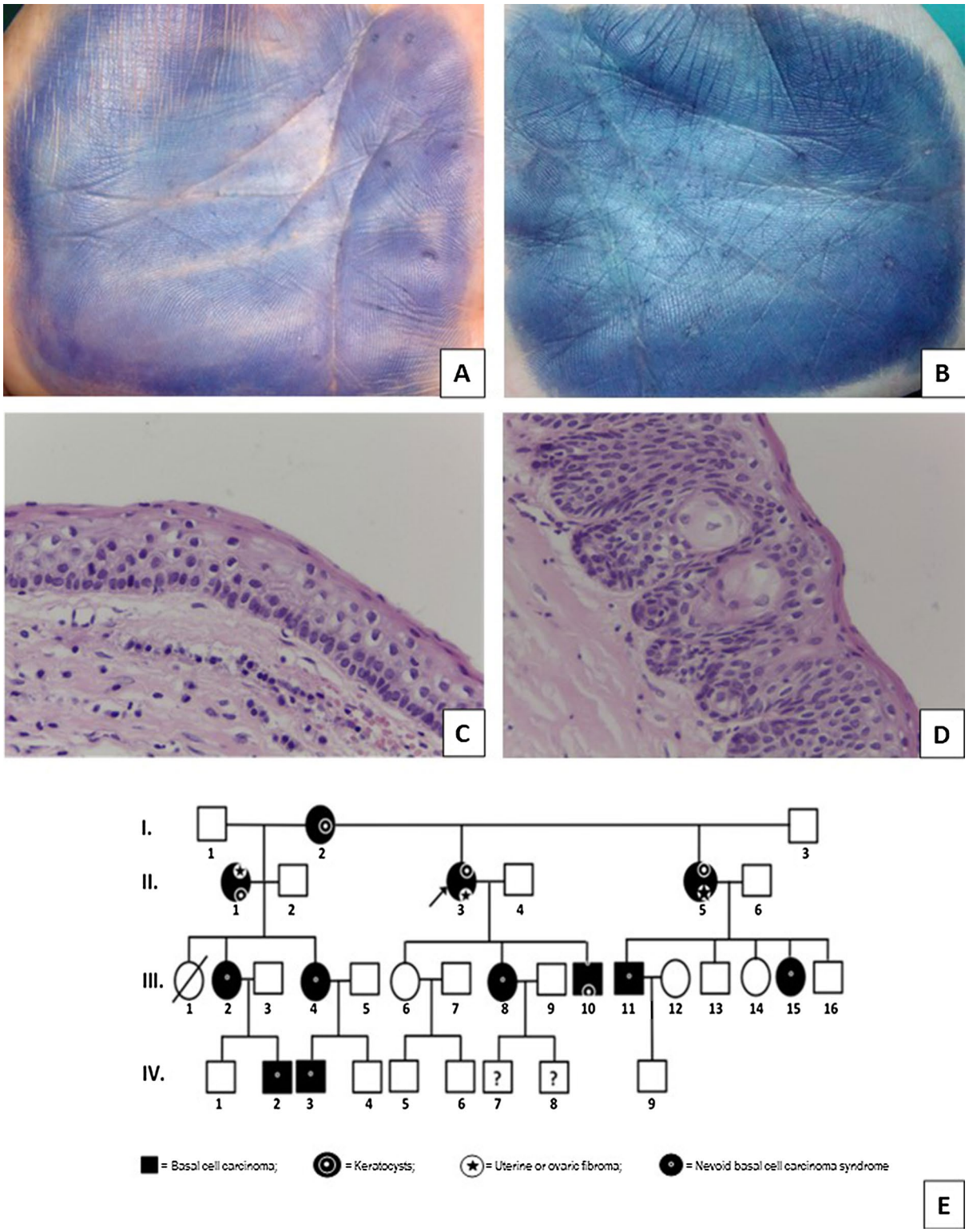

Fig. 4 Palmar pits, histopathology and pedigree of family 3 (**A**). Palmar pits of patient FAM.3. III.10. (**B**). Palmar pits of patient FAM.3. II.3. (**C**, **D**). Histopathology of OKC of patient FAM.3. II.3. (**E**). Pedigree of family 3

74% and 71% of the cases, respectively. Patients from both dental clinics and medical hospitals had OKC before 20 years of age and the most frequent location was in the mandible in the molar area and mandibular ramus [3, 12, 14–17].

The importance of early detection of OKC lies in its potentially aggressive local behavior, which can lead to deformation of the jaws, pathological fractures, infections and other complications that could be mutilating for the patient. Additionally, the diagnosis of OKC among children and adolescents can contribute to the diagnosis of NBCCS, allowing the prevention and early diagnosis of BCC and other neoplasms. The OKCs, formerly classified as odontogenic tumors, are relatively common lesions in Chilean series of jaw cysts [19]. Along with this, OKCs associated with NBCCS are generally multiple and have a higher frequency of recurrences [8]. In the present series, there were two children who were consulted because of infections in their jawbones. Radiographic studies showed that they both had multiple radiolucent areas, which were later diagnosed by histopathology as OKC. In the case of the family who had already been diagnosed with NBCCS (family 3), the three evaluated members had OKC at the time of examination, even though multiple OKCs had previously developed. In all described cases in the present study, conservative treatment was performed by decompression and surgery. For adult patients with NBCCS, a successful pharmacological treatment of OKC with vismodegib, an HH pathway inhibitor, has recently been reported by Ally et al. [20]. However, the use of these products for children requires additional studies, because they interact with molecules involved in craniofacial development. Ally et al. also recommend the use of MRI to study OKC instead of conventional radiographic techniques to prevent radiation and reduce the risk of developing BCC [20]. In the present work, the use of MRI identified two OKCs that had not been detected on panoramic radiographs.

Palmar pits were found among 100% of patients in the present report, which are also characteristics that have been reported with high frequency in several series [2, 14, 21]. In the study by Shanley, the number of palmar pits doubled after dipping hands in water, demonstrating that for the assessment of palmar pits, it is advisable to use a technique that highlights the presence of these dimples, as the pits measured from only 1–3 mm and may go unnoticed by the naked eye [17]. In this study, 0.5% toluidine blue was used for staining the palms [13], which allowed us to see the palmar pits that in many cases could not be identified before the use of the dye. In the work of Kimonis, the palmar pits were detected among patients aged 5 months to 77 years. Therefore, the pits would be an age-independent sign of NBCCS. Among the advantages of the evaluation of palmar pits are its low cost and being a non-invasive examination without any adverse effects for the patient.

Regarding the BCC, in our work, this neoplasia was observed in two cases of patients of about 50 years of age who have experienced multiple lesions, but this tumor was not detected among patients less than 17 years old. In the study by Shimada in which most NBCCS patients were teenagers, a low percentage of BCC was found, which is consistent with the general population of Japan where the incidence of BCC of patients without the syndrome is low [14]. In the series of South Africa, a low incidence of BCC was also observed among patients with NBCCS. Perhaps this is due to the small number of Caucasians, who are the most affected by BCC [3]. Moreover, in the study by Shanley, 76% of patients, including a high percentage of Caucasians, were diagnosed with BCC and 47% were less than 20 years old [17]. In the study by Kimonis, comparing the development of BCC in Caucasians and African-American patients, 50% of white patients developed BCC at the age of 21.5 years compared to African-Americans, 20% of whom presented the lesions at the same age [12]. There are few reports on Latin American population. The present study suggests that the development of BCC among patients with NBCCS in this ethnic group would occur at similar ages to those observed in Asian and African ethnic groups. As reported in the literature, there is an increased incidence of BCC with age, so these patients should be constantly checked to detect possible development of this neoplasm.

Among patients with NBCCS, a high percentage of craniofacial disorders such as macrocephaly, hypertelorism, prominent forehead, cleft palate and hypodontia have been reported [2, 16]. In the present group of patients, in addition to the OKC, macrocephaly, prominent forehead and tooth agenesis were observed. None of these patients had lip or cleft palate, which has been reported in the NBCCS in percentages ranging between 4 and 9% [2, 21], even though this condition has been reported in up to 29% [22]. In our country, one case of lip and cleft palate associated with NBCCS has been reported [22].

Among the results of this study, we found that two patients were the first affected members of their families with NBCCS, while the remaining three patients belonged to the same family in which autosomal dominant inheritance was observed. In a recent study by Evans [21], it was found that 26% of cases of NBCCS corresponded to de novo mutations, so the identification of clinical markers becomes more important in these patients without family history.

In the present work, ovarian fibroma was detected in the cases of three women with NBCCS, including the youngest patient who was diagnosed with the lesion at 10 years of age. Kimonis considers the ovarian fibroma as a minor criterion, which when asymptomatic goes unnoticed in many cases [12].

When a patient under 20 years of age has a histopathological diagnosis of odontogenic keratocyst, according to

the 2011 Consensus Statement on Basal Cell Nevus Syndrome, it should be considered as a triggering sign of suspicion to rule out NBCCS, since it is considered a major diagnostic criterion. In these cases, other major diagnostic criteria must be evaluated, such as: basal cell carcinomas before the age of 20 years or an excessive number of basal cell carcinomas unrelated to previous sun exposure or skin type; palmar or plantar pits; lamellar calcification of the falx cerebri, medulloblastoma and first degree relative with the syndrome. The diagnosis of NBCCS can be made when a patient has any of three combinations: (1) one major criterion and confirmed PTCH1 mutation, (2) two major criteria, or (3) one major criterion and two minor criteria [23].

In dental clinical practice, faced with the finding of radiolucent areas in the maxillary bones compatible with cystic lesions, it is imperative to reach an accurate diagnosis of these lesions. As already mentioned, if the histopathological diagnosis in children or adolescents is OKC, NBCCS should be ruled out. If major or minor diagnostic criteria are identified in anamnesis, the patient will require a multidisciplinary evaluation to determine if they have the syndrome and, if present, an early diagnosis will allow the use of management protocols that will improve the quality of life of these patients [23]. The finding of multiple OKCs should also raise suspicion for NBCCS, and major and minor diagnostic criteria should be evaluated to confirm or rule out the syndrome. In this regard, there are some reports of patients with multiple non-syndromic OKC [24, 25].

In summary, the five cases of Latin American origin that presented with NBCCS had single or multiple OKC, most often located in the mandibular area. One family had autosomal dominant inheritance and the cases of other two families were sporadic, possibly representing de novo mutations. Basal cell carcinomas were not observed in the cases of the three adolescent patients.

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Data availability The anonymized data evaluated during the present study will be available from the corresponding author upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This work is part of a research project approved by the Ethics Committee of the Faculty of Dentistry of the University of Chile.

Informed consent Each patient and in the case of children their parents signed an informed consent authorizing their participation. Young people between 12 and 18 years of age signed an informed assent.

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