The Saudi Dental Journal 36 (2024) 38–43

Contents lists available at ScienceDirect

The Saudi Dental Journal

journal homepage: www.ksu.edu.sa
www.sciencedirect.com

Pediatric odontogenic keratocyst and early diagnosis of Gorlin syndrome: Clinicopathological aids

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ARTICLE INFO

Keywords:
Early diagnosis
Odontogenic keratocyst
Clinicopathological
Histological

ABSTRACT

Odontogenic keratocysts (OKCs) are a common presentation in almost all patients with nevoid basal cell carcinoma syndrome (NBCCS) or Gorlin syndrome, irrespective of race. In most patients with NBCCS, OKC presents as multiple lesions affecting the jaws which makes it a signpost for the investigation of patients with the syndrome. In approximately 40% of pediatric patients, the initial presentation is that of a single OKC, which may often result in missing the diagnosis of NBCCS. This is particularly common in patients without clinically apparent NBCCS-related manifestations. This review examines the clinicopathological features that clinicians and oral pathologists may look for in pediatric patient with OKC and OKC surgical specimens that may serve as indicators for the diagnosis of NBCCS. Although these features do not diagnose NBCCS by themselves, they may significantly help in initiating the diagnostic process at an early stage with an obvious benefit to the child and relatives.

1. Introduction

Gorlin syndrome (Gorlin-Gorltz syndrome or nevoid basal cell carcinoma syndrome [NBCCS]; OMIM #109400) is a relatively rare autosomal dominant inherited multisystem disorder characterized by a spectrum of lesions or malformations spanning the skeletal, cutaneous, endocrine, neurological, ophthalmic and genital locations. A few of these lesions typically present during childhood whereas most develop later in adulthood. Among the most clinically significant lesions in Gorlin syndrome (herein referred to as NBCCS) are basal cell carcinomas (BCC), medulloblastoma and odontogenic keratocyst (OKC). Clinically, NBCCS is diagnosed by fulfilling diagnostic criteria consisting of lesions divided into major and minor manifestations (Evans et al., 1993, Kimonis et al., 1997, Bree and Shah 2011) or through genetic testing of the family members of a patient with established NBCCS. Early diagnosis of NBCCS is important for carrying out recommended surveillance and preventing iatrogenic induction of BCC during the management of early lesional features in the disease (such as avoidance or lessening of radiation exposure and frequent CT scans at an early age (Akbari et al., 2018), and seeking modalities other than x-irradiation for the treatment of patients with medulloblastoma (Gorlin 1999), -all aimed at preventing the development of BCCs). In addition, early diagnosis and treatment of NBCCS-related OKCs may be crucial for maintaining adequate jaw function (Fujii and Miyashita 2014), followed by the need to institute orthodontic therapy to address the occlusal and esthetic consequences of such treatments, as well as to eliminate or reduce any negative impact on maxillofacial growth (Feghali et al., 2022). Early diagnosis of NBCCS is often hampered by the absence of some important lesions until late adolescence or adulthood (Lo Muzio 2008, Gold et al., 2021), no previously diagnosed family members in over a quarter of cases (Akbari et al., 2018), significant rarity (only 1–5 % of NBCCS) of medulloblastoma (an early lesion recently classified as a major criterion) (Bree and Shah 2011, Palacios-Álvarez et al., 2018), and variation in presentation of lesions among different racial groups e.g. BCCs between Caucasians (common) and East Asians (rare) (Endo et al., 2012, MacDonald 2015).

In the maxillofacial regions, many patients with NBCCS develop multiple OKCs affecting one or both jaws as intraosseous cystic lesions with a predilection for the posterior mandible. It tends to appear during childhood or early adolescence in NBCCS. However, a significant number of pediatric patients are diagnosed with solitary OKC at the time of their first presentation in the clinic and may not show other NBCCS manifestations that are clinically apparent to clinicians (Karhade et al., 2019). While the majority of OKCs are not NBCCS-related, some clinical and histological features of NBCCS-related OKC have been found to be relatively good indicators of the suspicion and eventual diagnosis of the syndrome. Such features may be particularly important in patients

Peer review under responsibility of King Saud University. Production and hosting by Elsevier.
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https://doi.org/10.1016/j.sdentj.2023.10.012
Received 27 August 2023; Received in revised form 16 October 2023; Accepted 17 October 2023
Available online 18 October 2023

whose initial physical presentation is a solitary OKC, especially in Asians and Africans. The purpose of this review was to highlight the clinicopathological features of OKC, especially solitary OKC, which may sensitize clinicians and oral pathologists to be more vigilant and better play their role in the early diagnosis of NBCCS.

2. Gorlin syndrome

NBCCS is attributed to germline mutations in patched 1 (*PCTH*1) gene. Suppressor of fused (*SUFU*) and *PCTH2* genes have also been associated with this syndrome. They all encode proteins active in the sonic hedgehog (SHH) signaling pathway (Fujii and Miyashita 2014, Nosé and Lazar 2022). *SUFU* mutations appear to be associated with OKC-deficient NBCCS whereas *PTCH*2 are rarely associated with milder phenotypes of the syndrome (Fujii and Miyashita 2014). In NBCCS, the mutation is inherited in an autosomal dominant pattern, with almost complete penetrance and variable intrafamilial and interfamilial expressivity, with 20–30 % being de novo mutations in probands (Jones et al., 2011).

With wide variation in different studies, the prevalence of NBCCS is generally accepted to be approximately 1/60 000 (Gorlin 1999). Some investigators have found a similar prevalence (Pratt and Jackson 1987, Evans et al., 1993), while others have found a much lower prevalence (Shanley et al., 1994, Ahn et al., 2004) within their local population. It has an almost equal sex distribution (Spiker et al., 2023). It affects all races, but Africans and Asians are significantly less affected (Spiker et al., 2023). The classification of the diagnostic criteria (major and minor) was coded by Evans *et al* (Evans et al., 1993) (Table 1) and later modified by Kimonis *et al* (Kimonis et al., 1997) (Table 1, footnote) in the 1990 s. The most recent modification was proposed in a consensus statement in 2011 (Bree and Shah 2011) (Table 1, footnote), although this has not found universal acceptance within the expert community as including medulloblastoma as a major criterion may reduce the specificity of the criteria in patients undergoing radiation therapy for medulloblastoma without NBCCS (Evans and Farndon 1993). Based on the consensus statement, a diagnosis can be established by using two major criteria or one major and two minor criteria or one major criterion and genetic testing. A recent study highlighted the difficulty of early diagnosis of NBCCS using current clinical criteria in the absence of a family history and molecular testing, indicating that the median age of meeting the clinical diagnostic criteria is late adolescence (16.8 years) (Gold et al., 2021).

Table 1
Diagnostic criteria for naevoid basal cell carcinoma syndrome. * #.

A diagnosis can be made when 2 major or 1 major and 2 minor criteria are fulfilled.
Major criteria
(1) Multiple (>2) basal cell carcinomas (BCC) or one under 30 years, or > 10 basal cell naevi.
(2) Any odontogenic keratocyst (proven on histology), or polyostotic bone cyst.
(3) Palmar or plantar pits (3 or more).
(4) Ectopic calcification: lamellar or early (<20 years) falx calcification.
(5) Family history of NBCCS.
Minor criteria
(1) Congenital skeletal anomaly: bifid, fused, splayed, or missing rib, or bifid, wedged, or fused vertebra.
(2) Occipitofrontal circumference > 97th centile, with frontal bossing.
(3) Cardiac or ovarian fibroma.
(4) Medulloblastoma.
(5) Lymphomesenteric cysts.
(6) Congenital malformation: cleft lip and/or palate, polydactyly, eye anomaly (cataract, coloboma, microphthalmia).

The diagnostic criteria as proposed by Evans et al (Evans et al, 1993).
*In the Kimonis et al modification (Kimonis et al, 1997), among the major criteria is one BCC occurring under 20 years (not 30 years). Basal cell nevi and polyostotic bone cysts were removed. Rib abnormality was added to major criteria and removed from minor criteria. The minor criteria were similar apart for exclusion of lymphomesenteric cysts.
#In the consensus statement (Bree and Shah, 2011), major criteria now include only OKC before the age of 20 years and upgrading of medulloblastoma to a major criterion and moving rib abnormalities back to minor criteria group, in addition to inclusion of lymphomesenteric cysts. Genetic confirmatory testing was also advocated for suspected cases that do not meet the diagnostic criteria.

3. Odontogenic keratocyst (non-syndromic and syndromic)

OKC is among the most common and consequential odontogenic cysts, constituting approximately 10 % of jaw cysts, and is noted for its locally aggressive behavior (Boffano et al., 2022). It is believed to arise from remnants of the dental lamina (Toller 1972), although an alternative origin derived from the oral epithelial basal layer has been suggested (Stoelinga 2003, Boffano et al., 2022), with the latter being particularly more likely in NBCCS-related OKC (Stoelinga 2022). Most cases occur within the second and fourth decades of life and are almost twice more common in males than in females (August et al., 2003, Kolokythas et al., 2007). The lesion has a strong posterior mandibular predilection (65–85 %) (Kolokythas et al., 2007). While OKC can occur in any tooth-bearing part of the jaw, the most preferred sites in the maxilla are the molar and incisal regions (Boffano et al., 2022). Radiographically, most lesions are unilocular with only approximately 30 % presenting with multilocular radiolucency (Boffano et al., 2022). Mixed radiolucent-radiopaque lesions are rarely encountered (Boffano et al., 2022).

Histopathologically, OKC typically shows a uniformly thick squamous epithelial lining (approximately 5–10 cells thick); surface parakeratinization, often with corrugation; and a palisaded columnar or cuboidal basal layer with hyperchromasia. The cyst lumen is often filled with desquamated keratin. The epithelial component (lining) is overlaid with a thin fibrous connective tissue wall (Fig. 1).

NBCCS-related OKC appears a decade younger at the time of diagnosis than the non-syndromic type and is often multiple (Lo Muzio 2008). OKC is present in more than 90 % of the patients with NBCCS (Ahn et al., 2004, Lo Muzio 2008), and is often the first manifestation of this syndrome (Carlson et al., 2015). Maxillary presentation may be relatively more common than in non-syndromic OKC (Karhade et al., 2019). OKC is the most consistent and representative sign of NBCCS in the first and second decades of life, in addition to being free of any racial predilection (Lo Muzio 2008). Histopathologically, NBCCS-related OKCs are associated with high rates of satellite (daughter) cysts and solid islands of proliferating odontogenic epithelium including those with ameloblastoma-like features (Woolgar et al., 1987, Bello 2016). The

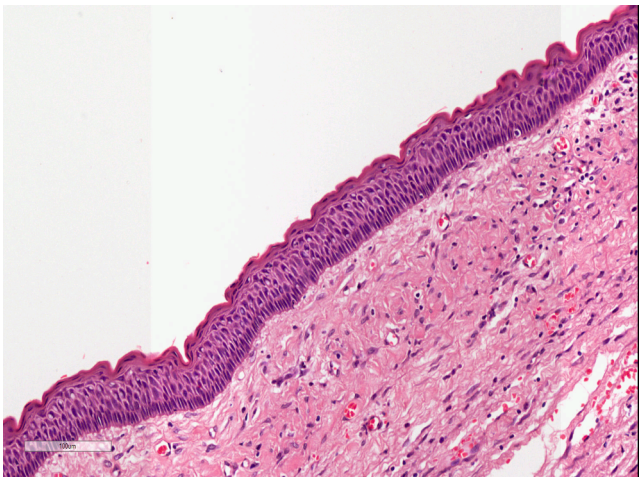

Fig. 1. Typical odontogenic keratocyst with the epithelium showing luminal corrugated parakeratinization and basal layer palisading. The epithelial lining-connective tissue wall interface is flattened and the cyst wall shows no inflammation.

clinicopathological features of NBCCS-related OKC that may be helpful in initiating the diagnosis of NBCCS are discussed below.

4. Multiple odontogenic keratocysts

The presentation of multiple OKCs (>1 cyst), either new or recurring, particularly in children or young adults, is one of the strongest pointers for the early diagnosis of NBCCS. Such NBCCS-related OKCs usually do not abate until 30 years of age (Mustaciuolo et al., 1989). They can range from 1 to 30 lesions with an average number of five (Lo Muzio 2008, Feghali et al., 2022). Prior to initiating the processes for NBCCS diagnosis, it is important that the cysts are histopathologically diagnosed as OKC. In our experience, some patients presenting with multiple synchronous cystic lesions have none or only one of them being OKC (with the others mostly non-keratinized or rarely orthokeratinized). These patients lacked other manifestations and were not diagnosed with the syndrome after investigation. Other patients with multiple histopathologically confirmed OKCs were eventually diagnosed with this syndrome (Bello 2016). The diagnosis of multiple OKC in a child or any other patient should automatically initiate an investigation for NBCCS, which should be included in the pathology report by the oral pathologist. Interestingly, multiple non-syndromic OKCs can occur (Stoelinga 2022). Conversely, 44 % of newly diagnosed pediatric patients with NBCCS may present with a single OKC. This presentation emphasizes the need for enhanced clinical vigilance of NBCCS among clinicians treating childhood OKC (Karhade et al., 2019). Many of these patients often go on to develop multiple OKCs during follow-up.

Further complicating the diagnostic dilemma for clinicians, multiple OKCs, by definition, do not imply that they should present synchronously at any given time, but that lesions develop over the patient's lifetime (Kalia et al., 2011). Therefore, the presence of multiple synchronous OKCs at presentation (seen in approximately 60 % of NBCCS patients) should be considered highly suggestive of NBCCS, which necessitates further clinical investigations and when necessary, genetic testing (Karhade et al., 2019). In some children, multiple OKCs at presentation followed by recurrence and/or development of new lesions on follow-up may be the only manifestation, with the diagnosis of NBCCS aided by confirmatory genetic testing (Santander et al., 2018). This underlines the central role played by multiple OKCs in the early diagnosis of NBCCS, particularly in children who have yet to develop other manifestations, or may never develop them even in adulthood.

Recurrent lesions and a relative increase in the maxillary presentation are closely related to multiple OKCs. NBCCS-related OKCs have recurrence rates ranging from 30 to 60 % (Gorlin 1987), which are significantly higher than those of non-syndromic OKCs (Ahn et al., 2004, Karhade et al., 2019). In a previously undiagnosed patient, the presence of two or more recurrences is indicative of NBCCS (Lo Muzio et al., 1999). As OKC is more likely to be present in the maxilla in NBCCS than in non-syndromic OKC (Karhade et al., 2019), the question is whether this is sufficient to initiate the early diagnosis of NBCCS in a solitary OKC case. The low threshold for the diagnosis of NBCCS suggests that this is an option. However, clinicians and investigators have not advocated for treating maxillary or mandibular OKC with any difference in this regard.

Overall, multiple OKCs, maxillary presentation and recurrence are good predictors of NBCCS in children. They should trigger the processes required for early diagnosis. However, unless all OKC cases are clinically and genetically screened for NBCCS at presentation (which may not be cost-effective or feasible), close to half of the cases may be missed in patients who present with only a single OKC and no other manifestations upon first clinical contact (Karhade et al., 2019). Based on previous studies (Woolgar et al., 1987, Bello 2016), it can be suggested that there could have been a notable reduction on the number of pediatric solitary, NBCCS-related OKC that would have been missed (regarding investigation and diagnosis of NBCCS) if certain histological features were considered in the evaluation of the surgical specimen submitted after the treatment of the solitary OKC.

5. Histopathological considerations in solitary OKC and Gorlin syndrome

It is generally agreed that OKC occurring in NBCCS is histologically indistinguishable from non-syndrome-related OKC (Bresler et al., 2016, Nosé and Lazar 2022, Stoelinga 2022). This is entirely accurate, and NBCCS cannot be diagnosed by microscopic examination of OKC only. However, if used as an aid to initiate further investigation of NBCCS in a pediatric patient with a solitary OKC without any other visible clinical manifestations, histological analysis of the excised keratocyst may be quite suggestive of NBCCS. The presence of numerous daughter cysts, solid islands of proliferating odontogenic epithelium, and solid epithelial islands with ameloblastoid features is more frequently observed in NBCCS-related OKCs than in their non-syndromic counterparts (Browne 1971, Brannon 1977, Woolgar et al., 1987, Bello 2016). Additionally, basal epithelial budding when present along with any of these histological features may substantially indicate the likelihood of NBCCS in a patient (Woolgar et al., 1987). While these morphological features may be seen in non-syndromic OKC, they are usually far less likely and almost always significantly fewer than those seen in NBCCS in young patients (Woolgar et al., 1987, Bello 2016). Morphologically, in addition to being numerically high and occupying a significant proportion of the cyst wall (Fig. 2), daughter cysts in NBCCS present a picture similar to the previously described solid variant of OKC (Vered et al., 2004) within the wall of the OKC (if the large parent keratocyst is disregarded). Some bear little resemblance to the parent OKC, with a flattened epithelial lining. Others retain the classic features of an OKC (Woolgar et al., 1987).

Additionally, NBCCS-related OKCs are more likely to present with an actively proliferating odontogenic epithelium in children (Woolgar et al., 1987) with or without the presence of numerous daughter cysts (Fig. 3). This may occur in the form of long rows or clusters of proliferative, often basaloid, anastomosing epithelial structures. Occasional central degeneration giving rise to microcysts may be observed. In addition, some of these proliferations may have features typical of ameloblastoma islands (Fig. 3). This latter features is rare; however, when present, should strongly indicate the need for further investigation of NBCCS. A relatively large comparative study found all seven cases with this feature were diagnosed with NBCCS whereas the feature was entirely absent in non-syndromic OKCs (Woolgar et al., 1987). The pathologist may not make the mistake of diagnosing this as a hybrid lesion of ameloblastoma with OKC or as a keratoameloblastoma, as the dominant feature is the presence of a large OKC, proliferating epithelium or daughter cysts, and few ameloblastoid epithelial structures. The budding of the basal epithelial cells of the OKC lining into the connective tissue wall may also be an additional clue to the possibility of NBCCS, although this is equally common in non-syndromic OKC (Woolgar et al., 1987) (Fig. 4). The presence of numerous inactive odontogenic rests has also been found to be significantly increased by some investigators (Woolgar et al., 1987), but this has not been confirmed by others (Bello 2016). It has been shown that these histomorphological features were more common in maxillary OKCs in NBCCS by proportion (Woolgar et al., 1987). However, by absolute numbers, they are more common in the posterior mandible because OKC prevalence is decisively skewed towards the latter (Woolgar et al., 1987). In our experience, this is quite accurate. However, it appears wise to disregard jaw location and initiate early diagnostic procedures for NBCCS in pediatric solitary OKCs without any other apparent NBCCS-related manifestations.

6. Early diagnosis of NBCCS with solitary OKC

Although initiating the diagnosis of NBCCS in children and teenagers is immediately indicated in multiple OKC presentations, it is often less indicated in those with a single OKC. The ideal scenario would be to investigate all pediatric OKCs for the possible presence of NBCCS. A simple investigative protocol at a Brazilian center for all patients with OKC resulted in the discovery of many previously undiagnosed cases of

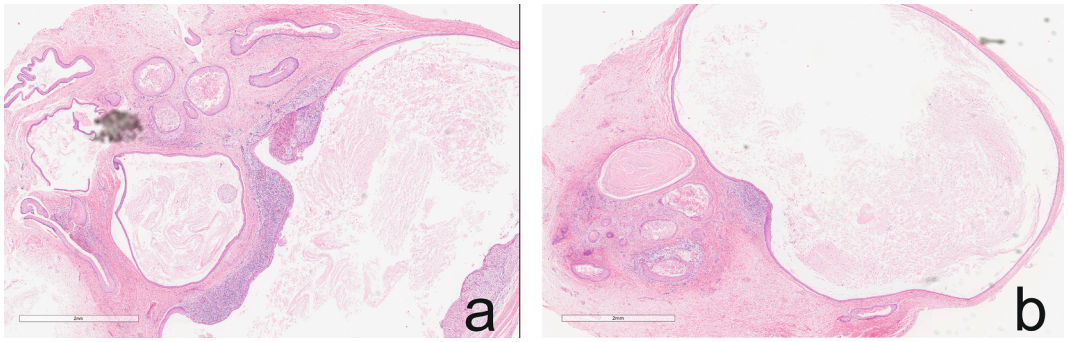

Fig. 2. Sections from a 15-year-old female patient with Gorlin syndrome with numerous daughter cysts of varying shapes and sizes in relation maxillary and mandibular odontogenic keratocysts.

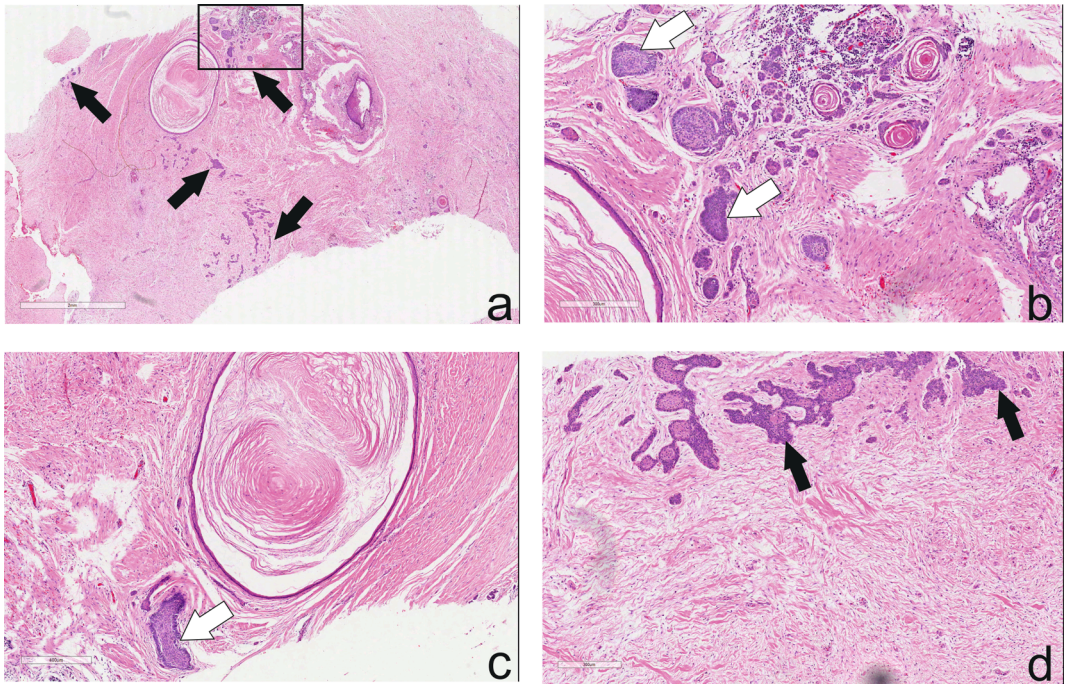

Fig. 3. Section from the cyst wall of a 10-year-old male patient presenting with posterior mandibular odontogenic keratocyst. There is a fairly large daughter cyst (main cyst is not included here) with prominent proliferating odontogenic epithelium (**black arrows**) with some undergoing cystification and some displaying ameloblastic features (**white arrows**). The patient was only investigated for, and diagnosed with Gorlin syndrome 4 years later when he presented with a new lesion on the anterior mandible. Fig. 3b Represent the area captured in the box in Fig. 3a.

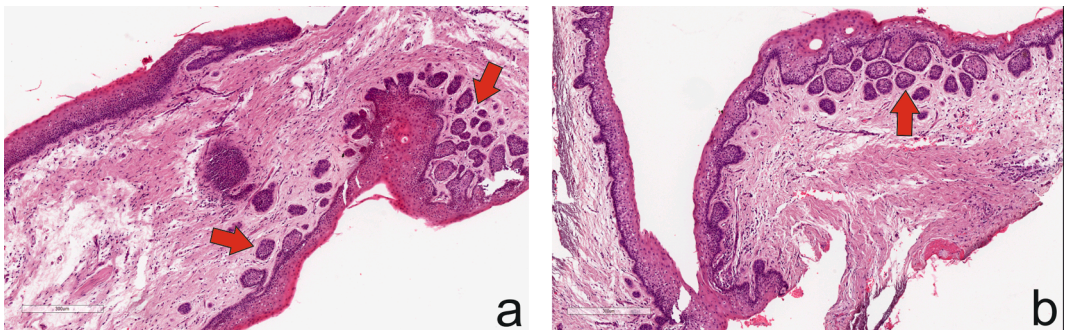

Fig. 4. Basal epithelial budding (**red arrows**) in odontogenic keratocyst.

NBCCS (Visioli et al., 2010). A screening protocol for NBCCS is needed in all cases of pediatric OKC in order to initiate treatment and genetic counseling for the patient and family members of those with the syndrome. NBCCS is a disease with varying manifestations, which in some cases, will never meet the clinical diagnostic criteria despite the presence of the disease. OKC is the most universal presentation across all races (Lo Muzio 2008). Where it may not be practical to thoroughly investigate all cases of pediatric solitary OKCs, the index of suspicion can

be increased by using some clinical and histomorphological features of OKC to improve early diagnosis. Early diagnosis of pediatric NBCCS is low and a significant number of cases may be missed owing to the paucity of diagnostic criteria at presentation, in addition to solitary OKC (Karhade et al., 2019). The difficulty associated with the diagnosis of pediatric NBCCS has recently prompted researchers to develop new criteria (using statistical optimization) to assist clinicians (Gold et al., 2021). An attempt was made to delineate early-onset lesions and propose criteria that should prompt the consideration of NBCCS in children (Gold et al., 2021). The overall goal of early diagnosis is to carry out recommended surveillance; to prevent the development of cutaneous BCC due to the use of radiation in patients (Gorlin 1999, Akbari et al., 2018); and to educate the patient to avoid UV radiation that may also result in BCC. Early diagnosis also helps with anticipating the development of new OKCs, managing them early and instituting simple orthodontic treatment to promote adequate jaw function (Fujii and Miyashita 2014) and improve occlusal and esthetic outcome (Feghali et al., 2022).

7. Conclusion

Pediatric patients with undiagnosed NBCCS and a single OKC without any other apparent clinical manifestations at presentation may have the syndrome diagnosed at an early stage by combining the clinical and histological features of OKC which will prompt further investigation. This is especially advised when it is not practicable to routinely investigate all presenting OKCs for association with NBCCS. Oral and maxillofacial pathologists may play a role in this process by thoroughly examining enucleated or jaw-resected OKC for features such as excessive daughter cysts, proliferating odontogenic epithelium, including those with ameloblastoid features and basal cell budding. There should be a high index of suspicion suggestive of NBCCS, especially when a solitary OKC exhibits a combination of these histopathological features. The features are not diagnostic of NBCCS but may serve to induce further investigation, including genetic testing.

Ethical statement

This work did not involve active participation of human subjects nor active use of patient material. It is exempted from ethical approval as part of original work on keratinizing cysts with approval no. FR/0279.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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