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# Role of Nevoid Basal Cell Carcinoma Syndrome (NBCCS) in Malignant Transformation of Odontogenic Keratocyst (OKC)

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**ABSTRACT**

Odontogenic Keratocyst (OKC) is a cyst lesion characterized by potential for malignant transformation, high recurrence potential, and occurrence as multiple lesions. Malignant transformation is mainly associated with Nevoid Basal Cell Carcinoma Syndrome (NBCCS), also known as Gorlin-Goltz syndrome, a genetic disorder caused by mutations in the PTCH1 tumor suppressor gene (TSGs). PTCH1 mutation may contribute to alterations in certain TSGs, such as p16 and p53, leading to dysregulation of cell cycle control, especially in the G1-S phase. These alterations impair DNA repair mechanisms, promote abnormal apoptotic processes, and facilitate malignant progression, thereby contributing to the aggressive behavior of OKC. Therefore, this study aimed to determine the role of NBCCS in the malignant transformation of OKC.

**Keywords:** Odontogenic Keratocysts, Basal Cell Naevus Syndrome, Ptch1, Cell Cycle Regulation

**ABSTRAK**

Odontogenik Keratocyst (OKC) merupakan kista yang dilaporkan memiliki sifat dapat mengalami transformasi maligna, memiliki potensi kekambuhan yang tinggi dan cenderung terjadi pada lesi yang multipel. Transformasi maligna terutama dikaitkan dengan Nevoid Basal Cell Carcinoma Syndrome (NBCCS). NBCCS atau sindrom Gorlin Goltz adalah kelainan genetik yang disebabkan oleh mutasi pada gen PTCH1 yang mana gen tersebut merupakan TSG. Mutasi pada gen PTCH1 juga memicu mutasi pada TSG tertentu seperti gen p16 dan gen p53. Terjadinya mutasi pada TSG berpengaruh pada gangguan siklus sel, terutama pada fase G1-S sehingga menyebabkan DNA yang terkena mutasi tidak tereparasi (DNA repair) yang akan memicu terjadinya apoptosis patologis, akan berkembang menjadi keganasan dan akhirnya memicu agresifitas OKC. Penelitian ini bertujuan untuk mengetahui peran NBCCS pada transformasi maligna dari OKC.

**Kata kunci:** Kista Keratosis Odontogenik, Sindrom Nevus Sel Basal, Ptch1, Siklus Sel

## 1. Introduction

Maxillofacial surgery is commonly used in the management of cystic lesions of the oral cavity [1]. The cause is often unknown, but the sessions may arise from several factors, including inflammation, trauma, and growth disorders. Cysts are classified into two groups based on the epithelium lining the central cavity. Odontogenic variants are lined by odontogenic epithelium derived from the dental lamina and constitute the majority of jaw lesions of this type [2].

Odontogenic cysts associated with developmental processes include dentigerous, lateral periodontal, and gingival cysts in infants and adults, as well as Odontogenic Keratocyst (OKC) [3]. An OKC is a benign lesion that occurs in the maxilla or mandible and originates from remnants of the dental lamina or proliferation of basal cells within the oral epithelium [4]. Hystologically, it is characterized by an irregular thin layer of parakeratin on stratified squamous epithelium with hyperchromatic palisading basal cells [5]. OKC shows a characteristic clinical, radiological, and histological appearance and may attain considerable size while remaining asymptomatic. A high recurrence rate following treatment has been reported, and some cases are associated with syndromes such as nevoid basal cell carcinoma syndrome (NBCCS) [6].

The clinical feature of OKC that warrants particular attention is the high recurrence potential. This tends to occur in multiple lesions, especially when associated with NBCCS [3]. Based on observation, NBCCS, or Gorlin Goltz syndrome, is a hereditary disorder characterized by developmental abnormalities and a tendency to become neoplasms. Gorlin-Goltz syndrome is an autosomal genetic disorder caused by mutations of the Patches 1 gene (PTCH) [7].The encoded transmembrane receptor protein forms a complex with Smoothened (SMO) within the Sonic Hedgehog (SHH) signaling pathway and regulates SMO-mediated gene transcription. Since inactivation of the tumor suppressor gene/TSG (PTCH1) is a characteristic feature of OKC, the lesion is considered a benign cystic neoplasm rather than a simple developmental cyst [8]. Patients suspected of having NBCCS should undergo a complete dermatological examination as well as radiological tests, including baseline brain MRI, cardiac ultrasound, pelvic ultrasound (if female), spine radiography, and panoramic dental radiograph [9].

According to Karhade [10], 65 patients with OKC were evaluated at the Boston Children's Hospital from 2007 to 2018. Among the patients who were evaluated, 27 boys and 23 girls met the inclusion criteria. Furthermore, 18 (36%) and 32 (64%) were diagnosed with NBCCS and Nonsyndromic Odontogenic Keratocyst (NS-OKC), respectively. A total of eight out of 18 patients (44%) were diagnosed with NBCCS due to family history. The remaining 10 (55.6%) were diagnosed following confirmation of OKC by pathology and genetics. NBCCS patients were younger at presentation (9.3 vs. 13.0 years), had a higher mean number of cysts (1.7 vs. 1.0), and showed a greater recurrence rate (1.0 vs. 0.1 recurrences per patient) than non-syndromic OKC (NS-OKC) cases [10]. OKC is the most consistent and representative sign of NBCCS in the first and second decades of life, and has no racial predilection. Histopathologically, lesions associated with the syndrome are frequently characterized by numerous satellite cysts and dense proliferations of odontogenic epithelium, including areas presenting ameloblastoma-like features. This lesion plays a central role in the clinical course of NBCCS, often serving as the earliest detectable manifestation prior to the development of other features such as basal cell carcinoma and skeletal abnormalities [11].

Radiographically, OKC usually appears as a round or ovoid radiolucent border with smooth or scalloped margins. A valuable clue to differentiate between a dentigerous cyst and an OKC is the relationship of the lesion to the tooth. Dentigerous cysts are attached to the cementoenamel junction and envelop the crown, while OKCs are not pericoronal. Some more sophisticated technologies supporting the diagnosis of OKC are Computerized Tomography (CT) and Magnetic Resonance Imaging (MRI). CT scans of areas with increased attenuation are observed in the lumen of the cyst, which is the result of keratin accumulation and has a potential role in this diagnosis. The use of MRI can help differentiate OKC and ameloblastoma based on characteristic signal patterns [10]. In light of these considerations, the present review aims to explore the role of NBCCS in the potential malignant transformation of OKC through a literature-based analysis.

## 2. Subtopic

### *2.1. Odontogenic Keratocyst (OKC)*

The odontogenic keratocyst (OKC) is a benign lesion occurring in both the maxilla and mandible, arising from the basal cell layer of the remnants of the dental lamina within the oral epithelium [4]. The cyst requires special consideration due to locally aggressive behavior, high recurrence rate, and potential for malignant transformation [12]. Classification as an odontogenic developmental cyst reflects its clinical behavior, including recurrence after treatment, ability to attain large size without producing symptoms, and occasional association with syndromes such as NBCCS [6]. OKC is generally regarded as an odontogenic developmental lesion originating from the dental lamina [13].

OKC can occur at any age, with the highest incidence in the second to third decade of life and a peak age range of 50-70 years. Most studies have recorded a higher prevalence in men, and not all the patients have NBCCS. Only about 5% of cases occur as part of NBCCS, while multiple cases tend to manifest in younger individuals. OKCs have a well-defined radiolucency, with more or less rounded or scalloped margins. Most lesions appear as painless radiolucencies and are discovered incidentally [14]. Some are unilocular, but the majority are multilocular, and the margins are well-defined with a characteristic growth pattern. There is extensive back and forth spread throughout the medullary cavity with minimal expansion until the entire medulla is replaced. Furthermore, in a small proportion of cases, cysts may appear at the site of a failed tooth [6]. The most common treatment is enucleation or surgical resection for large lesions. Based on observation, recurrence is possible and can be reduced with appropriate treatment. This can be caused by incomplete cyst removal or the presence of daughter cysts. Finally, large lesions may be marsupialized and followed by enucleation[14].

### *2.2. Nevoid Basal Cell Carcinoma Syndrome (NBCCS)*

NBCCS or Gorlin-Goltz syndrome is a rare autosomal dominant genetic disorder caused by mutations in the PTCH1 gene, which plays a role in the SHH signaling pathway [15]. It can manifest in OKC and a variety of skeletal anomalies, and the syndrome is caused by mutations in the PTCH1 gene on chromosome 9q22.3. The gene is a TSG and modulates the cell cycle through the SHH pathway. Inactivation or mutation of the second copy of the gene is associated with the development of some OKC. Mutations in the same gene can also be identified in various other neoplasms associated with the syndrome. There are several clinical features in NBCCS, including a characteristic facial expression/appearance (facies) with frontal and parietal bossing as well as a wide nasal root, multiple OKCs in the jaw, skeletal anomalies (usually minor) such as bifid ribs (forked ribs), and an abnormal shape of the sella turcica. Among the most common and reliable findings supporting the diagnosis is the presence of palmar pits, which are small, round depressions measuring 1–2 mm in diameter on the palms and soles. These lesions result from focal keratin deficiency and may appear red or dark when filled with debris. Although palmar pits can occur in other conditions, the presence of three or more is considered a diagnostic feature of the syndrome [6]. Diagnosis of NBCCS is established by the presence of either two major criteria or one major criterion accompanied by two minor criteria. Individuals suspected of having NBCCS should undergo comprehensive dermatological evaluation and radiological assessment, including baseline brain MRI, cardiac ultrasonography, pelvic ultrasonography in females, spinal radiography, and panoramic dental radiography [9]. [19]

### *2.3. How NBCCS affects OKC*

OKC, associated with NBCCS, has an aggressive growth rate and tends to experience a high recurrence. Aggressive growth is caused by mutations in the PTCH1 gene, which is a TSG engaged within the SHH (Sonic Hedgehog Signaling Pathway) [16]. Most OKC are associated with NBCCS, and mutations in the PTCH1 gene are believed to promote aggressive cystic growth and contribute to the development of multiple lesions [17].

## 3. Discussion

OKC is characterized by an irregular thin layer of parakeratin on a stratified squamous epithelium with hyperchromatic palisading basal cells [5]. The cyst requires special consideration because it often appears to grow aggressively and has the potential for recurrence and malignant transformation [12]. OKC is a keratinized cyst that can occur in the jaw and has a characteristic clinical, radiological, and histological appearance. Recognition of this lesion is important because of the high recurrence rate, capacity to attain considerable size without producing symptoms, and association with certain syndromes / NBCCS [6].

OKC associated with NBCCS has aggressive growth rates due to mutations in the PTCH1 gene and is prone to high recurrence rates. The PTCH1 gene is a TSG in the SHH (Sonic Hedgehog Signaling Pathway) [16]. SHH signaling pathway is a regulator of important events during the development process of multicellular organisms (multicellular embryos) [18]. In the signaling pathway, the gene plays the role of an inhibitory receptor. Under normal conditions, PTCH1 inhibits the activation of the SMO protein, thereby maintaining controlled cell proliferation. Inactivating mutations in the gene can result in the loss of SMO's inhibitory function, increasing odontogenic epithelial cell proliferation, disrupting cell differentiation, and leading to the formation of early lesions in the form of OKC [19].

In a study conducted by Kadlub [17], most OKC associated with NBCCS presented as multiple lesions. Development of these lesions has been related to mutations in the PTCH1 gene, which promote aggressive epithelial proliferation and contribute to the formation of multiple cysts. Kadlub [17] further reported that all NBCCS-associated OKC in the study cohort contained daughter cysts, a feature associated with lesion aggressiveness. Daughter cysts refer to smaller cystic structures arising from the epithelial lining of the primary lesion or persisting after incomplete removal. The presence of these structures in NBCCS-related OKC is thought to reflect the underlying PTCH1-driven proliferative activity, which contributes to recurrence and multiplicity of lesions.

From a biomolecular perspective, the development of OKC when associated with NBCCS and its potential for malignant transformation may be related to events occurring during odontogenesis, beginning at the stage of tooth germ formation from the dental lamina. Persistence of dental lamina remnants during tooth development is considered a key factor contributing to the early initiation and proliferation of OKC. Physiological growth and developmental processes are governed by regulated cell cycle activity, which depends on effective intercellular communication mediated through signaling pathways. In OKC, NBCCS-associated mutations in the PTCH1 gene disrupt the SHH signaling pathway, resulting in abnormal transmission of cellular signals. This disruption may impair the regulation of the G1 to S phase transition in the cell cycle. The TSG p16 plays a critical role in this checkpoint control by binding to cyclin-dependent kinases (CDK4/6), thereby inhibiting progression of the cell cycle. Mutation of the p16 gene reduces this inhibitory function, allowing cells carrying PTCH1 mutations to bypass the G1/S checkpoint and proceed with uncontrolled proliferation. In addition, mutations in the TP53 gene further compromise cellular regulation. TP53 is essential for DNA repair and apoptosis induction in response to genomic damage. Loss of TP53 function results in impaired DNA repair mechanisms, allowing cells with genetic alterations to continue through the G2 and M phases without correction, leading to propagation of mutated cell populations. Although TP53 plays a role in apoptosis, its mutation leads to dysfunctional apoptotic regulation, contributing to the survival of abnormal cells rather than their elimination. Collectively, PTCH1, p16, and TP53 are classified as TSGs, and their inactivation results in loss of cell cycle control. Dysfunction of these genes leads to impaired checkpoint regulation, defective DNA repair, and dysregulated apoptosis, ultimately contributing to uncontrolled cellular proliferation. Previous studies have reported the involvement of these TSGs in OKC development [20]. Inactivation of PTCH1, p16, and TP53 is associated with increased proliferative activity, which may contribute to the aggressive behavior observed in NBCCS-associated OKC.

According to Pramatika [4], TSGs that played a role in the development of OKC are p16, p53, and PTCH1. Inactivation of p16, p53, and PTCH1 tends to cause apoptosis, which triggers the development of OKC. Therefore, OKC shows an increase in cell proliferation, possibly leading to aggressive cyst growth. Several studies have reported that the high recurrence rate of OKC associated with NBCCS is due to incomplete removal of the parent cyst layer. This causes odontogenic remnants after surgery and the growth of a daughter cyst [21]. The growth is also possibly related to the aggressiveness of the cyst, which can lead to multiple enlargements of the cystic lesion [22].

Among the reviewed journals, Indonesian literature has not specifically addressed OKC in association with NBCCS. Following a comprehensive examination of the subject, clinicians encountering cases suggestive of NBCCS need to adopt a multidisciplinary approach to management, including relevant specialties according to established criteria. For example, suspected medulloblastoma should warrant neurological referral, while ocular abnormalities classified among the minor criteria should be evaluated by an ophthalmologist.

## 4. Conclusions

In conclusion, among the reviewed literature, no specific discussion from Indonesia has addressed the relationship between OKC and NBCCS. Based on the thematic analysis, clinicians encountering cases suggestive of NBCCS were encouraged to adopt a multidisciplinary approach, including relevant specialties according to established diagnostic criteria. For instance, suspected medulloblastoma should be referred to a neurologist, while ocular abnormalities classified under the minor criteria should be evaluated by an ophthalmologist.

This literature review suggests that the aggressive behavior of OKC may be associated with mutations in the p16, p53, and PTCH1 genes related to NBCCS. Furthermore, OKC appeared to show a higher tendency toward malignant transformation, particularly in cases presenting as multiple lesions.

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**Figure**

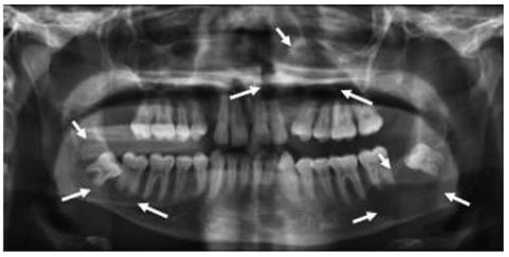

Figure 1. Multiple OKCs found on panoramic radiographs [23].

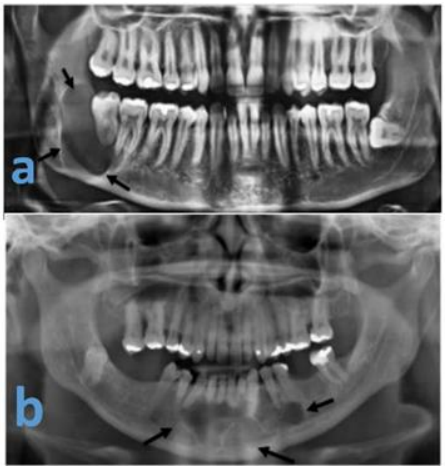


Figure 2. (a) OKC unilocular lesion associated with the third molar as shown in the arrow. (b) Multilocular OKC lesion which in 1 lesion appears lobulated [23].

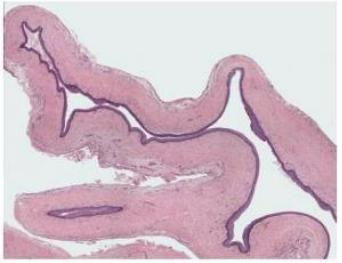

Figure 3. The outline of a folded cyst is typical of a satellite cyst. There is fibrous tissue that is not inflamed and thin [18].

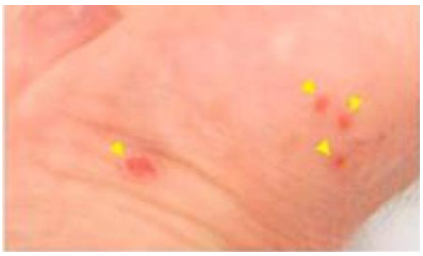

Figure 4. Multiple palmar pits in NBCCS patients [24].


Figure 5. Macrocephaly in pediatric and paternal patients with NBCCS [25].