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## Case Report

# Late-Onset of Keratocysts in De Novo Mutation c.1347+1G>A on Intron 9 PTCH1- (NBCCS) – Diagnosis and Therapy

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### ABSTRACT

**Introduction:** The occurrence of two main symptoms (calcification of the falx cerebri, odontogenic keratocysts, basal cell carcinoma) and a minimum of one secondary symptom is necessary for de-novo diagnosing a Basal Cell Nevus Syndrome (BCNS). Late diagnosing is usual if the primary symptoms are absent. Subtypes of BCNS may express phenotypes at different ages. Early recognition is needed. The adhesion of keratocysts to the basal bone layer varies, so different treatment options are standard.

**Aim:** A 47-year-old woman without clinical signs of BCNS except macrocephaly suffered from de-novo-mutation of the PTCH1 gene. Odontogenic keratocysts were recognized sporadically by CB-CT ten years later, as late-onset; Compared to subsequent generations, who often present the main symptoms in childhood. The indication of resection, marsupialization, or enucleation with or without Carnoy-solution is a clinical decision.

**Conclusion:** Despite 100% penetrance, intrafamilial expression of the clinical phenomenon is variable. In child morbidity, the parents' lifelong co-screening should be mandatory by radiological and clinical investigation. Late-onset KCOT should be resected en-bloc, including soft tissue movement. Enucleation has less morbidity for mandibular keratocysts near the nerve. Carnoy-solution helps minimize the risk of relapse.

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### Introduction

Gorlin-Goltz-Syndrome (basal cell nevus syndrome (BCNS)) is well-known for a prevalence of 1:50.000 to 1:150.000 and was first described by Gorlin *et al.* in 1960 [1]. It is a hereditary disease, an autosomal dominant trait characterized by high penetration and variable phenotypical expression [2]. A direct molecular genetic test confirms germline mutation in the PTCH1 gene chromosome 9q22.32. A multidisciplinary approach is necessary since the clinical symptoms often begin in adolescents, in the case of medulloblastomas, even in early childhood [3, 4]. Patients older than 20y have calcification of the falx [5]. Pathognomonic for BCNS are keratocystic odontogenic tumors (KCOT) in the jaws and multiple basal cell carcinomas. Skeletal abnormalities are pits, bifid ribs, hypertelorism, and macrocephaly. They

should be carefully detected [6-9]. For maxillofacial regions, a CB-CT is favourable for diagnostic reasons [10, 11].

### Aim

Parental generations should have genetic counseling by a specialist after detecting a mutation of the long arm of the chromosome 9q22.3 (PTCH1) in subsequent generations. To detect main symptoms like calcification of the falx cerebri, odontogenic keratocysts, basal cell carcinomas, and secondary symptoms (e.g., macrocephaly, cleft lip and palate, spine/rib abnormalities or polydactyly). Therefore, secondary symptoms often appear earlier and should receive more attention to avoid the extent of the destruction. There are various options for treating keratocysts: marsupialization enucleation, and block resection [12, 13].

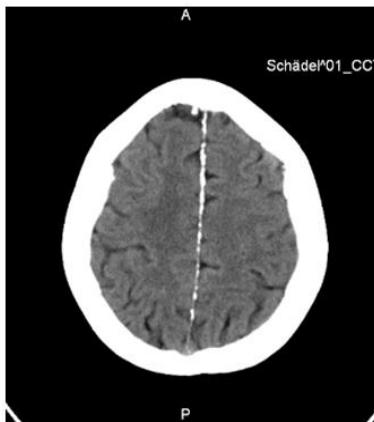
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Late-onset KCOT should be resected en-bloc, including soft tissue movement. Some authors recommend Enucleation for mandibular keratocysts near the nerve [14-18]. Carnoy-solution helps minimize the risk of relapse [13, 19-21].

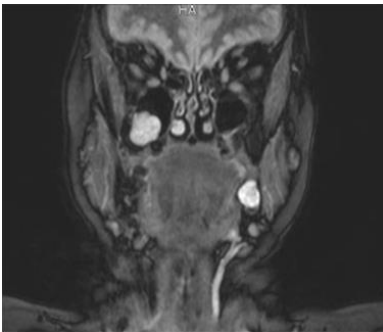
## Case Presentation

### I Diagnosis

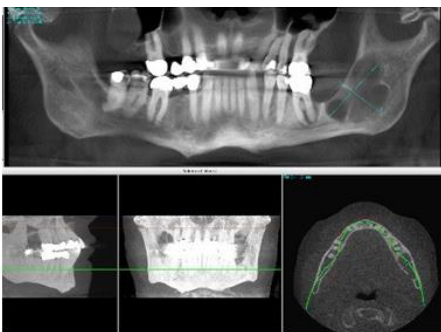
A 47-year-old woman suffered from a de novo mutation c.1347+1G>A on Intron 9 PTCH1-Gene and suspected BCNS. Diagnostical staging results in main symptoms: Calcification of the falx cerebri (Figure 1) and odontogenic keratocysts (Figures 2 & 3). So far, no basal cell carcinomas and point-shaped pits in the palmoplantar skin have appeared. Evident as secondary symptoms macrocephaly, strabismus, hypertelorismus, and bifid ribs appeared.



**Figure 1:** CT-Scan from the head with calcification of the falx cerebri at the age of 57 years.



**Figure 2:** Front- plane NMR of the mother at the age of 57 years.



**Figure 3:** CBCT: multiple keratocyst (left mandible and right posterior sinus maxillaris).

### II Treatment

Due to the strong adhesion of the maxilla keratocysts, we resected en-block with piezo- surgery [Piezosurgery® touch, Saw OT7A, Mectron-Deutschland, D-Köln]. For 3 minutes, we plugged a cotton swab soaked in freshly prepared Carnoy's solution [absolute alcohol 6 mL, chloroform 3 mL, glacial acetic acid 1 mL, ferric chloride 0.1 gm/mL; Engelbrecht Labortechnik, Edermünde, Germany] as chemical cauterization [20, 21].



**Figure 4:** KOT right maxilla with resorption of the anterior wall of the sinus.

For facial reconstruction, we used the Bichat fat pad for closure. The keratocysts showed macroscopically clinically different colorations with partly yellowish discoloration. Enucleation removed the multicystic keratocysts in the mandible. We used Carnoy-solution for intraluminal injection and post excavatum as chemical cautery of the bony cavity [19]. Tooth 36, which was in the cyst cluster, was osteotomized. We filled the cavity by using the PRGF technique, according to Anitua *et al.* 2012 [22].



**Figure 5:** En-bloc-resection of KOT in the right maxilla.



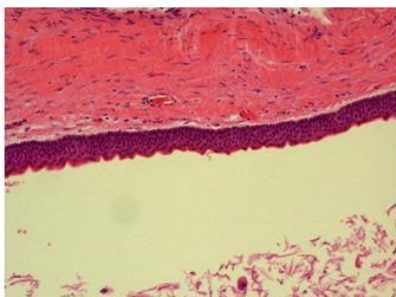
**Figure 6:** Clinical view of the multilocular KOT in the left mandible after enucleation.



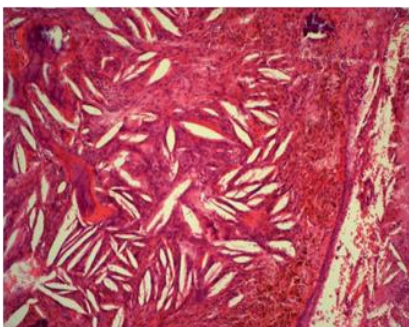
**Figure 7:** Chemical cauterization of the KOT-cavity with Carnoy-solution on absorbent cotton.

## Histological Examination of KCOT

The multilayer squamous epithelium is in line and has an orthokeratotic part of cystic walls (Figure 8). The surface is wave-shaped and palisade like reserve cells. The basement membrane is intact. Horn materials and macrophages peeled off in the lumen. Subepithelial and alternately dense and perivascular accentuated lymph plasma cell infiltrate. Areas with curly collagenous fiber tissue include sparse myelinated nerve fibers. The bony parts show vital osteocytes. The bone lamellae have slightly irregular putty lines and loose collagen fiber tissue. They accumulated sparse associations of a multilayered epithelium with a giant cell reaction around cholesterol voids (Figure 9).



**Figure 8:** Histological findings of syndromic KCOT (magnification of x 150 H.E.) with regular multilayer squamous epithelium with palisade like up lined reserve cells.



**Figure 9:** Histological findings of the altered KCOT (magnification of x 240 H.E.) with loose collagen fiber and giant cell reaction around cholesterol voids.

## Discussion

### I Diagnosis

KCOT are frequently diagnosed incidentally [1, 5, 13, 23]. To avoid extensive lesions, frequent dental check-ups and multimodal therapy are necessary [24-26]. Furthermore, genetic counseling of the entire family is recommendable due to the dominant inheritance. The mother's 11-year-old boy had early onset of multiple keratocyst, macrocephaly, hypertelorism, and calcification of the falx cerebri [25]. The sister was not affected by the BCNS but showed bifid ribs like her mother. The family was informed about the high risk of recurrence of keratocysts and basal cell carcinoma development.

Diagnoses are often backward detected, as described by Yordonova *et al.* 2007, who investigated late detection of multiple keratocysts of a 50-year-old mother after screening a BCNS in her 18-year-old daughter

[27]. If BCNS is suspected, family examinations sometimes show pair mutations. In the case-report described by Hedge *et al.*, a 38-year-old mother was co-screened with her eight-year-old daughter, who showed odontogenic keratocytes [28]. A meta-analysis of the syndromic keratocystic odontogenic tumor is presented by Antonoglu *et al.* 2014 [29]. Individuals with BCNS mutations showed a wide range of clinical variations. Pastorino *et al.* (2005) investigated the genotype/phenotype correlation in BCNS and concluded that carrier and type of mutation did not influence when the patients developed oral keratocysts or basal cell carcinoma. They recommend lifetime supervision in the case of BCNS [30]. Twin-examination shows multiple keratocysts in almost identical areas, as described by Anchlina *et al.* (2015) [31].

### II Treatment

The surgical procedure should enable the combination of minimized morbidity and a low recurrence of the keratocysts [32]. Various therapy options are available for this with increasing intervention effort: enucleation, enucleation with peripheral ostectomy, enucleation with Carnoy-Solution resection [18, 33-39]. The pooled weighted overall treatments of KOT was 16.6%, according to Al-Moraissi *et al.* (2017) [32]. There is significant heterogeneity among the studies. The weighted event rate of pooled recurrence for 17 studies is 23.1% [32]. For enucleation with peripheral ostectomy, they found a recurrence rate of 17.4% by evaluating eight studies (n= 378). Some countries do not allow Carnoy-solution (CS) including chloroform, according to Dashow *et al.* 2013, because of the precancerous potential of chloroform [21]. So modified Carnoy-solution without chloroform was used (MC). After 12-51 month follow up (n=210), MC treated patients significantly more relapses (19.2%) compared to CS patients (8.3%). Chiripathomsakul *et al.* had a recurrence rate of 22.6%. 71.4% of the relapses occurred within five years [24]. A systematic review of 35 pooled studies (n=576) results in recurrence rates of 11.5% [32]. A systematic review of Cochrane-analysis concludes en-bloc or marginal resection as the ultima ratio [40]. A recurrence rate of 8.4% (n=92) in case of resection is estimated [32]. Stoelinga (2001) and Stoelinga & Bronkhorst (1987) recommend resection including soft tissue margin because of satellite cells and cystic remnants in the surrounding tissue [41, 42]. An opinion shared by other authors [6, 9, 12, 24, 25, 32].

### Conclusion

Clinical expression of symptoms is variable despite a penetrance of 100%. In the case of child morbidity, the parents' lifelong co-screening should be mandatory by radiological and clinical investigation. Radical resection of late-onset KCOT appears to be a sure option in syndromic cases, including soft tissue movement. For non-syndromic cases, the literature advocates enucleation with the application of Carnoy-solution or as first line-treatment to minimize the risk of relapse.

### Consent

The patient gave written consent for publication. The author ensure that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The manuscript is in line with the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical

Journals and aim for the inclusion of representative human populations (sex, age, and ethnicity) as per those recommendations.

### Competing Interests

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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None.

### Abbreviations

**BCNS:** Basal Cell Nevus Syndrome  
**CBCT:** Cone Beam Computed Tomography  
**CS:** Carnoy Solution  
**GGs:** Gorlin-Goltz-Syndrome  
**H.E.:** Hematoxylin-Eosin-stained  
**KCOT:** Keratocystic Odontogenic Tumor  
**MC:** Modified Carnoy-Solution  
**NBCCS:** Nevoid Basal Cell Carcinoma Syndrome  
**NMR:** Nuclear Magnetic Resonance  
**OPT:** Orthopantomography  
**PTCH1:** Protein Patched Homolog 1

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