CASE REPORT

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Nevoid Basal Cell Carcinoma Syndrome with Beaten Copper Appearance of Skull

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ABSTRACT Nevoid basal cell carcinoma syndrome(NBCCS) or Gorlin-Goltz syndrome is a rare disorder with autosomal dominant inheritance and multisystem involvement. It is characterized by developmental defects including bifid ribs and palmar pits and is prone to various lesion formations such as basal cell carcinoma and odontogenic keratocyst. There is also a tendency for tumor formation such as medulloblastoma, fibroma, rhabdomyoma, leiomyosarcoma. The diagnosis is based on major and minor clinical and radiological criteria. Beaten copper appearance(BCA) is the radiological appearance that occurs as a result of gyral pressure sites occurring in the skull bones due to increased intracranial pressure(ICP). According to our knowledge, there has been no mention of this radiological finding in NBCCS reported to date. This article presents an NBCCS patient with BCA in the skull without an increase in intracranial pressure and hypophosphatasia.

Keywords: Gorlin-Goltz syndrome; skull; beaten copper appearance

Nevoid basal cell carcinoma syndrome (NBCCS) or basal cell nevus syndrome or Gorlin-Goltz syndrome is a rare disorder with autosomal dominant inheritance and multisystem involvement. The syndrome was first reported by Gorlin and Goltz in 1960.[1] Its prevalence has been reported between 1/57,000 and 1/164,000. Males and females are affected at the same rate.[2] A triad has been identified with concerning the syndrome; multiple basal cell carcinomas (BCC), odontogenic keratocysts (OKCs) and skeletal anomalies.

The mutation of the PTCH gene on the long arm of chromosome 9 is blamed for the syndrome, which is known to be genetic. As a result of this mutation, organogenesis and odontogenesis are disrupted.[3] The syndrome is seen in one-third of the cases as a result of de novo mutations.[4]

OKCs, basal cell carcinomas (were seen in early childhood), mandibular prognathism, calcification of falx cerebri, frontal bossing, macrocephaly (with or without hydrocephalus), palmar and plantar pits, vertebral and costal anomalies, cleft lip/palate, cardiac and ovarian fibromas can be seen together with this syndrome. Six major and six minor criteria were determined (Table 1). A combination of two major or one major and two minor criteria is diagnostic.[5]

OKCs may be the first finding for NBCCS diagnosis, and maxillofacial radiologists should be careful about multiple OKCs.

Imaging modalities of OKCs include conventional radiography, cone beam computerized tomography (CBCT), computerized tomography (CT), and magnetic resonance imaging (MRI). The protocol recommendation includes thin-section CT/CBCT with multiplanar reformats.

OKCs in NBCCS usually comprise unilocular or multilocular radiolucencies. Radiographical view of OKC is well-defined and cortically limited, scalloped

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TABLE 1: Diagnostic criteria in NBCCS (Kimonis, et al.).

Major criteria
Multiple (>2) basal cell carcinoma.
Younger than 20 years odontogenic keratocysts of the jaws (proven by histopathology)
Three or more palmar or plantar pits
Calcification of falx cerebri
Bifid,fused or markedly splayed ribs
First degree relatives with NBCCS
Minor criteria
Macrocephaly (with or without hydrocephaly)
Congenital malformation (cleft lip or palate, frontal bossing, coarse face, hypertelorism)
Other skeletal abnormalities (Sprengel deformity, marked pectus deformity, marked syndactyly of the digits.
Radiological abnormalities (bridging of sella turcica, vertebral anomalies, modeling defect of the hands and feet, or flame-shaped radiolucencies of the hands or feet)
Ovarian fibroma
Medullablastoma

or hydraulically shaped. While the internal structure is completely radiolucent, several septa may give a multilocular appearance. The changes that may occur in the surrounding structures can be listed as follows; occasional tooth displacement and root resorption, apical displacement of tooth when in pericoronal position, extension into and filling of the maxillary sinus, inferior displacement of the mandibular nerve canal.

The findings of OKCs on CT/CBCT are as follows; scalloping of the endosteal surface of cortices, hydraulic expansion in the maxilla and upper ramus. Perforation of cortices suggests an indication of soft tissue involvement. Contrast-enhanced CT (CECT) images do not show enhancement.

T1-WI MR images of OKCs show intermediate signal intensity (due to internal keratinaceous debris) and T2-WI heterogeneous low to high signal intensity. T1WI C + images do not show solid components and the rim enhancement is either absent or thin.[6]

Ectopic calcification of falx cerebri, tentorium cerebelli, and bridged sella may also be detected radiologically.[7]

Beaten copper appearance(BCA) is the radiological appearance that occurs as a result of gyral pressure sites occurring in the skull bones due to increased intracranial pressure (ICP).

Craniosynostosis, hydrocephalus and intracranial masses are examples of situations where ICP increases. Also, this appearance is typical for cases of hypophosphatasia. If ICP increases at adult age, it will be controversial whether the bones of the skull can adapt.

According to our knowledge, although macrocephaly and hydrocephalus is a well-documented finding for NBCCS, beaten copper appearance has not yet been identified.

This article presents an NBCCS patient with BCA in the skull without an increase in intracranial pressure.[8]

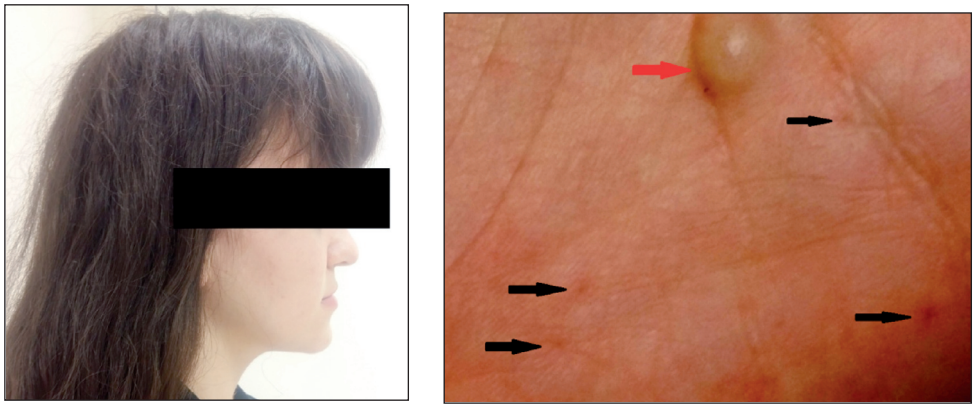

FIGURE 1: a) Prognathia inferior on extraorally view. **b)** Palmar pits(black arrows) and cutaneous cyst(red arrow).

CASE REPORT

A 16-year-old female patient was admitted to our clinic with the chief complaint of prognathism. In medical history, it was learned that she had undergone an operation in her foot twice due to basal cell carcinoma, and in her dental history, she had a canine tooth-related cyst operation from the left maxilla. Extraoral examination revealed mandibular prognathism, palmar pits, and cutaneous cyst (Figure 1a, b). Intraoral examination revealed migration in teeth 21, 22, 24 and 25. There was a polidiastemas in the maxilla and mandible, and 23 was not observed on the dental arch.

Well-defined and cortical limited unilocular radiolucency was seen in the bilateral mandible posterior regions and tuberosity of right maxilla region on panoramic radiography. The unicystic lesion in the posterior region of the left mandible was associated with an impacted 3rd molar tooth germ. In addition, radiolucency of the surgical scar tissue was observed in left upper canine tooth region and this tooth was also not observed radiologically (Figure 2). CBCT images showed bilaterally well-defined and cortical limited hypodense areas in the mandible (Figure 3a). The tuberosity of the right maxilla was also well-defined and the cortical limited hypodense area was present (Figure 3b).

Multiple radiolucencies in the jaws, history of BCC excision, and coexistence of mandibular prognathism aroused the suspicion of NBCCS. The family history was questioned, but not present.

Anteroposterior skull and thorax radiographies were requested to assess the presence of splayed ribs and calcification of falx cerebri. Thorax radiography showed markedly splayed right 2 and 4, left 2, 3, and 4. ribs (Figure 4). Anteroposterior skull radiography showed calcification of falx cerebri. Also, showed a beaten copper appearance of the skull, which was previously unrelated to this syndrome (Figure 5). MRI findings were normal, hydrocephalus was not detected (Figure 6). Ponticulus posticus was detected incidentally in CBCT images taken for the planning of treatment (Figure 7a, b).

While cysts on maxilla and right mandible were excised, cyst in the left mandible was marsupialized,

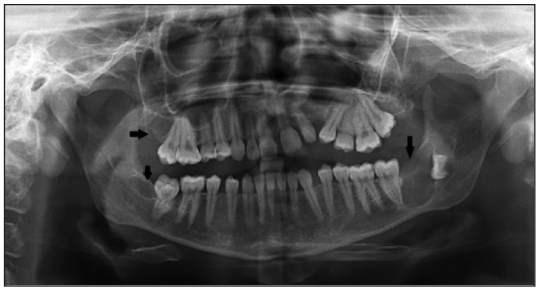

FIGURE 2: Panoramic radiography is showing unilocular, well-defined radiolucent lesions.

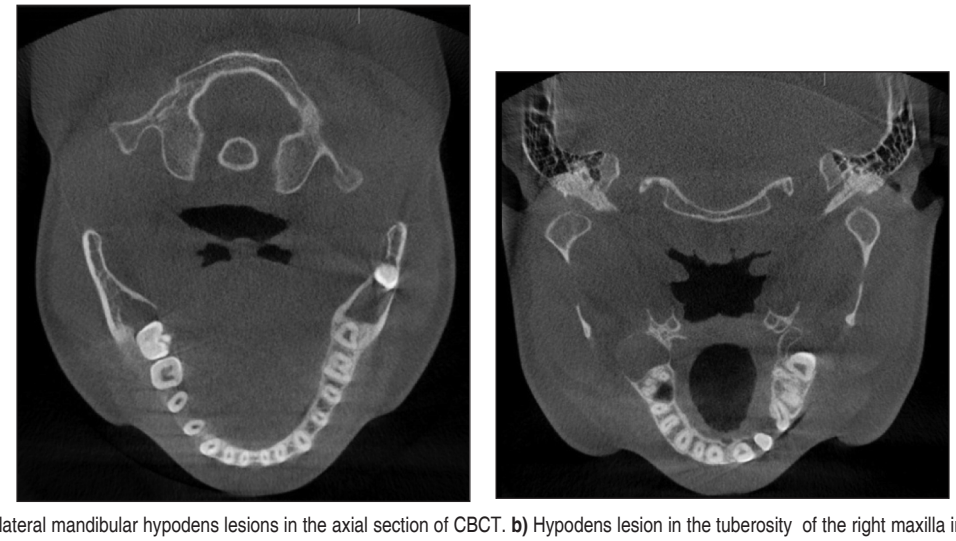

FIGURE 3: a) Bilateral mandibular hypodens lesions in the axial section of CBCT. **b)** Hypodens lesion in the tuberosity of the right maxilla in the axial section of CBCT.

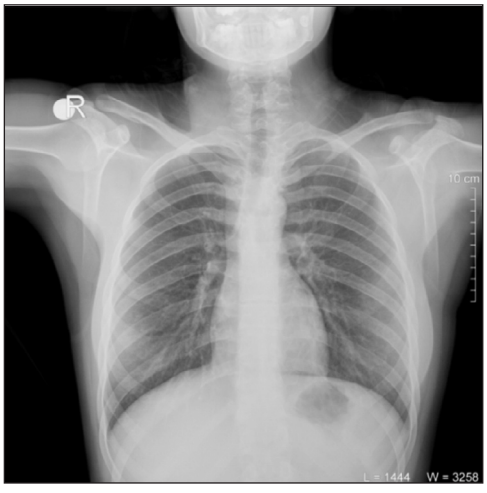

FIGURE 4: Thorax radiography is showing markedly splayed of right 2 and 4, left 2, 3, and 4. ribs.

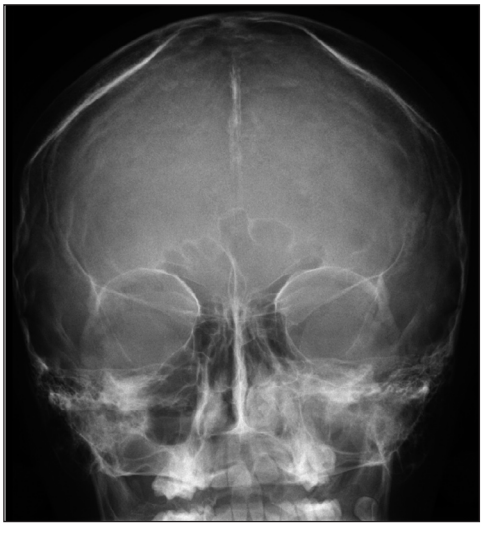

FIGURE 5: Extraoral radiography showing falx cerebri calcification and beaten copper appearence of skull.

They were sent for pathological examination with an initial diagnosis of OKC.

Microscopically, the epithelial lining is composed of uniform layer stratified squamous epithelium, 5 to 8 cells in thickness. The basal layer is well defined and palisaded. The case was diagnosed as OKC (Figure 8).

In the present case, calcification of falx cerebri, markedly splayed ribs, multiple OKCs in the jaws, plantar pits, and ponticulus posticus were seen. Four major criteria confirmed the NBCCS. The patient was referred for genetic counseling.

"Informed consent" was taken from the patient to use their records as data in scientific studies.

DISCUSSION

NBCCS is an autosomal dominant genetic disorder with multiorgan involvement in the first three decades of life. Sporadic and familial cases have been reported equally. It affects males and females at the same rate.[9] There was no familial history in our case and she is 16 years old.

Many body regions, such as the skeletal system, skin, eyes, craniofacial region, nervous system, may be affected, but all these systems are very rare in a single patient.[10] Our patient had a history of BCC excision, mandibular prognathism, calcification of falx cerebri, splayed ribs, palmar pits, cutaneous cyst, beaten copper appearance of skull, ponticulus posticus and multiple OKCs.

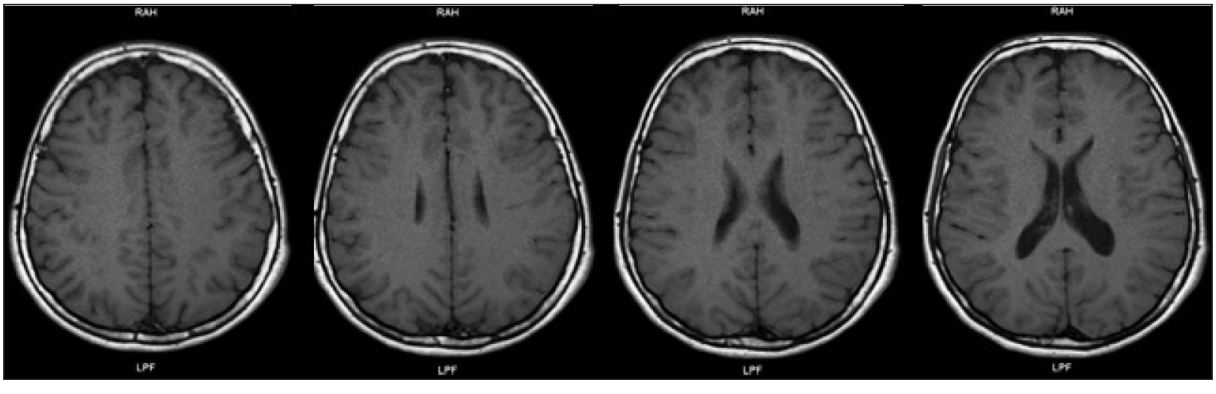

FIGURE 6: MRI images of the patient (axial section).

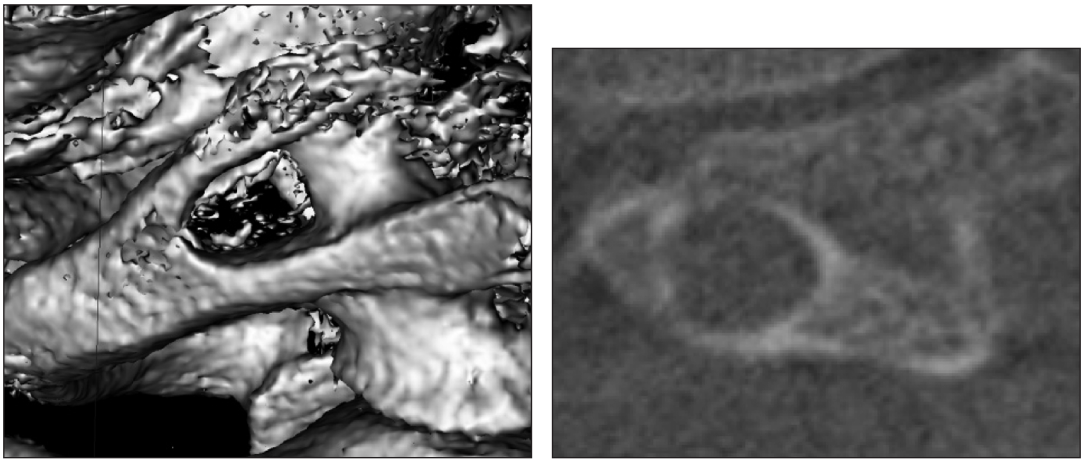

FIGURE 7: a) Ponticulus posticus on CBCT 3D reconstruction image. **b)** Ponticulus posticus on CBCT sagital section image.

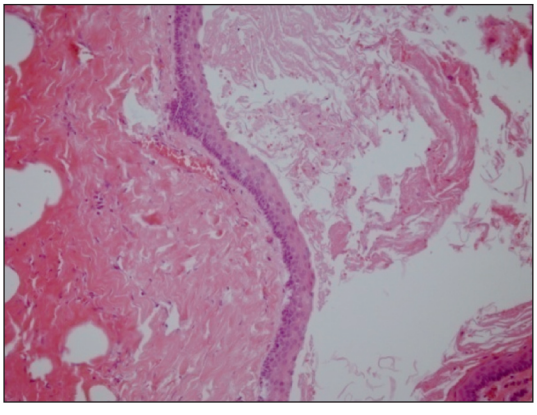

FIGURE 8: Uniflamaed fibrous wall lined thin, regular, stratified squamous epithelium, without rete ridges (HEX200).

OKCs were included in the tumor classification by WHO (World Health Organization) in 2005 for reasons such as PTCH gene mutation, aggressive growth, and recurrence after treatment. But, the mutations in OKCs are not limited to PTCH, as mutations in CDKN2A, TP53, MCC, CADMI, and FHIT have also been reported. At the same time, the OKC may regress by decompression, but the neoplasms do not. WHO has not definitively stated that OKCs are not neoplastic but in 2017 with today's evidence, it was included in the cyst classification again.[11]

OKCs are intraosseous cysts of the jaws. There are two different types; The most common sporadic solitary lesions are multiple OKCs, a component of NBBCS. These two types of OKCs have distinct differences (Table 2).[5,12]

The most common site of OKCs associated with NBCCS is the maxillary molar region. In our case, multiple cysts were bilaterally located in the mandible molar region and the right maxilla. There was scar tissue in the left maxilla posterior region following a prior excision at this location. Histopathological examination confirmed the presence of OKC. The radiological character of OKCs is well-defined, unilocular radiolucent lesions and is usually associated with unerupted teeth.[10]

The imaging protocol of OKCs primarily involves thin-section CT/CBCT with multiplanar reformats. The bone algorithm best describes the periphery. OKC doesn't show enhancement in contrast-enhanced CT because it does not have solid content. MRI can help to differentiate from other lesions. Radiological differential diagnosis should be made by the simple bone cyst, ameloblastoma, radicular cyst, and dentigerous cyst.[6]

TABLE 2: Syndromic/Nonsyndromic OKCs.

	Syndromic OKC	Nonsyndromic OKC
Age	Younger	Middle or older aged
Cyst	Multiple	Solitary
Region	Posterior maxilla (generally)	Posterior mandible (generally)
Recurrens	Higher(%82)	Lower (%61)
Epithelium	Less thickness	More thickness
Odontogenic islands	More frequent	Less

OKCs have two different treatment methods: conservative and aggressive. The conservative method involves simple enucleation and marsupialization. The aggressive method involves peripheral osteotomy and resection followed by chemical curettage with Carnoy's solution.[13] Radiographic follow-up is very important for detecting the recurrence of jaw lesions and new pathologies. In our case, as in the general cyst treatment approach, the relatively large cysts in the left mandible were marsupialized while the small cysts were excised.

Looking at current literature, in NBCCS cells, it is presumed that haploinsufficiency of PTCH1 results in the overflowing of hedgehog signal to induce diverse developmental abnormity. Loss of heterozygosity of PTCH would afterward cause poly-tumors like OKC, BCC, and medulloblastoma.[14]

In 2012, the Food and Drug Association in the USA adopted a new drug, vismodegib, for BCC therapy, confirming an effective treatment despite several adverse effects. Vismodegib blocks the growth of new BCC in patients with NBCCS. Adverse effects and the development of resistance to the drug are negative situations. some revisions can be made in the future for eliminating these negatives.[15]

Since the report of Gorlin and Goltz, much has been learned about this disease. In addition to diagnostic criteria, many new findings have been added to the spectrum of clinical and radiological findings of NBCCS. These include bilateral coronoid hyperplasia, curvature of the shoulders, supernumerary teeth, talon tubercle, low-pitched voice, and ponticulus posticus.[16,17]

There are different skull appearances that can be associated with varied syndromes like beaten copper skull in Crouzon syndrome and dolichocephalic skull in Marfan syndrome.

BCA is a type of radiological appearance of the skull associated with increased intracranial pressure and hypophosphatasia.[8] In our case none of this was present.

As far as we know, there has been no mention of this radiological finding in NBCCS patients reported to date. More case reports are needed to determine that this radiological finding is consistent with NBCCS.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Şuheda Erdem;* ***Design:*** *Şule Erdem;* ***Control/Supervision:*** *Ayşe Zeynep Zengin;* ***Data Collection and/or Processing:*** *Şuheda Erdem, Şule Erdem;* ***Analysis and/or Interpretation:*** *Ayşe Zeynep Zengin;* ***Literature Review:*** *Şule Erdem;* ***Writing the Article:*** *Şule Erdem, Şuheda Zengin;* ***Critical Review:*** *Ayşe Zeynep Zengin.*

REFERENCES

1. Gorlin RJ, Goltz RW. Multiple nevoid basal-cell epithelioma, jaw cysts and bifid rib. A syndrome. N Engl J Med. 1960;262:908-12. [Crossref] [PubMed]
2. Bresler SC, Padwa BL, Granter SR. Nevoid basal cell carcinoma syndrome (Gorlin syndrome). Head Neck Pathol. 2016;10(2):119-24. [Crossref] [PubMed] [PMC]
3. Baliga SD, Rao SS. Nevoid-basal cell carcinoma syndrome: a case report and overview on diagnosis and management. J Maxillofac Oral Surg. 2010;9(1):82-6. [Crossref] [PubMed] [PMC]
4. Muzio LL. Nevoid basal cell carcinoma syndrome (Gorlin syndrome). Orphanet J Rare Dis. 2008;3:32. [Crossref] [PubMed] [PMC]
5. Kimonis VE, Goldstein AM, Pastakia B, Yang ML, Kase R, DiGiovanna JJ, et al. Clinical manifestations in 105 persons with nevoid basal cell carcinoma syndrome. Am J Med Genet. 1997;69(3):299-308. [Crossref] [PubMed]
6. Koenig LJ, Tamimi D, Petrikowski CG, Perschbacher SE. Diagnostic Imaging: Oral and Maxillofacial E-Book. 2nd ed. Diagnostic Imaging. Philadelphia: Elsevier Health Sciences; 2017. p.1000.
7. Hegde S, Shetty SR. Radiological features of familial Gorlin-Goltz syndrome. Imaging Sci Dent. 2012;42(1):55-60. [Crossref] [PubMed] [PMC]
8. Bogdanović M, Radnić B, Savić S, Popović V, Durmić T. Copper-beaten skull appearance as a response of chronically increased intracranial pressure. Am J Forensic Med Pathol. 2019;40(1):58-60. [Crossref] [PubMed]

9. Evans DG, Farndon PA, Burnell LD, Gattamaneni HR, Birch JM. The incidence of Gorlin syndrome in 173 consecutive cases of medulloblastoma. Br J Cancer. 1991;64(5):959-61. [Crossref] [PubMed] [PMC]
10. Manfredi M, Vescovi P, Bonanini M, Porter S. Nevoid basal cell carcinoma syndrome: a review of the literature. Int J Oral Maxillofac Surg. 2004;33(2):117-24. [Crossref] [PubMed]
11. Wright JM, Vered M. Update from the 4th edition of the World Health Organization classification of head and neck tumors: odontogenic and maxillofacial bone tumors. Head Neck Pathol. 2017;11(1):68-77. [Crossref] [PubMed] [PMC]
12. Dominguez FV, Keszler A. Comparative study of keratocysts, associated and non-associated with nevoid basal cell carcinoma syndrome. J Oral Pathol. 1988;17(1):39-42. [Crossref] [PubMed]
13. Singh M, Gupta KC. Surgical treatment of odontogenic keratocyst by enucleation. Contemp Clin Dent. 2010;1(4):263-7. [PubMed]
14. Amakye D, Jagani Z, Dorsch M. Unraveling the therapeutic potential of the Hedgehog pathway in cancer. Nat Med. 2013;19(11):1410-22. [Crossref] [PubMed]
15. Rudin CM. Vismodegib. Clin Cancer Res. 2012;18(12):3218-22. [Crossref] [PubMed] [PMC]
16. Gupta SR, Jaetli V, Mohanty S, Sharma R, Gupta A. Nevoid basal cell carcinoma syndrome in Indian patients: a clinical and radiological study of 6 cases and review of literature. Oral Surg Oral Med Oral Pathol Oral Radiol. 2012;113(1):99-110. [Crossref] [PubMed]
17. Leonardi R, Santarelli A, Barbato E, Ciavarella D, Bolouri S, Härle F, et al. Atlanto-occipital ligament calcification: a novel sign in nevoid basal cell carcinoma syndrome. Anticancer Res. 2010;30(10):4265-7. [PubMed]