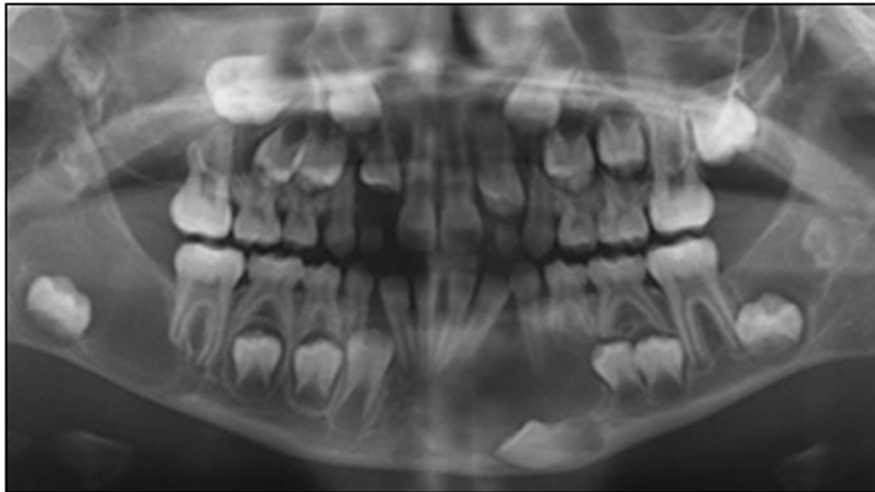


Multiple Cystic Lesions in a Child

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The following Case Challenge is provided in conjunction with the American Academy of Oral and Maxillofacial Pathology.

Case Summary

An 8 year-old African-American female was evaluated during a regular dental examination for multiple radiolucent lesions of the mandible and maxilla.

After you have finished reviewing the available diagnostic information, make the diagnosis.

The views expressed in this article are those of the authors and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.

Diagnostic Information

Medical and Dental History

The past medical and dental history to this point was unremarkable. She was asymptomatic and in good general health, had no known drug allergies, and was not taking any medications. The lesions were an incidental finding on the radiographic survey during a routine examination. At the time of examination, no expansion of the jaws was noted.

Radiographic Findings

A panoramic radiograph revealed multiple large, well-defined, multilocular radiolucencies located in each quadrant of the maxilla and mandible. The large multilocular cysts associated with the right and left mandibular molars have smooth corticated margins and involve most of the ascending ramus.

Surgical Findings

Clinical examination of the surgical specimen for the right posterior mandible and right posterior maxilla revealed large rubbery masses of soft tissue resembling deflated cystic structures (Figure 2). Incompletely formed mandibular molar teeth were included with the surgical sample.

Incisional Biopsy Findings

The excisional biopsy specimen shows on histologic examination numerous cystic spaces lined by convoluted, undulating squamous epithelium forming complex cystic spaces (Figure 3). Loose fibrovascular connective tissue surrounds the epithelial lining.

Focal areas of the specimen showed the epithelial lining with a complete separation from the supporting connective tissue (Figure 4) which transitions to areas of intact attachment with the connective tissue.

A low-power view shows the characteristic wavy, parakeratinized layer surfacing the stratified squamous epithelial lining (Figure 5, 40x) with desquamated keratin seen within the luminal area. A high-power view shows the prominent palisading and hyperchromatic appearance of the tall columnar basal cells (Figure 6, 200x). The epithelial lining can be seen to be six to eight cell layers in thickness.

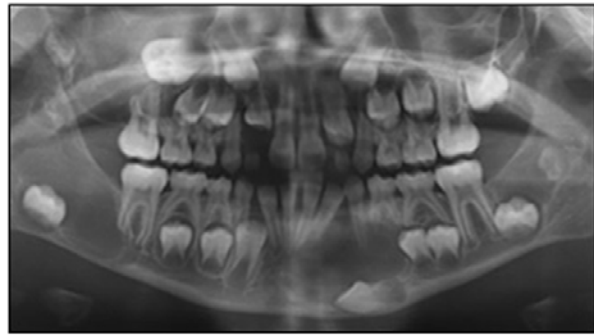


Figure 1. Panoramic radiograph demonstrating bilateral lesions involving the body, angle, and ramus areas of the mandible. Maxillary and mandibular third molar tooth buds, left mandibular canine, mandibular second molars, and right maxillary second molar appear displaced.



Figure 2. Soft tissue removed from the right (2a) and left (2b) posterior mandible displaying incompletely formed molar teeth and soft tissue resembling collapsed cysts.

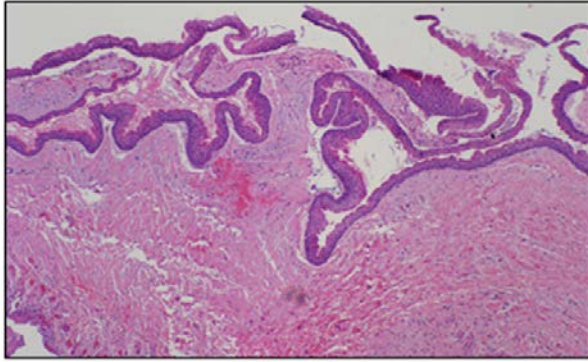


Figure 3. A low-power photomicrograph (40x) showing a proliferation of squamous epithelium forming complex cystic spaces.

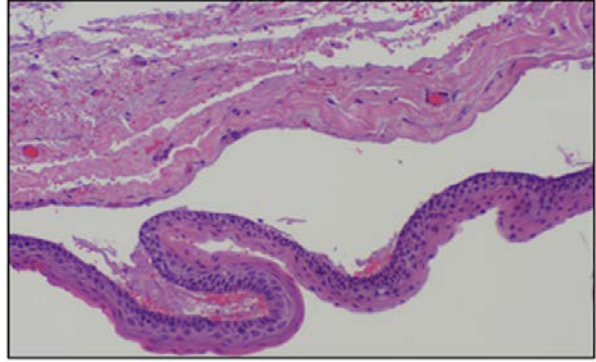


Figure 4. Separation of the epithelium from supporting connective tissue is clearly evident. (100x)

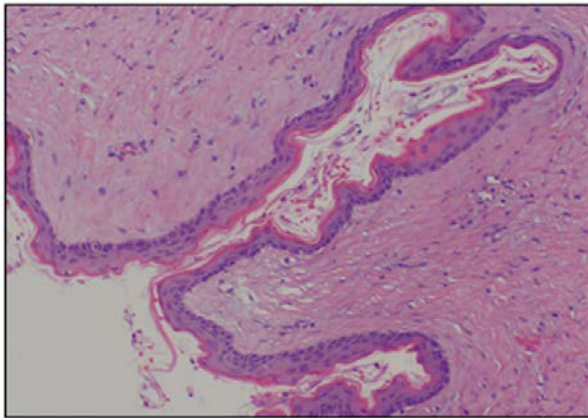


Figure 5. Wavy parakeratin along the surface, desquamated keratin within the luminal area. (40x)

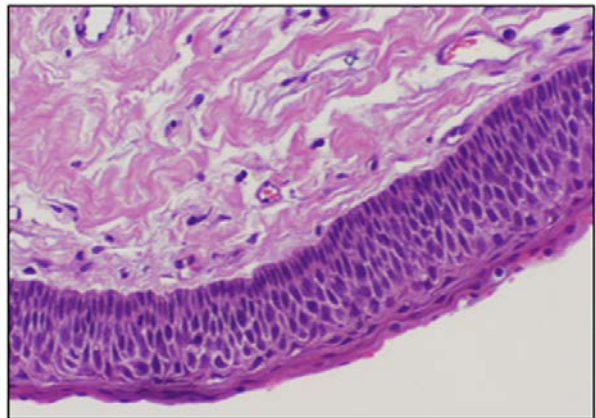
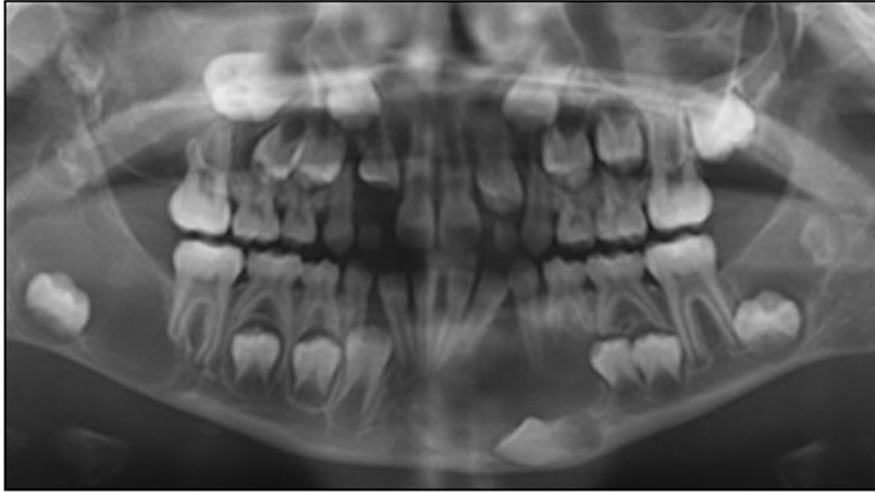


Figure 6. Hyperchromatic and palisaded columnar basal cells, are typical features. (200x)

Can you make the diagnosis?

An 8 year-old African-American female was evaluated during a regular dental examination for multiple radiolucent lesions of the mandible and maxilla.



Select the Correct Diagnosis

- A. Cherubism
- B. Central Giant Cell Lesion (Granuloma)
- C. Ameloblastic Fibroma
- D. Nevoid Basal Cell Carcinoma Syndrome (Gorlin Syndrome)

Cherubism

Choice A. Sorry, this is not the correct diagnosis.

Cherubism is a benign, slow-growing disease of childhood found in patients between the ages of 2 and 12 and is characterized by a distinctive bilateral mandibular involvement. These lesions follow a pattern of variable but progressive enlargement usually until the time of puberty, whereupon they partially or fully regress. The typical radiographic appearance of cherubism presents as bilateral, multilocular lesions with significant expansion that involves the mid-face. The epicenter always involves the posterior aspect of the mandible, but a majority of cases

additionally involve the posterior maxilla, with rare cases reported in axial skeletal areas. In a majority of cases, typical radiographic imaging shows variably increased opacity, with computed tomography showing results consistent with expansion of the facial, as opposed to lingual, cortex, as well as an impression of a fibro-osseous matrix. Displacement of teeth, leading to malocclusion, is a distinctive characteristic. The distinctive clinical and radiographic features are more diagnostic than the histopathologic findings in cases of cherubism due to the histologic similarity with a central giant cells lesion (granuloma).

Please re-evaluate the information about this case.

Central Giant Cell Lesion (Granuloma)

Choice B. Sorry, this is not the correct diagnosis.

Central giant cell lesions of the jaws begin as asymptomatic, benign neoplasms with an unknown etiology. The lesions typically occur in the second or third decade, with females affected slightly more often than males. Central giant cell lesions have a predilection for the mandible and are more common in the anterior region of the jaws, with mandibular lesions frequently extending across the midline. The lesion may initially present on a routine radiographic examination, or become evident as a result of painless but visible expansion of the jaws. Perforation of the cortex is rare, with extension into surrounding tissues even rarer still. The radiographic appearance ranges from small, unilocular, radiolucent lesions to those showing

large, multilocular radiolucencies, possibly with adjacent tooth resorption or tooth movement. Multiple lesions are rarely encountered, but when found, have been associated with what is termed Noonan-like/multiple giant cell lesion syndrome. It is likely that this is a variant of Noonan syndrome rather than a separate entity.

Treatment is usually managed by thorough curettage, although those lesions considered more aggressive may require resection to ensure a complete cure. Additional modalities of treatment have included intralesional steroid injection administered on a weekly basis for six weeks or daily administration of calcitonin through dermal injections or a nasal spray for up to 12 months. Long-term radiographic follow-up is necessary given the 15–20 percent potential for recurrence.

Please re-evaluate the information about this case.

Ameloblastic Fibroma

Choice C. Sorry, this is not the correct diagnosis.

Ameloblastic fibroma is considered a neoplasm of neoplastic mesenchymal as well as epithelial elements without the formation of dental hard tissues such as dentin and enamel. This entity tends to arise as the result of an aberration in odontogenesis, typically found to arise in children or young adults, with the mean age being 14 years of age. Typically found following a routine radiographic examination, ameloblastic fibroma presents as an asymptomatic, slow-growing but expansile lesion, with the vast majority of cases (80 percent) being found in the posterior mandible. These cases are normally located in the first permanent molar area, as well as the second primary molar area. Rarely, an isolated case is found in the posterior maxilla, with the anterior maxilla location being even rarer still.

The radiographic appearance is that of a well-defined, but expansile lesion with a smooth border most often found about the crown of an impacted tooth. Often, the periphery of the lesion will display a slightly sclerotic rim. The appearance can be that of a unilocular or multi-locular lesion where infiltration into bone is usually not present.

Treatment options have included multiple modalities, but as ameloblastic fibroma behaves in an indolent fashion, conservative treatment encompassing complete surgical enucleation has been suggested as the best treatment of choice when coupled with periodic radiographic follow-up. Although recurrence rates have been reported in the 20 percent range, their reappearance does not portend a more ominous outcome.

Please re-evaluate the information about this case.

Nevoid Basal Cell Carcinoma Syndrome (Gorlin Syndrome)

Choice D. Congratulations! You are correct.

NOTE: It should be noted that following the histologic findings and subsequent examination, this patient was found to have an ovarian fibroma.

Although refined by numerous authors, Gorlin and Goltz¹ brought to light additional data and cases of, at that time, a little-recognized process that has become a stalwart topic in both medical and dental education. Nevoid Basal Cell Carcinoma Syndrome (NBCCS) is known by many different titles such as Gorlin Syndrome, Gorlin-Goltz Syndrome, and Basal Cell Nevus Syndrome, to only name a few of the variations. Dr. Gorlin himself opposed the above descriptors as well as the eponym, although he did not have a solution to the problem.²

This syndromic process is often recognized early in life due to a characteristic facial appearance in addition to the variable myriad of developmental abnormalities and neoplasms. Between 50 and 70 percent of patients present with a calvaria of greater than 60 cm in circumference,^{2,3} which also is highlighted by frontal bossing noted in 25 percent of patients, as well as a pouting lower lip. Significant skin manifestations are seen in the form of basal cell carcinomas, numbering from few to thousands, that appear mainly between puberty and 35 years of age as pink or brown papules that are isolated or found in groups.^{3,4} Whereas 15 percent of patients show the skin lesions before puberty, only 10 percent of patients over 30 years of age have none.³ These lesions are rarely found below the waist and mainly involve the face, back, and chest; can become aggressive; and can be seen with local invasion.² Approximately 0.4 percent of all cases of basal cell carcinomas represent nevoid basal cell carcinoma syndrome.⁵ Of note, 2 percent of patients younger than 45 years of age with basal cell carcinomas have the syndrome,⁶ with additional reports^{7,8} suggesting that the minimal prevalence was 1 per 57,000. Facial milia are scattered among the basal cell carcinomas in at least 50 to 60 percent of cases and are especially prominent around the eyes, eyelids, nose, malar region, and upper lip.² Approximately 65 percent of patients present with palmar and/or plantar pits that are 1–2 mm in size,

although the palmar location is more common.³ Visualization of these is aided by the patient placing his/her hands in warm water for 10 minutes. In addition, large, often multiple epidermal cysts arise on the arms and chest in 35 to 50 percent of affected patients.

A very recognizable clinical sign is the presence of multiple odontogenic keratocysts (keratocystic odontogenic tumor), which range from 1 to 30 in number. Mandibular lesions outnumber those in the maxilla by 3:1, with both locations showing cysts 10 to 20 years earlier than those in nonsyndromic patients.² The cysts peak in number in the second and third decades but continue throughout as large, destructive lesions that cause little in the way of symptoms but can show extensive tooth displacement. A significant aspect of these cysts is the propensity for recurrence, leading to treatment management dilemmas as approximately 30 to 60 percent of cases recur.⁹ Multiple factors play a part in this recurrence rate, such as incomplete removal due to satellite microcysts or remaining epithelial islands found along the periphery in the connective tissue stroma.

Patients with NBCCS are seen to be of above average height and also show enlarged mandibular coronoid processes. A radiographic image is a helpful diagnostic tool as 55 to 95 percent of this group will show lamellar calcification of the falx, whereas that finding is seen in only 55 percent of the general population.³ Skeletal abnormalities present as splayed, bifid, or fused ribs in a majority of NBCCS patients, along with kyphosis and spina bifida occulta, which have been reported in a range from 10 to 60 percent of cases.¹⁰ Although only a very minor component of the syndrome, medulloblastoma that is seen in a child, especially during the first two years of life, or younger than five years of age, is highly suspicious for the syndrome as medulloblastoma normally appears at age seven or eight. Males may exhibit hypogonadism, whereas approximately 15 percent of females may clinically show ovarian fibromas or present with such a finding on ultrasound examination.² Ovarian fibromas associated with the syndrome may show calcifications and are most often bilateral. When compared to the general population, cardiac fibromas of the left anterior ventricular wall are not uncommon findings in children younger than 10 years of age with the syndrome.

NBCCS is the result of mutations in the PTCH1 gene and is transmitted as an autosomal dominant trait with complete penetrance and variable expressivity.¹¹ The PTCH1 gene, important in coding for proper growth and development, has been mapped to the long arm of chromosome 9, with the product of this gene acting as a tumor suppressor gene that becomes mutated in the syndrome. The gene modifies the Hedgehog signaling pathway and becomes mutated not only in the syndrome, but also in ordinary basal cell carcinomas.² This gene acts in the absence of Sonic Hedgehog, the ligand, as a cell cycle regulator that normally inhibits expression of genes controlling cell fate, patterning, and growth. Additionally, the Hedgehog signaling pathway plays an important role in mammalian embryonic development of structures such as the neural tube, axial skeleton, limbs, lungs, skin, hair follicles, and teeth.¹²

Diagnosis of NBCCS can be made in the presence of two major criteria or one major and two minor criteria:¹³

Major Criteria

- Multiple (>2) basal cell carcinomas, or one appearing at age <20 years
- Odontogenic keratocysts of the jaws proven by histopathology
- Palmar or plantar pits (three or more)
- Bilamellar calcification of the falx cerebri
- Bifid, fused, or markedly splayed ribs
- First degree relatives with NBCCS

Minor Criteria

- Macrocephaly determined after adjustment for height
- Congenital malformation: cleft lip or palate, frontal bossing, “coarse face,” moderate or severe hypertelorism

- Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits
- Radiological abnormalities: bridging of the sella turcica, vertebral anomalies such as hemivertebrae, fusion or elongation of the vertebral bodies, modeling defects of the hands and feet, or flame-shaped lucencies of the hands or feet
- Ovarian fibroma
- Medulloblastoma

If a family history of the disease is known, a thorough examination should be conducted at birth or shortly thereafter to evaluate for the presence of a large head, frontal and temporal bossing, cleft palate, eye anomalies, bifid ribs, or vertebral anomalies. A neurological examination also is suggested to evaluate for the presence of medulloblastoma and should be performed every six months until at least seven years of age.¹¹ Additionally, a yearly panoramic radiograph is suggested after the age of eight and should be coupled with a skin examination. Long-term examination and treatment will involve multiple specialties. Odontogenic keratocysts may show continued recurrence even in the presence of eradication of those that are radiographically present and have apparently been treated appropriately. Extensive surgical resection and reconstructive procedures may lead to significant jaw deformity. Only a small proportion of basal cell carcinomas become invasive, but results from several epidemiologic studies have indicated that a strong positive correlation with exposure to UV radiation exists; therefore, UV protection and avoidance of radiotherapy are paramount.¹¹ In total, the most common presenting signs of NBCCS are non-life threatening, save for medulloblastoma, although the disfiguring aspects can be life altering.

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