Hamartoneoplastic Syndromes

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KEYWORDS

• Hamartoma • Gorlin-Goltz • Peutz-Jeghers • Gardner syndrome • Multiple endocrine neoplasia • Sturge-Weber • Neurofibromatosis • Tuberous sclerosis

KEY POINTS

- Hamartomas are benign malformations presenting as an excess of normal tissue within the tissue of origin.
- Although some syndromes show a clear genetic transmission, the underlying reasons for many of these abnormalities are not fully understood.
- The hamartomatous syndromes are usually associated with other neural, cutaneous, skeletal, or developmental malformations.
- The orofacial signs and symptoms often precede systemic displays of the syndromes. Thus, oral and maxillofacial surgeons are in a unique position to identify and aid in diagnosing many of the hamartoneoplastic syndromes.

Gorlin syndrome (nevoid basal cell carcinoma syndrome)

- Genetics
  - Nevoid basal cell carcinoma syndrome (NBCCS) includes more than 100 signs and symptoms involving the skin, central nervous system, and skeletal system. The inheritance pattern is autosomal dominant. It is caused by a chromosome 9q22 microdeletion. Forty percent of new mutations arise spontaneously and the trait has complete penetrance with a widely varied expressivity.[1] In general, this syndrome and many others are noted to support the double-hit theory, the first hit being genetics and the second hit being some environmental insult.[2]
- Clinical features
  - Also known as Gorlin-Goltz syndrome, NBCCS includes multiple symptoms of the skeletal system, central nervous system, and skin. Manifestations commonly include nevoid basal cell carcinomas, odontogenic keratocysts (OKCs), skeletal anomalies, and bifid ribs.[1]
  - People affected with NBCCS tend to be very tall, and 70% of patients have a characteristic facies caused by enlarged occipitofrontal circumference. Ocular hypertelorism is also, along with prominent supraorbital ridges, a broad nasal base, and mandibular prognathism. Cleft lip and/or palate occur in about 5% of cases. Congenital blindness may also occur.[1,3]
  - Skin involvement includes nevoid basal cell carcinomas. In contrast with classic basal cell carcinomas, these lesions tend to appear at an early age (before 35 years old), in multiples, and on areas of skin not exposed to the sun. Palmar/planar pits present along the ventral surfaces of hands and feet in more than half of cases, with a higher frequency among elderly affected individuals.[4]
  - Reproductive system abnormalities can occur, such as bilateral calcifying ovarian fibromas or ovarian fibrosarcoma.[1]
  - Calcification of the falx cerebri and tentorium cerebelli is common, as well as calcification of the dura and the pia mater and the choroid plexus. Although neurologic abnormalities are frequent, the incidence of intellectual disability is around 3%.[1,4]
  - Common skeletal abnormalities include bifid, missing, splayed, fused, or hypoplastic ribs. Kyphoscoliosis may be present along with spinal bifida occulta. Lytic pseudocystic bone lesions are usually seen in the bones of the feet and hands. They can also affect the arms, legs, pelvis, and skull.[1]
  - As mentioned earlier, odontogenic keratocysts of the jaw are often the first clinically detected feature, and 85% of cases are affected before the third decade of life. Originating from the remnants of the dental lamina, the OKCs are large, expansile, and generally asymptomatic. However, the cysts may be associated with an unerupted tooth causing cortical expansion, tooth mobility, and displacement and invasion of nearby structures. The mandible is 3 times more likely to be affected than the maxilla, but OKCs can occur in both jaws simultaneously. The posterior molar/ramus area is the most common site to be affected in the mandible and the second molar region is the most common site of the maxilla. OKCs may present as multilocular or unilocular lesions, and the recurrence rate after surgical treatment is high, ranging from 30% to 60%.[1–4]
  - Diagnosis of the OKC is normally done from a histologic sample of the lining. Two types of stratified squamous epithelium can line OKCs: parakeratinized or, more

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rarely, the orthokeratinized type. Also typically displayed are a well-defined basal epithelial layer, palisaded nuclei, no rete ridges, and prominent epithelial rests. Inflammatory cells are commonly found in the underlying connective tissue. Syndromic OKCs have a higher rate of satellite cysts. Ameloblastoma and squamous cell carcinomas of the jaw can, rarely, arise from OKCs.[2,4]

- Differential diagnosis
  - Diffuse osteoma cutis, basaloid follicular hamartomas (associated with myasthenia gravis), Bazex syndrome, Rombo syndrome, multiple seborrheic keratoses in patients with adenocarcinoma. Multiple jaw cysts may be mistaken for dentigerous cysts or isolated OKCs. Severe calcifications of many organs may also suggest pseudohypoparathyroidism.[1]
- Treatment considerations for the oral and maxillofacial surgeon
  - OKCs are typically the first presenting feature of the syndrome so radiographic examination of skull and jaws is indicated. Biopsy of the skin lesions confirms clinical presentation of nevoid basal cell carcinomas, whereas OKCs may be distinguished histologically. OKCs associated with NBCCS tend to develop multiple new cysts and may be confused with recurrence of previous lesions. Because syndromic OKCs present at an earlier age than sporadic cysts, with the multiplicity of lesions and potential for recurrence, management by the maxillofacial surgeon continues into adulthood because lifelong follow-up is anticipated (Figs. 1 and 2).[2–4]

Gardner syndrome

- Genetics
  - Gardner syndrome (GS) has been found to be associated with the extracolonic manifestations of adenomatous polyposis of the colon (APC). The germline mutation associated with GS is localized to a gene on the long arm of chromosome 5. GS is present with APC with an incidence of 1 in 4000 to 1 in 12,000. Although the wide spectrum of extracolonic manifestations depicts the variable expressivity of the genotypic abnormality, GS represents a more complete phenotypic expression of the APC genotype.[5] Spontaneous mutations can arise, because 30% of cases occur because of a new dominant mutation.[1]
- Clinical features
  - The classic presentation of GS is a collection of multiple intestinal polyps (adenomatosis), widespread osteomas and abnormalities of the facial skeleton, epidermoid cysts, and desmoid soft tissue tumors. Extracolonic features typically precede the intestinal polyposis.[6] Although the early symptoms of APC are not well defined, soft tissue and other benign tumors in a child or adolescent may indicate the possible onset of GS followed by adenomas in the colorectal region.[7]
  - Osteomas of the jaw are most often found throughout the facial bones and are slow growing and reach a limited size. Appearing with well-developed haversian systems on radiograph,[1] the enostotic lesions may coalesce with other lesions. Other bones, such as the radius, ulna, and tibia, may be affected, and lesions appear as small osteomas with cortical hyperostosis.[5]
  - Approximately 58% to 88% of all individuals affected by ACP-GS have characteristic bilateral lesions of the retina, known as congenital hypertrophy of the retinal pigment epithelium.[8]
  - Skin lesions include epidermoid cysts, desmoid tumors, and fibrous hyperplasia. Epidermoid cysts are generally small, always benign, and occur in about half of cases of GS. They occur most often on the extremities, face, and scalp, typically manifesting in adolescence, and they precede the intestinal polyposis. Often unnoticed by patients, development of skin cysts may serve as an indication for further investigation for intestinal abnormalities. Desmoid tumors appear in 3.5% to 5.7% of patients,[9] typically near other surgical sites such as the abdominal cavity. Desmoid tumors are rare in the general population, so discovery in a patient should lead to an investigation of the colon for other signs of GS.[10]
  - Gastrointestinal system manifestations are required for diagnosis, and these multiple intestinal adenomatous

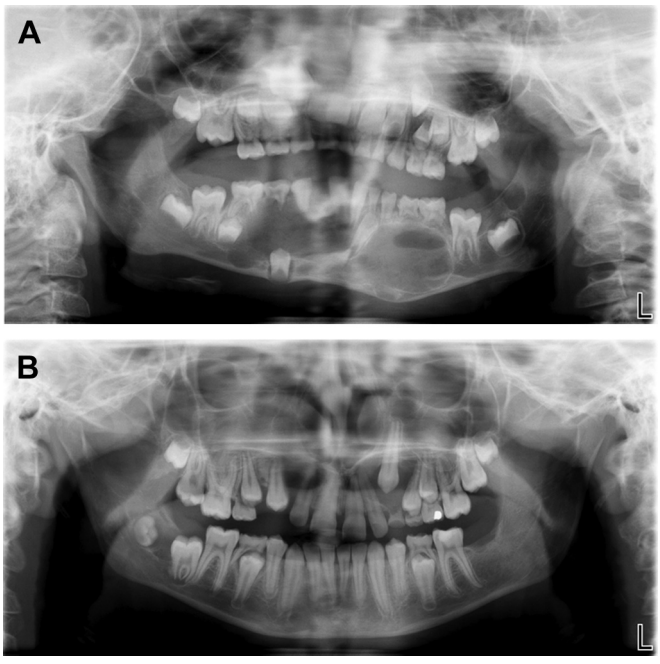

Fig. 1 (*A*, *B*) Panoramic radiographs of siblings with multiple OKCs as seen in Gorlin-Goltz syndrome.

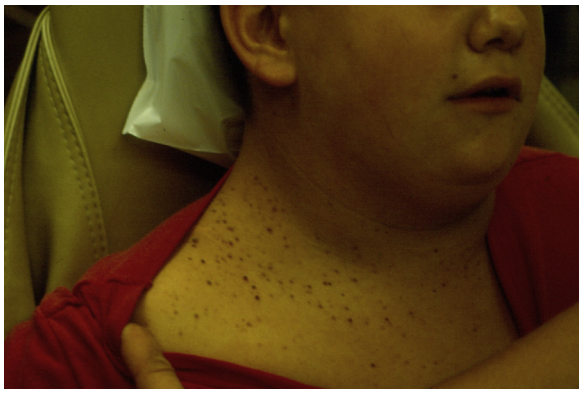

Fig. 2 Multiple basal cell nevi in a patient with Gorlin syndrome. (*Courtesy of* D. DeLuke, DDS, MBA, Richmond, VA.)