Case Report

Genetic mutations in Gorlin-Goltz syndrome

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Gorlin-Goltz syndrome is a rare multisystemic disease inherited in a dominant autosomal at a high level of penetrance and variable expressiveness. It is mainly characterized by basal cell carcinoma, odontogenic keratocyst and skeletal anomalies. Diagnosis is based upon established major and minor clinical and radiographic criteria and gene mutation analysis. This article presents a case of Gorlin-Goltz syndrome, its genetic predisposition, diagnosis and management.

Key words: Gorlin-Goltz syndrome, Nevoid basal cell carcinoma, odontogenic keratocyst, palmar plantar pits

Introduction

Gorlin-Goltz syndrome also known as Nevoid Basal cell carcinoma syndrome was first reported in 1894 but delineated by Gorlin and Goltz in 1960, as a classical triad composed of multiple basal cell carcinoma, keratocystic odontogenic tumors in the jaws and bifid ribs. A spectrum of other neurological, ophthalmic, endocrine and genital manifestations are known to be variably associated. The incidence is estimated to be 1 in 50,000 with both male to female ratio being same.[1]

Pathogenesis of the syndrome is attributed to abnormalities in the long arm of chromosome 9 (q22.3-q31) and loss of mutations of human patched gene (PTCH1 gene). The PTCH1 gene consists of 23 exons, which span 34 Kb. It encodes a transmembrane glycoprotein composed of 1447 amino acids, with 12 transmembrane domains and two large hydrophilic extracellular loops with Sonic Hedgehog (SHH) ligand binding occurs. However, mutations in other genes such as Patched 2 (PTCH 2), Smmothened (SMO) and Sonic hedgehog (SHH) have reported in isolated cases of basal cell carcinoma and medulloblastoma.[2]

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Case Report

A 12-year-old female patient was referred to dental clinic with a chief complaint of swelling on the left side of the upper jaw since 4 months by a local medical practitioner. Patient was concerned about the facial deformity and denied any other associated symptoms. Patient's medical, family, dental and personal history was noncontributory.

On general physical examination, the patient was moderately built and nourished, presenting with normal gait and satisfactory vital signs. There were multiple palmar pits brownish black in color present on the palms of both her hands [Figure 1]. There was a diffuse swelling in the left middle third of the face with no secondary changes noted over it. On palpation, there was local rise in temperature; the swelling was tender and soft in consistency. A solitary left submandibular lymph node was palpable, tender, soft in consistency and mobile.

There was a swelling in the left buccal vestibule causing vestibular obliteration in region of 22 and 63 extending distally unto 26. Mucosa over the swelling showed no secondary changes. On palpation the swelling was tender and soft in consistency with areas of decortication. Aspiration yielded thin straw-colored fluid.

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Based on the history and clinical findings, a provisional diagnosis of dentigerous cyst in relation to 63 was given and a differential diagnosis of odontogenic keratocyst considered. The patients was subjected to the following radiographic examination. Intraoral periapical radiograph in the region of 22, 63 and 26 showed a well-defined radiolucency with sclerotic borders in the periapical region extending from 22 to 26. The radiolucency was not associated with impacted teeth. The radiograph also showed missing 23, 24, 25. Anterior maxillary occlusal radiograph showed similar well-defined radiolucency in the region of 22, 63, 26 [Figure 2].

Orthopantomograph revealed multiple, unilocular well-defined radiolucencies with sclerotic borders located in maxilla and mandible [Figure 3]. The presence of multiple cysts in the jaws, associated with unerupted teeth, raised a suspicion of Gorlin syndrome and other relevant investigations were done. The patient was then evaluated systemically for other anomalies of the skeletal, cardiovascular or central nervous system. Ophthalmologic examination incidentally revealed Bitot spots in both the eyes. An incisional biopsy of the swelling in left side of maxilla was advised. Histopathological examination of specimen revealed stratified squamous parakeratinized epithelium with palisading pattern of columnar cells along with keratin flakes suggestive of odontogenic keratocyst [Figure 4]. Since the criteria of multiple cysts in the jaws (one of them being odontogenic keratocyst), multiple palmar pits, were present, a final diagnosis of Gorlin syndrome was given.

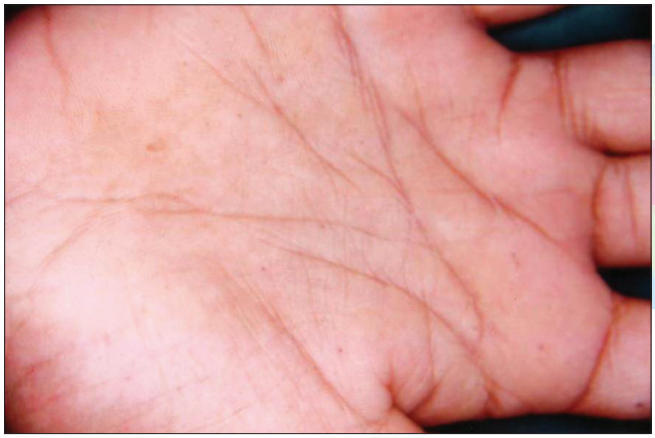

Figure 1: Multiple palmar pits on the hand

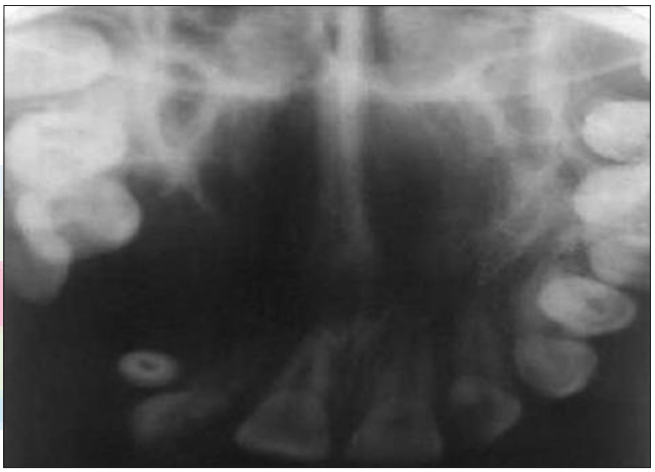

Figure 2: Anterior maxillary occlusal view

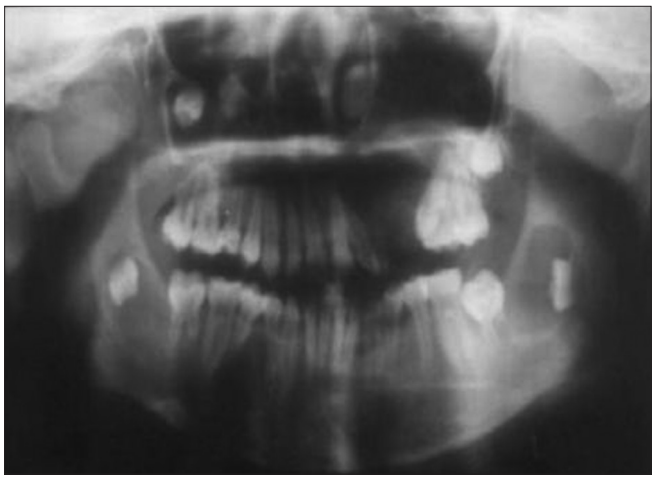

Figure 3: Orthopantomograph showing multiple jaw cysts in relation to impacted and unerupted teeth

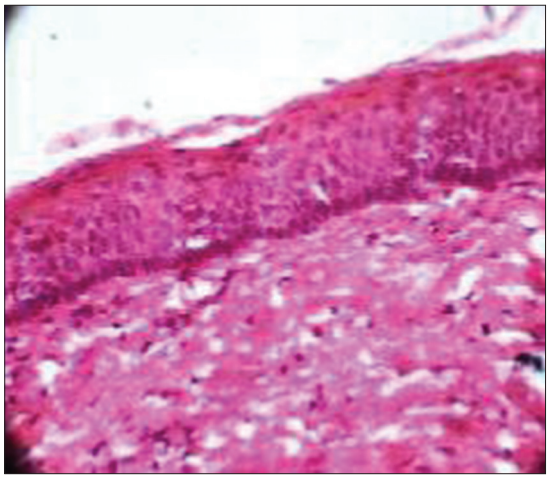

Figure 4: Histological section showing stratified squamous parakeratinized epithelium with palisading pattern of columnar cells along with keratin flakes suggestive of odontogenic keratocyst under high power (×40)

Discussion

The syndrome is synonymous with Nevoid basal cell carcinoma, Jaw cyst bifid rib basal cell nevus syndrome, Nevoid basalioma and Gorlin syndrome, Fifth phacomatosis.[3] Early diagnosis of Gorlin-Goltz syndrome is important due to susceptibility of affected people to multiple neoplasms in early age. The diagnostic criteria for Nevoid basal cell carcinoma can be established when two major or one major and two minor criteria as described below are present.[1,4]

Major criteria

- More than two basal cell carcinoma or one in patient <20 years old
- Any odontogenic keratocyst of the jaw;
- Three or more palmar or plantar pits;
- Bilamellar calcifications of falx cerebri;
- Bifid or fused ribs;
- Positive family history of Nevoid basal cell carcinoma.

Minor criteria

- Congenital malformations (cleft lip or palate, polydactylism or eye anomaly cataract, coloboma, microphthalmos);
- Macrocephaly;
- Radiologic anomalies (bridging of the sella turcica, vertebral anomalies, flame-shaped lucencies of the hands and feet);
- Ovarian fibroma;
- Skeletal anomalies (Pectus deformity, Sprengel deformity, syndactyly of digits).

Odontogenic keratocysts – These are constant features of this syndrome and are present in about 75% of the patients. They develop during the first decade of life, usually after the 7th year and reach the peak during 2nd and 3rd decade. This approximately is a decade earlier than the much more common isolated odontogenic keratocyst not associated with the syndrome.[5] It is most commonly seen in the mandibular – molar-ramus region. Their high mitotic index suggests greater proliferative potential of the epithelial lining for cyst expansion due to proliferating cell nuclear antigen (PCNA) and its recurrence.[5-7] In young patients, the cysts can cause displacement of developing teeth and may be associated with unerupted teeth and occasionally cause root resorption. In spite of widespread extension throughout the jaws, they are asymptomatic, unless secondarily infected. They are detected on routine dental checkups and rarely cause pathological fractures. Although rare, ameloblastoma and squamous cell carcinoma have arisen from these cysts.[5] Our patient showed multiple impacted teeth in the maxilla and mandible, one of them in the left side of the maxilla being associated with unilocular radiolucency, which was histologically proven as odontogenic keratocyst.

Palmar and/or plantar pits are present in about 65% of the patients. They are asymmetrical, ranging from 2 to 3 mm in diameter and 1 to 3 mm in depth. These pits usually develop late in the second decade but could be seen in patients as young as 5 years of age. They are caused by partial or complete absence of dense keratin in sharply defined areas. They become more evident when patient's hands or feet are placed in warm water for several minutes. Basal cell carcinomas may arise from these pits. Multiple palmar pits became evident when we placed our patient's hands in warm water.[2,5]

A dermatologist should maintain ongoing surveillance of superficial basal cell carcinomas without hair follicle involvement are treated by topical use of 0.1% tretinoin cream and 5% fluorouracil applied to affected area twice daily.[5] The use of oral retinoids (isotretinoin –3.1 mg/kg/day) or combined oral etretinate (0.5-1 mg/kg/day) is also suggested. Superficial basal cell carcinomas have also been managed by electrodessication and curettage. Photodynamic therapy by use of photosensitizing dye given intravenously or topically has also been advocated. Radiation therapy must be avoided, as it can cause invasion of basal cell carcinoma years later.[4]

Frequent dental visits are also obligatory. Jaw keratocysts are often recurrent and demand repeated surgical excisions. Antenatal diagnosis is possible with ultrasound scans and DNA analysis extracted from fetal cells after amniocentesis or chronic villus sampling. Thus, a genetic counselor is a critical component of the ongoing care of the patient.[8]

As new research is performed, the availability, sensitivity and specificity of molecular testing may further improve offering the opportunity for better survival rates.

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