International Journal of Medical and Pharmaceutical Case Reports
3(4): 101-106, 2015; Article no.IJMPCR.2015.044
ISSN: 2394-109X

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Gorlin Goltz Syndrome – A Case Report from Bosnia and Herzegovina

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AP and SM wrote the draft of the manuscript and supervised the work. Authors AK and BH provided the case and the figures. Authors SKV and MKF managed literature searches and contributed to the correction of the draft. Author AJ designed the figures and managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/IJMPCR/2015/17120
Editor(s):
(1) Syed A. A. Rizvi, Department of Pharmaceutical Sciences, College of Pharmacy, Nova Southeastern University, USA.
Reviewers:
(1) Anonymous, Kenya.
(2) Anonymous, USA.
Complete Peer review History: http://www.sciencedomain.org/review-history.php?iid=994&id=38&aid=8708

Case Study

Received 26th February 2015
Accepted 19th March 2015
Published 6th April 2015

ABSTRACT

Gorlin-Goltz syndrome (GGS) is an uncommon inherited disorder characterized by numerous basal cell carcinomas, odontogenic keratocysts and musculoskeletal malformations. A spectrum of other neurological, ophthalmic, endocrine and genital manifestations is known to be variably associated with this triad. Diagnosis of the syndrome is based on major and minor criteria. It is important to make an early diagnosis and a proper management of GGS to reduce the severity of complications

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including cutaneous and cerebral malignancy.
We present a case of GGS in a 39-year-old male who met three major and several minor criteria.

Keywords: Gorlin Goltz syndrome; nevoid basal cell carcinoma syndrome; basal cell carcinomas; palmar pits; odontogenic keratocysts; calcifications of the falx cerebri.

ABBREVIATIONS

Gorlin-Goltz syndrome (GGS); Nevoid basal cell carcinoma syndrome (NBCCS).

1. INTRODUCTION

Gorlin-Goltz syndrome (GGS), also referred to as the nevoid basal cell carcinoma syndrome (NBCCS), is an infrequent multisystem disease inherited in a dominant autosomal way, which shows a high level of penetrance and variable expressiveness [1]. Abnormalities of the skin, the skeletal system and the central nervous system are the most common. Ocular, genitourinary and cardiovascular disorders may occur [2-4]. Various low-frequency neoplasms, such as medulloblastomas, meningiomas, and ovarian and cardiac fibromas have been also reported [5].

The incidence of this syndrome is estimated to be 1 in 50.000 to 1.50.000 in general population but may vary with region. Males and females are equally affected [1].

In recent time important advances have been taking place in the knowledge of the genetic characteristics of this syndrome, existent clinicopathologic variants and its different manifestations [2,4].

Several reports have appeared in the medical literature describing this syndrome. However, GGS has never been reported from Bosnia and Herzegovina. We report here one such patient diagnosed at our department.

2. PRESENTATION OF CASE

We report a case of a 33-year-old male presented to our department with numerous basal cell carcinomas (BBCs) on his face and trunk that began in the age of puberty. Because of recurrent skin carcinomas with or without pigment he has been repeatedly treated surgically with transient result. During 2013 and 2014 several tumors from his face, chest, and back were removed; histopathology identified all as BCCs. Our patient denied any similar changes in members of his family or closer relatives. Routine laboratory tests were normal.

Presence of dysmorphic facial features like relative macrocephaly with a head circumference of 63 cm (normal is 57 cm in males), mild frontal bossing, broad nasal bridge, ocular hypertelorism and strabismus, and mandibular prognathism were observed (Fig. 1, A). Dermatological status showed multiple BCCs on patient's face, neck und trunk together with numerous basal cell nevi (Fig. 1, B and D). There were multiple pin-point sized palmar pits brown coloured and measuring 1-3 mm in diameter present on both his hands (Fig. 1, C). We also found several skeletal malformations such as sprengel deformity (high scapula), thoracis scoliosis (1, B) and pectus excavatum (Fig. 1, D).

Considering the possibility of the NBCCS with the above features, further investigations were carried out.

Orthopantamogram revealed an irregular homogenous radiolucency present in the right mandible approximately of 2 cm in diameter, in association with dens impactus in region 48. Another well defined cystic radiolucency of 1 cm diameter in the mandible in relation to 31 and 41 was also seen (Fig. 2, A). Head radiography revealed calcifications of the falx cerebri (Fig. 2, B). Computed tomography showed ectopic calcification of the falx cerebrai (Fig. 2, C) and tentorium cerebelli (Fig 2, D).

Based on the clinical, radiographic, and histologic findings and referring to the established diagnostic criteria for nevoid BCC syndrome, the patient was diagnosed as having GGS syndrome.

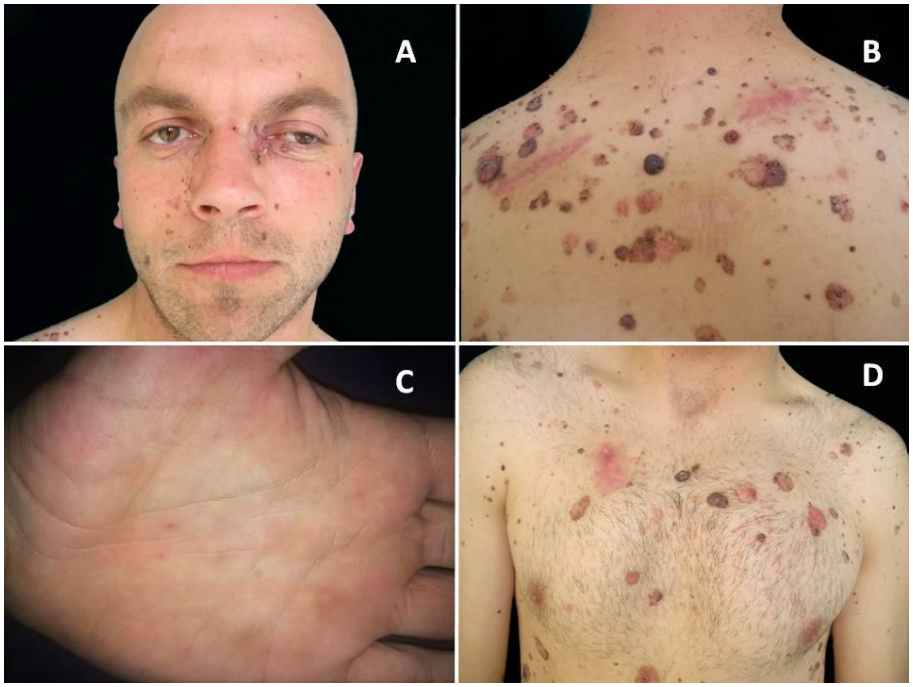

Fig. 1. Clinical features of NBCCS. Facial appearance of patient showed dysmorphic facial features, including relative macrocephaly, mild frontal bossing, broad nasal bridge, ocular hypertelorism and strabismus and mild mandibular prognathism (A), multiple BCCs, basal cell nevi (B, D), sprengel deformity and thoracis scoliosis (B), muliple palmar pits (C), pectum excavatum (D)

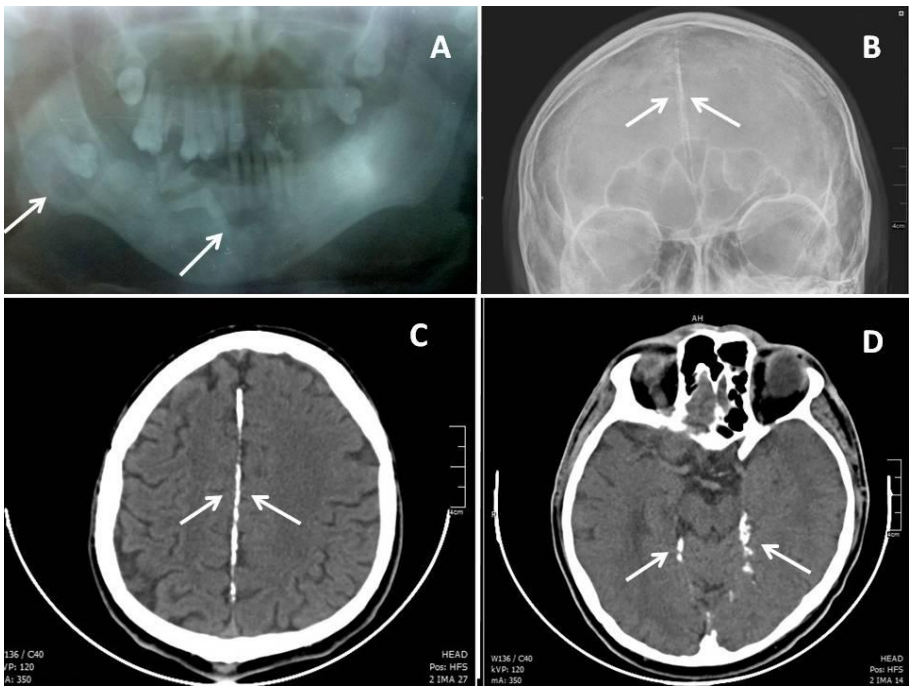

Fig. 2. Imaging findings of NBCCS. Orthopantomograph showing multiple cysts lesions in mandibule (A), radiograph of skull showing calcification of falx cerebri (B), computed tomography showed ectopic calcification of the falx cerebrai (C) and tentorium cerebella (D)

3. DISCUSSION

GGS is a rare autosomal dominant disorder that involves multiple organ systems, including the skin, jaws and skeleton. The pathogenesis of this syndrome is attributed to abnormalities linked to the long arm of chromosome 9 (q22.3-q31) human patched gene (PTCH1 gene) with no apparent heterogeneity. PTCH1 gene is significant in controlling growth and development of normal tissues and thus its mutation comprises a key event for the development of this syndrome including neoplasms [6]. This gene was first isolated in 1996 as the human homolog of the Drosophila PTCH1 gene, simultaneously in Australia and in the USA. Since than, several mutations of the PTCH1 gene have been identified in patients with GGS [7].

Evans et al. [8] first established major and minor criteria for diagnosis of this rare entity, later modified by Kimonis et al. in 1997 [9]. According to them, diagnosis can be established when two major or one major and two minor criteria are present as described below:

3.1 Major Criteria

I. More than two BCCs or one under the age of 20 years.
II. Any odontogenic keratocyst (proven on histology).
III. Three or more palmar or plantar pits.
IV. Bifid, fused, or markedly splayed ribs.
V. Bilamelar calcification of falx cerebri and tentorium cerebelli.
VI. Positive family history of NBCCS.

3.2 Minor Criteria

I. Macrocephaly adjusted for height.
II. Skeletal anomalies: Hemivertebrae, scoliosis, sprengel deformity (high scapula), pectus excavatum or pectus carinatum.
III. Radiological abnormalities like bridging of sella turcica, vertebral anomalies, and modelling defect of hands and feet.
IV. Medulloblastoma.
V. Ovarian Fibroma.
VI. Congenital malformations: Cleft lip or palate, polydactylism or eye anomalies (cataract, coloboma, and microphthalmus).

BCCs are the most common finding in GGS. The highest incidence rate is observed in people between puberty and age 35, although it was also observed in children ages 3 to 4 years. The number of BCC lesions varies from several to thousands, their diameter ranges from 1 mm to 10 mm, and they may have various forms from skin-coloured nodules or papules to ulcerating plaques. They are usually located on the face (especially periocular areas and eyelids), neck, and upper part of the trunk, but they may also be found on skin not exposed to the sun [1]. BCCs in this syndrome behave in the same manner as sporadic BCCs. In general, it is after puberty that the BCCs become aggressive and invade locally [10]. The histopathology of nevoid BCCs cannot be differentiated from that of ordinary sporadic BCC [1]. The predisposition of these patients to suffer from cutaneous cancers appears to be due to the fact that the mutated cells are more susceptible to sunlight, due to inefficacy of the mechanisms that repair UV-induced DNA damage [11]. Our patient is a case of multiple BCCs who had the diagnosis 20 years ago and who underwent 2 resections for local recurrences during that period.

Palmar and plantar pits are specific signs of this syndrome, occuring in 85% of patients over the age of 20 years [2]. These alterations are caused by the lack of a partial or complete absence of the corneal stratum. They are permanent, asymmetrical and unpalpable, with a depth ranging from 2 to 3 mm are a strong diagnostic indicator whenever found in a child [4].

Odontogenic keratocysts (OKCs) are often among the first signs of GGS, being present in 90% of patients younger than 10 years of age. Recently and based on the intrinsic growth potential of its epithelial coating, they have been re-classified and called odontogenic keratocyst tumours, and they have been included in the odontogenic neoplasias [12]. OKCs have more predilections for mandible especially molar ramus region. As previously mentioned, our patient presented with the main complaint of mild expansion and in radiography several radiolucent lesions were observed in the mandibule. OKCs associated with NBCCS have higher recurrence rates compared to solitary OKCs. It is believed that the aggressive behavior and high rate of recurrence of OKCs associated with GGS is due to a higher rate of proliferation of the epithelial lining [13].

Calcification of the falx cerebri is the most common radiologic finding in GGS, occurring in 65-92% of individuals and seen on anteroposterior skull radiographs [3].

The clinical spectrum of the 9q 22.3 microdeletion is variable and the clinical findings depend somewhat on the size of the microdeletion. Our patient does not show features associated with the 9q 22.3 microdeletion including delayed development, intellectual disability, overgrowth of the body (macrosomia), and physical abnormalities.

In our case three major manifestations such as BCCs, palmar pits and ectopic calcifications of the falx cerebri, were identified. OKCs, although seen on orthopantamogram, were not histologically proven as our patient refused surgical treatment. In addition, several minor manifestations such as macrocephaly, frontal bossing, broad nasal bridge, hypertelorism and mandibular prognathism, skeletal anomalies (sprengel deformity, pectus excavatum, scoliosis), were identified and diagnosed as GGS.

Management of our patient was directed towards his current symptomatic presentation including multiple BBCs. Treatment involved removal of tumors by surgical excision. The patient was advised strict photoprotection along with oral isotretinoin (0.75 mg/kg/day) as chemoprevention.

4. CONCLUSION

Early recognition of the disease and evaluation of signs and symptoms are important to reduce the severity of complications including cutaneous and cerebral malignancy and oromaxillofacial destruction due to jaw cysts. Because of the different systems affected, a multidisciplinary approach of various specialists like pediatricians, specialists in genetics, dermatologists, dentists, maxillofacial surgeons, etc., is required for a successful management.

CONSENT

All authors declare that 'written informed consent was obtained from the patient (or other approved parties) for publication of this case report and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=994&id=38&aid=8708