Gorlin-Goltz syndrome

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SUMMARY

Gorlin-Goltz syndrome, also known as basal cell nevus syndrome, is an uncommon, autosomal dominant inherited disorder, which is characterized by numerous basal cell carcinomas, maxillary keratocysts, and musculoskeletal malformations. Occasionally, it is associated with aggressive basal cell carcinomas and internal malignancies. Early diagnosis and treatment are essential, as well as genetic counseling. A patient with characteristic symptoms of nevoid basal cell carcinomas and a review of the literature are presented.

Introduction

Gorlin-Goltz syndrome, also known as basal cell nevus syndrome, is an uncommon, autosomal dominant inherited disorder, which is characterized by numerous basal cell carcinomas (seen in 50–97% of people with the syndrome), maxillary keratocysts (present in about 75% of patients) and musculoskeletal malformations. It was first reported by Jarisch and White in 1894. Binkley and Johnson in 1951, and Howell and Caro in 1959 suggested a relationship between basal cell epitheliomas and developmental malformations. Robert J. Gorlin and Robert W. Goltz described the distinct syndrome, consisting of the presence of multiple nevoid basal cell epitheliomas, jaw cysts, and bifid ribs (1).

The incidence of this disorder is estimated to be 1 in 50,000 to 150,000 in the general population, varying by region (2). It appears in all ethnic groups, but most often in whites; males and females are equally affected (3). Along with multiple basal cell carcinomas (BCC), jaw cysts and musculoskeletal anomalies are lesser-known manifestations of this disorder involving the skin, central nervous system, ophthalmic, endocrine, urogenital system, and so on (4–7).

Case report

We present a 47-year-old male patient that visited our clinic for the first time in June 2002. He had skin changes, predominantly on photoexposed areas, allegedly starting 1 year ago. The examination revealed numerous (over 50) papules and nodes predominantly on his face, but also on the skin of the chest and back, up

KEY WORDS

basal cell carcinoma, Gorlin-Goltz syndrome, pathogenesis, new data

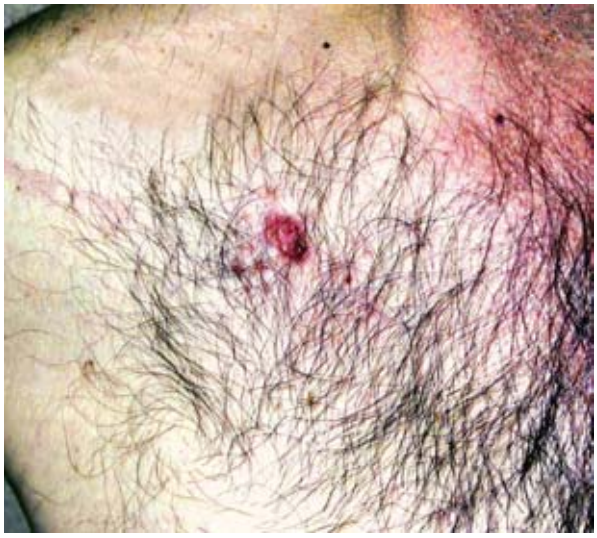

Figure 1: Same patient, basocellular carcinoma on the chest.

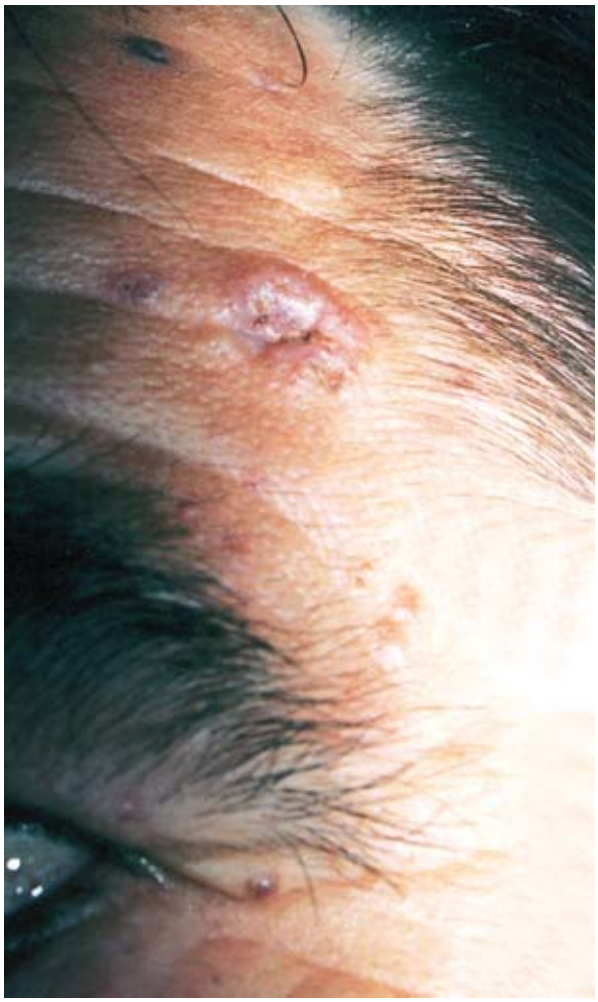

Figure 2: Basocellular carcinoma in frontal region.

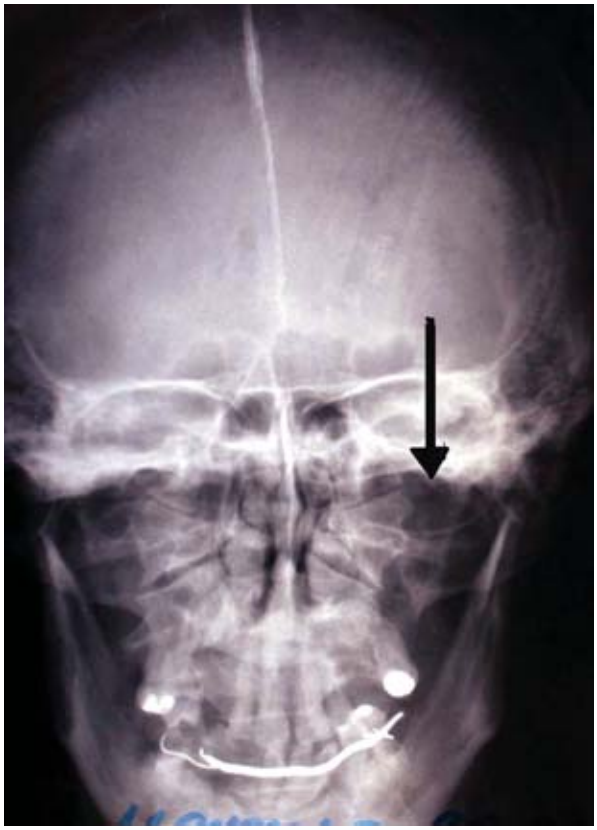

Figure 3: A cyst in the left maxillary region.

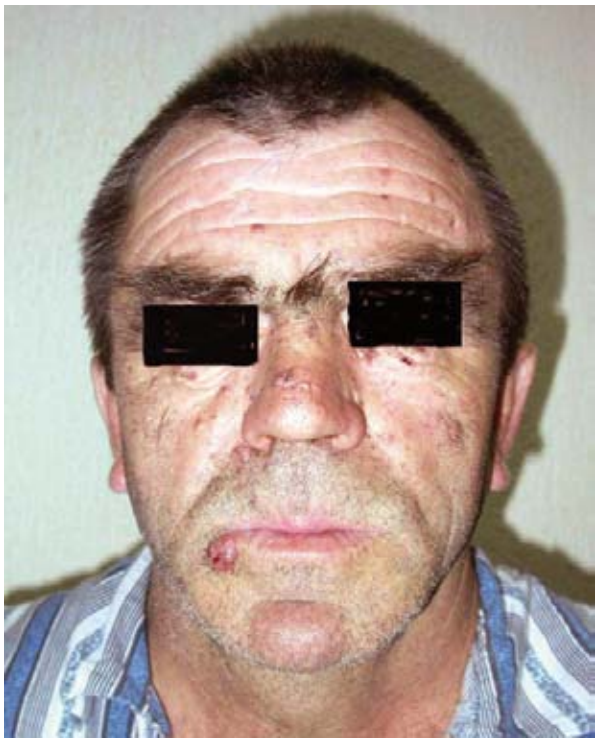

Figure 4: Same patient, last visit, five years later.

to 1 cm in diameter (Fig. 1). Some of these were shiny and dome shaped, and some had pearly borders and were covered by a crust (Fig. 2). The skin of his palms and soles was hyperkeratotic with tiny pits. Inspection revealed a coarse face with dense, fused eyebrows, and frontal prominences.

Radiographic examination showed a calcified falx cerebri and a cyst in the left maxillary region (Fig. 3). No further bone anomalies were observed. Routine laboratory tests were normal. Ultrasound examination of the abdomen did not show any abnormalities. Histopathologic examination of a nodule excised from the frontal region confirmed the diagnosis of basal cell carcinoma, and we established the diagnosis of Gorlin-Goltz syndrome. Our patient denied any similar changes in members of his family or closer relatives.

During 2002 and 2003 several tumors from his face, chest, and back were removed; histopathology identified all as basal cell carcinomas. Our patient's most recent visit to the Clinic for Dermatology and Venereology in Niš was in March 2006. He complained of an abrupt development of numerous nodules, especially on his face. The largest was a tumor on his lower lip (Fig. 4). It was excised and histopathology confirmed a basal cell carcinoma. During this last hospitalization, we repeated the laboratory tests and ultrasound examinations, which were normal. Computerized tomography of the head, chest, and abdomen did not show other abnormalities. We insisted on regular checks-ups.

Discussion

Gorlin-Goltz syndrome is autosomal dominant with a high penetrance and variable expressivity. It is caused by mutations in the patched tumor suppressor gene (PTCH), a human homologue of the Drosophila gene mapped to chromosome *9q21-23* (1, 4). Chromosomal mapping and genetic studies suggest that the underlying basis for this disease is an abnormality in the Hedgehog(Hh) signaling pathway. The role of this pathway in embryogenesis is well known. The PTCH gene product is part of a receptor for the protein called Sonic Hedgehog (SHH), which is involved in embryonic development (8). More recent investigations reveal the role of the Hh pathway in cell cycle regulation in adults. In the Drosphila model, the primary receptor for the Hh signaling pathway has two transmembrane protein components: Patched (Ptc) and Smoothened (Smo). In the absence of Hh protein, the Ptc protein inhibits the Smo. Under normal conditions, Hh, when present, binds Ptc, releasing Smo to affect downstream events such as cell growth and differentiation. Based on this model, inactivation of Ptc or constituitive activity of Smo or Hh could lead to overactivity of Smo, resulting in neoplasm formation (1).

The diagnostic criteria for nevoid basal cell carcinoma were established by Evans et al., and modified by Kimonis et al. in 1997 (3). According to them, diagnosis of Gorlin-Goltz syndrome can be established when two major or one major and two minor criteria are present as described below (2, 3):

I. Major criteria:
– More than two basal cell carcinomas or one basal cell carcinoma at younger than 30 years of age or more than 10 basal cell nevi.
– Any odontogenic keratocyst (proven on histology) or polyostotic bone cyst.
– Three or more palmar or plantar pits (present in about 65% of patients).
– Ectopic calcification: Lamellar or early at younger than 20 years of age.
– Falx cerebri calcification.
– Positive family history of nevoid basal cell carcinoma.

Some authors take plurilamellar appearance of the falx cerebri calcification as a pathognomonic symptom of Gorlin-Goltz syndrome (9).

II. Minor criteria:
– Congenital skeletal anomalies; fused, splayed, missing, or bifid ribs, wedged or fused vertebrae.
– Occipital-frontal circumference more than 97%.
– Cardiac or ovarian fibroma.
– Medulloblastoma.
– Lymphomesenteric cysts.
– Congenital malformations such as cleft lip or palate, polydactylism or eye anomalies (cataract, coloboma, microphthalmus).

Other diagnostic findings in adults with Gorlin-Goltz syndrome are:

I. Skeletal anomalies:
Hemivertebrae, scoliosis, syndactyly, polydactyly, shortened 4th metacarpal.

II. Craniofacial anomalies:
Frontal bossing: increased size of calvaria (occipitofrontal circumference 60 cm or more in adults); brachycephaly; macrocephaly, coarse face, heavy fused eyebrows; broadened nasal root; calcification of the falxes; tentorium cerebelli calcification; bridged sella turcica; low positioning of occiput; congenital blindness due to corneal opacity; congenital or precocious cataract or glaucoma; coloboma of iris, choroids, or optic nerve; convergent or divergent strabismus; and nystagmus.

III. Neurological anomalies:
Agenesis/dysgenesis of corpus callosum; congenital hydrocephalus; meningioma; mental retardation; schizoid personality.

IV. Oropharyngeal anomalies:
Cleft lip/palate; high arched palate or prominent ridges.

V. Anomalies of the reproductive system
VI. Cardiac anomalies

Tumors accompanying this syndrome include parathyroid adenoma, adrenal cystic lymphangioma, ovarian fibroma, and other neoplasms. This syndrome is followed by multiple complications, predominantly aggressive basal cell tumors invading surrounding structures, or distant metastases, causing death. Medulloblastoma causes death during infancy. Recurrence of odontogenic keratocysts causes varying degrees of jaw deformity.

Diagnosis and therapy of this syndrome require a multidisciplinary approach (dermatologists, surgeons, dentists, maxillary surgeons, and neurologists). It consists of removal of tumors (surgical excision, topical chemotherapies, and laser ablation) and adequate treatment of maxillary cysts. A new treatment strategy, based on the understanding of the Hh signaling pathway and the premise that tumors arise due to its overactivity, supposes that inhibition of this pathway with specific pharmacological treatment might suppress tumor growth (1). Patients with Gorlin-Goltz syndrome require consistent sun protection. Genetic counseling that considers the genetic risks is advisable for all patients with this syndrome, both familial and sporadic.

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