GORLIN SYNDROME – CASE REPORT

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Abstract

Gorlin Syndrome is a dysembrioplastic disease with dominant autosomal genetic transmittance, with strong penetrance, caused by mutations of the PTCH1 gene. This genodermatosis is characterized by the concomitant or short-term appearance of multiple basocelular tumors (BCC).

We present a case of polymorphous basal cell carcinomatosis found in a patient with congenital hydrocephaly and grade II oligophrenia, with 46 XY del 20p- karyotype, whose clinical features allow us to diagnose him with Gorlin syndrome.

The diagnosis is sustained by the presence of mutations on the PTCH1 gene found on chromosome arm 9q (q22.3-q31).

Case report

We report the case of a 44-year-old man, socially assisted, coming from rural areas, with uncontrolled exposure to the sun.

Reasons for admission: Numerous pigmentary, pearly tumors located at the facies, cervical and trunk area.

Heredo-collateral history: The father with pro-state cancer.

Keywords:
Gorlin syndrome; basal cell epitheliomatosis; PTCH1 gene mutations; treatment.

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Introduction

Gorlin Syndrome is a dysembrioplastic disease with dominant autosomal genetic transmittance, with strong penetrance, caused by mutations on the PTCH1 gene. This genodermatosis is characterized by the concomitant or short-term appearance of multiple basocelular tumors (BCC).

There are many variants of basal cell carcinomatosis: Multiple Arning-Fuchs Carcinoma (Multiple Superficial Wite Epitheliomas); multiple polymorphic disseminated epitheliomas (described by Pautrier); Multiple BCCs, Ferrari form. Also, multiple BCCs are found in Bazex-Dupré syndrome, Muir-Torre syndrome, Rombo syndrome or xeroderma pigmentosum, where they are present along with spinocellular carcinomas and rarely along with melanomas or other malignant tumors.

We present a case of multiple polymorphous basal cell carcinomatosis in a congenital hydrocephaly patient and Grade II oligophrenia, with karyotype 46, XY del 20p-, whose clinical features allow us to diagnose him with Gorlin syndrome.

The certainty of this syndrome’s diagnosis is given by the identification of mutations in the PTCH1 gene located on chromosome 9 (q22.3-q31).
**Personal pathological history:** Operated for intestinal occlusion nine years before presentation.

**Disease history:** The first tumor formations occurred at the age of 11 years, initially at the level of the posterior thorax, later at the facial, cervical and other areas of the trunk. Over time, multiple tumors have been excised, with slow wound healing and formation of atrophic scars.

**Clinical examination:** 62 kg patient, 179 cm tall, with macrocephaly, frontal bosom, hypertelorism and broad nose base plus moderate sternum excavation (Figure 1). Multiple post-surgical excision scars of tumors located on the trunk and cephalic extremity.

The thorough dermatological examination revealed 117 tumors with dimensions ranging from 0.5-11 cm. All the tumors were pigmented, with a pearly border, well-defined, with a depressed center, some of which had the image of "skin buried" lesions. Some factions were ulcerated. They were present in the cephalic extremity and the trunk (Figures 2, 3 and 4). We also noticed a diffuse palmar-plantar hyperkeratosis.

The patient presented multiple infectious dental outbreaks and dental defects (Figure 5).

The lab results were within normal range, except the karyotype, which revealed 46 XY del 20p- (Figure 6).

**Treatment:** Under local anesthesia with lidocaine 1%, we performed the biopsy of one tumor and we curetagged and electrocauterized, at the patient’s request, the lesions located on the face. The histopathological examination described the ap-
appearance of solid ulcerated basal cell carcinoma (Figure 7).

The patient was discharged with the recommendation of rigorous photoprotection and dermatological control on a quarterly basis, occasionally intervening on aggressive tumors.

**Discussions**

Several varieties of basal cell carcinomatosis are described in the medical literature (1):

- Arning-Fuchs Multiple Carcinoid (Wite Multiple Epitheliomas), which occurs in the form of a monomorphic eruption of superficial BCCs (erythematous type, rarely pagetoid) in number of 10-25. Tumors are preferentially located on the trunk. They do not appear on pre-existing injuries and the involvement of external factors is insignificant. It seems that an individual predisposition is important.

- Multiple polymorphic disseminated epitheliomas described by Pautrier-manifests itself like a sub-rash of 100-200 BCCs of various types; pagetoid and/or erythematous, pearly, nodular, ulcerated, pigmented, affecting the trunk, buttocks, and possibly the face.

- The multiple BCC form described by Ferrari. Its individualization is questionable, much like the form described by Pautrier.

A series of genetically determined syndromes creates conditions for the emergence of multiple BCCs (2, 3).

- Bazex-Dupré syndrome, with autosomal dominant genetic transmission. The clinical picture associates follicular atrofoderma, hypotricosis (congenital or of early onset), hypohidrosis, possibly pilar keratosis and pigmentation disorders. Patients develop multiple BCCs.

- Muir-Torre Syndrome. It presents sebaceous tumors, keratoacanthomas and various visceral tumors with low malignancy. BCCs with sebaceous differentiation are common.

- The genetic transmission is autosomal dominant.

- Rombo syndrome, in which multiple BCCs are present, numerous milium cysts on the face, vermiculite atrophy, hypothyroidism, trichoepitheliomas, and peripheral vasodilatation with cyanosis.

- Gorlin syndrome, known under various other names: basal cell nevomatosis, Gorlin and Goltz syndrome, neoplastic basal cell nevus syndrome, basal cell carcinoma syndrome, basal cell neural syndrome, basal cell hamartoma syndrome or simple basal cell hamartomas.

Gorlin syndrome has an autosomal dominant genetic transmittance, with strong penetration. Even so, approximately 30% of cases lack a positive family history, in which case we talk about de novo PTCH1 gene mutations. Both sexes are af-
fected in approximately equal proportions (M/F is 1/1.3) (4). The African population has fewer cuta-
neous tumors compared to the white population. A retrospective study conducted in Africa over a
40-year period, that evaluated 15 patients with Gorlin syndrome, revealed that only 20% of them
had skin tumors (5).

Gorlin syndrome’s prevalence was estimated at 1/56000 in England and 1/164,000 in Austra-
lia (6). The PTCH1 gene is located on the long arm of chromosome 9 (q22.3-q31), acting as a tumor-
suppressor gene (7, 8). This gene was isolated as a human gene homologous to the Drosophila
PTCH1 gene, where it plays an important role in body segmentation (9). In humans, it intervenes in
normal tissue growth and development.

The PTCH1 gene contains 23 exons and 34 kb. It encodes a transmembrane glycoprotein com-
posed of 1447 amino acids, with 12 transmem-
brane domains, and two extracellular hydrophilic
large loops where they seem to bind Sonic Hedge-
hog ligands (SHH) (9, 10). If a mutation occurs in
PTCH1 and the second loop is not formed, SHH
cannot bind. Thus, the product of the PTCH1 gene
acts as a membrane receptor for the SHH signal and
represses the transcription (in certain cells) of the genes encoding signaling proteins belong-
ing to the transforming factor (TGF)-beta and the
Wnt family. PTCH1, in the absence of its SHH ligand,
acts as a regulator of the normal cell cycle, inhibi-
ting downstream expression of genes that control
cell growth, differentiation and fate (8, 10). In the
case of C-terminal truncation caused by a mutation
in PTCH1, these genes are no longer repressed.

The Hedgehog signaling pathway plays a cru-
cial role in organ genesis in the early years of life
and becomes almost inactive in adults, where it
retains only tissue repair functions. Its central com-
ponents are three ligands (Sonic Hedgehog, Indiana
Hedgehog and Desert Hedgehog), a negative regu-
lation receptor (PTCH) and a positive regula-
tion receptor (SMO), oncogenic factors associated
with glioma (GLI) and transcription factors (Gli 1, 2
and 3).

In the absence of a HH binding agent, PTCH in-
hibits SMO activity, preventing the insertion into
cellular cylinders. Transcription factors are seized
inside the cytoplasm via the action of certain medi-
ating proteins, such as protein kinase A (PKA). In
this place also, GLI are subject to a specific clea-
vage, which results in the translation inhibition of
the target genes by the HH pathway. When activat-
ed, GLI is the final effector of the HH signaling
pathway, inducing the expression of specific genes
involved in regulating cell differentiation, prolifera-
tion and survival.

Another factor that favors HH in oncosis is
phosphatidylinositol-3-kinase (PI3K), while S6-kinase 1 (S6K1) and atypical protein kinase C
(aPKC) facilitate GLI-dependent transcription. Also,
PI3K activates 3-inosinoside-dependent kinase
(PDK1), which activates S6K1, which promotes Gli-
dependent transcription by Gli-phosphorylation,
thereby preventing an interaction that activates
target genes by the action of GLI. A HH target gene
is aPKC, which phosphorylates Glis in other regions
other than S6K1. As a result, Glis binding to DNA
occurs, generating a positive feedback that ampli-
ifies GLI-dependent transcription in basal cell car-
cinomas (11).

The involvement of the FOXE1 gene in cutane-
ous carcinogenesis has recently been demonstra-
ted. This is part of a large family of transcription
factors characterized by a DNA binding domain.
The expression of this gene is controlled by the ex-
pression of the HH/GLI signaling pathway. FOXE1
was initially isolated from keratinocytes, but its
role in epidermis development is not fully known.
Recent studies have shown that FOXE1 is a target
gene for Gli2. Considering the critical role of Gli2
in follicular cell proliferation and in carcinogene-
sis, the co-expression of both in normal skin and
in the skin of patients with Gorlin syndrome sug-
gests that FOXE1 might be involved in mediating
the proliferative effect of Gli2 in vivo (12).

Molecular biology of cancer in Gorlin syndrome
is similar to that of retinoblastoma and undergoes
Knudson’s theory in which for cancer develop-
ment, normal cells must acquire two mutations,
one inherited from the germline and a second
acquired during development at the second nor-
mal allele (13, 14). Loss of heterozygosity at the
PTCH1 locus was observed in nearly 90% of cases
with basal cell carcinomas.

Over 150 mutations have been identified, most
of them being deletions, insertions, nonsense mu-
tations and misinterpretation. Approximately 70%
of the germline mutations of PTCH1 are rearrange-
ments, and over 80% of these mutations appear to
produce truncated protein, suggesting that deve-
lopmental abnormalities occurring in Gorlin syn-
drome may be due to haploinsufficiency (15, 16).
Recently, mutations in the PTCH1 gene have been
reported as errors in recombinational repair pro-
cesses (17).

Gorlin’s syndrome is an autosomal dominant
hereditary disease, requiring the presence of a
single mutant PTCH1 gene. An affected heterozy-
gous person has a risk of transmitting the disease
to 50% of his offspring. The risk for family mem-
bers varies, about 70-80% of people diagnosed
with Gorlin syndrome having an affected parent
and about 20-30% of the probants carrying a de
novo mutation. The risk for a probationer’s brother
depends on the status of the parents: if a parent
of a proband is affected, the risk to the brothers is
50%. If the parents are not clinically affected and
the mutation that causes the disease cannot be de-
Case presentation

tected in the parents’ DNA, the breeds have a low but higher risk than the general population due to the possibility of somatic mosaicism or germ mosaicism (10). The molecular diagnosis with the identification of mutations in the PTCH1 gene confirms the syndrome.

Gorlin syndrome is a complex dysplasia that associates multiple basal cell hamartomas with various other dysplasias (maxillo-dental, bone, nerve, ocular, etc.). Basal-cell hamartomas generally occur at puberty or during the 2nd or 3rd decades of life. There are small translucent, hemispherical tumors with a smooth and telangiectasic surface of 1-10 mm diameter, similar to BCC beads. There may also be larger-sized hyperpigmented nodules. The lesions are situated on the face, chest, abdomen and more rarely, on the limbs.

Other skin signs are the palmar (rarely plantar) Wells, described by Word, represented by crateriform wells, 1-3 mm in diameter, sometimes with a prominent keratosis border. There may be a discrete diffuse palmo-plantar hyperkeratosis as in our patient’s case. There have also been described epidermoid cysts and milium grains predominantly on extremities.

Bone manifestations consist of maxillary cysts (60-90% of cases), and rarely abdominal abnormalities (bending changes, sinusoids, bifurcated ribs, partial agenesis), cifoscoliosis, spina bifida, pectus excavatum, shortening of the fourth metacarpian, etc. The patient with basal cell nevomatosis has an olympian forehead, hypertelorism, hydrocephaly. There may be ocular changes (congenital lesions, ocular tumors), neurological (intracranial calcifications, callous bodies agenesis, meningioma, medulloblastoma), endocrine (pseudohypoparathyroidism, hypogonadism) etc. Mental retardation is present in 5% of cases (18).

In a study of 105 basal cell nevomatoses, the authors (19) investigated the frequency of clinical and radiological abnormalities. They found odontogenic cysts in 74%, palm and plant depressions in 87%, macrocephaly in 50%, hypertelorism in 42%, frontal bosoms in 27% of the cases. Almost 64% of the patients presented with calcifications of the cerebral fossa and four of them had medulloblastoma.

In another study (20), conducted on 22 patients with Gorlin syndrome, except basal cell hamartoma who were present in all cases, the authors encountered palmar wells (45%), odontogenic cysts (62%) and calcifications of the cerebral fossa (66%).

The diagnosis criteria defined by Evans et al. (1993) and modified by Kimonis et al. (1997) are as follows:

- Major criteria
  1. Multiple BCCs (> 2) or a basal cell tumor that occurred before 20 years of age;
  2. Odontogenic keratocysts of the jaw, confirmed histopathologically;
  3. Soles or palm wells (three or more);
  4. Bilateral calcification of the cerebral fossa;
  5. Bifid, united or enlarged ribs;
  6. Grade I relatives with Gorlin syndrome;

- Minor criteria
  1. Macrocephaly;
  2. Congenital malformations: frontal bosom, moderate/severe hyperplasia, split palate or split lip;
  3. Other skeletal defects: sindactilia, pectus excavatus;
  4. Radiological abnormalities of saddle, vertebra, and in the hands and feet;
  5. Ovarian fibroma;

The diagnosis of Gorlin syndrome involves the presence of two major criteria or one major and two minor criteria. According to the above criteria, our case can be diagnosed with Gorlin syndrome.

Basal-cell carcinomas in the patient with Gorlin syndrome occur since childhood and continue to appear throughout life. In most cases the histopathological aspect is basal cellular carcinoma with pillar differentiation (2).

Different treatment methods are used (21-23): surgical excision, Mohs surgery, ablative laser therapy (CO2 laser or Erbium: Yag), PDT, cryosurgery. Locally 5-FU 5% or Imiquimod 5% cream can be applied. Radiotherapy is contraindicated. Oral retinoids can inhibit the development of new tumors.

BCCs treatment in Gorlin syndrome remains a great challenge for the practitioner. There is not enough evidence to impose a specific therapeutic method. Aggressive tumors should be surgically-removed and superficial tumors should be treated with other therapeutic methods, in order to preserve the healthy skin. MAL-PDT would be a good option (18). These patients should be evaluated periodically, due to the risk of developing new BCCs. The early recognition of the syndrome is essential for establishing photoprotection. The development of other malignancies, including medulloblastoma (occurring in 5-10% of cases) (20), aggravates the vital prognosis.

The new therapeutic methods involve the use of oral HH signaling pathway inhibitors. Of these, FDA approved Vismodegib in 2012 and Sonidegib in 2015. Both medicines are currently used for the treatment of advanced or metastatic basal cell carcinoma but have no clear specification for their use in the treatment of Gorlin’s syndrome. A 2012 study of 42 patients with Gorlin syndrome following treatment with vismodegib (150 mg/day for 18 months) showed a 70% reduction in the number of tumors eligible for surgical treatment. However, the same study also showed a tendency to relapse after cessation of treatment and a large number of
Conclusions

• The appearance of a numerous basal-cell carcinomas on a young subject, located on the photo-exposed areas and also on the non-photoexposed areas, evokes a syndrome with genetic determinism, which may be Gorlin syndrome.

• Repeated excision of tumors leaves unsightly scars; therefore, at least for superficial lesions, non-surgical methods should be used to conserve as much as possible of the skin surface.

• in Gorlin’s syndrome, B basal cell carcinomas first appear in childhood and adolescence, but continue to develop throughout life, so regular controls and rigorous, early and continuous photoprotection are needed.

• Complex clinical manifestations call for a multi-disciplinary approach to these cases involving the dermatologist, neurologist, endocrinologist, orofacial surgeon. Genetic counseling is mandatory.

Conflicts of interest: none declared.

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Patient consent obtained.

Bibliography


