



Gorlin-Goltz syndrome

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Abstract

Gorlin-Goltz syndrome is a rare multisystemic disease inherited in an autosomal dominant pattern. It is characterized by numerous basal cell carcinoma of the skin, jaw cysts, and skeletal anomalies such as frontal bossing, vertebral anomalies, palmoplantar pits, and falx cerebri calcification. There is a tendency to tumors including medulloblastoma, fibroma, rabdomyoma, leiomyosarcoma etc.. The diagnosis is based on major and minor clinical and radiologic criteria. Early diagnosis and treatment are of utmost importance in reducing the severity of long-term sequelae of this syndrome. In this article, we present a 15-year-old boy who was admitted to our clinic with brown-black papules and plaques on his scalp and was thought to have Gorlin-Goltz syndrome. He had a history of medulloblastoma that was treated with surgical resection followed by cranial radiotherapy and unilateral retinoblastoma. We present this case, because association of Gorlin-Goltz syndrome and retinoblastoma has not been described previously in the literature and we aimed to draw attention to radiation-induced basal cell carcinomas.

Keywords: Basal cell carcinoma, Gorlin-Goltz syndrome, medulloblastoma, retinoblastoma

Introduction

Gorlin-Goltz syndrome is a rare genetic disease with autosomal dominant inheritance that leads to multi-organ disorder. Its prevalence is approximately 1/50 000-150 000 though it varies by regional and ethnic distribution. The disease, which was reported in 1894 for the first time by Jarish and White, was subsequently labeled as Gorlin-Goltz syndrome because its signs and symptoms were collected by Gorlin and Goltz (1). The clinical findings that may be observed in this syndrome include odontogenic keratocysts in the jaw, which generally develop in the first 30 years of life, basal cell carcinomas (BCC) from early childhood, palmar and plantar pits, falx cerebri calcification, frontal bossing, macrocephaly, broad nasal bridge, mild mandibular prognathism, vertebral anomalies, cleft palate, cleft lip, highly arched

palate, eye anomalies, and tumors including medulloblastoma and fibromas in the ovaries and heart (2). In this disease, which shows high penetrance and variable expressivity, the “protein patched homolog” (PTCH) gene mutation is held responsible for the etiology (1). In one third of subjects, the disease occurs as de novo mutations. A mutation in the PTCH gene, which is located in chromosome 9q22.3, leads to overexpression of the “sonic hedgehog” (SHH) pathway and as a result, malignancies and BCC occur (2). Six major criteria and six minor criteria were specified in the diagnosis. The presence of two major or one major and two minor criteria is required to make the diagnosis (Table 1). The major criteria include more than two BCC or occurrence of BCC below the age of 20 years. In patients aged above 20 years, the frequency of BCC is 51.4%, whereas it is 71.7% in patients aged above 40 years. Thus, BCC

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occurring in childhood is notable and should raise suspicion in terms of accompanying syndromes (3).

Retinoblastoma is the most common malignant intra-ocular tumor of childhood, most commonly observed between the ages of one and three years (4). The association of retinoblastoma and Gorlin-Goltz syndrome, which was found in the history of our patient, has not been reported in the literature before as far as we know. In our patient who had a history of basal cell carcinoma associated with medulloblastoma and retinoblastoma, three tumors were found in childhood. In a case of early-onset Gorlin-Goltz syndrome reported recently in the literature, a total of three tumors including BCC, fetal rhabdomyoma, and an adnexial tumor-like skin tumor, were found in a 22-month-old female patient (5).

In this case presentation, we report our patient who was diagnosed as having Gorlin-Goltz syndrome with clinical, histopathologic, and radiologic findings because of the rarity of the syndrome, and we aimed to draw attention to its association with retinoblastoma and to BCCs that may develop following radiotherapy.

Case

A 15-year-old male patient presented to our Dermatology Clinic with numerous brown protuberances. In his history, it was learned that he underwent surgery and received radiotherapy because of medulloblastoma at the age of three years, enucleation was performed in the right eye because of retinoblastoma at the age of 10 years, he underwent surgery because of a BCC located in the right palpebra at the same age, and was recently found to have mandibular and maxillar cysts on X-rays obtained owing to dental deformations. The family history revealed no pathology except for recurrent BCC in the mother. On physical examination, the patient's height was found as 151 cm (<3 percentile) and his weight was 52 kg (3-10 percentile). Macrocephaly, bitemporal flattening, frontal prominence, high arched eyebrows, hypertelorism, broad nasal bridge, highly arched palate, and dental deformations were present (Picture 1). No pathologic finding was observed in the palmoplantar areas. In his dermatologic examination, numerous brown-black, well-circumscribed, domed papules and plaques with diameters ranging between 4 and 8 mm were found in the frontal, temporal, and parietal areas (Picture 2). Other system examinations were normal.

On histopathologic examination of a full-thickness biopsy specimen obtained from the patient's lesion, a

Table 1. Diagnostic criteria of Gorlin-Goltz syndrome

| Major Criteria | |
|----------------|---|
| 1. | Presence of more than two BCCs or a history of one BCC below the age of 20 years |
| 2. | Odontogenic keratocysts of the jaw (confirmed histologically) |
| 3. | Three or more palmoplantar pits |
| 4. | Falx cerebri calcification |
| 5. | Bifid or combined costae |
| 6. | Presence of a diagnosis of Gorlin-Goltz syndrome in a first-degree relative |
| Minor Criteria | |
| 1. | Macrocephaly |
| 2. | Congenital anomalies, cleft lip-palate, frontal bossing, coarse face, hypertelorism |
| 3. | Skeletal anomalies; Sprengel deformity, pectus deformity, syndactylia |
| 4. | Radiologic anomalies; cella turcica bridging, vertebral anomalies including hemivertebra and combined vertebral corpi, flame-like lucency on hand and foot X-rays |
| 5. | Ovarian fibroma |
| 6. | Medulloblastoma |

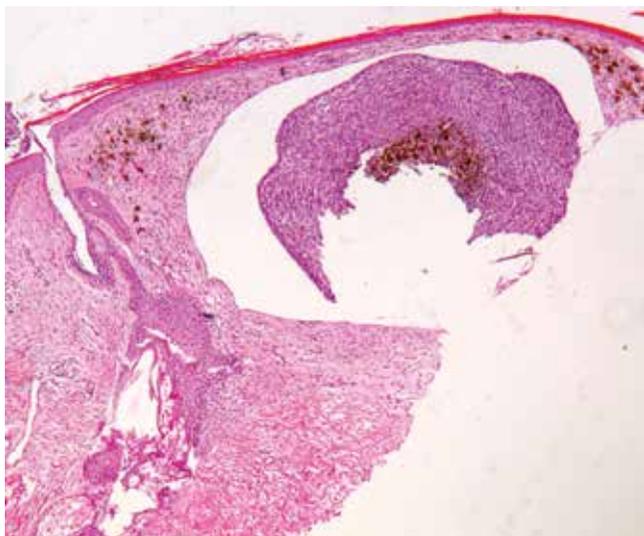
BCC: basal cell carcinoma



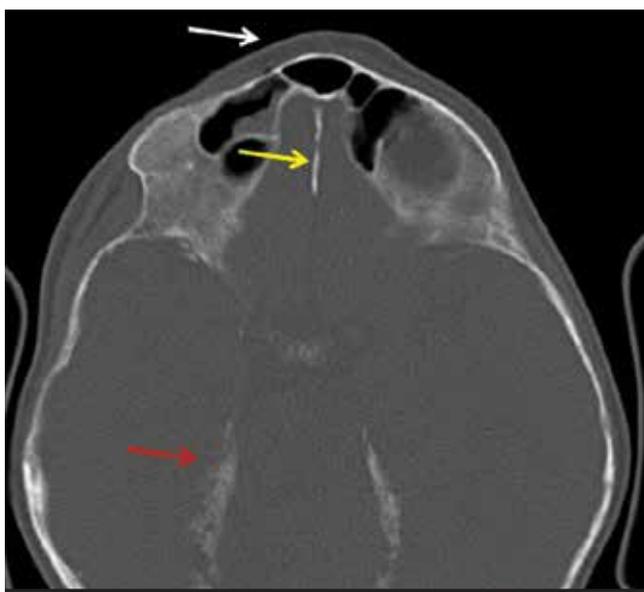
Picture 1. Malformations in the teeth



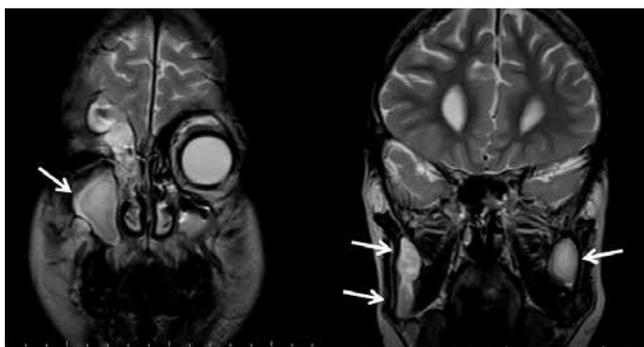
Picture 2. Brown-black papules and plaques in the fronto-temporal areas



Picture 3. Tumoral structure composed of basaloid cells, palisade arrangement in the periphery, melanin accumulation and retraction artifact, H&E x50



Picture 4. Frontal bossing (white arrow) and calcifications in the interhemispheric falx (yellow arrow) and tentorium cerebelli (red arrow) on the axial computerized tomography section



Picture 5. Numerous odontogenic keratocysts (white arrow) on sections of coronal T2A magnetic resonance imaging

tumoral structure composed of basaloid cells was observed in the dermis and the cells showed palisade arrangement in the edges. Additionally, melanin accumulation and retraction residues were found (Picture 3). The pathologic findings were compatible with BCC. Routine biochemistry tests, complete blood count, thyroid function tests, parathormone, prolactin, follicle-stimulating hormone, luteinizing hormone, testosterone, and cortisol levels were within the normal limits. A cardiologic examination, electrocardiography, and echocardiography revealed no pathology. Cranial computerized tomography (CT) revealed frontal bossing; and basal ganglia, falx cerebri, and tentorium cerebelli calcifications (Picture 4). Coronal magnetic resonance imaging (MRI) revealed keratodontogenic cysts (Picture 5). Costa anomalies were not found on vertebral radiographs and an appearance compatible with spina bifida occulta was found in the T1 processus spinosus. Hand-foot X-rays were normal. The patient was diagnosed as having Gorlin-Goltz syndrome with numerous BCC, falx cerebri calcifications, maxillar and mandibular keratodontogenic cysts, frontal bossing, highly arched palate, broad nasal bridge, hypertelorism, and a history of medulloblastoma. Topical imiquimod treatment was initiated for the multiple BCCs. Personal information related with the patient and his family has not been shared in the article and consent was obtained from the family.

Discussion

Our patient was diagnosed as having Gorlin-Goltz syndrome with numerous BCCs and falx cerebri calcifications, which are among the major criteria, and macrocephaly, frontal bossing, hypertelorism, and presence of medullablastoma, which are among the minor criteria. Panoramic X-ray of the teeth revealed multiple cysts and MRI revealed odontogenic keratocysts, but a histologic evaluation could not be made because consent could not be obtained.

The most prominent tumor in Gorlin-Goltz syndrome is BCC; therefore, this syndrome is also called nevoid BCC syndrome. Basal cell carcinomas show an increase with advanced age (3). It generally occurs between adolescence and the age of 35 years. Occurrence in childhood indicates that the syndrome may have a severe course. Basal cell carcinomas have an aggressive course after adolescence and may show local invasion. The sizes and number of carcinomas show variance in different patients. Clinically, the skin is observed in different forms ranging from papules to ulcerated plaques and may be confused with nevus, acrochordon, and heman-

gioma (1, 2). The lesions are most commonly observed around the eye, on the palpebrae, cheeks, and upper lips (6). In our case, BCC was observed before adolescence and lesions started from the frontal regions and palpebral, and subsequently extended to the parietal and temporal regions.

Odontogenic keratocysts may be observed with a rate reaching up to 75% in patients with Gorlin-Goltz syndrome. They are generally found incidentally as a result of radiologic examinations and may be the first sign of the syndrome. Recurrence rates reaching up to 60% have been reported after treatment (6). Falc calcification is observed in 65% of patients and this calcification is not found in early childhood (3). Medulloblastoma is observed in 5-10% of patients and it usually occurs in the first two years of life. In the general population, it peaks at the age of 7-8 years. Therefore, early-onset medulloblastoma should raise suspicion in terms of Gorlin-Goltz syndrome. Radiotherapy administered for medulloblastoma induces BCCs in the area of radiation, as in our patient (2). Palmoplantar pits are observed in 50-65% of patients. They have a diameter of 2-3 mm and a depth of 1-3 mm. They occur on the palms and soles as a result of partial or complete loss of dense keratin. They generally occur in the second decade and increase in number as age advances (1, 6). Palmoplantar pits were not observed in our patient. Skeletal, genital, ophthalmic, and cardiac anomalies may be observed in patients (6). Tendency to tumors (brain tumors including mainly medulloblastoma, ovarian, and cardiac fibroma, rhabdomyoma, leiomyoma, amenoblastoma, seminoma, surrenal tumors, Hodgkin's lymphoma, non-Hodgkin's lymphoma) may be observed (2). Our patient had a history of operated retinoblastoma for which an association in Gorlin-Goltz syndrome has not previously been reported in the literature. Retinoblastoma is an embryonic neoplasia originating from the retina that occurs as a result of mutations in the RB1 gene, which is a tumor-suppressor gene located in the 13q14 region. Ninety percent occur before the age of five years. Retinoblastoma occurs sporadically or by inheritance depending on genetic properties. Hereditary retinoblastoma is observed in one third of all cases. The tumors occur in both eyes with a rate of 85%. Hereditary retinoblastoma shows autosomal dominant inheritance with 90% clinical penetrance. In sporadic retinoblastoma, the tumor generally develops in one eye as a single focus. However, hereditary mutations may be found in 15% of unilateral retinoblastomas (4, 7). Unilateral retinoblastoma in our patient suggested sporadic development. Secondary tumors de-

veloping after cranial radiotherapy have been reported (8). However, to the best of our knowledge, a case of retinoblastoma developing after radiotherapy has not been reported in the literature. Therefore, it was difficult to differentiate if the retinoblastoma in our patient was a tumor that developed secondary to radiation or was related with tendency to tumor, which is observed in this syndrome.

In the differential diagnosis, Bazex-Dupre-Christol syndrome, Muir-Torre syndrome, Rombo syndrome, multiple papular trichoepitheliomata, and xeroderma pigmentosum should be considered. Bazex-Dupre-Christol syndrome is characterized by follicular atrophoderma, hypotrichosis, and hypohydrosis in addition to multiple BCCs. Odontogenic cysts, skeletal anomalies, neurologic and radiologic anomalies, palmoplantar pitting, which are found in Gorlin-Goltz syndrome, are not observed in Bazex-Dupre-Christol syndrome. Muir-Torre syndrome is a genodermatosis in which multiple sebaceous adenomas, multiple keratoakantomas, and gastrointestinal malignancies, which are not observed in Gorlin-Goltz syndrome, are observed in association. Rombo syndrome manifests with vermiculate atrophoderma in the face, hypotrichosis, cyanotic erythema in the hands and feet, multiple BCCs, and trichoepitheliomata (9).

A multi-center approach is necessary in the diagnosis and treatment in patients with Gorlin-Goltz syndrome because different clinical attitudes may be observed in a life time. Genetic consultancy is important and a definite diagnosis can be made with a gene mutation test (2). Early diagnosis may allow patients to receive conservative treatment instead of complex therapies and render other family members aware of potential genetic risks (6). These patients should absolutely be protected from the sun because ultraviolet rays increase the risk of BCC. Multiple BCC may develop in patients who previously received radiotherapy because of medulloblastoma. These scalp tumors may show an aggressive course and early diagnosis is essential. Therefore, radiotherapy should be avoided as much as possible (2). The classic treatment for basal cell carcinomas is surgical excision, but CO₂ laser, electrocauterization, cryotherapy, and photodynamic therapy may be used when too many lesions are present and when recurrence occurs. In addition, imiquimod cream 5%, topical 5-fluorouracil and vismodegib in locally-advanced and metastatic forms are other treatment options (9, 10). We initiated imiquimod cream 5% three days a week in our patient, observed regression in the lesions after one month, and still continue this treatment.

Family members of patients with Gorlin-Goltz syndrome should be screened in terms of morbidity. Clinical findings related with this syndrome were not found in the first-degree relatives of our patient, whereas BCC was found only in the mother. However, the clinical and phenotypic findings of the mother did not suggest Gorlin-Goltz syndrome.

In conclusion, patients with Gorlin-Goltz syndrome should be informed about the possibility of BCC, which may be induced by cranial radiotherapy, protected from the sun, and be regularly followed up by dermatology, neurology, and dentistry departments.

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