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Background: Basal cell carcinoma of the skin is the most common malignant cancer worldwide. It is characterized by a low grade of malignancy and it gives very rare metastases to lymph nodes or internal organs. It is also a typical symptom of Gorlin syndrome, which is characterized by multiple basal cell carcinomas, calcifications in the central nervous system and palmar or plantar pits. Mutations in the PTCH gene are responsible for the development of this syndrome, and its inheritance is autosomal dominant. The estimated frequency of Gorlin syndrome is 1/57 000 – 256 000.
Case report: The authors present a case of a 34-year-old man with Gorlin syndrome and metastasis of basal cell carcinoma of the face to the submandibular lymph node. Though there are some reports of high radiosensitivity in patients with this syndrome, in this case postoperative radiation treatment was used. Inter- and post-treatment observation did not confirm an early or late postradiation reaction higher than score 2 on the EORTC/RTOG scale. Within 20 months after the treatment no new malignant lesions of the irradiated skin were noticed.
Discussion: In the literature there are fewer than 300 cases of basal cell carcinoma metastases, of which only 3 concern patients with Gorlin syndrome. On the basis of the case presented the authors suggest that early and late radiation toxicity in Gorlin syndrome patients is not as high as previously believed.

Key words: Gorlin syndrome, basal cell carcinoma, metastasis.

Metastasis of basal cell carcinoma to lymph nodes in a patient with Gorlin syndrome – case report and literature review

Tomasz Bajon[1], Ewa Adamiak[1], Maciej Krawczyński[2]

[1]Greater Poland Cancer Centre, Poznan
[2]Department of Medical Genetics, University of Medical Sciences, Poznań

Background

Basal cell carcinoma (BCC) is the most common invasive cancer of the skin and affects mostly people excessively exposed to ultraviolet light. The incidence of this cancer increases with age and is higher in Caucasians. This tumour is characterized by a low degree of malignancy, slow growth, a typical location on skin exposed to the sun (face, neck) and extremely rare metastases to the lymph nodes or internal organs [1].

There is also a genetically determined tendency to develop this cancer, first described in 1960 by Gorlin and Goltz in *The New England Journal of Medicine* [2]. The syndrome is sometimes called the fifth phakomatosis, Gorlin or Gorlin-Goltz syndrome, and in English literature nevoid basal cell carcinoma syndrome (NBCCS). The main features of this syndrome is the presence of multiple BCC in the early decades of life (< 30 years of age), frequent occurrence on skin protected from sunlight (back, buttocks), and odontogenic keratocysts of the jaw, calcification of the falx cerebri and anomalies of the ribs [3]. Criteria for clinical diagnosis were described in 1997 by Kimonis *et al.* [4]. The estimated prevalence varies from 1/57 000 to 1/256 000, with a male-to-female ratio of 1 : 1. The lowest incidence of the disease is described in Italy [5]. Gorlin syndrome is caused by mutations in the PTCH1 tumour suppressor gene, whose locus was mapped to the long arm of chromosome 9 (q22.3-q31) [3].

In the literature there are fewer than 300 reports of BCC metastases [6] and only 3 of them concern patients with Gorlin syndrome [7-9].

Case report

A 34-year-old male was referred to the Department of Radiotherapy with a diagnosis of BCC of the facial skin after the surgical removal of a tumour and metastatic lymph node.

The patient was born after an uncomplicated pregnancy and uneventful delivery. He was the first child of unrelated parents of normal stature, who were generally healthy and not exposed to teratogenic or mutagenic factors. The patient has two daughters – the elder has multiple pigmented naevi. Previously in the family there has not been diagnosed any genetically determined diseases.

Since 17 years of age the patient has been repeatedly treated with surgery and cryosurgery for BCC of the face (especially around the nose and eyelids), back and buttocks, and since 24 years of age he has been operated on for odontogenic keratocysts of the jaw and mandible three times. At the age of 29 he underwent surgical excision of nodular lesions on the right and left foot. Histological examination identified these lesions as dermatofibroma.

At the age of 33 there were diagnosed tumourous lesions of the nose skin and enlarged lymph node in the left submandibular area, which was removed surgically. Postoperative histological examination showed BCC with metastasis to one lymph node.

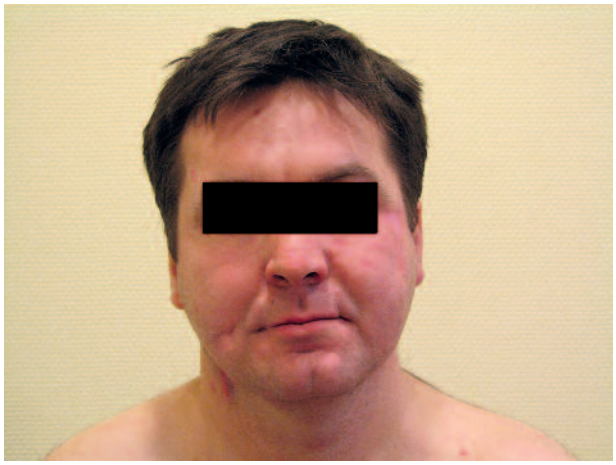

Fig. 1. Broad face and nasal bridge and cicatrices after excisions of multiple basal cell carcinomas in patient with Gorlin syndrome

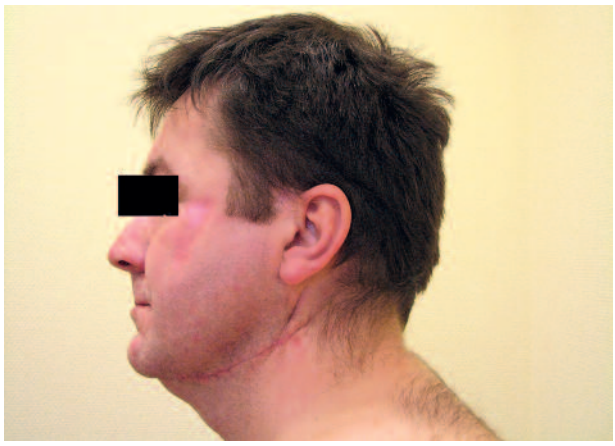

Fig. 2. Prominent jaw and cicatrices after excisions of multiple basal cell carcinomas and submandibular lymph nodes in patient with Gorlin syndrome

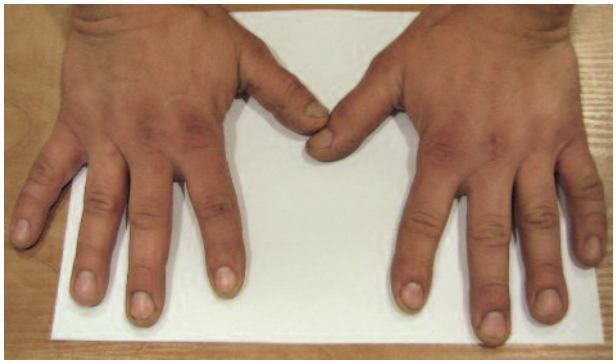

Fig. 3. Shortening of distal phalanges of thumbs in patient with Gorlin syndrome

A physical examination in our department found multiple pigmented naevi on the skin of the whole body, and scars from previous operations. There was also found a broad face with temporal bossing and a broad nasal bridge (Fig. 1), a prominent mandible (Fig. 2) and shortening of the distal phalanges of the thumbs (Fig. 3). Genetic consultation confirmed the diagnosis of Gorlin syndrome.

Because of the metastasis to the lymph node it was decided to irradiate the lymphatic nodes of the neck with 6 MV photons to the dose of 50 Gy and 60 Gy on the right and left side respectively. Treatment was planned with 7-field coplanar IMRT technique based on computed tomography images. Irradiation was performed on a Clinac linear accelerator. Due to reports of increased sensitivity to ionizing radiation in patients with Gorlin syndrome, this patient was subjected to strict medical supervision during the treatment. There was noticed only moderate toxicity of the skin on the neck and a small xerostomia (grade 2 and 1 respectively according to the EORTC/RTOG scale). Late treatment toxicity consisted of mild xerostomia (also grade 1 according to the EORTC/RTOG scale). 20 months after irradiation there were not noticed any new lesions on the skin covered by radiotherapy. However, there were diagnosed new BCC in the skin of the nose. Currently, the patient remains under the care of oncology and genetic counselling.

Discussion

The phenotype of Gorlin syndrome is characterized by high variability. The main clinical symptom is multiple basal cell carcinoma. In addition, disorders may concern almost all systems: central nervous, vascular, respiratory, genitourinary, digestive and musculoskeletal system.

BCC in patients with Gorlin syndrome develops between puberty and 35 years of age [10], but the earliest reported lesions were diagnosed in 3-4-year-old individuals [11, 12]. The average age of onset is 25 years of age. Only 40% of black patients manifest skin cancer, while in Caucasians it develops in up to 90% of cases [3]. The number of neoplastic lesions of the skin varies from a few to about one thousand. BCC in Gorlin syndrome occurs particularly frequently in the skin area, which is typical for sporadic BCC. However, characteristic is the coexistence of skin cancer in the area protected from sunlight, such as the back and buttocks. In the literature there is also described vulvar basal cell carcinoma [13]. Histopathology and biology of these lesions are similar to those of sporadic BCC. Metastases are extremely rarely observed. The literature includes only about 300 cases of metastatic BCC, of which only three relate to patients with Gorlin syndrome. The most common sites of metastases are regional lymph nodes, lungs, bones and bone marrow. Metastases reported in patients with Gorlin syndrome were located in the bone marrow [9] and lung [8]. The case described by Winkler and Guyuron [7] concerned cancer spread to the pleura, diaphragm and heart. Due to the small number of cases of metastases, there is no clear indication in the literature regarding adjuvant therapy for patients with metastatic BCC. The originally used chemotherapy based on bleomycin, vincristine and methotrexate or prednisone was ineffective [15]. However, a rapid response was described in patients with lung metastases after treatment with cisplatin in combination with paclitaxel [16]. In cases of single metastases to the regional lymph nodes a good response to treatment was also seen after radiotherapy [17]. The average overall survival for patients with metastatic BCC is estimated at 8 months [18] and only in the case of metastases to regional lymph nodes

Table 1. Clinical diagnostic criteria of Gorlin syndrome according to Kimonis

Major criteria	Minor criteria
Multiple BCCs (> 2) or one under 20 years of age	Macrocephaly determined after adjustment for height
Odontogenic keratocysts of the jaws proven by histopathology	Congenital malformations: Cleft lip or palate Temporal bossing "coarse face" hypertelorism
Palmar or plantar pits (more than 2)	Skeletal abnormalities: syndactyly of the digits Sprengel deformity pectus deformity
Bilamellar calcifications of the falx cerebri	Radiological abnormalities: bridging of the sella turcica vertebral anomalies (hemivertebrae, fusion or elongation of the vertebral bodies) flame-shaped lucencies of the hands or feet
Rib anomalies: bifid ribs fused ribs markedly splayed ribs	Ovarian fibroma
First degree relatives with Gorlin syndrome	Medulloblastoma

is it significantly longer at 3.6 years [15]. Due to the lack of clear data on the optimal treatment of metastatic BCC, in the presented case the authors decided to irradiate neck lymph nodes. Despite the reports of the possibility of inducing secondary skin cancers in the irradiated field in patients with Gorlin syndrome, in the presented case there was not observed any new BCC in the area of radiotherapy during the 20-month follow-up.

In addition to BCC in Gorlin syndrome patients there were also described a number of skin symptoms: palmar and plantar pits (30 to 65% of cases), multiple naevi (in 30-50% of patients before 20 years of age), nodular or patch lesions, epidermal cysts on the trunk and extremities (50% of cases) [3]. In the described case multiple skin naevi have been noted since childhood and multiple BCC of the face, neck, hands, back and buttocks. The other mentioned skin lesions were not observed. The presence of skeletal abnormalities may be helpful in the diagnosis of Gorlin syndrome. The most frequently reported anomalies are odontogenic keratocysts of the jaw, which occur in up to 90% of cases [5]. There were often reported defects of the ribs (30 to 60% of patients) such as: bifid, fused, splayed or missing ribs [5]. Among the abnormalities of the vertebral column the dominant disorder is spina bifida (60%) [14] and scoliosis in 40% of cases [5]. Characteristic is also an abnormal skull configuration – frontal, biparietal or temporal bossing occurs in about 70% of patients [5]. In the above presented case the skeletal symptoms were limited to recurrent odontogenic keratocysts of the jaw and mandible.

Typical abnormalities for Gorlin syndrome in the central nervous system include: calcification of the falx cerebri (70-85% of cases) [5], calcification of the tentorium cerebelli (20-40%) [5] and the diaphragma sellae (60-80%) [19]. These signs do not manifest clinically, but are an important part of the diagnosis. In a large radiological study by Lambrecht *et al.*, the lamellar calcification of the falx cerebri was considered as a pathognomonic symptom of Gorlin syndrome [20]. There is also reported increased occurrence of medulloblastoma in patients with Gorlin syndrome. The estimated prevalence of this cancer is 1-2% of all cases [11] and usually it is diagnosed at an earlier age than the sporadic tumour (1-2 years old), more frequently in males. O'Malley and colleagues have described multiple BCC in the skin area irradiated in childhood during treatment for medulloblastoma [21]; hence the authors suggest that radiotherapy should be avoided in Gorlin syndrome patients.

Multiple cutaneous neoplasia has led to suggestions that Gorlin syndrome may be associated with a higher incidence of other cancers. A literature review showed more frequent incidence of brain tumours such as astrocytoma, meningioma, craniopharyngioma and oligodendroglioma [3], as well as Hodgkin and non-Hodgkin lymphoma [22]. There is also described significantly higher incidence of fibroids of ovary (25-50% of patients) [11] and heart, particularly the left ventricle [23], non-cancerous ovarian cysts [23], cysts of lung [3], eyeball and optic nerves [11].

Studies on large groups of patients with Gorlin syndrome indicated a much more frequent incidence of eye disorders (estimated average frequency is 20%) than in the general population. Hyperopia is diagnosed in as many as 70% of patients. Slightly less frequent are: exophthalmos, nystagmus, convergent strabismus, congenital cataract, and the above-mentioned cysts of the iris and optic nerve [5, 11].

The phenotype of Gorlin syndrome is caused by mutations of the PTCH1 gene, which was first isolated in 1996 simultaneously in the United States and Australia [24, 25].

This gene was mapped to the long arm of chromosome 9 in the region 22.3-31. The PTCH1 gene belongs to the group of tumour suppressor genes and its function is to control growth and development of normal tissues [3]. The gene product is a transmembrane glycoprotein composed of 1447 amino acids with 12 transmembrane domains and two extracellular loops to bind with ligand – the sonic hedgehog homolog (SHH) protein which is involved in organogenesis. Mutations in the PTCH1 coding parts of the extracellular domains result in no binding to the SHH and the absence of cell division inhibition [26]. PTCH1 mutations are transmitted in an autosomal dominant manner with high penetrance and variable expressivity [27].

Currently in Poland there are not commercially available molecular tests to detect mutations in the PTCH1 gene. Only a few laboratories perform such tests worldwide. Diagnosis of Gorlin syndrome is based on clinical criteria established by Kimonis *et al*. [4] (Table 1). For confirmation of the disease, it is necessary to meet two major or one major and one minor criteria. In the described case finding multiple BCC before 20 years of age and odontogenic keratocysts of the jaw allowed Gorlin syndrome to be diagnosed. Due to the non-specificity of most symptoms in patients without family history of Gorlin syndrome the diagnosis is made when multiple BCC appear (usually in the third decade of life). Early clinical diagnosis is also very difficult in the offspring of individuals with Gorlin syndrome. Indications for molecular diagnostics include only offspring with medulloblastoma for which radiotherapy is considered.

Conclusions

The differential diagnosis with Gorlin syndrome should be performed in all cases of multiple basal cell carcinoma. Criteria for clinical diagnosis are based on a precise physical and radiological examination, which are available in all medical centres.

Despite the few reports about metastatic basal cell carcinoma, such a possibility should always be taken into account during the examination.

The presented case suggests that both early and late toxicity of radiotherapy for patients with Gorlin syndrome are not significantly greater than in the general population.

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Address for correspondence

Tomasz Bajon
Greater Poland Cancer Center
Garbary 15
61-866 Poznan
e-mail: tomasz.bajon@wco.pl