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Late Onset of Multiple Basal Cell Carcinomas in a Patient with Gorlin-Goltz Syndrome Previously Treated for Hodgkin's Lymphoma

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Abstract

Development of multiple basal cell carcinomas is commonly associated with immunosuppression or genetic disorders. The latter include congenital diseases such as Gorlin-Goltz syndrome, also known as nevoid basal cell carcinoma syndrome, or basal cell nevus syndrome. It is an autosomal dominant inherited disorder characterized by the development of multiple basal cell carcinomas at an early age and a variable combination of other phenotypic abnormalities that result in multiple organ involvement. The susceptibility gene was mapped to chromosome 9q22.3–3.1. Like other tumor suppressor genes, PTCH1 gene shows frequent deletion and a whole variety of other mutations. A high rate of new mutations and the variable expressivity of the condition make full diagnostic assessment difficult, especially in mildly affected individuals with no family history of the condition. It has been postulated that the presence of two major features or one major feature with two minor features classify a condition as Gorlin-Goltz syndrome.

We present a 42-year-old male patient with a 6-year-long history of multiple smooth and/or rough skin patches and plaques on the back and shoulders. Some of the lesions gradually progressed and increased in number without any sensation. Dot-like, flesh-colored and brownish pits were found on the patient's palms. Further investigations revealed many musculoskeletal and craniofacial congenital abnormalities such as pectus excavatum, frontal and parietal bossing, exotropia, ectopic teeth (impacted tooth), mandibular hyperplasia, broad nose. Histopathological examination by light microscopy of biopsies taken from the nodular and patchy skin lesions showed findings typical for basal cell carcinoma. Family history revealed no members with similar health disorders.

The patient was treated for Hodgkin's lymphoma with chemotherapy and radiation therapy 20 years before, with good therapeutic results, and no additional treatment was administered in the last ten years.

The treatment for multiple basal cell carcinomas included: 5% imiquimod cream, 5 days a week, for 12 weeks. After 12 weeks of treatment, the nodular lesion and all the superficial lesions cleared. One month later the lesions disappeared completely without any residual signs. The patient was advised to use adequate photoprotection and to avoid future uncontrolled sun exposure. On follow-up visits during a three year period, no recurrent or new lesions indicative for BCC were seen.

This is a case with late-onset multiple BCC in a patient with Gorlin-Goltz syndrome and a history of prior Hodgkin's lymphoma. To the best of our knowledge hitherto only two cases of Hodgkin's lymphoma in patients with Gorlin-Goltz syndrome have been reported in the literature. We also present therapeutic results of topical imiquimod for multiple basal cell carcinomas with no recurrent lesions over a three-year follow-up.

Key words

Basal Cell Nevus Syndrome; Carcinoma, Basal Cell; Neoplasms, Multiple Primary; Comorbidity; Hodgkin Disease; Diagnosis; Aminoquinolines; Treatment Outcome

Basal cell carcinoma (BCC) is the most common skin cancer, known for its local malignancy, relatively slow growth, rare metastases and overall good prognosis *quo ad vitam*. In patients with multiple BCC, immunosuppression or genetic disorders need to be considered. The latter include

congenital diseases such as Gorlin-Goltz syndrome, Bazex-Dupré-Christol syndrome, Rombo syndrome, Oley syndrome and xeroderma pigmentosum (1, 2, 3).

Gorlin-Goltz syndrome (GGS), also known as nevoid basal cell carcinoma syndrome (NBCCS), or basal cell nevus syndrome, is an autosomal dominant hereditary cancer syndrome which includes development of multiple basal cell carcinomas (BCCs) at an early age and a variable combination of other phenotypic abnormalities that result in multiple organ involvement. The NBCCS gene was mapped to chromosome 9q22.3–3.1 during the identification of mutations in the patched (PTCH1) gene of patients with NBCCS. Like other tumor suppressor genes, PTCH1 gene shows frequent deletion and a whole variety of other mutations. A considerable part (more than one third) of patients are found to have new mutations (2, 4, 5). A high rate of new mutations and the variable expressivity of the condition makes full diagnostic assessment difficult, especially in mildly affected individuals with no family history of the condition.

The clinical features of this syndrome involve a whole variety of organs and systems including the skin, skeleton, neural, dental and genital structures, eyes, etc. Thus far, distinctive symptoms and signs have been divided into major and minor criteria (2, 4, 6, 7). It has been postulated that the presence of two major features or one major feature with two minor features classify a condition as GGS (2, 8-10).

Major criteria

- More than 2 BCCs or 1 BCC in patients under the age of 20 years
- Odontogenic keratocysts of the jaw (histologically proven)
- Three or more palmar or plantar pits
- Bilamellar calcification of the falx cerebri
- Bifid, fused, or splayed ribs
- First-degree relative with GGS/NBCCS

Minor criteria

- Macrocephaly
- Congenital malformations - cleft lip/palate, frontal/temporoparietal bossing, coarse face, hypertelorism
- Skeletal abnormalities - Sprengel deformity, pectus excavatum/carinatum, syndactyly
- Radiologic abnormalities - bridging sella turcica, vertebral anomalies
- (hemivertebrae, fusion or elongation of the vertebral bodies), defects of the hands and feet, flame-shaped lucencies of the hands and the feet
- Ovarian fibroma/fibrosarcoma or medulloblastoma.

Besides the aforementioned clinical and radiologic categories, many different manifestations and symptoms have been reported in association with GGS:

Cutaneous anomalies: cutaneous dyskeratosis, keratotic papules, other benign dermal cysts and tumors, milia and comedones, palmar and plantar keratosis, dermal calcification.

Musculoskelet anomalies: polydactyly/oligodactyly, scoliosis/kyphosis, brachymetacarpalism, cervical ribs, absent ribs, flat feet, pelvic calcification, spina bifida, arachnodactyly, hallux valgus, cortical defects in long bones.

Craniofacial and orofacial anomalies: brachycephaly, choroid cysts (ventricles), prominent supra orbital ridge, broad nasal root, palatal or maxillary sinus fibroma, high-arched palate, prominent palatine ridges, malocclusion (maxillary hypoplasia, mandibular hyperplasia), fibrosarcoma of the jaws, impacted teeth and/or agenesis, ectopic teeth, ameloblastoma.

Ophthalmic anomalies: wide nasal bridge, strabismus/exotropia, dystopia canthorum, glaucoma, choroidal/optic nerve coloboma, congenital amaurosis/blindness/opaque cornea, ptosis, cataracts, chalazion.

Neurological anomalies: mental retardation, agenesis of corpus callosum, congenital hydrocephalus.

Sexual anomalies: hypogonadism, supernumerary nipple, cryptorchidism, calcified ovarian cysts, female distribution of the pubis hair, sparse growth of beard in men, gynecomastia.

Other anomalies: inguinal hernia, renal anomalies, lymphomesenteric cysts, left ventricular fibroma (neonatal), cardiac fibroma.

The BCC (most frequently on the face and sun-exposed parts of the body) is one of the most important criteria for setting the diagnosis of GGS.

BCCs can vary in number and develop in various stages of the disease, but most often appear between puberty and 35 years of age. The early onset of BCCs defines the disease and often lead to the underlying syndrome diagnosis (4).

There is no unified treatment for skin manifestations of GGS, particularly tumors, papules, plaques or patches. Generally, the treatment is surgical (curettage, electrodesiccation, excision, Mohs micrographic surgery, ablative laser therapy). Many studies have been carried out to assess the applicability and efficacy of alternative, less invasive treatment modalities such as cryotherapy, photodynamic therapy, and topical drugs such as 5-fluorouaracil and imiquimod.

We report a patient with a late onset of multiple BCCs and GGS, presenting with cutaneous, craniofacial, orofacial, ophthalmic and musculoskeletal symptoms. Our case also shows a successful treatment of BCCs in GGS with imiquimod.

Case report

A 42-year-old male patient was ademitted to the Department of Dermatology of the Medical University of Plovdiv, Bulgaria, with multiple smooth and/or rough skin patches and plaques that appeared and spread over his back and shoulders for the last 5-6 years. Some of the lesions gradually progressed and increased in number without any sensation, particularly a small tumor over the largest plaque which slowly developed in the last two years. The patient was treated for Hodgkin's lymphoma with chemotherapy and radiation therapy 20 years before, with good therapeutic results, and no additional treatment was administered in the last ten years. Family history revealed no data about similar health disorders among his relatives.

On examination, the patient presented with multiple smooth, scaly or partly crusty, slightly pigmented or reddish patches and plaques of varying sizes (5 – 35 mm) as well as keratotic papules on the back and shoulders (Figure 1). A nodular tumor (10x12 mm) with crusty and ulcerous center was found in the central part of the largest superficial plaque located in the thoracolumbar area (Figure 2). Pearly papules and comedones were seen in the periphery and on the surface of some lesions. Dot-

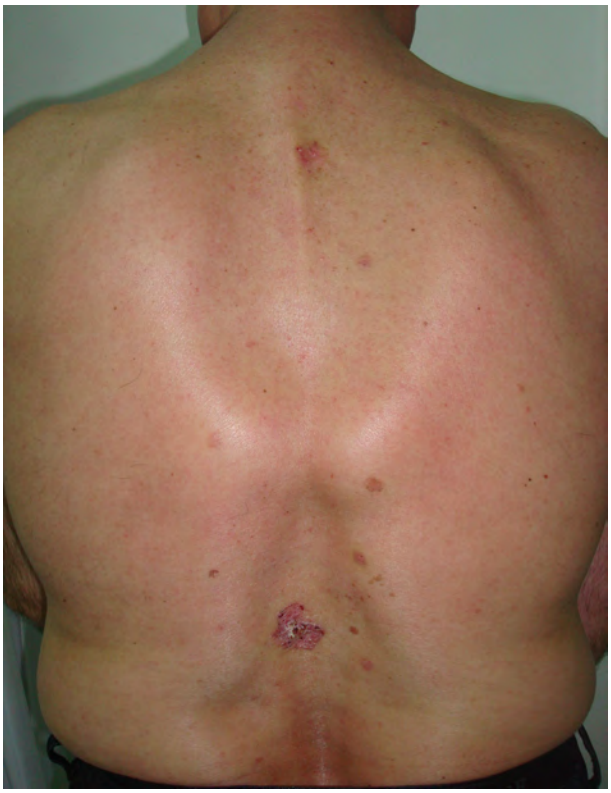

Figure 1. Multiple smooth, scaly or partly crusty, slightly pigmented or reddish patches and plaques over the back and shoulders; prominent paravertebral protuberances on the back

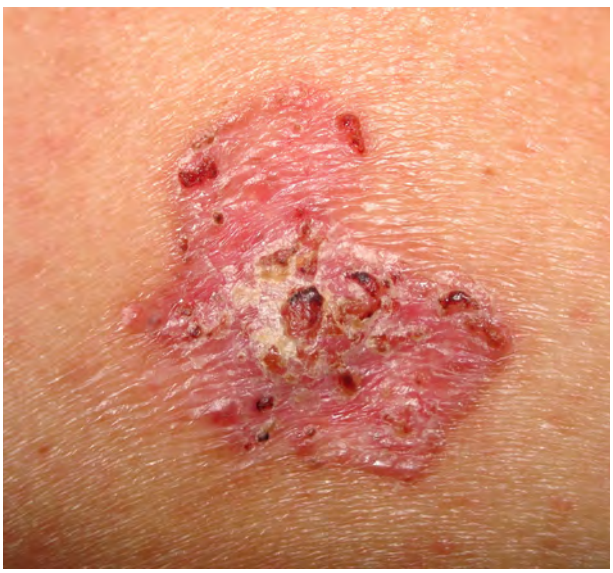

Figure 2. A solitary tumor (10x12 mm) with a crusty and ulcerous center in the central part of the largest superficial plaque in the thoracolumbar area

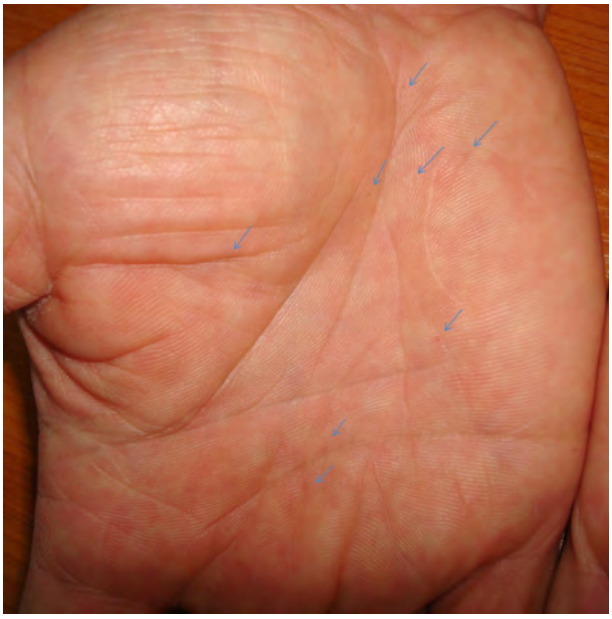

Figure 3. Dot-like, flesh-colored and brownish pits over the palms

like, flesh-colored and brownish pits were discovered on the palms (Figure 3).

Further investigations revealed musculoskeletal abnormalities such as pectus excavatum, back deformity (other than Sprengel's deformity), with prominent paravertebral protuberances (Figure 1) and thoracolumbar kyphosis (Figure 4). Craniofacial and congenital anomalies were also present: frontal and parietal bossing, exotropia, ectopic teeth (impacted tooth), mandibular hyperplasia, broad nose. A cardiologist disclosed aortic stenosis and regurgitation, and severe aortic valve calcification. The findings were consistent with post-radiation pericarditis and aortic valve changes probably induced by therapy on Hodgkin's lymphoma.

Histopathological examination by light microscopy of biopsy specimens, taken from the nodular tumor and patchy lesions, showed findings typical for BCCs. The superficial BCCs were small islets of basaloid tumor cells (Figure 5) limited against normal epithelium, in contact with papillary dermis, but without evident invasion into the deeper dermis. Nodular BCC was characterized by well circumscribed islets of uniform cells with large, hyperchromatic, oval nuclei and little cytoplasm, aligned in a palisade pattern at the periphery of nests and localized in the dermis, where interposed clefts between the cell nests were discovered as retraction artifact (Figure 6).

Figure 4. X-ray showing thoracolumbar kyphosis

Bearing in mind the preceding Hodgkin's lymphoma and the aggressive treatment the patient received, further hematological, biochemical and immunological laboratory tests were performed, but no abnormalities were found. Flow cytometry failed to identify immunosuppression, apart from an activated cell-mediated immunity: lymphocyte blood count 3.969 x 10^9/L (normal range 1 - 2.8 x 10^9/L), T-lymphocytes (CD3+) 2.155 x 10^9/L (normal range

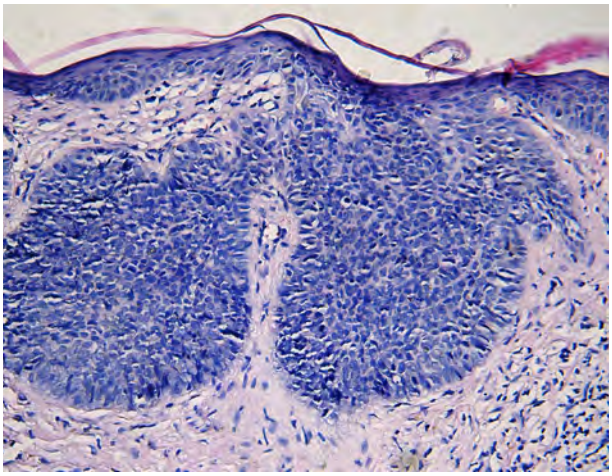

Figure 5. Histopathology examination of the biopsy taken from one of the patchy lesions demonstrated on light microscopy features of the superficial BCCs: small islets of basaloid tumor cells without evident invasion into the deeper dermis (HE x 40)

0.69 - 2.54 x 10^9/L), T- helper/inducer cells (CD3+ CD4+) 1.630 x 10^9/L (normal range 0.41 - 1.59 x 10^9/L), T suppressor/cytotoxic cells (CD3+ CD8+) 0.514 x 10^9/L (normal range 0.19 - 1.14 x 10^9/L), total B-cell count (CD19+) 0.599 x 10^9/L (normal range 0.09 - 0.66 x 10^9/L), NK cells (CD3+ CD56+) 1.143 x 10^9/L (normal range 0.09 - 0.6 x 10^9/L), CD4/CD8 index 3.17 (normal range 0.9 - 3.6).

Multiple BCCs were treated with topical: 5% imiquimod cream, 5 days a week, for 12 weeks. The nodular lesion was preliminarily treated with cautery/electrodesiccation. Our patient's compliance was good; the treatment was well-tolerated, and only a mild erythema was found in the treated areas. After 12 weeks of treatment the nodular lesion and all the superficial lesions cleared. One month later, the lesion disappeared completely without any residual signs. Biopsy from the site of the previous nodular tumor and the specimen from one of the other superficial lesions, taken one month after discontinuing the therapy, showed a histological eradication of the malignant structure and a process of scarring with fibroelastic tissue formation and reduction in cellularity.

The patient was advised to use adequate skin photoprotection and to avoid future uncontrolled sun exposure. On follow-up visits during a three year period, no recurrent or new lesions indicative for BCC were seen.

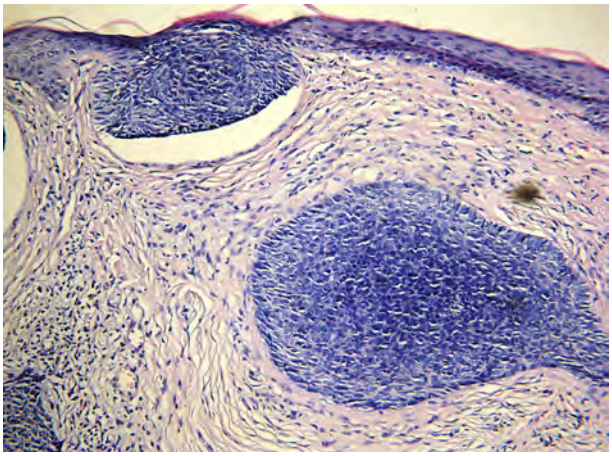

Figure 6. Histopathology examination of biopsy specimens taken from the nodular tumor revealed marked circumscribed nodular islets of uniform cells with large, hyperchromatic, oval nuclei and little cytoplasm, aligned in a palisade pattern at the periphery of the nests and localized in the dermis (HE x 100)

Discussion

The GGS, described by R. Gorlin and R. Goltz in 1960 (11) as an association of basal cell epithelioma, jaw cyst and bifid ribs, was earlier described, partially and independently, by W. Jarisch (12) and J. C. White (13) in 1894, then by G. W. Binkley and H. H. Johnson in 1951 (14).

Later on, many case reports added new characteristics to the primary description of this congenital disorder with a wide variety of basic manifestations (15-19).

Besides NBCCS and basal cell nevus syndrome, there were quite a number of other terms (e.g., nevus epitheliomatodes multiplex; nevoid basal-cell epithelioma, jaw cysts and bifid rib syndrome, etc.) given to GGS, each indicating particular features found in an individual or a group of patients (2, 20).

BCCs represent one of the major clinical problems of this syndrome due to their multitude, wide distribution and early invasion of deep structures, notwithstanding any particular predilection for sun exposed areas. Apparently, clinicians and investigators have been concerned with various features exhibited in this syndrome (4, 8, 21).

In our case, we found two major (multiple BCCs and palmar pitting) and two minor criteria (frontal/

parietal bossing and pectus excavatum) from the basic list found in publications of Evans et al. (8) and Kimonis et al. (7). Furthermore, we disclosed a number of additional abnormalities such as keratotic papules over the back and shoulders, an extraordinary back deformity having markedly prominent paravertebral protuberances, not consistent with the Sprengel's deformity, thoracolumbar kyphosis, exotropia, ectopic teeth (impacted tooth), mandibular hyperplasia, and broad nose.

The variety of clinical features seen in our case, according to a group of authors and R. Gorlin himself, are likely the result of an inborn error in developmental metabolism determines causing multiformity of symptoms (16). Moreover, further reports have only broaden the list of abnormalities found in affected individuals (18, 20, 22-25).

Interesting cardiology findings in our patient included aortic stenosis and regurgitation, whereas severe aortic valve calcification was interpreted as the consequence of a post-radiation pericarditis and aortic valve changes due to radiotherapy applied for Hodgkin's lymphoma. Besides, the BCCs in our patient developed much later. Actually, the association of GGS with lymphoma is very rare and we found only two cases of Hodgkin's lymphoma in patients with GGS in the literature (26, 27). It is postulated that the gene for GGS may act as a tumor suppressor gene perhaps for many types of cell lines and may explain the diversity of tumors (28, 29, 30). Despite the preceding malignant disorder and aggressive radiologic and cytotoxic treatment, our patient was not immunosuppressed. We believe that this pattern of immune reactivity supported the patient's skin own defense mechanisms against the congenital predisposition to cancer development, given the sun exposure abuse reported in his history.

The common therapy for BCCs in GGS includes surgical excision, cryosurgery, electrodesiccation, curettage, and Mohs micrographic surgery (6, 31-35), although these procedures do not ensure tumor eradication in all cases (31, 36, 37, 38). It is known that in patients with multiple or extensive lesions surgical procedures are not always manageable (35), being rather traumatic and painful, time consuming and/or may result in disfigurement. Non-surgical alternatives are recommended for tumors located at sites inappropriate for surgical intervention, due to their lower overall costs and more esthetically acceptable outcomes. Photodynamic therapy (37) is used in patients with wide-ranging skin cancers. Ablative lasers have been successfully used with minimal scarring for particular lesions on the face and other specific locations (39).

Topical drugs such as imiquimod (1, 40-44), 5-fluorouracil (45, 46, 47) and retinoids (46, 48, 49) have been reported with variable results, showing high cure rates in superficial BCC, but much lower efficacy in more extensive lesions. Topical medications appear to be appropriate in patients with superficial BCCs and therefore have been used with some success in GGS, thus becoming the armamentarium of choice among treatment modalities (37, 50, 51, 52).

Topical 5% imiquimod cream monotherapy for superficial BCC and adjuvant therapy following electrodessication of nodular BCC, proved to be a successful treatment modality in our patient, who is tumor-free three years after treatment. Some authors suggest that imiquimod adjuvant imiquimod after surgery shows double activity: it removes residual tumor tissue and provides a better esthetic outcome (32-34, 53, 54, 55). It seems that imiquimod induced inflammation may participate in the clearance of BCC to some extent (33, 50).

Investigations of imiquimod efficacy showed that regression of BCC after imiquimod treatment is related to immune-mediated processes (56). It has been discovered that 5% imiquimod upregulates the release of cytokines such as interferon-alpha and -beta (IFN-α IFN-β), tumor necrosis factor alpha (TNF-α), interleukin-1 (IL-1) alpha and beta, IL-6, as well as natural killer cell activity and nitric oxide secretion from macrophages (57). It has also been established that imiquimod upregulates the cell-mediated immune response via indirect stimulation of IFN-gamma (Th-1 cytokine), activates Langerhans cells to promote antigen presentation (58), toll-like receptor 7, which itself activates nuclear factor kappa B to stimulate production of IFN-alpha and cytokines IL-12 and IL-18. Subsequently these cytokines induce IFN-gamma release by naïve T-cells, producing a Th1-type immune response and a stimulation of cytotoxic T lymphocytes, providing a long-term immune memory. Imiquimod has no direct interaction with

tumor cells, but induces pro-inflammatory cytokines production and in this way stimulates both the human innate and cell-mediated immune system response to malignant cells (50).

Nowadays, new diagnostic and treatment protocols are being developed for non-melanoma skin cancer for their future management and prevention (5, 6, 21, 36, 59, 60).

Conclusion

This is a case with late-onset multiple basal cell carcinomas in a patient with Gorlin-Goltz syndrome and a history of prior Hodgkin's lymphoma. To the best of our knowledge hitherto only two cases of Hodgkin's lymphoma in patients with Gorlin-Goltz have been reported in the literature. We also present therapeutic results of topical imiquimod for multiple basal cell carcinomas with no recurrent lesions over a three-year follow-up.

Abbreviations

BCC - basal cell carcinoma
GGS - Gorlin-Goltz syndrome
NBCCS - nevoid basal cell carcinoma syndrome

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Kasna pojava multiplog bazocelularnog karcinoma kod pacijenta sa Gorlin-Golcovim sindromom prethodno lečenog od Hočkinovog limfoma

Sažetak

Uvod. U slučaju pojave multiplih bazocelularnih karcinoma potrebno je kod pacijenta isključiti postojanje imunosupresije i/ili genetske predispozicije. Kada su genetska oboljenja u pitanju, na prvom mestu treba ispitivanje usmeriti na kongenitalni Gorlin-Golcov sindrom, poznat i pod nazivom nevoidnog bazocelularnog sindroma ili nevusnog sindroma bazalnih ćelija, koji predstavlja nasledni autozomno-dominantni karcinomski sindrom, a podrazumeva razvoj multiplih bazocelularnih karcinoma u ranim godinama života i varijabilnu kombinaciju drugih fenotipskih abnormalnosti koje rezultiraju zahvatanjem više organa. Odgovorni gen je mapiran na hromozomu 9q22.3–3.1. Kao i drugi supresorski geni, PTCH1 gen pokazuje učestalu deleciju i čitav niz drugih mutacija. Visok stepen novih mutacija i varijabilna ekspresivnost čine kompletnu dijagnostičku procenu teškom, naročito kod osoba sa blagom kliničkom slikom i bez pozitivne porodične anamneze.

Prisustvo dva glavna kriterijuma ili jedan glavni i dva sporedna kriterijuma definišu pacijente sa Gorlin-Golcovim sindromom. Glavni kriterijumi su: više od dva ili jedan bazocelularni karcinom kod pacijenata mlađih od 20 godina; odontogenetske keratociste vilice – histološki potvrđene; tri ili više palmarnih ili plantarnih udubljenja – rupica; bilamelarna kalcifikacija falksa velikog mozga; bifidna, fuziona ili raširena rebra; rođaci prvog stepena sa sindromom. Sporedni kriterijumi su: makrocefalija; kongenitalne malformacije – rascep usna/nepce, fronto/temporoparijetalna ispupčenja, krupno i grubo lice, hipertelorizam; skeletne malformacije – Sprengel deformiteti, pektus ekskavatum/karinatum, sindaktilija; radiografske abnormalnosti – premošćavanje sele turcika, vertebralne abnormalnosti (hemivertebre, fuzija i elongacija vertebralnih tela), defekti na kostima šaka i stopala, rasvetljenje u obliku plamena na stopalima i šakama; ovarijalni fibromi/fibrosarkomi ili meduloblastomi.

Prikaz slučaja. Prikazujemo 42 godine starog pacijenta, muškog pola, sa šestogodišnjim postojanjem promena u vidu multiplih glatkih i/ili grubih plakova na koži leđa i ramena. Pojedine od ovih promena su vremenom postepeno progredirale i postale brojnije, nisu bile praćene subjektivnim simptomima. Na dlanovima je uočeno prisustvo tačkastih udubljenja crvenkastosmeđe boje. Daljim ispitivanjima otkriveno je prisustvo mnogih mišićno-skeletnih i kranio-facijalnih kongenitalnih abnormalnosti, kao što su pektus ekskavatum, fronto/parijetalna ispupčenja, egzotropija, impaktirani zubi, mandibularna hiperplazija, širok nos. Histopatološkim pregledom bioptiranog materijala uzetog sa nodularne i ostalih pločastih promena na koži utvrđeno je prisustvo dijagnostičkih kriterijuma tipičnih za bazocelularni karcinom. U porodici nije bilo obolelih srodnika.

Pacijent je lečen pod dijagnozom Hočkinovog limfoma sa hemioterapijom i radijacionom terapijom pre 20 godina. Postignuti su dobri terapijski rezultati, tako da se pacijent nalazio u remisiji poslednjih deset godina. Protočnom citometrijom nije utvrđeno stanje imunosupresije u trenutku pregleda.

Lečenje multiplih bazocelularnih karcinoma sprovedeno je 5% imikvimod kremom, pet dana u nedelji, tokom 12 nedelja. Nodularni tumor je prethodno tertiran elektrokoagulacijom. Mesec dana kasnije došlo je do potpunog povlačenja promena bez ikakvih rezidua.

Pacijentu je savetovano da koristi fotoprotekciju i da izbegava nekontrolisanu ekspoziciju sunčevim zracima. Tokom naredne tri godine na kontrolnim pregledima nisu uočeni znaci recidiva.

Diskusija. Prema kriterijumima koje su predložili Evans i saradnici , kao i Kimonis i saradnici, naš pacijent je ispunio dva glavna kriterijuma za postavljanje dijagnoze (multipli bazocelularni karcinomi i tačkasta udubljenja na dlanovima) i dva sporedna kriterijuma (fronto/parijetalna ispupčenja i pektus ekskavatum). Štaviše, mi smo otkrili brojne dodatne nepravilnosti kao što su: keratotične papule

na leđima i ramenima, izuzetan deformitet leđa sa jako izraženim paravertebralnim protuberancijama koji se razlikovao od Sprengelovog deformiteta, torakolumbalna kifoza, egzotropija, dentalna ektopija, mandibularna hiperplazija i širok nos.
Zaključak. U radu je prikazan slučaj kasne pojave multiplih bazocelularnih karcinoma kod osobe muškog pola sa Gorlin-Golcovim sindromom i sa anamnezom o ranije lečenom Hočkinovom limfomu. Prema nama dostupnoj svetskoj literaturi do sada su objavljena dva slučaja Hočkinovog limfoma kod osoba sa Gorlin-Golcovim sindromom. Uspešan terapijski efekat lokalne primene imikvimod krema u lečenju multiplih superficijalnih bazocelularnih karcinoma potvrđen je odsustvom recidiva tokom praćenja pacijenta naredne tri godine.

Ključne reči

Sindrom bazocelularnog nevusa; Bazocelularni karcinom; Multiple primarne neoplazme; Komorbiditet; Hodžkinova bolest; Dijagnoza; Aminokuinolini; Ishod terapije