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CLINICAL REPORT

Successful Treatment of Multiple Basaliomas with Bleomycin-based Electrochemotherapy: A Case Series of Three Patients with Gorlin-Goltz Syndrome

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Gorlin-Goltz syndrome is a rare multisystemic disease, characterized by numerous basal cell carcinomas. The ideal approach for patients with the syndrome would be a treatment with a high cure rate, minimal scarring, short healing time and mild side-effects. Electrochemotherapy is a novel therapeutic option that ablates tumours with electrical current and simultaneously administered anticancer drugs. Three patients with Gorlin-Goltz syndrome were treated with electrochemotherapy using intravenous bleomycin. Clinical response was obtained in 98 (99%) of the lesions, 86 (87%) of them showed complete response. In 2 tumours, regression was confirmed with histological examination. Long-term cosmetic results were excellent. We consider electrochemotherapy to be an additional tool in the therapeutic armamentarium for Gorlin-Goltz syndrome, and suggest using it as early as possible in selected patients to avoid disfiguring scarring.
***Key words: electrochemotherapy; Gorlin-Goltz syndrome; bleomycin*.**

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Gorlin-Goltz syndrome (basal cell naevus syndrome) is a rare multisystemic disease inherited in a dominant autosomal way, which shows a high level of penetrance and variable expression. The disease is caused by mutations in the *PTCH1* gene on chromosome 9q22, the *PTCH2* gene on 1p32, or the *SUFU* gene on 10q24-q25 (1–3). The syndrome is characterized by numerous basal cell carcinomas (BCCs), often presenting as early as the second or third decade of life. Other typical signs are palmoplantar pits, acral epidermoid cysts and skeletal abnormalities. The facial appearance is characterized by a large skull, frontal bossing, hypertelorism and enlarged mandible. Single or multiple odontogenic keratocysts can develop in the mandible or, less often, in the maxilla, as shown on radiological examinations. The falx cerebri may be calcified and corpus callosum agenesis can occur. In very rare cases, medulloblastoma, ovarian fibroma or other benign hamartomatous or neoplastic lesions can develop (4, 5). One of the main challenges in Gorlin-Goltz syndrome is the management of the high number of BCCs, especially when presenting on the head and neck region. In addition, these skin tumours are often classified as high-risk and can invade deeper structures (6). Currently, cryotherapy, surgery and systemic retinoids are the most commonly used treatment modalities, while topical imiquimod and photodynamic therapy (PDT) have emerged as alternatives. The ideal approach for patients with Gorlin-Goltz syndrome would be a treatment with minimal scarring, short healing time and mild side-effects, which, at the same time, result in a high cure rate of any skin tumours while preserving the healthy tissue surrounding the tumour (5). Novel oral synthetic inhibitor molecules, GDC-0449 and LDE225, have been found to be highly effective in blocking the activities of the Hedgehog-ligand cell surface receptors PTCH and/or SMO which might represent new therapeutic approaches for Gorlin-Goltz syndrome (http://clinicaltrialsfeeds.org/clinical-trials/show/NCT01350115) (7).

Electrochemotherapy (ECT) is a novel therapeutic option that ablates tumours with electrical current and simultaneously administered anticancer drugs. During the surgical procedure, electric pulses deliver non-permeant or poorly permeant chemotherapeutic agents specifically into the tumour cells and at the same time increase their local cytotoxicity. It has been proved to provide long-lasting control of various cutaneous and subcutaneous neoplasia with minimal side-effects and good cosmetic results (8–12). The European Standard Operating Procedures of Electrochemotherapy (ESOPE) was the largest prospective, randomized, multicentre study demonstrating ECT to be an effective and safe anticancer treatment using various drugs and administration methods (13).

Based on the characteristics of ECT and the promising results reported in the literature, we aimed to use it as an alternative to other standard treatments in three patients with Gorlin-Goltz syndrome.

CASE REPORTS AND METHODS

Gorlin-Goltz syndrome was diagnosed in our patients (mean age 58.6 years, range 51–63) based on medical history of

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early appearing skin tumours, on physical and on radiological examinations. We did not perform genetic screening. Prior to treatment, all patients presented with numerous (mean number: 33) BCCs in our clinic. The skin tumours were localized on the face, scalp, trunk and extremities, and were clinically classified as superficial, nodular, ulcerated or plaque type. Frontal bossing was characteristic in all patients, hypertelorism in two of them. The 51-year-old man (patient 1) had palmar pits, multiple osteolytic cysts in the mandible and maxilla, and intracranial calcification of falx cerebri. The 62-year-old man (patient 2) had extensive scarring of previous surgical excisions and flap repairs. The 63-year-old woman (patient 3) had twice undergone meningioma resection.

The patients had been treated with surgery, cryotherapy, PDT, intralesional interferon, topical 5-fluorouracil and systemic acitretin in the past, with varying success. Patient no. 3 had undergone systemic isotretinoin treatment without appreciable benefit, and oral acitretin was stopped because of hair loss and gingival bleeding.

The patients gave written informed consent before treatment, which was approved by the local ethics committee. Treatments were carried out in the Department of Dermatology and Allergology, University of Szeged, Hungary.

Treatment was carried out according to the ESOPE guidelines (13, 14) (between June 2009 and January 2011). All 3 patients received intravenous bleomycin-based ECT at a dose of 15 mg/m^2 using the Cliniporator TM device (IGEA Ltd, Modena, Italy). Depending on the size and nature of the tumours, different types of electrodes were connected to the electroporator device. For smaller exophytic tumours plate electrodes (Type I) were applied, whereas for cicatrizing lesions needle electrodes were used. In case of small nodules less than 1.0 cm in diameter, electrical pulses were delivered by parallel arrays (Type II), for larger nodules by hexagonal array needle electrodes (Type III). Electrical pulses were delivered to the tumour during the pharmacokinetic peak, which is the time period of 8–28 min following the intravenous administration of bleomycin (15). If the tumour was larger than the gap between the electrodes a second run of electric pulses was delivered by repositioning the electrode until complete tumour electroporation was obtained. The electrical parameters of treatment (amplitude, duration, number of electric pulses, repetition frequency) were dependent on the type of the electrodes.

Due to the high number (25–38) of skin tumours treated during the same session general sedation with endotracheal intubation or larygeal mask was used. If necessary the sessions were repeated at 2-monthly intervals. Following ECT, all patients were monitored in hospital for one day. During the follow-up period patients were examined and photographed twice during the first month, monthly for the next 6 months, and thereafter every second month. Response to treatment was assessed at least 60 days after intervention (8).

Complete response (CR) was determined as no palpable tumour detected, while partial response (PR) was defined as a decrease of more than 50% in the largest diameter of the lesion (16). Less than 50% reduction and up to 25% increase in the above measurements was defined as no change (NC). Progressive disease (PD) was defined as an increase in diameter by more than 25%. Skin biopsies were taken from two treated lesions showing CR for histological evaluation of tumour response.

RESULTS

The total number of treated tumour was 99, ranging from 25 to 38 per patient. A mean of 27 tumours were treated per session under general sedation. (One patient underwent 4 treatment session, while the others had only one.) Twenty-eight (28%) tumours were localized in the head and neck region, and 71 (72%) on the trunk and extremities. The diameter of tumours ranged from 0.3 to 2.2 cm (mean 0.94 cm) (Table I). The response rate of treated tumours was 99%. We observed CR in 86 tumours (87%), PR in 12 tumours (12%). In one of the treated tumours we did not find any change (1%). Excellent cosmetic results were achieved meeting the expectations of our patients (Figs 1 and 2). None of the CR lesions relapsed during follow-up (2–20 months).

Table I. *Treated tumour size*

Tumour size	<0.5 cm^3 small	0.5–1 cm^3 medium	>1 cm^3 large	Total
Diameter, cm, median (range)	0.8 (0.3–0.98)	1.1 (1–1.15)	1.8 (1.2–2.2)	0.94 (0.3–2.2)
Tumours, *n* (%)	64 (65)	30 (30)	5 (5)	99

Biopsies were taken 3 months after treatment from two treated lesions (face, back), where clinically no residual tumour could be detected. The 2 samples showed similar histopathological features (Fig. 3). The epidermis was flattened and showed regenerative changes with focal subepidermal clefting. Scar tissue replaced the previous tumour in the dermis. In the scar of the facial sample, one small intradermal residual BCC nest buried, focal bone metaplasia, microcalcification and obliterated blood vessels were detected. There was no tumour remnant in the sample taken from the back.

In accordance with other reports in the literature, one day after treatment we observed mild and transient side-effects: erythema and slight oedema around treated lesions, and sore muscle due to muscle contractions at the time of pulse delivery (17). Due to the low doses of bleomycin used during ECT no systemic side-effects

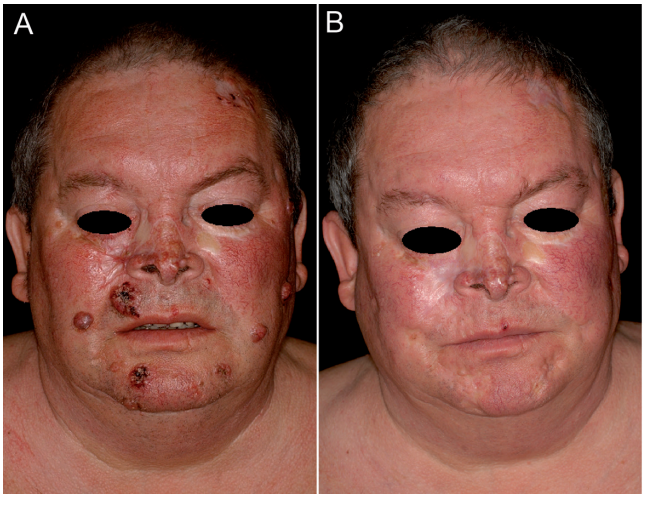

Fig. 1. Patient no. 2, with high-risk tumours on the face. (A) Before electrochemotherapy (ECT) treatment and (B) after 4 sessions of ECT. Published with approval from the patient.

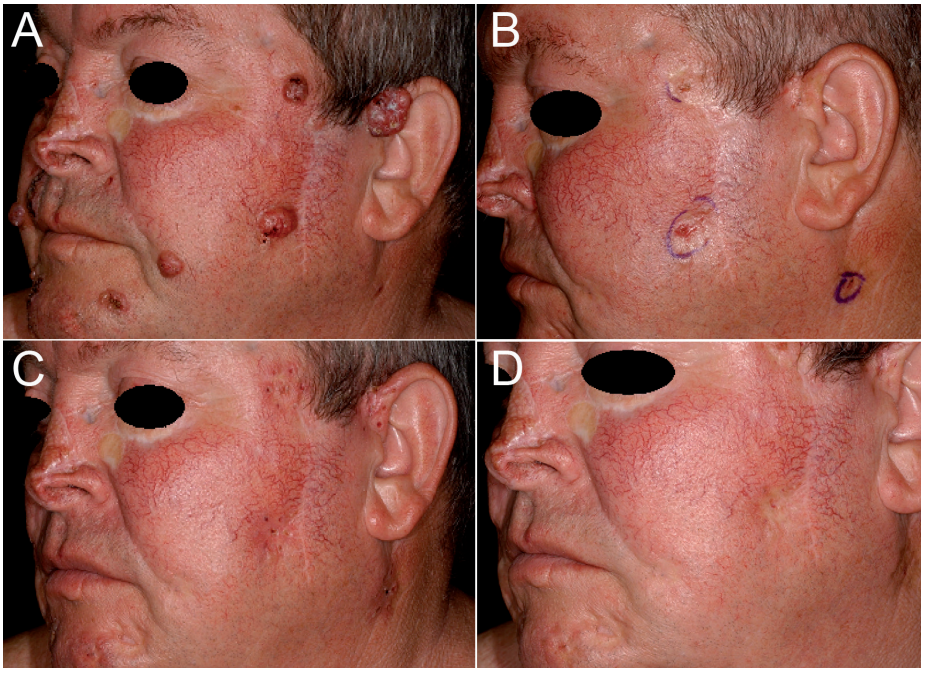

Fig. 2. Patient (same as in Fig. 1) with high-risk tumours on the face. (A) Before electrochemotherapy (ECT). (B) Partial response after 2 sessions of ECT. (C) Marks of the needle electrodes on the left temple and cheek 2 weeks after 4 sessions of ECT. (D) Complete response 10 months after 4 sessions of ECT. Published with approval from the patient.

were observed. Marks from the needle electrodes could be seen for approximately one month (Fig. 2C); central or complete necrosis of the treated lesions was visible for about 2–3 weeks. The short-duration general sedation (25–32 min) with analgesic support was well tolerated by the patients, and no pain was reported.

DISCUSSION

Three patients with a total of 99 BCCs on the face and trunk were treated with ECT according to the ESOPE guidelines using intravenous bleomycin. Clinical response was obtained in 99% of the lesions, 87% of them showed CR. In 2 tumours, regression was confirmed with histological examination. Patients were very satisfied with the long-term cosmetic results (Figs 1 and 2).

Electroporation increases the cell membrane permeability, allows bleomycin direct access to cytosol and causes mitotic catastrophe through DNA damage in the tumour cells, while sparing the surrounding tissues leading to good cosmetic results (18–21). Clinical efficacy of ECT has previously been reported as a primarily palliative intervention for progressive disease, with few studies using it for curative therapy. Most of these trials treated a small number of BCCs using intralesional bleomycin (9, 11, 22–25).

The cost-effectiveness of ECT was evaluated and confirmed in the control and treatment of cutaneous and subcutaneous advanced neoplasms (26). Concerning BCC treatment we do not have such comparisons.

Cryosurgery is a frequently used treatment option in Gorlin-Goltz syndrome with high cure rate (99%) and few complications, but in contrast to ECT mainly superficial BCCs can be treated (5). Surgical removal of multiple tumours in the face can cause extensive and sometimes disfiguring scarring.

Based on our results we conclude that ECT under general sedation is a good choice to treat BCCs in Gorlin-Goltz syndrome, especially in patients presenting with multiple high-risk skin tumours. We did not experience any recurrence on treated tumours in the follow-up (10–28 months). Healing time is short; side-effects are

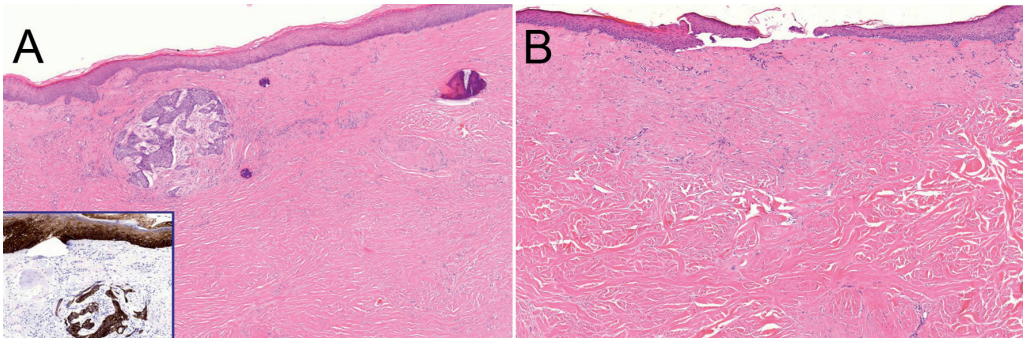

Fig. 3. Histological findings in the residual scars. (A) Biopsy of the face: extensive scar tissue in the dermis with residual basal cell carcinoma nest and with bone metaplasia and microcalcification (haematoxylin-eosin). The epidermis and the tumour show cytokeratin MNF116 positivity (*insert*). (B) Biopsy of the back: flattened epidermis with clefting and scar tissue in the dermis.

mild and transient. Numerous tumours can be treated at the same time with curative intent, and sessions can be repeated if necessary.

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The authors declare no conflicts of interest.

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