Electrochemotherapy: a Valid Treatment for Gorlin-Goltz Syndrome

The Gorlin-Goltz syndrome, also known as nevoid basal cell carcinoma (BCC), has a variable prevalence, estimated from 1/57,000 to 1:256,000 inhabitants (1). It is a rare autosomal dominant disorder due to a genetic mutation in the PTCH tumor suppressor gene localized to 9q22.3 chromosome (2).

In order to make a diagnosis of Gorlin-Goltz syndrome, some diagnostic criteria have to be taken into account. The most important criteria are the presence of pigmented BCCs, odontogenic keratocysts, palmar and/or plantar pits, and ectopic calcifications of the falx cerebri. Together with these major criteria, more than 100 minor clinical signs have been described. Diagnosis can be established when two major or one major and two minor criteria are present (3) (Table 1).

Basal cell carcinomas are seen in 50%-97% of all cases. Some differences have been described between the BCCs of patients not affected by the syndrome and those with the syndrome. In the latter, they are more likely to be multiple lesions, polymorphic in nature, in either sex, and even areas not exposed to sunlight can be affected (4). They are not histologically different, but show a higher rate of recurrence after treatment than in non-syndrome patients. The cosmetic consequences are more important because of their multiplicity (5).

There are many therapeutic alternatives for BCCs. Surgical excision is the first usual approach, but sometimes for multifocal or large size lesions, this is not the best choice.

Electrochemotherapy (ECT) is a tumor ablation modality for cutaneous and subcutaneous lesions from different malignancies, including BCC. This combines conventional chemotherapeutic drugs (bleomycin or cisplatin) with cell electroporation.

Table 1. Diagnostic criteria for Gorlin-Goltz syndrome

Major criteria	• Multiple basal cell carcinomas or one occurring under the age of 20 years. • Histologically proven OKCs of the jaws. • Palmar or plantar pits (three or more). • Bilamellar calcifications of the falx cerebri. • Bifid, fused, or markedly splayed ribs. • First degree relative with nevoid basal cell carcinoma syndrome.	**Minor criteria**	• Macrocephaly (adjusted for height). • Congenital malformation: Cleft lip or cleft palate, frontal bossing, coarse face moderate or severe hypertelorism. • Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, marked syndactyly of the digits. • Radiological abnormalities: Bulging of sella turcica, vertebral anomalies such as hemi vertebrae, fusion or elongation of vertebral bodies, modeling defects of the hands and feet, or flame-shaped hands or feet. • Ovarian fibroma. • Medulloblastoma.

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Since 1995, literature reports very good rates of response, up to 90%, of cutaneous and subcutaneous metastases treated with ECT and bleomycin administered intravenously or intralesionally (6).

A 43-year-old man was referred to our Department. He had a large painless, erythematosus and ulcerated plaque on the scalp, which had first appeared two years earlier and was growing slowly. The size of the lesion ranged from 5 cm to 10 cm in diameter (Fig. 1). An incisional biopsy was performed and the diagnosis of BCC was made.

Clinical examination revealed the presence of other BBCs localized on the trunk and preauricular region. Other BBCs had been previously removed from his scalp, face, leg and abdomen; most of these procedures entailed complex surgical closures, which were undertaken by plastic surgeons.

There was also pitting on palmar and plantar surfaces and typical skeletal malformations such as frontal bossing, depressed nasal bridge, prominent supraorbital ridges and mandibular prognathism.

The diagnosis of Gorlin-Goltz syndrome was made. Surgery was excluded due to the tumor extension. So, after careful consideration, we decided to refer the patient to a sitting of electrochemotherapy. It was performed with deep sedation; bleomycin was administered intravenously at a dose of 15 mg/m^2. We used an electric pulse generator, the Cliniporator®, and a hexagonal needle electrode of 20 mm in length (IGEA S.r.l.). After eight minutes, the electrode was inserted directly into the lesion, covering the whole area. Sequences of eight pulses of 680 V for nodule were delivered at a frequency of 5 KHz and duration of 100 µs. The treatment was finished at 20 minutes after the end of the infusion, to ensure an adequate concentration of bleomycin in tumoral tissues. After ECT, the patient was kept under observation for 24 hours.

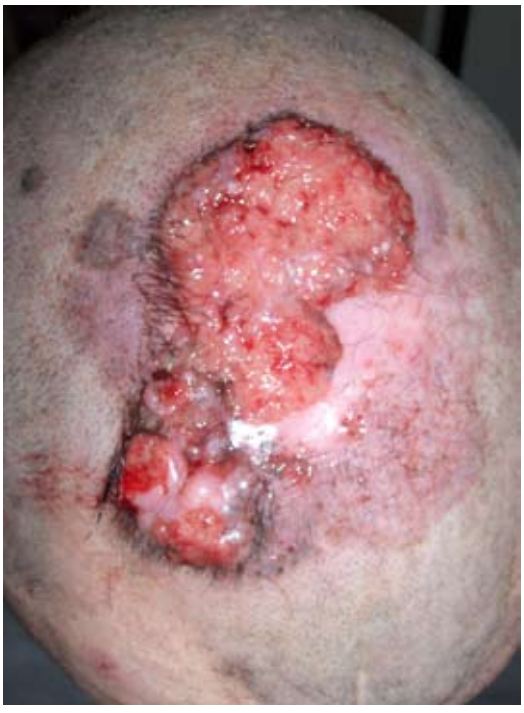

Figure 1. Erythematous and ulcerated plaque 5 cm x 10 cm on the scalp

Initially, the treated surface appeared erythematous and edematous. Later, a superficial necrotic eschar had formed on the nodule for about four weeks, when complete re-epithelialization was observed. The patient had residual pain on treatment areas for less than two weeks, then it decreased after anti-inflammatory therapy.

After one-month follow up, we decided for a second treatment to achieve complete remission. This ECT session was performed with the same criteria as the first one. After two weeks, the lesion had almost vanished and the surface had become flattened; after four weeks, we observed complete response of the treated area, understood as no palpable tumor detected (7). Other BBCs, superficial at the time of diagnosis, were treated with cryotherapy and imiquimod 5%.

In the following months, we followed up the patient and we treated new suspected hotbeds with several sessions of cryotherapy. After four-year follow up, there was clinical evidence of complete recovery and no sign of local relapses (Fig. 2).

Therapy for clinical manifestations of Gorlin-Goltz syndrome is not a simple treatment.

Basal cell carcinomas in this syndrome have a multiple-modality treatment: surgical excision, Mohs micrographic surgery, electrodesiccation, topical fluorouracil, cryotherapy, topical imiquimod and photodynamic therapy, and carbon dioxide laser vaporization (8). Multiple BBCs, present in this disease, require numerous surgical procedures that over time leave them with multiple disfiguring scars.

Surgical intervention, although efficient, may be too painful and discomforting and may increase morbidity, especially if it has to be frequently performed. For this reason, we decided to use ECT.

Electrochemotherapy combines the electropulsation of tumor cells (by local application of electric pulses) and the administration of antineoplastic drugs such as cisplatin or bleomycin (either intravenous or intratumoral). The permeability of the cancer cells to these poorly permeating anti-tumor drugs is transiently increased up to hundred-fold. This approach

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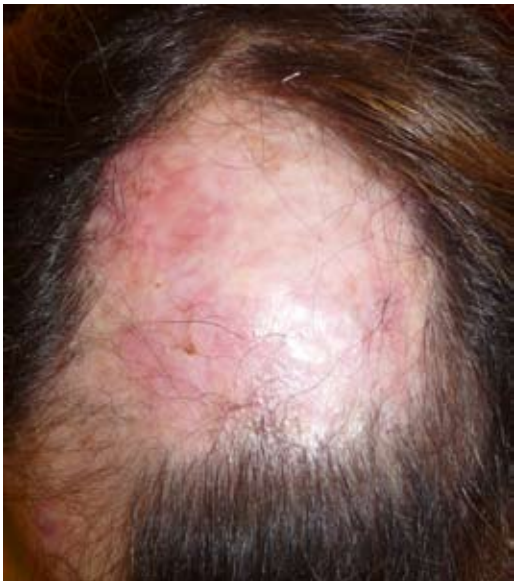

Figure 2. Complete remission and no sign of local relapses after four years of follow up

has been shown to be highly effective in providing local control of cutaneous or subcutaneous tumors, regardless of their histologic origin, while maintaining a very low toxicity profile and high patient compliance (9).

Recent discoveries suggest that in addition to the direct cytotoxic effect of ECT on tumor cells, there may also be an indirect effect on the tumor, decreasing the blood flow with consequent extensive tumor necrosis (10). It has also been proposed that ECT might allow tumor antigen shedding and local inflammation, thus attracting immune antigen-presenting cells (11).

In our case, we have obtained complete response, showing that ECT is feasible and effective on unresectable BCCs. The advantages of this therapy are its simplicity, the short duration of treatment sessions, insignificant side effects, and repeatability. In addition, ECT has the advantage of achieving good local tissue preservation, less scarring and a good cosmetic outcome, thus improving the quality of life.

We think that ECT may represent a treatment of choice in cases of multiple and unresectable BCCs in this pathology.

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