Metastatic Basal Cell Carcinoma With Squamous Differentiation

Report of a Case With Response of Cutaneous Metastases to Electrochemotherapy

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Background: Metastatic basal cell carcinoma is a rare disease with poor prognosis. Palliative therapeutic approaches include surgery, radiotherapy, and/or chemotherapy. These treatment modalities are invasive and risky and associated with relevant adverse effects. Electrochemotherapy is a recently described therapy that relies on the permeation of cancer cell membranes by electrical pulses to enhance cytotoxic drug penetration. It has been successfully used in the treatment of primary and metastatic skin cancers. We report a case of metastatic basal cell carcinoma in which electrochemotherapy was effective in inducing local regression of skin metastases.

Observations: A 75-year-old man presented with a pigmented, deeply infiltrating nodule in the right axilla manifesting as basal cell carcinoma with squamous differentiation at histopathologic examination. Despite 2 wide surgical resections involving lymphadenectomy with axillary vein substitution and systemic chemotherapy, a progressive metastatic spreading, both cutaneous and visceral, occurred in the following 2 years. Three successive sessions of electrochemotherapy with bleomycin sulfate were then performed on isolated skin metastases. The treatment was well tolerated and led to a rapid clinical and histologic regression of the treated lesions.

Conclusion: Electrochemotherapy is an effective and well-tolerated adjunct to the therapeutic options in metastatic basal cell carcinoma, characterized by an advantageous risk-benefit ratio and minimal downtime.

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BASAL CELL CARCINOMA (BCC) is the most common cutaneous malignant neoplasm, accounting for up to 80% of nonmelanoma skin cancers, with increasing incidence rates in recent years. Basal cell carcinoma is characterized by a slow, local growth, with distant metastases being exceedingly rare (frequency range estimated at 0.0028%-0.55%). Metastatic spread most often involves local lymph nodes (70%), but lung, skin, and bone metastases are also described. The prognosis of metastatic BCC is poor, with a median survival time after diagnosis of 8 months. Currently available treatment options for metastatic BCC include surgery, radiotherapy, and chemotherapy, alone or in combination.

Electrochemotherapy (ECT) is a recent therapeutic technique that relies on pulsed, high-intensity electrical currents (electroporation) to reversibly increase cell membrane permeability, thus enhancing the penetration of cytotoxic drugs into tumor cells. Although several chemotherapeutic agents have been proposed, bleomycin sulfate, systemic or intralesional, has shown the greatest antitumor activity when used in conjunction with electroporation. Electrochemotherapy with bleomycin has been successfully used in primary skin tumors, such as in Kaposi sarcoma and in selected cases of primary squamous and BCC as well as in the palliative treatment of cutaneous metastases of melanoma and squamous cell carcinoma. We report a case of metastatic BCC in which ECT has proven useful in the treatment of cutaneous metastases.

REPORT OF A CASE

A 75-year-old man was seen at our clinic for a 3-year history of an enlarging skin lesion in his right axilla. Medical history disclosed local radiotherapy for hidrosadenitis and a progressive hypoesthesia of the right arm in recent months. Physical examination revealed a pigmented nodule (1.5 x 1.0 cm) fixed to the deep planes, in an area of atrophic, scarred skin. A wide cutaneous excision, along with an axillary lymphadenectomy, was performed. Intraoperatively, a deeply infiltrating mass embedded in fibrous tissue, reaching the adventitia of the axillary vein, was apparent. Findings from histopathologic examination showed a BCC with squamous differentiation infiltrating the perivascular soft tissues. Lymph nodes were negative for tumor cells.
After 1 year, a local relapse occurred, consisting of perilesional cutaneous and subcutaneous nodules in the lymphedematous arm and axilla. Echotomography of the axillary vault was consistent with deep soft tissue persistence. A wide surgical excision of the axillary soft tissues with partial resection of the axillary vein (substituted with saphena) was performed. After 1 additional year, clinical and instrumental follow-up examination (echotomography, computed tomography, and positron-emission tomography) revealed mediastinal, lung, and bone metastases. Progressive, massive lymphedema of the upper right arm, with extensive cutaneous and subcutaneous involvement by multiple nodular and plaque lesions, mostly ulcerated, led to severe functional impairment, greatly worsening the patient’s mobility and quality of life. In particular, a large, ulcerated, neoplastic plaque developed in the right axilla, in the site of the original lesion. Systemic chemotherapy using cisplatin and fluorouracil was started, with only partial and temporary results.

Because of the risks and morbidity of palliative surgery, we decided to test the usefulness of ECT to control the cutaneous diffusion of the tumor and to reduce the patient’s disability. A few cutaneous metastatic nodules were chosen for initial testing because of their limited extension and superficial location. In the first therapy session, 2 nodular lesions on the right arm (Figure, A) and 1 on the back were selected for ECT with intraleSIONAL bleomycin according to the previously published standard operating procedures.1 Briefly, the tumor volume was calculated from the major diameter ($a$) and the next longer diameter perpendicular to $a$ ($b$), according to the formula $V = \frac{ab^2 \pi}{6}$. The patient was prepared with local anesthesia (perilesional infiltration of 1% mepivacaine hydrochloride) and general analgesia (ketorolac tromethamine, 30 mg intravenously) and vital parameters were monitored during the procedure.

Bleomycin sulfate was injected in the 2 lesions according to the tumor volume (250 IU cm$^2$ for tumor volumes $>1.0$ cm$^3$; 500 IU cm$^2$ for tumors 0.5-1.0 cm$^3$; and 1000 IU cm$^2$ for tumors $<0.5$ cm$^3$), followed by electroporation (Cliniporator; IGEA, Carpi, Italy). Briefly, within 2 minutes of bleomycin injection, a 7-needle (18-mm) hexagonal electrode (1.6-cm diameter) was inserted in the skin around each lesion and a run of 8 square-wave electrical pulses (730-V amplitude, 5000 Hz, 100 microseconds per pulse) was delivered. Pulse deliverance was monitored to assure the effectiveness of the applied electrical field (1.5 A). Mild pain due to muscle contraction was experienced by the patient during the pulse delivery, with no residual pain after treatment. In the following days a rapid response was observed, with ulcerative necrosis of the 2 lesions followed by progressive tumor shrinkage, resulting in clinical healing in 1 to 3 months (Figure, B). Regression of the tumor nodules was histologically confirmed with skin biopsy performed after 2 months, which revealed dermal fibrosis in the absence of tumor nodules (Figure, C-D). A second ECT session with intraleSIONAL bleomycin was performed 1 month later on 3 different nodules, with...
a similar response. A further ECT session with intravenous bleomycin sulfate (15 000 IU/m², followed by electroporation within 8-28 minutes) performed 2 months later on several other cutaneous lesions of the right arm and trunk again yielded a complete clinical regression of the lesions.

Three months later, sudden extensive deep venous thrombosis of the legs complicated by intestinal perforation and acute renal failure led to a rapid death. No autopsy was performed. Until the patient’s death, no sign of tumor recurrence was detected in all the treated sites.

A few clinical and histologic characteristics are considered predictive of metastatic risk in BCC. It is believed that long-standing lesions, large (>10 cm) solitary or multiple primary tumors, head and neck localization, and a history of radiation therapy are risk factors for developing metastases. Aggressive histologic patterns, such as the basosquamous, morpheic, and adenocystic variants, as well as perineural invasion, have also increased metastatic potential. The characteristics of our case of metastatic BCC (long-standing lesion developing on radiodermatitis, with a basosquamous histologic pattern) are consistent with the literature reports. In our patient, tumor progression with both regional and distant diffusion occurred in spite of wide surgical excisions. Later, the response to systemic chemotherapy in controlling tumor spread was poor.

Electrochemotherapy has been demonstrated to be an effective and well-tolerated therapy for solid tumors in both experimental and clinical studies. In several clinical trials, ECT with bleomycin gave the best response rates in BCC among a variety of primary and secondary skin tumors, with a complete response in up to 94.4% of cases after 1 treatment session. We then decided to use ECT with bleomycin in our patient as a palliative treatment to reduce the tumor burden and patient's discomfort. After the first favorable results with intraleisional bleomycin, we moved to intravenous administration to treat more lesions per session. In the choice between intraleisional and intravenous administration, one should consider both the possible differences in drug delivery to the tumor (eg, in cases of impaired circulation) and practical therapeutic and technical issues (eg, number of nodules to be treated, dose-related adverse and toxic effects, timing between drug administration, and electroporation). Both modalities of ECT in our case proved successful in the local control of BCC skin metastases in clinical conditions (ie, number, dissemination, and closeness of lesions, severe lymphedema of the limb), whereas other approaches, such as surgery or radiotherapy, would have been unsuitable and hazardous due to the high risk of ulceration, bleeding, infection, and delayed healing. A complete healing by secondary intention was observed within 3 months, with minimal adverse effects. The therapeutic response occurred without any increased morbidity for the patient in tissue-sparing and low-risk conditions due to the minimal doses of bleomycin, local anesthesia, and absence of surgical wounds. Our case represents, to our knowledge, the first to test the potential role of ECT as palliative therapy in metastatic BCC. Electrochemotherapy allowed for the rapid treatment of multiple lesions, greatly reducing the risks, downtime, and adverse effects linked to surgery, radiotherapy, and systemic chemotherapy.

In conclusion, ECT represents an effective, safe, and well-tolerated adjunct to the therapeutic options in difficult-to-treat cutaneous tumors, and it is worthy to be considered in selected cases in which the extension of the lesions or the patient’s conditions contraindicate traditional techniques.

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