

Intralesional Cisplatin for the Treatment of Cutaneous B-Cell Lymphoma

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The Cutting Edge: Challenges in Medical and Surgical Therapeutics

REPORT OF A CASE

A 56-year-old white woman presented with a solid erythematous nodule on her scalp that had developed 6 years earlier. She denied having a fever, losing weight, or sweating during the night. Her medical history was notable for epilepsy, which was adequately controlled with phenothiazine and chlorpromazine therapy. When a solitary nodule first appeared on the patient's head 6 years earlier, a biopsy specimen revealed nodular, dense B-cell infiltrates without blasts, nuclear atypias, or mitoses. Therefore, the lesion had been regarded clinically and histologically as a B-cell pseudolymphoma. The patient was subsequently treated with potent topical corticosteroid creams and local psoralen-UV-A, but within 2 years the preexisting nodule became larger and 2 further nodules appeared despite the therapy. After topical chemotherapy using carbomustine and topical corticosteroids, the patient had a partial response consisting of a reduction in tumor size, but the tumors recurred after a few months.

The results of a physical examination showed that she had 4 dense, erythematous, smooth nodules with a median size of 3 cm on the frontal and parietal areas of her scalp accompanied by alopecia (**Figure 1**). No enlarged lymph nodes were palpable.

The results of a histopathological examination of the nodules revealed a dense nodular infiltrate extending throughout all dermal layers into the subcutaneous fat, exhibiting a follicular pattern that was separated from the epidermis by an uninvolved grenz zone. Cytomorphologically germinal center-derived cells with pale cytoplasm, pleomorphic nuclei, and a few atypical mitoses were found (**Figure 2**). The cells stained for B-cell markers including CD20 (Figure 2), CD79a, and proliferation-associated Ki-67 marker. Immunohistochemical staining for κ and λ light chains of immunoglobulins showed a restricted reactivity of the tumor cells for the immunoglobulin κ light chain. Genotyping with amplification of immunoglobulin-heavy specific regions using a polymerase chain reaction did not reveal a monoclonal B-cell population. A chest x-ray film, an abdominal ultrasonogram, and a computed tomographic head scan showed no abnormal findings. In

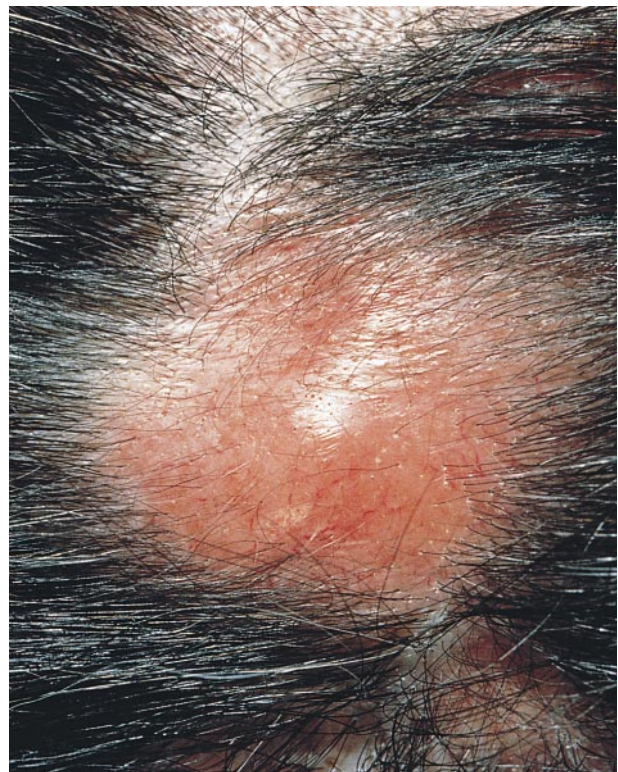


Figure 1. Erythematous nodule of cutaneous B-cell lymphoma on the parietal area of the patient's scalp before treatment with intralesional cisplatin gel.

addition, examination of peripheral blood and a bone marrow biopsy specimen showed no evidence of an extracutaneous lymphoma.

Based on histopathological and clinical findings, the diagnosis of a follicle center cell lymphoma of the head and neck, a subtype of a primary cutaneous B-cell lymphoma, was made.

THERAPEUTIC CHALLENGE

Because the patient refused radiotherapy and excision of the tumoral nodules, and because other therapeutic ap-

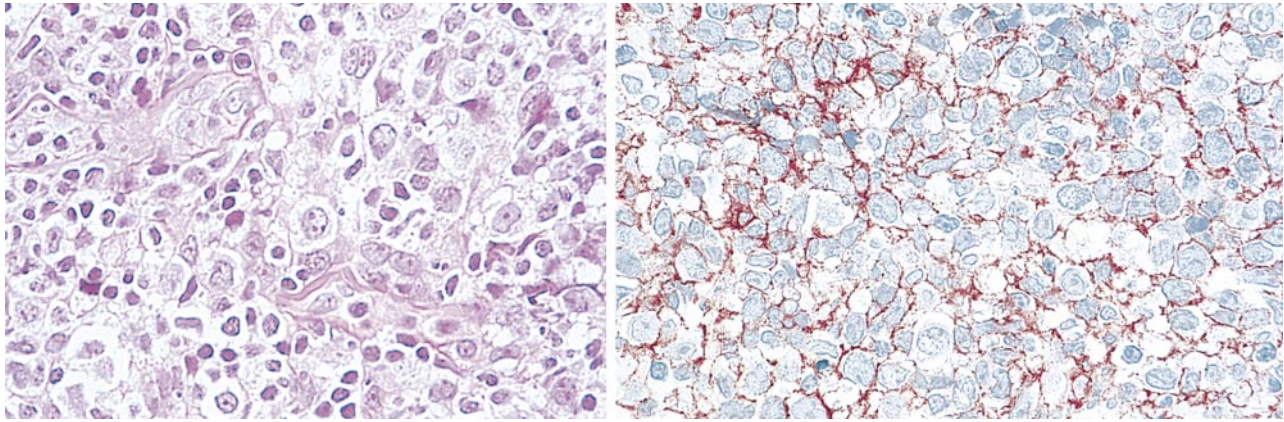


Figure 2. Cutaneous B-cell lymphoma. Left, Centroblasts, centrocytes, and small B-lymphocytes (hematoxylin-eosin, original magnification $\times 640$). Right, Immunohistochemical detection of CD20 expression (alkaline phosphatase antialkaline phosphatase complex, original magnification $\times 600$).



Figure 3. Necrosis in the area of treated nodules after the patient received the third injection of intralesionally applied cisplatin gel.



Figure 4. Reepithelialized area without recurrences of cutaneous B-cell lymphoma at 5 months' follow-up.

proaches such as topical corticosteroids, psoralen-UV-A, and carbomustine had failed to resolve the tumors, an alternate local treatment was needed.

SOLUTION

Local chemotherapy has been used as a therapeutic approach for various skin tumors. Experimental and early clinical trials indicated that intratumoral-injected cisplatin in a collagen-epinephrine gel could be a new potent local chemotherapy for various tumors, especially for those on the head and neck. Based on experience with patients who had other head and neck tumors, we injected 0.5 to 1.0 mL of 4 mg/mL of cisplatin with 0.1 mg/mL of epinephrine in a collagen-containing gel (IntraDose, Matrix Pharmaceutical Inc, Fremont, Calif) once per

week into 2 of the 4 tumoral nodules over a period of 5 weeks, with a total cumulative dose of 16 mg per nodule. After the third injection, the tumoral lesions became demarcated and necrotic (**Figure 3**). Two months after initiation of therapy, the necrotic tumor mass could be removed using curettage without surgical intervention or anesthesia. The resulting erosive wound area healed rapidly, leaving a hairless scar (**Figure 4**). After 5 months, no clinical recurrence of the lymphoproliferative infiltrates could be detected. However, untreated lesions continued to grow.

During the cisplatin-gel injection, the patient reported feeling pain at the injection site and slight nausea. After the third injection, swelling and an erythematous flush developed on the same side of her face after 1 hour, which persisted for many hours. The results of

serologic investigation and prick or scratch tests did not reveal a sensitization against collagen and epinephrine as components of the gel, although cisplatin was not tested because of its direct toxic effect. Pretreatment with oral antihistamines did not prevent a similar reaction after the fourth and fifth injections.

COMMENT

Follicle center cell lymphoma is the most common subtype of primary cutaneous B-cell lymphoma and is typically located on the head and neck.¹⁻³ Whereas a more aggressive variant located on the lower legs has been reported, most cases of cutaneous B-cell lymphoma are usually confined to the skin for many years and show a favorable prognosis despite the tendency to recur after treatment.^{3,4}

Because primary cutaneous B-cell lymphoma is a rare disease, there are no generally accepted standards for its treatment. Excision and/or radiotherapy are the primary therapeutic modalities, but successful treatment with topical or intralesional corticosteroids as well as local chemotherapy has been reported.^{5,6} Once the tumor has spread to extracutaneous sites, systemic chemotherapy is often necessary.^{3,7}

Cisplatin is used as a systemic chemotherapeutic drug either alone or in combination with other drugs in a regimen to treat several malignant neoplasms, such as testicular cancer, head and neck cancer, and other solid tumors.⁸ It exhibits cytotoxic properties because of the cross-linking of DNA molecules, resulting in a breakdown of DNA synthesis and induction of tumor cell apoptosis.^{8,9}

Cisplatin gel is a 3-component gel system consisting of a bovine collagen gel base containing cisplatin in a concentration of 4 mg/mL as the active cytotoxic drug and epinephrine, 0.1 mg/mL, to avoid rapid diffusion of cisplatin from the tumor and into the circulation. This composition results in an intratumoral concentration of cisplatin that is 10-fold greater than that after systemic intravenous injection of the drug. Veterinary data have demonstrated that intratumorally injected cisplatin gel is effective for the treatment of various tumors, including primary and secondary hepatic cancers and accessible head and neck cancer.^{10,11} Experimental data of ongoing studies in the treatment of human neoplasms, such as primary and secondary hepatic cancers and accessible head and neck cancer, reveal complete or partial response in 30% and 60% of treated lesions, respectively. Treatment of cutaneous lymphoma with intralesionally adminis-

tered cisplatin has not been reported before. The therapeutic effect can be expected after the third to fourth injection with formation of necrosis and subsequent demarcation of the tumoral lesion. The most common adverse effects of cisplatin injections include acute pain at the injection site during injection and nausea. Swelling and erythematous flushing as observed in our patient have rarely been reported (data from Marrix database, accessed 1997) and seem not to be due to an allergic reaction.

Intratumoral injection of cisplatin-epinephrine gel may be an alternative therapeutic approach for the treatment of primary cutaneous B-cell lymphoma.

Presented as a scientific poster at the European Society for Dermatological Research and the European Organization for Research and Treatment of Cancer meeting for Cutaneous Malignant Lymphomas, Berlin, Germany, September 1997, and published as an abstract in the Journal of Investigative Dermatology (1997;109:495).

Dr Kempf was a dermatology resident at the time the study was done.

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