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# Electrochemotherapy-induced Radiation Recall in a Cat

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**Abstract.** *Electrochemotherapy is gaining popularity for the treatment of malignancies of companion animals due to its efficacy and low cost. In this paper, we describe the successful treatment of a recurring fibrosarcoma in a cat by using cisplatin selectively driven within the tumor cells by trains of biphasic pulses. The cat's tumor did not recur over the following five months, however the cat did experience severe erythema at the site of previous irradiation, followed by moist desquamation and ulcer that required debridement and prolonged therapy with steroids and antihistaminic drugs. The symptoms and the response to symptomatic therapy were strongly suggestive of radiation recall. Electrochemotherapy (ECT) should be used with caution in previously irradiated areas. Further studies are warranted in this field due to its potential as a rescue for relapsing tumors.*

Soft tissue sarcomas (STS) are rather common feline tumors and have local aggressive behavior and a low tendency for distal spread (1-2). The standard therapy following surgical excision, due to their tendency to early recurrence, is radiation therapy (3-6). Recently, electrochemotherapy (ECT) has been proposed as an alternative adjuvant therapy with promising results (7, 8).

## Case Report

A 10-year-old castrated castrated domestic short hair cat was referred for a rapidly growing interscapular neoplasm. Accordingly to the owner, the mass grew in approximately 20 days. At presentation, the cat was quiet, alert and responsive, and had a 8×5×4 cm dorsal mass. A surgical biopsy was performed after the patient's sedation with a combination of medetodimine and ketamine as per manufacturers' instructions. Grossly, the neoplasm had a fibrous white cut surface with yellow flecks and foci of hemorrhage and necrosis with poorly defined borders. The sample was fixed in 10% formalin for histological analysis. Paraffin sections, 5 μm-thick, were prepared and stained with hematoxylin and eosin and hematoxylin-Van Gieson staining. The histopathology report gave a diagnosis of high-grade sarcoma as per injection sarcoma. Morphologically, the neoplastic cells were arranged in fascicles that intersected each other at acute angles. The areas of hemorrhage and necrosis, and the mitotic index of 8 per high power field, clearly indicated the high grade of the malignancy (Figure 1A).

The tumor was staged with a complete blood cell count, serum biochemical profile, urinalysis, test for feline leukemia virus (FeLV) and for feline immunodeficienty virus (FIV), chest radiographs (three projections) and abdominal ultrasonography. The cat was found to be FeLV and FIV negative; all the other hematological tests were within reference limits and the imaging studies did not show metastatic spread (data not shown). At this point, therapeutic options included surgical resection of STS (1, 2), coupled with systemic radiation therapy (3-6), or electrochemotherapy (7-9). The owner elected the cat to have surgery performed at the referring veterinarian and radiation therapy (57 Gy in 19 fractions delivered on a Monday through Friday schedule) at a referral institution.

One year after the completion of radiation therapy, the cat came back with a 2×3 cm cutaneous nodule at the previous tumor site. Fine-needle aspiration cytology was suggestive of tumor recurrence. At this time, since radiation was not an option due to the risk of damage to the normal tissues, it was proposed to associate surgery with adjuvant ECT. On the basis of the reported limited effectiveness of bleomycin-based ECT (10), it was decided to use cisplatin as the anticancer agent. The cat underwent surgery and was referred for ECT at the time of suture removal. The patient was

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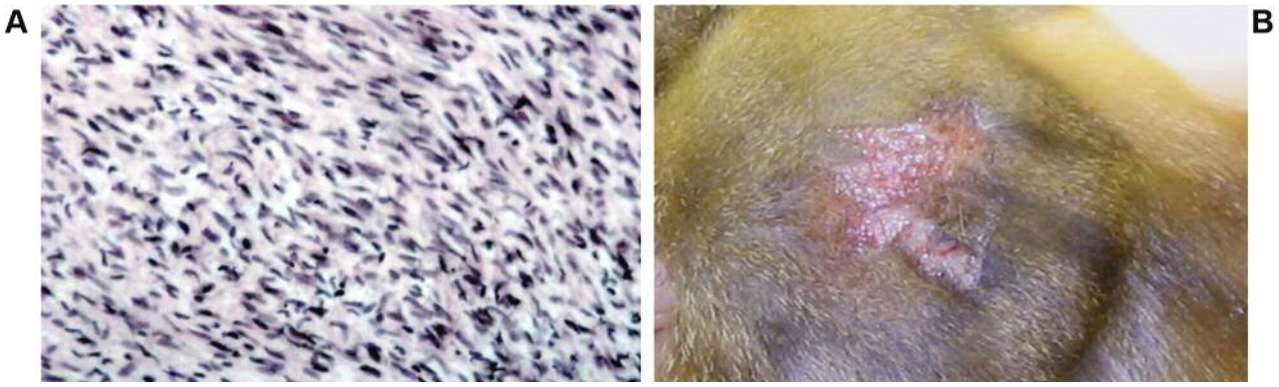


Figure 1. *A) Microscopic appearance of the lesion at the time of surgical biopsy, showing the neoplastic cells arranged in fascicles and the high mitotic index (hematoxylin and eosin, original magnification ×40). B) The patient showing cutaneous signs compatible with ECT-induced radiation recall.*

sedated with a combination of medetodimine and propofol as per manufacturers' instructions and the tumor bed was pretreated with a combination of hyaluronidase and lidocaine (LIDO-HYAL B Laboratori farmaceutici Giovanni Ogna & figli S.p.A., Milan, Italy), to dissolve the ground substance and to increase local analgesia (8). Five minutes after the injection of hyaluronidase, the tumor and 1 cm of normally appearing margins were infiltrated with cisplatin (Platinex vial 50 mg/100 ml, Bristol-Myers Squibb, Sermoneta (LT), Italy) at a concentration of 0.5 mg/ml (total dose 8 mg). Five more minutes after the infiltration of the antiblastic agent, trains of 8 biphasic electric pulses (EP) lasting 50 + 50 μs each, with 1 ms interpulse intervals, were delivered by means of caliper electrodes (11). Adherence was enhanced by using an electroconductive gel. The cat recovered from the treatment and received a second session one week later.

Three days after the completion of its ECT course the cat came back with a marked erythema at the site of ECT and the owner reported frequent scratching by the cat. During the physical exam the cat was very aggressive and vocalized upon palpation of the interscapular space. A 5×5 cm erythematous plaque with moist desquamation was noticed (Figure 1B). The tentative diagnosis was ECT-induced radiation recall (RR). The cat was discharged on symptomatic therapy consisting of oral antibiotics (enrofloxacin 5 mg/kg for 10 days) and prednisone (1 mg/kg). The cat had significant improvement consisting of decreased oozing and a marked reduction of the attempts to scratch. Unfortunately, after seven days, the lesion evolved into an open wound that required debridement (not shown). At this time, antihistaminic medication was added (cyproheptadine 2 mg *bid*). The wound healed within two weeks and the cutaneous symptoms receded within three more weeks. Four months later, the cat came as an emergency case due to progressively worsening neurological symptoms. The cat was tetraparetic, depressed, dehydrated and not responsive to stimuli; neurology consultation yield the diagnosis of multifocal spinal disease. Differentials included spinal lymphoma, spinal neoplasia, spinal malacia (potentially radiation induced). Due to the poor prognosis, at that time the owner elected euthanasia.

## Discussion

Electrochemotherapy is a new approach to solid neoplasms that associates the systemic or local administration of a chemotherapy agent with the application of square or biphasic electric pulses (EP) so as to increase the uptake of drug by the cancer cells, thus resulting in increased chemotherapy efficacy (7-9, 11-13). In the past five years, our group has successfully treated feline sarcomas, canine malignant melanoma and mast cell tumors with ECT, obtaining high percentages of complete remissions as well as a high number of long-term responders (7-9, 11-14). To the best of our knowledge, this is the first report of successful ECT for relapsing tumors after full course radiation therapy.

Radiation recall in humans is a redness, resembling severe sunburn, that can occur at the site of previous radiation when certain chemotherapy drugs are given (15). This effect of radiation recall can occur from 8 days to 15 years after radiation therapy (16). The majority of the drugs currently used in cancer therapy have been involved in the radiation recall phenomenon (17). A mixed non-specific inflammatory infiltrate seems to be the common histopathological criterion in previously published reports (17). During or shortly after certain anticancer drugs are given, the skin over an area that had received radiation turns red - a shade anywhere from light to very bright. The skin may blister and peel. This reaction may last hours or even days. Symptoms in humans can vary and include redness, tenderness, swelling, wet sores, peeling skin and discoloration after the skin has

healed. The proposed mechanism for this complication include altered drug(s) pharmacokinetics, depletion or epithelial stem cell or epithelial stem cell hypersensitivity (18-20). Treatment of radiation recall is symptomatic with an effort to avoid or treat secondary infections that may occur. Universally, corticosteroids or the use of non-steroidal anti-inflammatory agents, in conjunction with withdrawal of the offending agent, produce prompt improvement; however the radiation recall phenomenon often leads to significant dose reduction or even therapy discontinuation. Unfortunately, in our case, the episode of radiation recall, despite being resolved, led to a significant decrease in the patient's quality of life and makes further studies on this salvage technique most warranted, especially in view of the translation of similar protocols to humans.

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