Surgically induced tumor seeding in eight dogs and two cats

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Summary: *Surgically induced tumor seeding was diagnosed in 8 dogs and 2 cats. All animals had histologic confirmation of neoplasia in an unusual location or pattern, and a history of surgical manipulation of a similar histologic-type tumor at the site of seeding. Highly malignant carcinomas (8/10 animals) were the most common tumor type. Seeding occurred secondary to a variety of surgical procedures and in the face of various adjuvant therapies. Seeded tumors were recognized from 2 to 30 weeks after the causal procedure (median, 6 weeks). Survival times after the causal procedure ranged from 15 to 131 weeks (median, 45 weeks) and 8 of 10 animals died or were euthanatized because of seeded tumors.*

Tumor seeding is the mechanical spread of viable tumor cells by surgical or invasive diagnostic procedures resulting in subsequent cell growth and gross tumor formation. It has been described in people for many different tumor types and secondary to various causal procedures.[1-10] The mechanisms and biology of tumor seeding have also been studied.[11-15] Because of this awareness, even introductory human surgery textbooks emphasize oncologic surgical technique and apprise medical students of the potential for tumor seeding.[16-18] In contrast, there are only anecdotal reports of tumor seeding in animals, and limited veterinary discussion of oncologic surgical technique. The purpose of the study reported here was to describe and characterize tumor seeding in animals.

Materials and methods

The criteria used for entry of an animal into the study were histologic confirmation of neoplasia in an unusual location or pattern, history of surgical or invasive diagnostic manipulation of a similar histologic-type tumor at the site of seeding, and no special precautions taken to prevent tumor seeding (ie, protective drapes or glove and instrument changes). Eight dogs and 2 cats with seeded tumors were identified between February 1980 and January 1988 at the Veterinary Hospital of the University of Pennsylvania (VHUP; No. 1 and 2), at a surgical referral practice in Atlanta (No. 3), and at North Carolina State University College of Veterinary Medicine (NCSU-CVM, No. 4 to 10.) Animals were identified by the authors and other clinicians. The cases identified may represent a nonrandom population, and statistical analysis of the results was not possible.

Medical records were reviewed and information recorded regarding signalment; tumor histologic results, including tumor type and evidence of aggressiveness (lymphatic or vascular invasion, marked cellular anaplasia, or mitotic index >3 per high-power field); tumor stage at time of initial diagnosis; causal procedure of tumor seeding; location of seeded tumor(s), postoperative time to diagnosis of seeding; adjuvant therapy for treatment of the primary and seeded tumor; and survival time from causal procedure. Additional information on survival and disease recurrence was obtained by telephone from the owner or referring veterinarian, or by reexamination at NCSU-CVM.

Results

Carcinomas were most common (8/10 animals); 5 animals had carcinomas of the urinary tract, 1 had a squamous cell carcinoma of the pinna, 1 had an anal sac adenocarcinoma, and 1 had a basal cell carcinoma. In several cases, the tumors had marked cellular anaplasia, lymphatic or vascular invasion, or a mitotic index >3 per high-power field (8/10 animals). Tumor staging by use of the World Health Organization TNM classification[19] at the time of the causal procedure was variable. Five animals had stage I or local disease (T_{1-2} N_0M_0), 4 animals had stage II or regional disease (T_{3-4} N_{0-3} M_0, or T_{1-4} N_{1-3} M_0), and cancer in

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one animal was not staged. The causal procedure was major surgery (>60 minutes' duration) in 6 animals, including three partial cystectomies, a limb-sparing procedure, pinna ablation, and an ear ablation; and minor surgery (≤60 minutes' duration) in 4 animals, including three incisional biopsies and one excisional biopsy. None had seeding after an invasive diagnostic procedure (eg, cutting needle biopsy, fine-needle aspirate). Location of seeded tumors was the primary incision site in 9 animals (6 on abdomen, 2 on head, 1 on trunk) and the site of an autogenous bone graft in 1 animal. Postoperative time to diagnosis of seeding ranged from 2 to 30 weeks (median, 6 weeks). Adjuvant therapy (chemotherapy, radiotherapy, or hyperthermia) was used in 5 animals at the time of the causal procedure, and in 7 animals at the time of tumor-seeding diagnosis. Survival times from the causal procedure ranged from 15 to 131 weeks (median, 45 weeks). Eight of 10 animals (all except No. 6 and 9) died or were euthanatized because of their seeded tumors.

Case examples—Negative contrast cystography revealed a large, irregular mass involving the cranioventral bladder wall (Fig 1) in an 11-year-old spayed Alaskan Malamute (case 1) examined at VHUP. A partial cystectomy was performed. Regional lymph nodes and abdominal organs were grossly normal at surgery. Histologic examination of the resected tissue revealed transitional cell carcinoma. Tumor cells extended through the muscle layers of the bladder to the serosal surface, and vascular invasion was evident. Postoperative adjuvant chemotherapy was used for 5 weeks (30 mg doxorubicin/m^2 on day 1 and 100 mg cyclophosphamide/m^2 on days 3 to 6, repeated weekly).

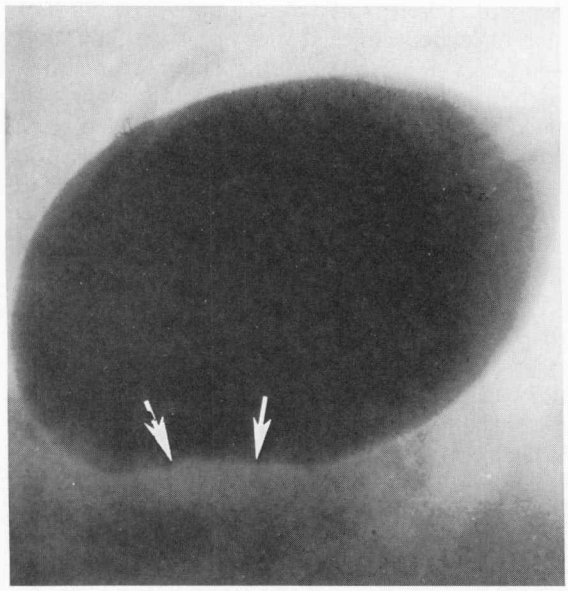

Figure 1—Negative contrast cystogram of a dog (case 1) with large irregular mass in the cranioventral bladder wall (arrows).

Figure 2—Mass in laparotomy incision (transitional cell carcinoma) 21 weeks after causal procedure (case 1).

Twenty-one weeks later, the dog was admitted to VHUP with a 13-cm firm mass in the caudal part of the incision line (Fig 2). Histologic examination of a punch biopsy specimen revealed the mass to be a transitional cell carcinoma. Double-contrast cystography revealed no abnormalities. The abdominal wall mass was resected and no adjuvant therapy was used. At 60 weeks after the initial surgery, the dog was again admitted to VHUP with a rapidly growing 15-cm mass on the ventral midline over the initial laparotomy incision. Results of histologic examination of the mass confirmed a transitional cell carcinoma. The mass was again resected and no adjuvant therapy was used. At 131 weeks after the initial surgery, the dog was euthanatized because a transitional cell carcinoma had regrown at the site of the incision line. At necropsy, there was no evidence of neoplasia in the bladder or elsewhere.

A 5-year-old, spayed Great Dane (case 2) was admitted to NCSU-CVM for evaluation and treatment of a suspected osteosarcoma. A firm mass that caused signs of pain was over the distal portion of the left radius, and the dog was partially weight-bearing on the limb. Radiography of the left carpus revealed a mixed productive and lytic lesion in the

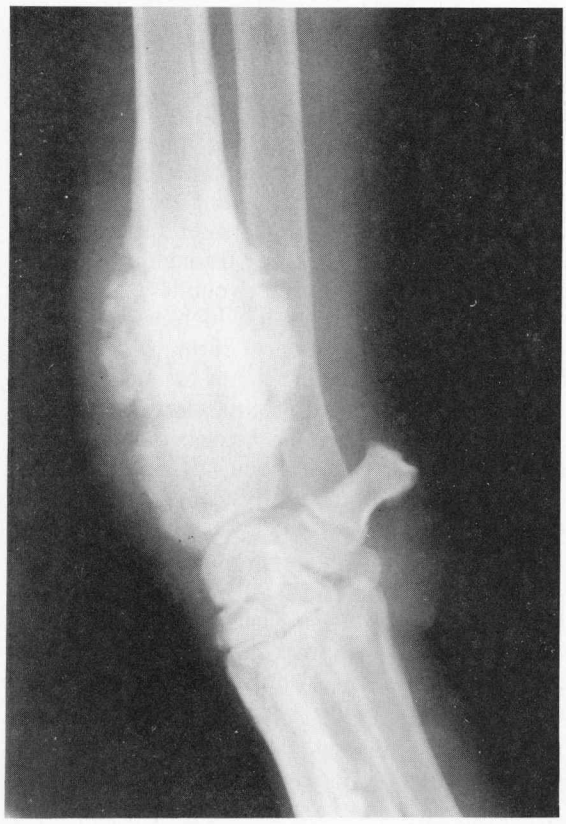

Figure 3—Lateral radiograph of left carpus of a dog (case 2). A mixed lytic and productive lesion is evident in the distal portion of the radius.

distal portion of the radius (Fig 3). Nuclear bone scanning with ^{99m}technetium methylene diphosphonate revealed increased tracer uptake in the area of the distal portion of the left radius only. Multiple biopsy samples were taken from the lesion.[a] The tumor was identified as an osteosarcoma, and osteoblasts appeared large and highly anaplastic. The dog was treated with megavoltage radiation therapy (40 Gy total dose divided into 4-Gy fractions given on Mondays, Wednesdays, and Fridays), and intra-arterial chemotherapy (70 mg cisplatin/m^2 given at radiation treatments 1 and 10). Three weeks after treatment, the dog was returned for a limb-sparing procedure. The distal portion of the left radius was resected and replaced with a cortical allograft. A pancarpal arthrodesis was performed by use of a bone plate to rigidly fix the allograft. An autogenous cancellous bone graft was harvested from the left ilium and placed around the allograft. Results of histologic evaluation of the resected tissues confirmed a diagnosis of osteosarcoma with only marginal resection. Two weeks after surgery, infection of the allograft was diagnosed. Despite 16 weeks of intensive wound management and antibiotic treatment, infection persisted. The cortical allograft was removed and replaced with a cancellous autograft harvested from the tibial crests and the proximal portion of the right humerus. At 30 weeks after surgery, the dog was admitted for evaluation of a left hindlimb lameness. The dog had a 6 × 9-cm firm swelling over the wing of the left ilium. Radiography of the pelvis revealed a mixed lytic and productive lesion in the left wing of the ilium. Examination of multiple biopsy specimens[a] revealed osteosarcoma of the left ilium. No further treatment was given. Six weeks later, the dog was euthanatized. Necropsy findings included a 15 × 15-cm osteosarcoma of the wing of the left ilium (Fig 4), with no other evidence of neoplastic disease.

[a]Jamshidi Biopsy Needle, Kormed Inc, Minneapolis, Minn.

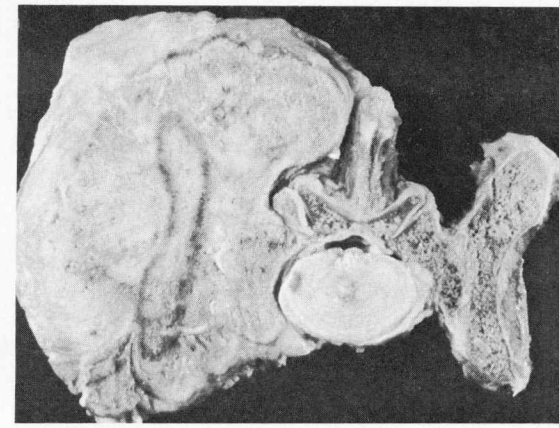

Figure 4—Cross-section of ilial osteosarcoma at postmortem examination (case 2).

Discussion

Tumor seeding in the 10 animals of this report is similar to tumor seeding in human beings. Histologically aggressive carcinomas, particularly of the urinary tract, were the most common tumor types seeded in our study as they are in people.[1-4,6,9,13,20] In animals and human beings, tumor staging at time of diagnosis did not correlate with the occurrence of tumor seeding, and seeding frequently occurred even with adjuvant therapy.[1,10,20] The location of seeding for human beings and animals was most commonly at the primary incision site; however, distant seeding, as in animal 5, has been described in human beings.[5,7,20,21] In the animals of this report, all tumor seedings were evident by 8 months after surgery, and most were evident by 3 months. In people, many cases are also recognized within 8 months of the causal procedure,[1,2,4,5,7,10] although others do not occur until years later.[1,2,5,10,20,21] Animals in our study and human beings[1,2,5,21] frequently died from their seeded tumors, with no evidence of disease at the primary tumor site and often with no evidence of metastatic disease.

Tumor seeding in our animals was caused by major or minor surgical procedures. There were no instances of seeding secondary to an invasive diagnostic procedure. In contrast, most recent tumor

seeding incidents in people have occurred secondary to invasive diagnostic procedures, particularly cutting needle biopsies.[1,3,4,8,9] In the past, seedings occurring after surgery were reported,[6] but are now less common presumably because most physician surgeons are trained to avoid inducing tumor seeding, and are likely to take greater steps to prevent it.

The occurrence of tumor seeding depends on at least 3 factors: cell biology of the seeded tumor, environmental milieu in which the cells are deposited, and number of cells seeded. Important biologic characteristics of tumor cells contributing to seeding are poor contact inhibition, cell-to-cell adhesiveness and cohesiveness, and a high clonogenic and proliferative potential.[1,11,12] Hence, a tumor with more malignant-type cells would be more likely to seed, as demonstrated clinically in animals and people. It is not known what factors make the environmental milieu favorable for tumor cell growth, although local blood supply and nutrient and waste transport are important. Isolation from or resistance to host immune responses and adjuvant cancer therapies would also favor tumor growth.[22-24] Protection from the immune system is possible by host failure to recognize the tumor as foreign, or a large tumor burden overwhelming the immune system. Protection from adjuvant therapies may develop because of poor vascular supply decreasing cytotoxic drug delivery, chemotherapy-resistant cell clones, or local tissue hypoxia reducing radiotherapy effectiveness. The number of contaminating cells correlates with the occurrence of tumor seeding.[11,12] Inoculations of 1 to 10 million cells are necessary for tumor growth in 13 to 24% of people.[22-24] In studies in rats, as few as 100 seeded cells caused tumor growth in 25% of inoculations, and fine-needle aspirates commonly seeded 1,000 to 10,000 cells into the needle tract.[11,12] Case descriptions of tumor seeding in human beings, secondary to fine-needle aspirates, suggest that fewer than 1 million cells can cause tumor seeding in people.[3,8] The actual number of cells seeded depends on tumor cell cohesiveness, amount of stromal cells in a tumor, and degree of tumor disruption.[1,11] For example, major surgical disruption of a highly malignant urothelial carcinoma would be more likely to result in seeding than a fine-needle aspirate of a well differentiated fibrosarcoma.

Because confirmation of surgically induced tumor seeding is impossible, two other sources for similar growth patterns after surgery must be considered. Inflammatory oncotaxis refers to the apparent predisposition for cancer cells to be deposited and grow in sites of inflammation.[25-29] Inflammation may facilitate tumor cell entrapment by forming clots, increasing capillary stickiness, and disrupting endothelial intercellular barriers.[25-29] Tumor cell chemotactic factors might also be released during the inflammatory response. Metastases have been described from primary tumors not treated surgically to injection sites,[30] soft tissues traumatized by a plaster cast,[31] and remote surgery sites.[21]

The "path of least resistance" phenomenon is the proliferation of residual tumor within the surgical site and through the healing incision. Many tumors spread by growing between tissue planes, along vascular structures, and through other easily invaded spaces.[32] Surgical wounds and needle tracts produce tissue planes, which have a greatly increased capillary density during the healing phase. Incised tissue planes and increased vascularity provide an ideal setting for local tumor spread. Tumor seedings following complete wound healing are difficult to explain by this theory, but scars generally remain physically weaker than normal tissues, perhaps facilitating tumor ingrowth.

Although the unusual tumor growths in the animals in this report could be examples of inflammatory oncotaxis or growth along the path of least resistance, the presumptive diagnosis of tumor seeding was made on the basis of the 3 criteria given in this report.

Recommendations regarding therapy for seeded tumors cannot be made from results of this study; however, in two studies in people, better results were obtained with surgical excision than with other therapies.[10,20]

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Book Review: Mineral Levels in Animal Health: Diagnostic Data

This handbook provides the reader with information on low, normal, and high tissue and blood levels of 39 minerals, from aluminum to zinc, in both domestic and wild animal species. The contents are arranged alphabetically by element, then alphabetically by species. Generally, 1 page is devoted to each element for each species. Tabular data on tissue and blood levels of the mineral are found at the top of the page. This is followed by notes that vary among minerals and species, on dietary levels, deficiency signs, toxicity levels and signs, and so forth. Data are provided on both essential nutrients as well as toxic minerals.

The author states that the book is designed to aid veterinarians, pathologists, nutritionists, and other agricultural personnel. There is no question that this book provides, in 1 reference source, a wealth of information that will be of great value in interpreting the significance of measured values of minerals in animal tissues, both in cases of suspected mineral toxicoses and in evaluation of dietary imbalances of mineral nutrients.

In some cases, the accuracy of some of the notes can be questioned. Unfortunately, references are not included in the book, although the author claims that these will be published in a companion volume. When it becomes available, this will be an indispensable part of this work.

The $45 price for the handbook is high, but the book is worth the price for veterinary pathologists and toxicologists for whom a ready source of such information can be of value in interpreting the relevance of tissue mineral data.—*[Mineral Levels in Animal Health: Diagnostic Data. By Robert Puls. 240 pages; softcover, plastic-ring-bound. Sherpa International, PO Box 2256, Clearbrook, British Columbia, Canada V2T 4X2. 1988. Price $45. Bibliographies for volume, $65.]*—FRANCIS A. KALLFELZ