MY PATIENT IS ILL: IS IT FROM ITS TUMOR?

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Animals with tumors can, of course, be ill or become ill for reasons unrelated to their tumor. The clinician attending to a patient with a tumor needs to be careful not to jump to the conclusion that the patient's illness is a result of the tumor lest an opportunity to address a treatable disease be missed. In simple terms, cancer patients that are ill, or become ill, are usually sick because of their tumor, the treatment administered for the tumor, or something unrelated to the tumor. It can at times be difficult to determine which is responsible, but deciding that the patient is ill because of the tumor without more direct support for such a conclusion may lead to inappropriate treatment, and at worst, untimely or inappropriately timed euthanasia of the patient. This presentation will outline some considerations for cancer patients that become ill during and after treatment.

Illness related to tumor treatment

The mainstays of cancer therapy, surgery, chemotherapy and radiation therapy, can create clinical illness on their own. In the cancer patient that has had one or more of these primary treatments, the clinician needs to ask if elements of the treatment could be responsible for a clinical illness. Surgical complications are often seen early in the post-operative course, but occasionally can be seen weeks or months afterwards depending on the nature of the surgery and the surgical site. The author has seen surgical abscesses appear as nodules or masses on radiographic studies that led some clinicians to believe that the affected patient had developed metastatic disease. If there is any question as to whether a new finding on a patient represents re-emergence of a tumor, or represents a surgical complication, then it is appropriate to collect samples (cytology, biopsy, etc) or pursue other diagnostic investigation such as additional imaging studies to try to more clearly define the finding as neoplastic or non-neoplastic.

Complications of chemotherapy tend to be seen within expected post-treatment windows. The most clinically important complications of chemotherapy, in terms of illness-producing potential, are gastrointestinal signs such as inappetance, vomiting, or diarrhea, which can be features of the underlying tumor for some patients, and bone marrow suppression, especially neutropenia and thrombocytopenia. Familiarity with the typical time course of post-chemotherapy complications for the drugs that the patient has been treated with can help pin initial suspicion of clinical illness on the chemotherapy. Gastrointestinal signs after chemotherapy are most often seen within the first 72 hours after chemotherapy has been given, and typically resolve within the following 24-48 hours. Some exceptions include doxorubicin-induced colitis, which may not be seen until 5-7 days after doxorubicin has been administered, and vinca-alkaloid induced gastrointestinal ileus, which can persist for days or longer in affected patients. The time to neutrophil nadirs depends on the chemotherapeutic drug administered. Many of the commonly used chemotherapy drugs cause neutrophil nadirs around 7 days after administration. Cyclophosphamide, vincristine and doxorubicin all tend to be associated with nadirs at around 7 days, although a later nadir is possible for any given patient. Carboplatin nadirs are often seen around 10-14 days, but occasional animals will have nadirs around 19-21 days. It is also important to be familiar with the unique toxicities of the patient's chemotherapy drugs. Doxorubicin can cause myocardial dysfunction, cyclophosphamide causes sterile hemorrhagic cystitis, cisplatin induces nephrotoxicity, and hepatotoxicity can arise as a complication of lomustine administration. Patients presenting with clinical signs that could reflect unique drug toxicities should be considered in that light before assuming that clinical signs are a manifestation of their tumor. Conversely, patients presenting with clinical signs atypical of drug-induced complications should be viewed as having something other than drug-induced illness.

Even drugs that are not cytotoxic, but used for tumor treatment, can cause clinical signs unrelated to the tumor. Glucocorticoids, for example, are common components of protocols used in the treatment of hematopoietic malignancies (e.g. lymphoma, multiple myeloma) and mast cell tumors. The author has seen cases that

presented with clinical signs that reflected complications of chronic glucocorticoid treatment, such as diabetes mellitus/diabetic ketoacidosis, that made it difficult to determine if the patient was ill from tumor-related causes.

Radiation therapy is increasingly available for adjuvant and primary treatment of a large number of small animal tumors. Side effects of radiation therapy are often considered early or late, reflecting their timing relative to treatment. Early radiation therapy reactions most often affect tissues with a rapidly dividing cell population (e.g. skin and other epithelial tissues) and are typically seen within the first 12 weeks of starting or completing radiation therapy and reflect injury to organs or tissues within the radiation field. Common early reactions that can cause clinical signs include moist or dry desquamation of the skin, and diminished tear production when eyes are in or close to the radiation field. In the central nervous system (CNS), neurological abnormalities that reflect the region of the CNS that was irradiated can be seen as a consequence of the radiation therapy within weeks, or late effects can be seen months after radiation therapy. Neurological abnormalities that develop, or in some cases persist, after radiation therapy may have major overlap with the original clinical presentation of the patient. A common strategy that is used in such instances is to treat with glucocorticoids, but response to therapy does not guarantee that clinical signs are a result of radiation therapy. Irradiation of nasal tumors can be associated with rhinitis, causing nasal discharge and sneezing similar to what may have been seen at the time of tumor diagnosis. For areas such as the CNS and nasal cavity, resolving whether clinical signs are a result of radiation therapy or tumor recurrence or progression may require repeating cross-sectional imaging studies such as computed tomography or magnetic resonance imaging.

Patients with some tumors within the abdomen and pelvis are candidates for radiation therapy, and here again, complications of radiation therapy have the potential to mimic clinical signs of the tumor. At WSU, under some circumstances we will treat patients with bladder and urethral carcinoma with radiation therapy. Irradiation of structures within the pelvis can lead to strictures, cause signs of colitis such as tenesmus and frank blood in the stool, or lead to stranguria, similar to what may have been seen as part of the clinical presentation of a patient with urethral carcinoma. Here again, repeating imaging studies, or other diagnostics, may be essential to defining the clinical picture as tumor-related or treatment-related.

Illness unrelated to the tumor

In many animals with tumors, reappearance of clinical signs similar to those seen around the time of diagnosis can be a signal that illness is related to the tumor. Patients that had paraneoplastic syndromes as a part of their initial presentation commonly have reemergence of the paraneoplastic syndrome when their tumors recur. Thus, for example, patients with hypercalcemia secondary to a malignancy may exhibit polyuria and polydipsia during tumor relapse and reemergence of hypercalcemia. Patients with lymphoma will often (but not always) relapse with presentations similar to their original presentations. Thus, in the cancer patient that becomes ill, be cautious about attributing the new illness to the tumor if the presentation is quite different than the patient's original tumor presentation. This is particularly important if the patient had a tumor not usually associated with metastatic potential. For example, the author consulted on a WSU patient that had been treated for vaginal lymphoma. The dog had responded quite well to chemotherapy, and approximately a year after having completed its chemotherapy protocol, a moderate lymphocytosis was found on a routine CBC. The dog had no physical examination evidence of a vaginal mass similar to its initial presentation. Further investigation revealed that the dog had a travel history to states where canine monocytic ehrlichiosis is endemic, and the dog proved to have *E. canis*-induced lymphocytosis that responded as expected to doxycycline. This case emphasizes the need for a broad approach that accounts for the same features of the presenting problem that would be appropriate for the non-cancer bearing patient: history of the presenting problem, travel history, other drug treatments, response to treatments if administered, physical examination and pursuit of appropriate diagnostic tests. Of course, patients may develop clinical signs that are a consequence of metastatic disease when there has been good local control of a primary tumor, and these presentations can be quite different from the original tumor presentation. For the client willing to pursue diagnostic tests, it is reasonable to perform imaging studies such as thoracic and

abdominal radiography, or abdominal ultrasonography, to determine if newly observed clinical signs can be attributed to metastasis, or to something else.

Patients with tumors can have other, concurrent problems that are not clinically important at the time of tumor diagnosis and initial treatment but can contribute to clinical signs later. One value of thoroughly staging a cancer patient is identification of other co-existing medical problems. When the problems are documented, the medical record can serve as a reminder to consider the possibility that the patient with a tumor may be experiencing clinical signs related to other pre-existing problems. For example, the author has seen hepatic abscesses in a diabetic dog treated for lymphoma, thromboembolic disease in proteinuric patients, and pre-existing renal failure be clinically important contributors to malaise that could have been easily attributed to the patient's tumor.

Summary

The approach to a cancer patient that has become ill should really be no different than the approach to any other ill patient. Acquisition of a good history is important as it can give clues as to why the patient is now ill. For some patients, consideration needs to be given to the possibility that clinical signs reflect treatment complications. To give one's patients the benefit of the doubt if it is not clear that a problem is tumor-related or not, the clinician may need to pursue additional diagnostic testing. For some patients, incorporation of laboratory results, imaging studies, and cytology and/or histopathology will be needed to discriminate tumor from non-tumor related illness. Keeping an open mind could prevent inappropriate decisions for the patient that has, or had, a tumor.