J Vet Intern Med 2007;21:1401–1404

Successful Treatment of Acute Tumor Lysis Syndrome in a Dog with Multicentric Lymphoma

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A 6-year-old, female, spayed Scottish Terrier weighing 13 kg was referred to the Colorado State University Animal Cancer Center (CSU-ACC) for radiation therapy (RT) for refractory multicentric lymphoma. The University of Wisconsin (UW)-Madison protocol (cyclophosphamide,[a] doxorubicin,[b] vincristine,[c] asparaginase,[d] and prednisone[e])[1] was initiated 1 year before presentation at CSU-ACC. A complete remission was achieved after the 1st dose of chemotherapy and continued for the next 11 months. When relapse was detected, a modified UW-Madison protocol substituting actinomycin D[f] for doxorubicin was initiated. The dog received 1 cycle of this modified protocol before the disease progressed. Asparaginase was administered 1 week before presentation at CSU-ACC. Additional rescue chemotherapy protocols were considered, but the owners opted for RT referral in an attempt to reduce tumor burden.

The most predominant features on general physical examination were generalized lymphadenopathy, hepatomegaly, and splenomegaly. The dog was otherwise clinically normal without signs of gastrointestinal upset or lethargy. The dog was not receiving other medications. A CBC revealed mild thrombocytopenia (115,000/uL; reference range, 200,000–500,000/uL). A serum biochemistry profile obtained 1 week before presentation at CSU-ACC had high alkaline phosphatase (2,000 U/L; reference range, 23–212 U/L) and high alanine transferase (517 U/L; reference range, 10–100 U/L) activities. All other values were within reference range. Hepatomegaly and splenomegaly were evident on left lateral thoracic and abdominal radiographs obtained for RT planning.

The plan was to administer two 3-Gray fractions to the entire body on consecutive days. Whole body radiation was planned instead of the more common half-body RT protocol because of the concern that if only half the body was irradiated, the dog's disease would remain in the half of the body that was not irradiated. To help spare as much bone marrow as possible, the dorsal aspect of the cranium, the vertebrae, tail, and the distal radii, ulnae, and tibiae were not included in the radiation field. Acute tumor lysis syndrome (ATLS) after half-body radiation therapy in dogs with lymphoma has been documented.[2,3] In addition, this dog had several risk factors known to promote ATLS development, such as a large tumor burden and abdominal disease. The owners were counseled on the high risk of this dog developing ATLS because of the treatment modality employed as well as known risk factors this dog possessed. The owners opted to continue with the treatment plan. The dog received one 3-Gray fraction of 6-mV photons from a linear accelerator.[g]

Four hours after treatment, emesis and diarrhea developed. The dog was febrile (104.7°F; reference range, 99.0–102.5), tachycardic (140 beats per minute), and tachypneic (70 breaths per minute). Mucous membranes were pale pink and tacky with capillary refill time less than 2 seconds. Femoral pulses were weak. Results of a serum biochemistry profile during this time period revealed several abnormalities, including hyperphosphatemia (7.5 mg/dL; reference range, 2.1–6.0 mg/dL), hyperkalemia (7.5 mEq/L; reference range, 3.5–5.2 mEq/L), and decreased serum bicarbonate concentration (12.4 mEq/L; reference range, 16–25 mEq/L). These abnormalities led to a tentative diagnosis of ATLS. The blood urea nitrogen (BUN) and creatinine concentrations were within reference range, supporting the underlying cause of hyperphosphatemia and hyperkalemia to be ATLS rather than secondary to acute oliguria or renal failure.

The dog was administered 0.9% sodium chloride[h] IV at 70 mL/h with a metoclopramide[i] continuous rate infusion (CRI) at 2 mg/kg/day. The dog was also administered 0.1 mg/kg ondansetron[j] IV every 8 hours. Temperature, heart rate, respiratory rate, mucous membrane color, and capillary refill time were monitored hourly. The dog remained tachycardic, tachypneic, febrile, and had multiple episodes of vomiting and diarrhea throughout the night. Serum electrolytes and venous blood gas analysis were repeated at 4–8 hour intervals. Urine pH via dipstick was 8.0.

The day after irradiation serum biochemistry abnormalities included hyperphosphatemia (9.9 mg/dL), hypocalcemia (8.9 mg/dL; reference range, 9.2–11.7 mg/dL), hypoalbuminemia (1.4 g/dL; reference range, 2.5–4.0 g/dL), increased BUN concentration (52 mg/dL; reference range, 7–32 mg/dL) with normal creatinine concentration, and decreased serum bicarbonate concentration (8.2 mEq/L). The potassium concentration returned to reference range. CBC and coagulation panel abnormalities included thrombocytopenia (37,000/uL), prolonged prothrombin time (PT) (16.8 seconds; reference range, 7.5–10.5 seconds) and activated partial thromboplastin time (aPTT) (39.7 seconds; reference range, 8–11.8 seconds), high concentration of fibrin degradation products (FDP) (>20 ug/mL; reference range, <5 ug/mL), and D-dimers (>4.0 ug/mL; reference range, <0.5 ug/mL). Thrombocytopenia with increases in PT, aPTT, FDP and D-dimers led to the diagnosis of

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Submitted January 19, 2007; Revised March 16, 2007, May 6, 2007; Accepted June 25, 2007.

0891-6640/07/2106-0033/$3.00/0

disseminated intravascular coagulopathy (DIC),[4] so 2 units of fresh frozen plasma were administered. Hypoalbuminemia was likely secondary to capillary leakage from the DIC as well as hemodilution from fluids. Venous blood gas abnormalities included acidemia (7.16; reference range, 7.3–7.45) and decreased bicarbonate concentration (8 mM; reference range, 15–24 mM). This severe metabolic acidosis was treated with the addition of a sodium bicarbonate[k] CRI. Sodium bicarbonate (13 mEq) was administered during the 1st hour, then 6.5 mEq/h sodium bicarbonate was given for an additional 4 hours. The metoclopramide CRI was continued at the previous dose, whereas the ondansetron dose was increased to 0.2 mg/kg IV every 8 hours. The dog continued to vomit but with less frequency.

Two days after RT a venous blood gas analysis revealed normal acid-base status. The sodium bicarbonate CRI was discontinued, and the fluid type changed to Normosol R[l] with 20 mEq potassium chloride[m]/L added. Serum phosphorus, calcium, BUN, and albumin concentrations were normal. The total bilirubin concentration was high (3.2 mg/dL; reference range, 0–0.3 mg/dL). There was thrombocytopenia (94,000/uL), normal PT, and mildly high aPTT (13.1 seconds). The dog was administered low-dose heparin[n] at 75 U/kg SC every 8 hours to prevent a thromboembolic event secondary to DIC. Ondansetron and metoclopramide CRI were continued as the previous day. The dog appeared to be clinically improved with normal pulse, respiratory rate, temperature, urine output, and only 1 episode of vomiting the entire day.

Three days after RT, the ondansetron was discontinued because there were no episodes of vomiting. The dog was offered food and ate readily. Crystalloid fluid therapy and the metoclopramide CRI were continued, given the history of severe vomiting. The metoclopramide CRI was discontinued the next day. Low-dose heparin therapy was continued. The platelet count was normal 9 days after RT. The aPTT and total bilirubin returned to reference range 3 days after RT.

Based on peripheral lymph node measurements, the dog met criteria for a partial response, according to the Response Evaluation Criteria in Solid Tumors (RECIST) criteria,[5] 5 days after RT, and this reached near complete response by 13 days after RT. Hepatomegaly and splenomegaly also became less profound on abdominal palpation by day 5 after RT.

The dog was discharged from the hospital 6 days after RT. Low-dose heparin therapy as prescribed while in the hospital, and oral prednisone (1 mg/kg PO q24h for 14 days) was administered. She was reevaluated at CSU-ACC on days 9 and 13 after RT for blood work and lymph node measurements. Plasma FDPs and D-dimer concentrations were within reference range on day 13, so the low-dose heparin therapy was discontinued. Starting 13 days after RT, the dog received a combination chemotherapy protocol including doxorubicin, bleomycin, vinblastine, and dacarbazine. Progressive disease was noted after 3 months. Overall, the dog survived for an additional 4 months after being treated for ATLS and subsequent DIC.

ATLS is an oncologic emergency resulting from spontaneous, radiation- or chemotherapy-induced rapid lysis of malignant cells. As malignant cells are destroyed, intracellular contents such as phosphorus, potassium, and purines spill into systemic circulation exceeding the excretory capacity of the kidneys and producing life-threatening metabolic and electrolyte disturbances.

Malignant lymphocytes contain approximately 4 times the amount of phosphorus as normal lymphocytes because of their increased nucleic acid and ATP requirements.[6] The rapid breakdown of tumor cells results in profound hyperphosphatemia and subsequent hypocalcemia due to precipitation of calcium phosphate in tissues, including the renal tubules,[7] which can result in oliguric or anuric acute renal failure. Clinical signs of hypocalcemia such as tetany, cardiac arrhythmias, syncope, or seizures may also be evident. As tumor cells break apart, the major intracellular cation, potassium, moves into systemic circulation. Hyperkalemia may result in lethargy, weakness, bradycardia, syncope, or life-threatening cardiac arrhythmias.

Hematologic neoplasms have a high nucleic acid turnover because of increased DNA synthesis requirements.[8] Lysis of malignant cells results in a high concentration of purines in the peripheral blood. In humans, purines are catabolized by the liver through oxidation of hypoxanthine and xanthine to the end product uric acid.[7] As serum uric acid concentrations increase, urine uric acid becomes less soluble, enabling the formation of crystals in the renal tubules[7] and leading to acute renal failure. Dogs, with the exception of Dalmatians and English Bulldogs, oxidize uric acid to allantoin in the liver via the enzyme uricase.[3,9–11] This small difference in purine metabolism prevents most dogs from developing hyperuricemia. Theoretically, Dalmatians and English Bulldogs are more susceptible to ATLS-associated hyperuricemia because these breeds lack the uricase enzyme.

DIC occurs after ATLS.[3] Shock, systemic inflammation, and neoplasia are all triggers for DIC.[12–14]

Increases in the total bilirubin in this dog 2 days after RT may have been due to inflammation-induced cholestasis. Bile flow takes place by the osmotic activity of bile salts that are actively transported across the canalicular membrane.[15] Cytokines upregulated by inflammation, such as interleukin 1-β and tumor necrosis factor-α, interfere with hepatocyte membrane binding of bile salts, therefore decreasing bile salt uptake and subsequent transport into the bile canaliculi, resulting in cholestasis.[15] Inflammation-induced cholestasis was reported in veterinary patients with extrahepatic infections.[15] It is conceivable that a dog with ATLS-induced severe inflammatory response might also experience cholestasis because of the effect of inflammatory mediators on bile salt binding to the hepatocyte.

ATLS is a well recognized syndrome in human cancer patients.[16,17] Patients with hematologic malignancies are at higher risk for the development of ATLS than are patients with most solid tumors.[17] Chemotherapy, immunotherapy, corticosteroids, and RT precipitate ATLS.[18–21] Case reports implicating surgery, a prolonged

fever, and spontaneous occurrence of ATLS are documented as well.[22–24]

Several clinical factors are associated with increased risk for ATLS in humans.[7,17] Advanced disease with large tumor burden, high proliferative fraction, and abdominal involvement impose a greater risk. Because renal clearance is the primary mechanism for excretion of phosphate, potassium, and uric acid, pre-existing renal insufficiency or dehydration increases risk for the development of ATLS.

The focus in humans is on prevention of ATLS.[25] Patients with known risk factors for ATLS are pretreated with intravenous fluids and allopurinol, a xanthine oxidase inhibitor that blocks the conversion of hypoxanthine and xanthine to uric acid. By blocking uric acid production, the likelihood of hyperuricemia-induced acute renal failure is diminished. Allopurinol has become so commonly integrated into treatment regimes that the incidence of ATLS in human patients has diminished.[25] With the exception of the at-risk breeds discussed above, allopurinol is not indicated in most canine patients.[3,9–11] If a human patient experiences ATLS despite the aforementioned precautions, treatment recommendations include aggressive monitoring of the patient's vital signs, correction of electrolyte abnormalities, aggressive fluid therapy, and additional allopurinol.[25]

ATLS is rarely reported in dogs, possibly because dogs do not develop uric acid nephropathy, the primary underlying problem in human patients. It should be mentioned that it is much more common for dogs to develop sepsis as a treatment complication after chemotherapy rather than ATLS. When acute fever and collapse occur after chemotherapy, sepsis is by far the most common cause of these adverse events. It is unlikely that the dog in this report was septic because she had not received myelosuppressive chemotherapy recently, had a normal neutrophil count, and improved without antibiotic treatment.

ATLS can occur in tumor-bearing dogs receiving chemotherapy or RT.[3] Death ensued within 6–18 hours after the appearance of clinical signs of ATLS in the 3 dogs with lymphoma included in one case series. The appearance of clinical signs in those dogs ranged from 18 hours to 8 days after treatment. Laboratory abnormalities included hyperphosphatemia, hypocalcemia, hyperkalemia, azotemia, and severe metabolic acidosis. The presence of generalized microthrombi and infarcts on postmortem examination of 2 of the dogs suggests that DIC was a terminal event. Two of the 3 dogs included in this case series received half-body radiation therapy before the development of ATLS.

Half-body radiation therapy for dogs with lymphoma precipitates ATLS.[2] It could be inferred from these reports that this treatment modality could present a greater risk for the development of ATLS in dogs with lymphoma. In the dog examined in this report, the risk factors for ATLS included large tumor burden, abdominal involvement, and treatment with radiation therapy. One could also speculate that the risk might have been further increased in this dog through the administration of whole-body, rather than half-body, radiation therapy as had been described in the previous reports.

Aggressive treatment and monitoring were initiated once the clinical signs of ATLS developed in the dog examined in this report. The severe response in this dog might have been mitigated if fluids were administered before irradiation, especially since risk factors for the development of ATLS were recognized. Furthermore, the risk of ATLS could have been significantly diminished or ameliorated if a different treatment approach, such as rescue chemotherapy or a half-body RT protocol, was taken. Quick recognition of ATLS as well as aggressive monitoring and supportive treatment appear to have been important in this dog's recovery.

Footnotes

[a] Cyclophosphamide, Mead Johnson Oncology, Princeton, NJ
[b] Doxorubicin HCl, Pfizer Inc, New York, NY
[c] Vincristine sulfate, Genesia Sicor Pharmaceuticals, Irvine, CA
[d] Asparaginase, Merck and Company, Inc, West Point, PA
[e] Prednisone, Phoenix Pharmaceutical, Lincoln Park, NJ
[f] Actinomycin D, Merck and Company, Inc, West Point, PA
[g] Mevatron 6740, Siemens, New York, NY
[h] 0.9% Sodium chloride, Abbott Laboratories, Abbott Park, IL
[i] Metoclopramide, Wyeth-Ayerst, Madison, NJ
[j] Ondansetron, GlaxoSmithKline, Philadelphia, PA
[k] Sodium bicarbonate, Abbott Laboratories, Abbott Park, IL
[l] Normosol R, Abbott Laboratories, Abbott Park, IL
[m] Potassium chloride, Phoenix Pharmaceuticals, Lincoln Park, NJ
[n] Heparin sodium, Wyeth-Ayerst, Madison, NJ

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