CASE REPORT

Acute tumour lysis syndrome in a dog with B-Cell multicentric lymphoma

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A 5-year-old, spayed female German Shepherd dog was admitted to hospital with marked generalised lymphadenomegaly and splenomegaly. A stage Va B-cell multicentric lymphoma was diagnosed on clinical, cytological (lymph node, bone marrow), histological-immunohistochemical (lymph node excision) and imaging grounds. Since no satisfactory remission was achieved using a multi-drug chemotherapy protocol that included cyclophosphamide, vincristine, cytosine arabinoside, prednisolone, and subsequently supplemented by L-asparaginase, it was replaced by another protocol combining vincristine, L-asparaginase, prednisolone, cyclophosphamide and doxorubicin. Soon after the third weekly session of the second protocol, the clinical status of the animal deteriorated suddenly and severely, with a bleeding tendency, jaundice, hyperuricaemia, hyperphosphataemia, azotaemia, hyperbilirubinaemia and, presumptive disseminated intravascular coagulation. There was also complete regression of lymphadenomegaly. This report emphasises the clinicopathological features and the diagnostic peculiarities of the acute tumour lysis syndrome, which occurs uncommonly in dogs.

Key words: lymphoma, dog, acute tumour lysis syndrome
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ATLS	Acute tumour lysis syndrome
IV	Intravenously
SC	Subcutaneously

Acute tumour lysis syndrome (ATLS) is an oncological emergency precipitated by the release of intracellular substances such as purines, potassium and phosphorus into the bloodstream after rapid cytoreduction of bulky tumours.[1,2] It is a well-recognised emergency condition in humans undergoing chemotherapy or radiation therapy for Burkitt's lymphoma, acute lymphoblastic leukaemia or, less frequently, non-haemopoietic tumours.[3,4] It occurs rarely in veterinary medicine, with the majority of cases involving the dog.[5,6] To the best of our knowledge, only six canine cases and a single feline case have been reported; these animals belonged to various breeds and had received chemotherapy, radiation therapy or both, for multicentric (five dogs), mediastinal (one cat) or pulmonary (one dog) lymphoma.[5–8]

This article describes a dog with ATLS and illustrates the clinical, clinicopathological and diagnostic considerations of this rarely occurring but often lethal complication of lymphoma treatment.

Case report

A 5-year-old, spayed female, German Shepherd was presented with a 4-day history of exercise intolerance and selective appetite. Generalised peripheral lymphadenomegaly and splenomegaly were detected, in an otherwise normal physical examination. Complete blood count along with the microscopic evaluation of Giemsa-stained (Merck, Darmstadt, Germany) peripheral blood smears disclosed only a mild neutrophilic leukocytosis (Table 1). Serum biochemistry profile (Table 1) and urinalysis were unremarkable and the dog was tested negative by dot enzyme-linked immunoabsorbent assay for *Ehrlichia canis* (ImmunoComb, Biogal-Galed, Laboratories, Kibbutz Galed, Israel) and *Leishmania infantum* (Snap Leishmania Test Kit; IDEXX Laboratories Inc., One IDEXX drive, Maine, USA). Giemsa-stained, fine needle aspiration smears, obtained from the left prescapular lymph node, were dominated by lymphoblasts and prolymphocytes, comprising 85% of the nucleated cells. A lymphoblastic infiltrate (20% of the nucleated cells) was observed on cytological examination of a bone marrow aspirate. Thoracic radiographs were unremarkable, while abdominal ultrasonography revealed marked splenomegaly, mild hepatomegaly, and sublumbar-mesenteric lymph node enlargement.

The entire left popliteal lymph node was surgically excised, fixed in 10% buffered formalin, dehydrated and embedded in paraffin. Sections, 4 to 5 μm thick, were cut and stained with haematoxylin and eosin. Additional lymph node sections were stained with antibodies against CD3 (Dako A/5, Glostrup, Denmark) and CD79α (Dako A/5, Glostrup, Denmark) for T- and B-cell lymphocyte identification, respectively. On histological examination, a high grade lymphoblastic lymphoma was diagnosed, the entire cellular population of which reacted positive to CD79α, apart from less than 3% CD3 positive cells, thus leading to the documentation of a stage V (substage a) B-cell multicentric lymphoma.[9]

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At the owner's request to prolong the animal's survival time, an 8-week induction chemotherapy protocol,[10] including cyclophosphamide (Endoxan, Farmalex, Athens, Greece) at 50 mg/m^2 orally every 48 h, vincristine (Oncovin, Farmaserb, Athens, Greece) at 0.5 mg/m^2, IV, weekly, cytosine arabinoside (Aracytin, Vianex, Athens, Greece) at 100 mg/m^2, SC for 4 days and prednisolone (Prezolone, Minerva, Athens, Greece) at 50 mg/m^2, orally once daily, for 1 week, then 20 mg/m^2 orally every 48 h for 7 weeks, was instituted, resulting in partial remission, without apparent adverse drug effects. At the end of the 8-week period (63 days from the initial admission), intensification of chemotherapy was attempted with a single dose of L-asparaginase (Erwinase, Ipsen, Athens, Greece), at 10,000 IU/m^2, IM,[10] which again failed to induce complete remission. One month later and 90 days from the initial admission, another multiple-agent chemotherapy protocol combining (until the third treatment week) vincristine (0.7 mg/m^2, IV, at weeks 1 and 3), L-asparaginase (400 U/kg, SC, once at week 1), prednisolone (2 mg/kg, 1.5 mg/kg and 1 mg/kg orally, daily for weeks 1, 2 and 3, respectively), and cyclophosphamide (200 mg/m^2, IV at week 2)[11] was instituted because of progressive disease characterised by a relapsing lymphadenomegaly and palpable splenomegaly. No pre-treatment haematological, biochemical or urinalysis abnormalities could be detected, apart from a mild hyperuricaemia (Table 1). There was a less than 50% reduction of peripheral lymphadenomegaly, in addition to resolution of palpable splenomegaly, by completion of the 3rd weekly chemotherapy session.

Four days later (109 days from the initial admission), the dog was re-admitted in a moribund state, with jaundice, mucosal petechiae-ecchymoses and dramatic regression of lymphadenomegaly. Laboratory abnormalities consisted of non-regenerative anaemia, thrombocytopenia, azotaemia, hyperbilirubinaemia, elevated alkaline phosphatase and alanine aminotransferase activities, hyperphosphataemia, hyperuricaemia (Table 1) and lower than normal urine specific gravity (1.020). Routine coagulation profile (SCA 2000, Veterinary Coagulation analyzer, Synbiotics, San Diego, CA, USA) revealed a prothrombin time of 23 s (reference interval: 12 to 17 s), partial thromboplastin time of 190 s (reference interval: 70 to 102 s) and a concentration of fibrin(ogen) degradation products (FDP Plasma, Diagnostica Stago, Asnieres, France) in excess of 10 µg/dL (reference interval: < 5 µg/dL). These laboratory abnormalities led to the diagnosis of ATLS along with presumptive disseminated intravascular coagulation. Despite the efforts of the emergency service staff that included crystalloids (0.9% NaCl at 90 mL/kg for the first hour and then 10 mL/kg/h), a blood-typed and cross-matched whole blood transfusion, sodium heparin (Heparin, Leo, Athens, Greece) at 100 IU/Kg SC, the dog died 12 h after admission. Permission for necropsy was denied by the owner.

Table 1. Clinicopathological findings at two time points prior to, and at the onset of, acute tumour lysis syndrome in a dog with multicentric B-cell lymphoma.

	Reference interval	Day from initial admission		
		1	90	109
Haematology				
Haematocrit (L/L)	0.37–0.55	0.37	0.39	0.27
Haemoglobin (g/L)	120–180	125	136	91
White blood cells (×10^9/L)	6–17	17.7	13	18.7
Neutrophils (×10^9/L)	3–11	13.27	10.5	14.2
Bands (×10^9/L)	0–0.3	0	0.15	0.56
Lymphocytes (×10^9/L)	1–4.8	4.25	1.5	2.8
Monocytes (×10^9/L)	0.15–1.35	0	0.7	0.77
Eosinophils (×10^9/L)	0.1–1.25	0.18	0.15	0.37
Platelets (×10^9/L)	175–500	183	139	11
Serum biochemistry				
Total proteins (g/L)	60–80	60	66	60
Albumins (g/L)	25–35	35	34	ND
Creatinine (µmol/L)	44–132	106	107	201
Blood urea nitrogen (mmol/L)	2.5–10.7	7.1	13.5	19.4
Glucose (mmol/L)	4.4–7.1	7.4	7	4
Total bilirubin (µmol/L)	5.1–13.7	ND	5.6	180
Alkaline phosphatase (U/L)	50–210	58	225	2000
Alanine aminotransferase (U/L)	10–34	6	30	677
Phosphorus (mg/dL)	0.8–1.6	1.2	1.1	4.4
Calcium (mmol/L)	2.25–3	3.1	2.5	2.75
Potassium (mmol/L)	3.5–5.5	4.5	3.3	4
Uric acid (mmol/L)	0–59	ND	153	826

ND: not determined.

Discussion

The clinical and biochemical criteria for the diagnosis of ATLS in humans include rapid tumour regression, hyperuricaemia, hyperphosphataemia with or without azotaemia, hyperkalaemia, and occasionally hypocalcaemia.[1,3] Most of these criteria were met in the dog described here. Fulminating clinical deterioration, another feature of ATLS that was also witnessed in this case, may lead to a moribund state a few hours to 7 days after the administration of chemotherapy or radiotherapy.[5,7] Although the small number of published canine cases does not allow definite conclusions, it appears that animals with advanced disease (that is, stage IV or V of high grade lymphoma), high pre-treatment serum alkaline phosphatase activity, rapid tumour regression and, probably, pre-existing renal failure, are at higher risk.[7,12] These risk factors were present in this dog, apart from the elevated alkaline phosphatase activity and kidney disease, neither of which were documented during the period preceding the appearance of ATLS.

This dog developed ATLS during the second multi-drug chemotherapy, following the failure of the first protocol to achieve satisfactory remission. This may indicate that the aggressiveness of the chemotherapy precipitated the occurrence of ATLS, although the timing for its appearance is rather unpredictable. In

humans, even single agent protocols may induce the syndrome.[13] Lymphoma immunophenotype apparently does not correlate with the occurrence of ATLS in humans,[14] but there is no such information in the published veterinary cases. This issue may warrant further consideration, since canine B-cell lymphomas are considerably more chemoresponsive than their T-cell counterparts.[9]

Serum uric acid was much in excess of pre-treatment levels, a very uncommon finding in the dog due to its adequate uricase activity (apart from the Dalmatian breed).[1,7] Interestingly, a mild hyperuricaemia has been documented in dogs with lymphoma prior to treatment, which is not normally expected to increase significantly with uncomplicated chemotherapy.[5,15] Massive tumour cell lysis may have accounted for the dramatic elevation of serum uric acid concentration, probably aided by uricase depletion due to severe liver disease.[1] Serum hyperuricaemia (that is, in excess of 600 mmol/L) may cause obstructive nephropathy secondary to crystallisation of uric acid within the distal renal tubules and ureters, which would account for the acute renal failure seen in this dog.[1]

Hyperphosphataemia, probably the most consistent biochemical indicator of canine ATLS,[5,7] may appear in isolation or in the context of renal azotaemia.[5] In human lymphoma the intracellular concentration of phosphorus is 4 to 6 times higher than that of the normal lymphocytes and the same is probably true in canine lymphoma.[16] The fact that hyperkalaemia and hypocalcaemia were not documented in the dog of this report is in agreement with the current notion that they are not consistent findings in canine ATLS.[5,7] Although the underlying mechanism for the development of acute liver failure is not straightforward, the diffuse infiltration of the organ by malignant lymphocytes would be a reasonable explanation.[10] Notably, the steroid treatment could have accounted at least partially for the considerable increase of alkaline phosphatase activity.

Disseminated intravascular coagulation has occasionally been observed in terminally ill dogs with ATLS,[5] probably representing a paraneoplastic condition. The laboratory diagnosis of disseminated intravascular coagulation was based on the combination of thrombocytopenia, prolonged prothrombin and partial thromboplastin times, and elevated fibrin(ogen) degradation products,[17] although severe liver disease may also produce the same haemostatic abnormalities.[18] Undoubtedly, the measurement of D-dimers in blood plasma and postmortem histopathology may have confirmed the diagnosis of disseminated intravascular coagulation.[5]

Experience raised by the present as well as the few previously published cases of canine ATLS, indicate that predisposed patients (that is, those with lymphoma and high tumour burden) should be identified and closely monitored, especially during the induction chemotherapy period. Early recognition and institution of aggressive fluid therapy may reduce the mortality rate from ATLS.[5] Prophylactic treatment is frequently instituted in human patients considered at high risk for developing ATLS. Prophylaxis consists mainly of saline diuresis, urine alkalinisation by intravenous administration of sodium bicarbonate, as well as allopurinol and urate oxidase to diminish the production of uric acid.[1,19]

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