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Spontaneous rupture of the lymph nodes as a cause of haemoabdomen in two canine lymphoma patients

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Abstract: Non-traumatic haemoabdomen in dogs usually occurs due to abdominal neoplasia, coagulopathies or organ torsion. The most common sources of bleeding in neoplastic cases are the spleen and liver, but other abdominal organs can also be involved. However, in the available veterinary literature, ruptured lymph nodes are not described as a cause of haemoabdomen. In the present manuscript, two canine cases of intra-abdominal haemorrhage from ruptured lymph nodes secondary to B-cell lymphoma are described.

Keywords: dog; haemoperitoneum; multicentric lymphoma; neoplasia; nontraumatic haemoabdomen

Haemoabdomen is defined as the accumulation of blood within the peritoneal cavity and may be classified as traumatic or non-traumatic/spontaneous (Brockman et al. 2000). Clinical signs are related to acute blood loss and hypovolemic shock, and patients with spontaneous haemoabdomen may also present with lethargy, inappetence, abdominal distension, abdominal pain and vomiting (Pintar et al. 2003; Aronsohn et al. 2009).

Spontaneous haemoabdomen in dogs occurs due to abdominal neoplasia, coagulopathies or intra-abdominal organ torsion (Brockman et al. 2000). Neoplastic conditions that have been reported as a cause include splenic haemangiosarcoma, haemangioma, hepatocellular carcinoma, carcinomatosis, renal and adrenal malignancies, mesothelioma or hepatic metastasis of other tumours (Evans et al. 1991; Brockman et al. 2000; Pintar et al. 2003; Aronsohn et al. 2009; Gumber et al. 2011). Splenic rupture and haemoabdomen secondary to high-grade lymphoma and splenic marginal zone lymphoma have been recently reported (Stefanello et al. 2011; O'Brien et al. 2013; Azevedo et al. 2017), but no report of ruptured lymph nodes (LNs) as a cause of haemoabdomen is found in veterinary literature.

The prognosis of lymphoma patients is mainly dependent on the inclusion of chemotherapy (Vail et al. 2019). However, surgical intervention may be warranted in patients in which organ rupture is suspected (Stefanello et al. 2011).

The purpose of this manuscript is to describe two surgically explored cases of spontaneous haemoabdomen occurring after the rupture of the abdominal LN secondary to the lymphoma.

Case descriptions

CASE 1

A 6.5-year-old intact male American Staffordshire Terrier weighing 28.5 kg presented with acute onset of vomiting and sudden lethargy beginning two

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hours prior to admission. The dog had been treated for multicentric B-cell lymphoma by a referring veterinarian with a protocol using cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), which had ended two months prior to this admission.

At presentation, the dog exhibited pale mucous membranes, hypothermia (37 °C), a prolonged capillary refill time (CRT; approximately 3 s) and tachycardia (140 bpm) with a weak pulse. The abdomen was distended and painful upon palpation. The peripheral LNs were within normal limits. The complete blood count (CBC, ADVIA 120; Siemens, Germany) values at presentation are shown in Table 1. The biochemistry profile (RX Daytona, Randox, UK) was within normal limits, with a total protein concentration of 54 g/l (reference range 54–71 g/l). The emergency ultrasonography in the right lateral recumbency (Lisciandro 2011) revealed a small amount of fluid in the diaphragmatic-hepatic and hepatorenal views, and abdominocentesis was unsuccessful at that point. The coagulation profile, including the D-dimer levels, was within normal limits.

An intravenous (i.v.) catheter was inserted into the cephalic vein, and an isotonic crystalloid solution (Hartmann solution; B. Braun, Melsungen, Germany) was initiated at 10 ml/kg/h i.v. The analgesic treatment was provided with morphine (Morfin Hidroklorid Alkaloid; Alkaloid, Skopje, North Macedonia) at 0.1 mg/kg/h, lidocaine (Lidocaine; B. Braun, Melsungen, Germany) at 1 mg/kg/h and ketamine (Bioketan; Vetoquinol Biowet, Gorzow, Poland) at 0.1 mg/kg/h in a constant rate i.v. infusion (MLK CRIV), with the simultaneous administration of a 75-µg fentanyl transdermal patch (Durogesic; Janssen Pharmaceutica, Beerse, Belgium).

Table 1. The relevant haematology indicators of both patients

	Patient 1	Patient 2	Reference range
White blood cell count	23.11	17.76	5.2–13.9 × 10^9/l
Neutrophil	19.38	13.64	3.9–8 × 10^9/l
Lymphocyte	2.38	2.27	1.3–4.1 × 10^9/l
Monocyte	1.33	1.25	0.2–1.1 × 10^9/l
Red blood cell count	5.11	5.24	5.7–8.8 × 10^{12}/l
Haemoglobin	122	114	129–184 g/l
Haematocrit	37.22	34.04	37–57%
Platelet count	80	164	143–400 × 10^9/l

The ultrasonographic examination after four hours revealed a severely enlarged, heterogeneous spleen. The abdominal lymph nodes (LNs) were hypoechoic and severely enlarged. There was a large amount of free abdominal fluid. An abdominocentesis was performed, revealing fluid with a haematocrit of 41.65%. The thoracic radiographic examination results were within normal limits. At that point, the haematocrit level in the peripheral blood fell to 28%. Due to the progression of the haemoabdomen, the dog was scheduled for a diagnostic celiotomy. The fluid treatment was changed to fresh whole blood (starting at 2 ml/min and continued at 5 ml/min) and a crystalloid solution (NaCl 0.9%; B. Braun, Melsungen, Germany) was administered i.v. at 10 ml/kg/h, which was continued during the anaesthesia.

The patient was premedicated with Midazolam at 0.1 mg/kg and fentanyl at 0.2 µg/kg i.v., and the anaesthesia was induced with propofol (Propoven; Fresenius Kabi Ltd., Runcorn, England), titrated to effect (2 mg/kg). After the endotracheal intubation, the anaesthesia was maintained with sevoflurane (Sevoflurane Baxter; Baxter Healthcare Ltd., Norfolk, England) at 1.5% to 3% (vapour setting) in a mixture of oxygen (1 l/min) and air (1 l/min) delivered through a circular breathing system. The dog continued to breath spontaneously during the anaesthesia. The perioperative analgesia was performed with an MLK CRIV.

During the diagnostic celiotomy, after the aspiration of 450 ml of blood and the examination of the abdominal cavity, the jejunal LNs (Figure 1)

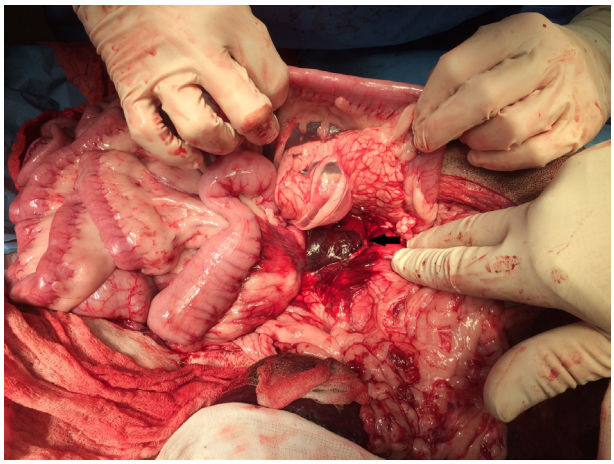

Figure 1. The severely enlarged, ruptured jejunal lymph node (arrow) after the successful haemostasis

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were ascertained as the source of the bleeding. They were rounded and up to 5 cm in diameter, and one was ruptured. The rupture was 3 cm long and 1 cm deep, and blood was oozing from the surface. Biopsies of the LNs, spleen and liver were taken, and the bleeding was stopped using an oxidised cellulose net (Surgicel; Ethicon SARL, Neuchatel, Switzerland). The abdomen was closed in a routine manner. The postoperative analgesia consisted of MLK CRIV, which was continued for 12 hours, and an additional 25-µg fentanyl transdermal patch (Durogesic; Janssen Pharmaceutica, Beerse, Belgium) was applied. Methadone (Comfortan; Dechra, Northwich, England) at 0.3 mg/kg q5h was applied subcutaneously three times in the postoperative period. Additionally, 100 ml of fresh whole blood was given postoperatively, after which the crystalloid solution was again changed to an isotonic crystalloid solution (Hartmann solution; B. Braun, Melsungen, Germany). The patient was discharged 2 days postoperatively.

The samples for the histopathology were fixed in 10% neutral buffered formalin and routinely embedded in paraffin blocks; the 4-µm-thick paraffin tissue sections were stained with haematoxylin and eosin (HE) and immunohistochemically labelled with antibodies against CD3 and CD20. The slides were deparaffinised and hydrated using a xylene-ethanol series. The antigen retrieval was performed by microwave treatment at a medium power (550 W) for 20 min in a 0.1 M citrate buffer (pH 6.0). The sections were incubated with a rabbit anti-human CD3 polyclonal antibody (DAKO, Glostrup, Denmark) diluted 1 : 300 and a rabbit anti-human CD20 polyclonal antibody (Invitrogen) diluted 1 : 400 for one hour at room temperature in a humid chamber. The endogenous peroxidase activity was quenched in a DAKO REAL™ Peroxidase-Blocking Solution (DAKO) for 30 min at room temperature. Subsequently, a DAKO REAL™ EnVision™ Detection System Peroxidase/DAB+, Rabbit/Mouse visualisation kit (DAKO) was employed according to the manufacturer's instructions. The sections were counterstained with Mayer's haematoxylin and mounted.

The histopathological examination of the jejunal LNs and spleen revealed complete effacement of the architecture by a diffuse infiltrate of lymphoid cells that expressed CD20 and were negative for CD3. In the liver, lymphoid cell infiltrates were mainly found in the periportal areas. The findings

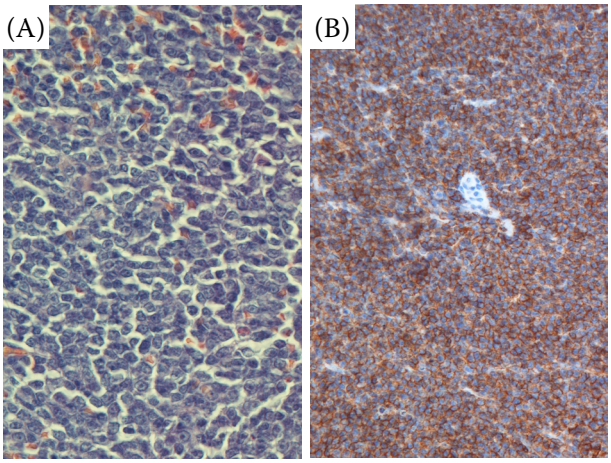

Figure 2. The histological and immunohistochemical photomicrographs of the jejunal lymph node. Haematoxylin and eosin (A), CD20 immunostaining (B)

were consistent with the diagnosis of an immunoblastic diffuse large B-cell lymphoma (DLBCL-IB) (Figure 2).

After the diagnosis, the dog continued the treatment at the referring veterinarian's office, receiving two additional cycles of the CHOP protocol. The patient was euthanised eight months after surgical intervention due to the progression of the disease.

CASE 2

A 13-month-old intact male Scotch Collie weighing 30 kg presented with weight loss and inappetence with a 2-week duration. Three days prior to admission, the dog started vomiting and exhibited voluminous mucous diarrhoea with haematochezia.

Upon presentation, the dog was attentive, febrile (40.2 °C), tachycardic (150 bpm) and exhibited slightly muffled heart sounds, had pale mucous membranes and had a CRT of 3 s. A firm and non-painful mass of approximately 15 cm in diameter was palpated in the cranial mesogastrium. The biochemistry profile (as in Case 1) was within normal limits, and the CBC results are shown in Table 1.

The ultrasonographic examination revealed extremely enlarged abdominal LNs with mixed echogenicity, while the liver, spleen and kidneys were of normal size and echogenicity. An abdominal effusion was not evident; hence, a fine needle aspiration biopsy (FNA) of the jejunal LN was

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performed, revealing a mixed population of lymphocytes and activated macrophages with severe blood contamination. The abdomen was checked ultrasonographically approximately 30 min after the FNA for possible bleeding, and no fluid collection around the site of aspiration could be seen.

Due to the non-diagnostic cytological examination, twenty hours after the initial presentation, a diagnostic celiotomy was performed, revealing severely enlarged and partly necrotic pancreaticoduodenal LNs and ruptured jejunal LNs, in addition to 150 ml of blood and several blood clots in the abdomen. An intraoperative FNA of the enlarged LN was performed, and the specimen was examined cytologically, revealing the diagnosis of lymphoma. The dog was euthanised intraoperatively with a 0.3 ml/kg of embutramide, mebezonium iodide and tetracaine hydrochloride injectable euthanasia solution (T61 ad us vet; MSD Animal Health GmbH, Lucerne, Switzerland) administered intravenously at the owner's request and submitted for necropsy.

At necropsy, pale tan, severely enlarged jejunal LNs measuring 19 × 9 × 5 cm were observed. On the surface of the enlarged jejunal LNs, multifocal small blood clots were observed. In addition, moderately to severely enlarged pancreaticoduodenal, sternal, and mediastinal and slightly enlarged superficial cervical LNs were found. The spleen was slightly congested. Samples of the LNs and spleen were taken for histopathology and were further processed as described in Case 1.

The histopathological examination of the LNs revealed the complete effacement of the architecture by a diffuse infiltrate of CD20-positive lymphoid cells. In the spleen, multifocal infiltrates of lymphoid cells were found predominately around the fading remnants of the germinal centres, but larger aggregates of lymphoid cells were also found. The findings were consistent with the diagnosis of a centroblastic diffuse large B-cell lymphoma (DLBCL-CB).

DISCUSSION

Lymphoma as the aetiologic factor of spontaneous haemoabdomen is not common, but it may occur with the spleen as the source of bleeding (Stefanello et al. 2011; O'Brien et al. 2013; Azevedo et al. 2017). Herein, we report the rupture of the jejunal LNs in two dogs due to diffuse large B-cell lymphoma. In the available veterinary literature, LNs have not previously been reported as the cause of haemoabdomen. However, there are reports in human medicine indicating the rupture of mostly metastatic LNs, resulting primarily from hepatocellular carcinoma (Seki et al. 2001; Terada et al. 2003; Oh et al. 2013), with other metastatic tumours being reported sporadically (Moore et al. 2010; Choi et al. 2017). This relatively common spontaneous rupture (10–18%) observed in human hepatocellular carcinoma occurs due to the extensive vascular structure and the relatively small amount of fibrous tissue in the tumour (Oh et al. 2013). In cases of spontaneous splenic ruptures in lymphoma patients, the suggested mechanisms are splenic enlargement, cellular infiltration, and eventual splenic infarction with associated capsular haemorrhage (Kumar et al. 2017). While the vascular and cavity structure of haemangiosarcoma explains the high prevalence of organ rupture in dogs, the rupture observed in our cases can be attributed to a small amount of fibrous stroma, the enlargement of the lymph nodes and a dense lymphoid infiltration. Although the FNA performed on the preceding day may be the reason for the LN rupture in the second case, the available literature generally indicates only small haematomas or minimal bleeding from a local site (Liffman and Courtman 2017), which were not confirmed in the control ultrasonographic examination performed approximately half an hour after the FNA. Significant bleeding after an abdominal FNA is not encountered even in patients with prolonged bleeding times, as demonstrated by Gazelle et al. (1992) in pigs treated with warfarin. Core biopsies of abdominal organs, which are more invasive than FNA, are associated with a higher chance of bleeding in canine patients with platelet counts below 80×10^9/l (Bigge et al. 2001). Although the coagulation profile of the second patient was not determined during the diagnostic workup, the dog's platelet count was well above the previously mentioned threshold; therefore, we do not believe that the FNA of the affected lymph node was the cause of haemoabdomen in this patient. In particular, we consider the finding of Kol et al. (2015) that approximately 80% of canine malignant lymphoma patients exhibit coagulation disorders consistent with hypercoagulability with an accelerated clot formation time, which would make the possibility of significant bleeding after FNA even lower.

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Since the use of ultrasonography in locating the source of the bleeding as well as differentiating malignant from benign lesions is limited (Pintar et al. 2003; Aronsohn et al. 2009; Gerboni et al. 2015), a diagnostic celiotomy with biopsies is indicated in cases of spontaneous haemoabdomen. Surgical management is aimed at the resection of the tumour, the control of the bleeding focus, the biopsy of the additional sites and the removal of the devitalised tissue (Brockman et al. 2000). In both patients, the bleeding was controlled; however, one of them was euthanised intraoperatively.

The prognosis of patients with haemoperitoneum due to lymphoma is, beyond the ability to achieve control of the bleeding, dependent on the inclusion of chemotherapy and the biologic behaviour of the tumour (Stefanello et al. 2011; O'Brien et al. 2013; Cozzi et al. 2018). The first patient with immunoblastic diffuse large B-cell lymphoma survived 8 months postoperatively, which is in accordance with the literature (Vail et al. 2019).

In conclusion it can be stated that massive enlargement of jejunal LN can occur in dogs with diffuse large B-cell lymphoma. The affected LNs may rupture and cause haemoabdomen, demanding surgical intervention.

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Conflict of interest

The authors declare no conflict of interest.

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