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Neoplastic disease

T-cell lymphoma involving the rectum of a dog

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ABSTRACT

A mediastinal mass was diagnosed in a 7-year-4-month-old neutered female mixed breed dog following a 3-week history of lethargy, hyporexia and pyrexia. Bi-cavitary imaging, needle aspirate cytology and flow cytometry confirmed WHO clinical stage IVb, intermediate to large T-cell lymphoma involving the mediastinum, liver and spleen. The dog initially responded to a multidrug chemotherapy protocol but clinical deterioration occurred 3 months later. The dog presented with anorexia, vomiting and diarrhoea, associated with marked faecal tenesmus and haematochezia, initially believed by the primary care practitioner to be related to chemotherapy toxicity. However, rectal examination revealed multiple sessile and pedunculated masses. Further diagnostic imaging, cytology and flow cytometry confirmed progressive disease, including T-cell lymphoma of the rectum. Histology and immunohistochemistry confirmed an infiltrate of intermediate-sized CD3-positive neoplastic cells that expanded the rectal mucosa. Rectal lymphoma is uncommon in dogs and previous cases have been B cell in origin. In this report we describe the clinical presentation and macro- and microscopic findings of a case of canine T-cell lymphoma involving the rectum.

Lymphoma is a common neoplasm in dogs and is anatomically classified into multicentric, mediastinal, alimentary and extranodal forms. Primary alimentary lymphoma is diagnosed when the predominant lesion lies within the gastrointestinal (GI) tract, with lymph node involvement confined to the lymph node chain draining that specific segment of the tract and without peripheral lymphadenopathy [1]. Alimentary lymphoma, whether primary or part of the wider pattern of disease, is uncommon in dogs, accounting for only 7% of all canine GI tumours [2] and 5–7% of all lymphomas [3,4]. It is often described as involving multiple segments of the GI tract, without further anatomical localization [3,5–7]. The T-cell lineage predominates in primary canine GI lymphoma [4–7] and carries a guarded prognosis with median survival times as low as 0.5–2.5 months [6,7].

Rectal neoplasia in dogs is predominantly benign and epithelial in origin [8]. Rectal lymphoma is rarely reported [9–14] and is most commonly a primary lesion at this site. By comparison with generalized alimentary lymphoma, rectal lymphoma has a better prognosis, with one study reporting a mean survival of 1,697 days (median not reached) [11]. When phenotype has been reported, a B-cell origin has been identified [11–15]. In this report we describe the clinical presentation and macro- and microscopic findings of a case of canine T-cell lymphoma involving the rectum.

A 7-year-4-month-old neutered female mixed breed dog weighing 27 kg, with a body condition score (BCS) of 6/9, presented following a 3-week history of intermittent pyrexia, lethargy, hyporexia and tachypnoea. There was no relevant previous history. Survey radiographs revealed a cranial mediastinal mass and the dog was referred for further assessment. At presentation, the animal was receiving paracetamol (10 mg/kg TID) and was bright, alert, responsive and mildly overweight. The rectal temperature was 38.5°C, heart rate 112 beats/minute, with a synchronous pulse, and resting respiratory rate 44 breaths/minute with no adventitial sounds. The remainder of the physical examination was unremarkable.

Routine haematology and clinical chemistry revealed a mild mature neutrophilia of 12.16×10^9/L (reference interval [RI] 3–11) and a moderate to marked increase in C-reactive protein (44.5 mg/L, RI 0–8.2) consistent with acute inflammation. Mild elevations in alkaline phosphatase (ALP) (210 IU/L, RI 26–107), gamma-glutamyltransferase (GGT) (14 IU/L, RI 0–10) and aspartate aminotransferase (AST) (56 IU/L, RI 12–49) activities were considered non-specific and of no clinical significance. Thoracic radiography confirmed a cranioventral, mediastinal mass with widening of the cranial mediastinum on the dorsoventral view, equivalent to four times the width of the vertebral column.

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Ultrasonography confirmed an approximately 4.8 cm diameter, heterogeneously hypoechoic mass in the left cranial mediastinum, which was poorly vascularized on Doppler interrogation. In the abdomen there was a 6.05 cm × 6.09 cm rounded and heterogeneously hypoechoic mass in the right division of the liver, with several variably sized, ill-defined, hypoechoic nodules in multiple lobes of the left division of the liver. The hepatic lymph nodes surrounding the porta hepatis were markedly enlarged, hypoechoic and rounded. Several variably sized, hypoechoic nodules were seen throughout the splenic parenchyma, ranging from 0.5 to 2.6 cm in diameter. Cytological examination of fine needle aspirates confirmed intermediate to large cell lymphoma of the mediastinum, spleen and liver. Flow cytometry performed on aspirates of the mediastinal mass confirmed CD4+/CD5+ T-cell lymphoma (Supplementary Tables 1 and 2). Cytological evaluation of the smaller splenic nodules was consistent with mild extramedullary haematopoiesis and lymphoid reactivity. A diagnosis of intermediate to large cell, WHO (clinical) stage IVb mediastinal/thymic lymphoma was made [16]. Bone marrow samples were not obtained.

A lomustine-based multidrug chemotherapy protocol was commenced (Supplementary Table 3). Dose reductions and omissions were made on the basis of published guidelines for haematological monitoring [17]. After initial resolution of clinical signs, the dog developed intermittent vomiting and diarrhoea at week 11. The animal was re-presented after having received symptomatic management by the primary care practice for 10 days, without resolution of clinical signs (low fat/high fibre diet; smectite clay [VBS Clay; VBS Direct Ltd, www.vbsdirect.co.uk]; maropitant [30 mg PO SID; Cerenia; Zoetis UK Ltd, www2.zoetis.co.uk]. At this time, the diarrhoea was accompanied by faecal tenesmus and haematochezia.

On examination, the dog was bright, alert, responsive and in good body condition (27.8 kg, BCS 5/9). Auscultation of the thorax and palpation of the abdomen were unremarkable. The right prescapular lymph node was firm, mobile and enlarged, measuring 3 cm in length. Rectal examination revealed multiple, firm, pedunculated and sessile nodules, approximately 0.5–1 cm in diameter, circumferentially located along the rectal wall, which were associated with bleeding and discomfort.

Further haematology and biochemistry were performed before sedation and repeat bi-cavitary imaging. The dog had a mild lymphopenia (0.6×10^9/L [RI 1–3]) and although erythrocyte parameters were within normal limits, there was evidence of a recent regenerative response (reticulocytes 103×10^9/L [RI 0–70]) with an associated polychromasia, consistent with the history of recent blood loss. C-reactive protein remained moderately increased (22.3 mg/L [RI 0–8.2]) and there were marked increases in the hepatobiliary markers (ALP 2,541 IU/L [RI 26–107] and ALT 884 IU/L [RI 14–67]) and, to a lesser degree, GGT (32 IU/L [0–10]) and AST (146 IU/L [12–49]). There were mild reductions in urea (2.2 mmol/L [RI 2.5–7.4]) and albumin (24 mmol/L [25–41]) levels, potentially associated with reduced hepatic function. These results were considered consistent with hepatobiliary disease or recent hepatotoxic drug therapy.

Although imaging demonstrated an apparent reduction in size of the mediastinal mass to approximately twice the width of the vertebral column, there was progression of the abdominal lymphadenopathy including coeliac, porta hepatis, aortic and sublumbar lymph nodes. The previously identified splenic and hepatic abnormalities remained largely unchanged. The more distally located rectal masses could be seen and were gently exteriorized to permit sampling. Cytology and flow cytometry on aspirates obtained from a rectal nodule (Fig. 1) confirmed intermediate- to large-sized CD4+/CD5− T-cell lymphoma (Supplementary Table 2). The lack of CD5 expression was interpreted as most likely an aberrant loss of expression by the neoplastic cell population.

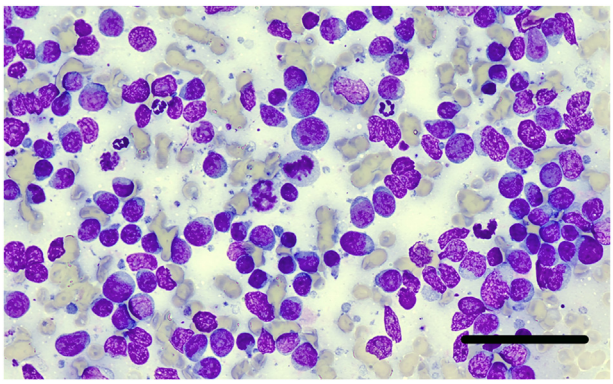

Fig. 1. T-cell lymphoma, rectum, dog. Cytology of rectal nodule. Fine needle aspirate contain predominance of similar intermediate to large lymphocytes, with paracentral round to irregularly indented nucleus, coarsely stippled chromatin (occasionally with 1–2 irregularly round prominent nucleoli) and small volume of mid-blue cytoplasm. Occasional cells have cytoplasmic projection ('hand mirror' appearance). Wright Giemsa. Bar, 50 μm.

The owner elected euthanasia and permitted necropsy. Representative sections of a panel of tissues were fixed in 10% neutral-buffered formalin for histological processing, staining with haematoxylin and eosin (HE) and immunohistochemistry (IHC) for CD3 and CD20 following standard protocols [18] (Supplementary Table 4).

At necropsy, an approximately 60 mm segment of the distal colon and rectum had a red mucosal surface and was expanded by flattened nodules that were predominantly pink but multifocally had a cream, depressed ulcerated central focus (Fig. 2). On cut surface these nodules had a cream, homogeneous appearance consistent with lymphoma. There was also a moderately firm, well-demarcated mass in the cranial mediastinum. The mass had approximate dimensions of 60 × 30 × 30 mm and had a smooth grey/pink capsule that was interpreted as a lymph node capsule. On cut section the neoplasm was homogeneously cream to pink and was interpreted as lymphoma. Gross changes consistent with

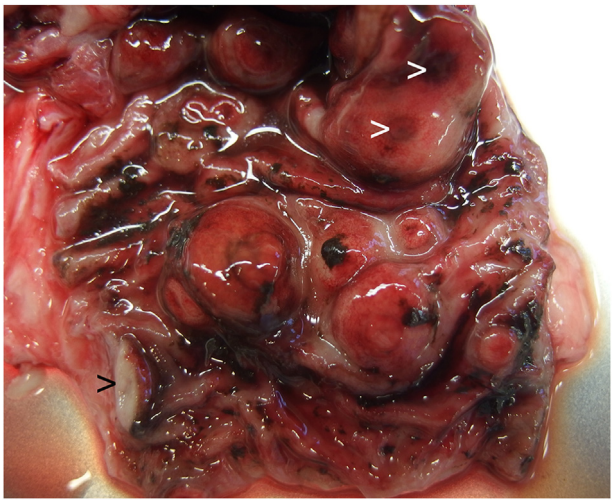

Fig. 2. T-cell lymphoma, rectum, dog. Segment (approximately 60 mm) of distal colon and rectum has red mucosal surface and is expanded by flattened pink nodules that multifocally have a depressed ulcerated centre (white arrowheads). Cream nodules on cut surface (black arrowhead).

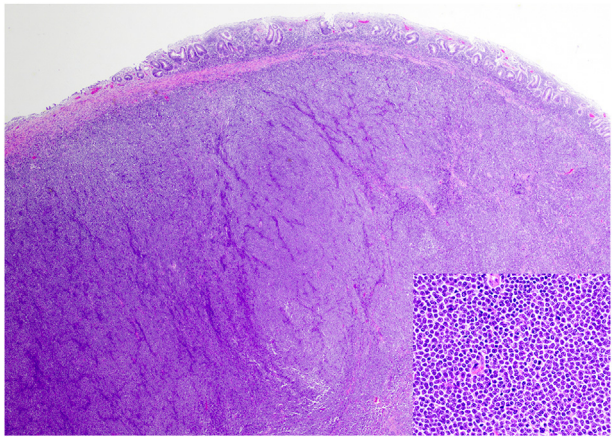

Fig. 3. T-cell lymphoma, rectum, dog. Rectal mucosa and submucosa thickened by flattened nodular to plaque-like neoplastic mass composed of neoplastic round cells with prominent nuclei. HE. ×20. Inset: detail of neoplastic cells. ×400.

lymphoma were also identified in the spleen, pancreatic, ileocaecocolic, colonic and renal lymph nodes, liver and caecum.

Histologically, the rectal mucosa and submucosa were thickened by a flattened nodular to plaque-like neoplastic mass that was up to 6 mm (fixed tissue) thick, unencapsulated, well-demarcated, densely cellular and infiltrative (Fig. 3). The neoplastic cells were arranged in dense sheets supported by a fine collagenous stroma, and were round with distinct cell borders and a small amount of eosinophilic cytoplasm. The nuclei were round with an approximate diameter equivalent to 1.5 erythrocytes, and had lightly to densely stippled chromatin and generally between one and four prominent basophilic nucleoli. There were 19 mitotic figures per 10 high-power fields (2.37 mm^2). There was moderate anisocytosis and anisokaryosis and a mild to less frequently moderate degree of nuclear pleomorphism. The overlying mucosa was segmentally ulcerated.

Most (>95%) of the neoplastic cells had moderate to intense cytoplasmic and membranous immunolabelling for CD3 (T-lymphocyte marker) (Fig. 4) and most were immunonegative for CD20 (B-lymphocyte marker). However, scattered throughout the neoplastic population and also in the adjacent lamina propria were moderate numbers of round cells that had strong cytoplasmic and membranous immunolabelling for CD20 were interpreted as non-neoplastic B lymphocytes (Supplementary Fig. 1). The mediastinal mass comprised a population of neoplastic cells with a similar arrangement and morphology to that in the rectum. However, in the tissue planes that were examined, most of the neoplastic mass was necrotic (Supplementary Fig. 2).

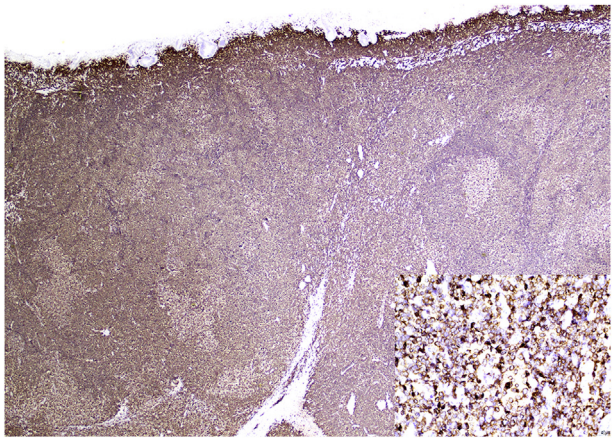

Fig. 4. T-cell lymphoma, rectum, dog. More than 95% of neoplastic cells have moderate to strong cytoplasmic and membranous immunolabelling for CD3. IHC. ×20; inset ×400.

The combined histology and IHC findings confirmed intermediate-sized T-cell lymphoma of the distal colon/rectum that also involved the mediastinum, spleen, pancreatic, ileocaecocolic, colonic and renal lymph nodes, liver and caecum.

Reports of rectal lymphoma in other animal species are rare but a case of CD3-positive large granular cell lymphoma has been described in a 21-year-old pony with neoplastic infiltrates in the rectum, mesenteric lymph nodes, mesentery, liver, caecum and colon [19]. Canine rectal B-cell lymphoma has also been reported [11–15]. The present case is notable for the T-cell phenotype, confirmed by flow cytometry and IHC. As rectal examination was not recorded on initial presentation, it is uncertain whether the rectal lymphoma was present at initial diagnosis. In a recent study of 82 dogs undergoing colonoscopy to investigate a rectal mass, 96.3% of the dogs had at least one clinical sign associated with the rectal mass, with a median duration of 5 months [8]. Masses were palpable in 86.6% of cases. This suggests that had the rectal involvement been present earlier in the disease course, clinical signs attributable to the neoplasm would probably have been present and, therefore, it can be inferred that in this case, rectal involvement most likely occurred as the disease progressed. This is an important distinction from the previously reported cases of canine rectal lymphoma in which the rectum was considered to be the primary site of the neoplasm [11,12,14,15].

Mediastinal lymphoma has been poorly described in animals and complete staging appears to be infrequently performed, resulting in a potential underestimation of the extent of disease [20]. In this case, mediastinal lymphoma with associated clinical signs occurred in the absence of peripheral lymphadenopathy and was thus deemed to be primary mediastinal lymphoma with involvement of the liver and spleen (stage IV). Conversely, the disease may have arisen simultaneously in these body systems. However, by convention, splenic and hepatic involvement are considered as secondary sites for staging purposes [16]. While clinicians may adopt a pragmatic approach to staging cases of lymphoma [21,22], discrimination between B-cell and T-cell lymphoma is clinically essential because of the variance in therapeutic management and prognosis [13,23–26]. T-cell lymphomas have higher levels of P-glycoprotein (*MDR1*/*ABCB1*) gene expression than the B-cell phenotype, therefore avoiding drugs exported by MDR1, such as doxorubicin and vincristine, is logical [26–28]. Furthermore, GI lymphoma may overexpress *MDR1* compared with other lymphomas [7,29]. Lomustine-based, alkylating-agent rich protocols are increasingly accepted as first-line treatment of non-indolent T-cell lymphoma over doxorubicin-based protocols such as CHOP, with evidence of therapeutic benefit based on historic controls [30–33]. The protocol used in this case study (Pittaway, personal communication) lacked the second alkylating agent procarbazine, the addition of which is likely to confer therapeutic benefit [34].

As previous reports support only B-cell phenotype in cases of canine rectal lymphoma, the discovery of rectal pathology in this case raised suspicions of a second malignancy, including a *de novo* B-cell lymphoma, which would have necessitated a potentially contradictory change in drug treatment. However, flow cytometry, utilizing minimum input material, permitted rapid phenotypic diagnosis of a simple relapse with rectal involvement in this case, which assisted the owner's decision-making around rescue therapy and the likelihood of clinical sign control.

Ethical statement

The authors certify that all relevant legal and ethical requirements were met with regard to the humane treatment of the animal described in this case report. Informed consent from the owner of the animal was obtained for the treatment of the dog and publication of this article.

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Declaration of competing interests

The authors declared no conflicts of interest in relation to the research, authorship and publication of this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcpa.2023.10.009.

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