Rectal lymphoma in 11 dogs – a retrospective study

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OBJECTIVES: To retrospectively evaluate the clinical behaviour and immunophenotype of lymphoma of the rectum in dogs.

METHODS: Eleven dogs diagnosed with lymphoma of the rectum on histopathology were retrospectively reviewed. Immunohistochemistry with CD3 and CD79a antibodies was performed at diagnosis or retrospectively.

RESULTS: Treatment protocol varied with six dogs undergoing surgery and adjuvant chemotherapy, two received chemotherapy after only incisional biopsy, one had surgical resection only, one was treated symptomatically and one dog was not treated. Chemotherapy treatment consisted of either a low-dose COP (cyclophosphamide - prednisolone - vincristine) protocol (four dogs) or a six-week CHOP-based (cyclophosphamide - vincristine - prednisolone - anthracycline) protocol (four dogs). Dogs that received chemotherapy lived significantly longer than dogs that did not receive chemotherapy (2352 versus 70 days). Median survival time was not reached, and there was an overall mean survival time of 1697 days. Immunohistochemistry was performed in 10 of 11 samples, and was consistent with B-cell lymphoma in all cases.

CLINICAL SIGNIFICANCE: Canine lymphoma of the rectum is associated with a favourable prognosis. Immunohistochemical evaluation of these lesions was consistent with B-cell lymphoma in all cases in which it was examined.

INTRODUCTION

Malignant lymphoma represents a diverse group of neoplasms, originating from lymphoid cells. The incidence was estimated to be between 13 and 24 per 100,000 dogs in 1978 (Jacobs 2002), while a UK-based study 20 years later calculated an age-adjusted incidence of 107 cases per 100,000 dogs (Dobson and others 2002).

Canine lymphoma subtypes are classified by a number of different schemes, including one based on anatomic distribution of lesions (Vail 2007). Gastrointestinal lymphoma is reported to comprise 5 to 7% of all canine lymphoma cases (Patnaik and others 1977).
Overall, gastrointestinal lymphoma is considered to be aggressive, poorly responsive to treatment and is associated with short survival times (Couto and others 1989, Frank and others 2007). However, there are reports of a number of individual long-term survivors with lymphoma of the colorectal area. A report of 29 dogs with gastrointestinal lymphoma included three dogs that received multi-agent chemotherapy (Couto and others 1989). One of these three dogs was diagnosed with colorectal lymphoma and was still in remission five years after diagnosis. Six of seven dogs suffering from gastrointestinal lymphoma in another study received chemotherapy (Miura and others 2004). One of these six dogs had a solitary rectal mass, while the remaining five suffered from small intestinal lymphoma. The dog with the solitary rectal mass was the only long-term survivor, and was lost to follow-up in complete remission one year after diagnosis. Seven dogs with rectal lymphoma were included in a series of canine rectal neoplasms, only three of them were treated surgically, and none received chemotherapy (Holt and Lucke 1985). One of three died within eight weeks, one was lost to follow-up 10 months after surgery without signs of recurrence, and the remaining dog was still alive 18 months after surgery. Six dogs with solitary large intestinal lymphoma were included in a final study, and only three dogs survived to discharge. Two had solitary rectal masses and were still alive 930 and 2520 days later, while one was euthanased four months after surgery (Frank and others 2007).

The purpose of this retrospective study was to describe the treatment and outcome of 11 dogs with lymphoma of the rectum. A secondary goal was to report the immunophenotype associated with dogs with lymphoma of the rectum.

MATERIALS AND METHODS

The data for this retrospective study were obtained from the clinical and pathological database of the Diagnostic Laboratory of the Animal Health Trust in Newmarket and the clinical database of the Queen’s Veterinary School Hospital, Cambridge, from 1998 to 2007. Patients were included if there was a histological diagnosis of lymphoma (incisonal or excisional biopsy) of a rectal mass and no evidence of distant spread was detected on clinical-stage evaluations. Grading of the lymphoma was done according to the mitotic rate, with grouping into low (0 to 2/HPF), medium (3 to 5/HPF) and high grade (>6/HPF) lymphoma (Carter and others 1986).

Immunohistochemistry was performed on one sample at the time of diagnosis. For the other samples, the original tissue biopsies were requested from the original pathology laboratories for labelling with B-cell (CD79a) and T-cell (CD3) markers.

The following data were obtained from the medical records: age, sex, breed, presenting complaint, clinical examination findings, haematology and serum biochemistry results, location of the mass within the rectum, abdominal and thoracic imaging results, endoscopic findings, bone marrow aspirate and biopsy results, treatment and survival time. The referring veterinary surgeons were contacted and were asked to provide follow-up information including date and cause of death.

Treatment

The COP-based protocol used in this study was a continuous low-dose protocol that is administered over two years (Dobson and Gorman 1994). Cyclophosphamide was substituted by chlorambucil (Leukeran, GlaxoSmithKline, 5 mg/m² q48h PO) or melphalan (Alkeran, GlaxoSmithKline, 5 mg/m² q48h PO) at the discretion of the clinician in charge if haemorrhagic cystitis or severe gastrointestinal side effects associated with the administration of cyclophosphamide (Endoxana, Pharmacia) occurred. Re-examination was performed by the referring veterinarians every four to six weeks, and consisted of a complete clinical examination (including rectal examination) and haematological analyses.

The CHOP-based protocol used during the study period was a six-week maintenance free pulse protocol (Table 1). Chemotherapy was discontinued after the initial six weeks if the patient appeared in complete remission on clinical and rectal examination. Repeat clinical examination was performed at each chemotherapy appointment. Dogs were re-examined every three months after the completion of the chemotherapy protocol and an abdominal ultrasound was performed on each of these occasions.

Surgical excision was classified as complete, incomplete or with narrow margins, which was described as less than 2 mm of tumour-free tissue noted on the tissue sample.

Statistical analysis

The Kaplan-Meier method was used to estimate the survival time with the date of histopathology submission as day 0. “Death due to disease” was defined as euthanasia due to symptoms related to regional lymphoma recurrence or postsurgical wound healing. “Death due to other reasons” was defined as euthanasia due to non-gastrointestinal clinical problems while the dog was in complete remission. Complete remission was defined by the absence of clinical signs and absence of abnormal tissue on rectal palpation.

Deaths that resulted from disease progression were considered events, while deaths which were assumed to be related to other problems than lymphoma were censored. Dogs that were still alive on October 1, 2011, were censored.

The difference in the survival distribution between dogs that did and did not receive chemotherapy was evaluated with the log-rank test. A P value of <0.05 was considered significant.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Drug treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 1</td>
<td>Haematology</td>
</tr>
<tr>
<td></td>
<td>0–70 mg/m² vincristine iv</td>
</tr>
<tr>
<td></td>
<td>30 mg/m² prednisolone PO sid</td>
</tr>
<tr>
<td>Week 2</td>
<td>Haematology</td>
</tr>
<tr>
<td></td>
<td>Urinalysis</td>
</tr>
<tr>
<td></td>
<td>200 mg/m² cyclophosphamide PO</td>
</tr>
<tr>
<td></td>
<td>20 mg/m² prednisolone PO sid</td>
</tr>
<tr>
<td>Week 3</td>
<td>Haematology</td>
</tr>
<tr>
<td></td>
<td>Echocardiography</td>
</tr>
<tr>
<td></td>
<td>30 mg/m² doxorubicin/epirubicin iv for dogs &gt;15 kg or 1 mg/kg doxorubicin/epirubicin iv for dogs &lt;15 kg</td>
</tr>
<tr>
<td></td>
<td>10 mg/m² prednisolone PO sid</td>
</tr>
<tr>
<td>Week 4</td>
<td>Haematology</td>
</tr>
<tr>
<td></td>
<td>Urinalysis</td>
</tr>
<tr>
<td></td>
<td>0–70 mg/m² vincristine iv</td>
</tr>
<tr>
<td></td>
<td>200 mg/m² cyclophosphamide PO</td>
</tr>
<tr>
<td>Week 5</td>
<td>Haematology</td>
</tr>
<tr>
<td></td>
<td>Urinalysis</td>
</tr>
<tr>
<td></td>
<td>30 mg/m² doxorubicin/epirubicin iv for dogs &gt;15 kg or 1 mg/kg doxorubicin/epirubicin iv for dogs &lt;15 kg</td>
</tr>
<tr>
<td>Week 6</td>
<td>Haematology</td>
</tr>
<tr>
<td></td>
<td>Echocardiography</td>
</tr>
</tbody>
</table>

Table 1. Six-week CHOP-based protocol

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The Kaplan-Meier analysis and log-rank test were calculated with SPSS 19 (IBM).

RESULTS

Signalment
Of the 11 dogs included in this study, 3 were neutered males, 4 neutered females, 3 entire males and 1 entire female. Ten different breeds were represented, with the Labrador retriever being the only breed that was represented twice. The median age at the time of histological diagnosis was 6.5 years (range 2.6 to 13.7 years), and the mean was 6.9 years. The median duration of clinical signs before diagnosis was seven days.

The details of each case are presented in Table 2.

Immunohistochemistry
Excisional biopsy was performed in six cases, while five underwent incisional biopsy.

Histology was performed at the time of initial diagnosis and was consistent with lymphoma in all 11 cases. Eight tissue samples were reviewed by one pathologist, and medium-sized, non-cleaved lymphocytes with scant to moderate amounts of eosinophilic cytoplasm and finely stippled evenly dispersed chromatin were reported in all samples.

All samples had diffuse lymphomatous infiltration and the mitotic rate of the neoplastic cells was low in two, medium in five and high in four dogs.

Immunohistochemistry was performed retrospectively in 9 of 11 cases and at the time of diagnosis in 1 case. All samples stained strongly positive for CD79a, indicating a B-cell origin, while only a minority (<1 to 20%) of cells stained with CD3. For one case the tissue sample could not be retrieved and no immunohistochemistry was available.

Clinical signs and initial staging
The most common presenting signs were haematochezia (n=7), mucochezia (n=4), tenesmus (n=3) and increased frequency of defection (n=4). Four dogs were presented for further investigation of a protruding mass on defection without any other clinical signs.

The local extent of the mass was diagnosed by digital rectal examination in six dogs, while abdominal ultrasound was necessary to localise the cranial margin in one dog. Four dogs underwent additional colonoscopy and proctoscopy, but no abnormalities other than the original mass were detected.

Haematology and biochemistry were unremarkable at presentation in all but one dog, which was mildly neutropenic (2·4×10^9/L, reference interval 4·0 to 12·0). This patient underwent bone marrow evaluations (aspirate and biopsy); there was no evidence of bone marrow infiltration at that date.

Thoracic radiographs (orthogonal views, 11 dogs) and abdominal radiographs (8 dogs) and/or ultrasound (11 dogs) were performed. No abnormalities were detected on thoracic or abdominal radiography. No abnormalities were noticed on abdominal ultrasound in nine dogs, while two dogs had mild changes noted in their regional lymph nodes. Mildly enlarged colonic lymph nodes, but with a normal echogenicity and shape, were detected in dog 1. These lymph nodes were considered normal in their appearance on repeat ultrasonographic examination.

Table 2. Patient characteristics, treatment and survival times of 11 dogs with lymphoma of the rectum

<table>
<thead>
<tr>
<th>Breed</th>
<th>Sex</th>
<th>Age at diagnosis</th>
<th>IHC</th>
<th>Initial staging</th>
<th>Surgery</th>
<th>Chemotherapy</th>
<th>Status</th>
<th>Follow-up (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Border terrier</td>
<td>FN</td>
<td>7-7 years</td>
<td>B-cell</td>
<td>Mildly enlarged colonic inn</td>
<td>Pull-through, clear margins</td>
<td>Pulse CHOP started 41 days post surgery</td>
<td>A</td>
<td>1818</td>
</tr>
<tr>
<td>Crossbreed</td>
<td>FN</td>
<td>4 years</td>
<td>B-cell</td>
<td>No metastatic disease</td>
<td>Pull-through, incomplete margins</td>
<td>Pulse CHOR 7 days post surgery</td>
<td>DDD</td>
<td>2172</td>
</tr>
<tr>
<td>3 Labrador retriever</td>
<td>M</td>
<td>8 years</td>
<td>B-cell</td>
<td>No metastatic disease</td>
<td>Pull-through, incomplete margins</td>
<td>COP* started 18 days post surgery</td>
<td>DDD</td>
<td>936</td>
</tr>
<tr>
<td>Basset</td>
<td>FN</td>
<td>2-8 years</td>
<td>B-cell</td>
<td>No metastatic disease</td>
<td>Pull-through, uncertain margins</td>
<td>COP*, started 17 days post surgery</td>
<td>DDD</td>
<td>88</td>
</tr>
<tr>
<td>4 CKCS</td>
<td>FE</td>
<td>2-6 years</td>
<td>B-cell</td>
<td>Not performed</td>
<td>Caudal laparotomy with midline pelvic osteotomy, incomplete margins</td>
<td>COP, started 31 days post surgery, stopped after 6 months</td>
<td>A</td>
<td>1805</td>
</tr>
<tr>
<td>5 Labrador retriever</td>
<td>MN</td>
<td>7-5 years</td>
<td>B-cell</td>
<td>No metastatic disease</td>
<td>Pull-through, clear margins</td>
<td>Pulse CHOP started 12 days post surgery, stopped after first vincristine</td>
<td>LTF</td>
<td>413</td>
</tr>
<tr>
<td>6 German shepherd</td>
<td>MN</td>
<td>3 years</td>
<td>B-cell</td>
<td>No metastatic disease</td>
<td>Caudal laparotomy with midline pelvic osteotomy, local spread to mesentery</td>
<td>None</td>
<td>DDD</td>
<td>15</td>
</tr>
<tr>
<td>7 Golden retriever</td>
<td>M</td>
<td>4 years</td>
<td>B-cell</td>
<td>No metastatic disease</td>
<td>None</td>
<td>COP*, started 38 days post biopsy</td>
<td>A</td>
<td>2663</td>
</tr>
<tr>
<td>8 WHWT</td>
<td>MN</td>
<td>13-7 years</td>
<td>B-cell</td>
<td>Hypoechoic medial iliac lymph nodes, normal size</td>
<td>None</td>
<td>Pulse CHOP (epirubicin), started 13 days post biopsy</td>
<td>DDD</td>
<td>117</td>
</tr>
<tr>
<td>9 Whippet</td>
<td>ME</td>
<td>6-5 years</td>
<td>B-cell</td>
<td>No metastatic disease</td>
<td>None</td>
<td>None</td>
<td>DDD</td>
<td>28</td>
</tr>
<tr>
<td>10 Border collie</td>
<td>MN</td>
<td>10 years</td>
<td>B-cell</td>
<td>No metastatic disease</td>
<td>None</td>
<td>Lactulose+prednisolone</td>
<td>DDD</td>
<td>172</td>
</tr>
</tbody>
</table>

IHC = Immunohistochemistry, COP* = Exchange cyclophosphamide with chlorambucil during protocol, FE = Female entire, ME = Male entire, FN = Female neutered, MN = Male neutered, WHWT = West Highland white terrier, CKCS = Cavalier King Charles spaniel, A = Alive, DDD = Dead due to other reasons, DDD = Dead due to disease, LTF = Lost to follow-up
one month into treatment. Dog 9 had hypoechoic but normally sized medial iliac lymph nodes at the time of diagnosis. The changes were considered to be consistent with reactive change in both dogs, and no aspirates or biopsies were performed.

**Treatment**

Treatment varied between cases and consisted of surgery alone (n=1), chemotherapy alone (n=2), or surgery combined with chemotherapy (n=6). After incisional biopsy and clinical staging, one dog was treated with lactulose and prednisolone only and one patient did not receive any treatment after diagnosis.

After surgical resection, the histological margins were reported to be incomplete in four dogs, clean in two dogs (dogs 1 and 6), and one dog had narrow margins (dog 5).

**Chemotherapy**

Six dogs received adjuvant chemotherapy, while two dogs received chemotherapy after incisional biopsy; both dogs went into complete remission after the first dose of chemotherapy.

A low-dose COP-based chemotherapy protocol was used in four dogs. One owner elected to discontinue the COP-based protocol six months into treatment while the dog was in complete remission (dog 5). Cyclophosphamide was substituted by chlorambucil in one dog and by melphalan in two dogs because of suspected drug-related side effects; one for haemorrhagic cystitis, one for vomiting and one for haemorrhagic diarrhoea.

Four dogs received the six-week CHOP-based pulse protocol. Only one dog relapsed 15 months after finishing the initial protocol (dog 2). Remission was regained by repeating the original six-week pulse protocol and no further recurrence was noted. This dog was euthanased because of tetraparesis due to a vertebral body tumour in C2 almost seven years after the initial diagnosis. One dog received only the first dose of vincristine as the owner requested discontinuation because of the development of severe diarrhoea.

**Outcome**

At the date of censor, one dog was alive, four had been euthanased because of progressive disease, three had been euthanased for causes that were assumed to be unrelated to lymphoma and three were lost to follow-up (after 414, 1909 and 2676 days). The mean and median follow-up times were 907 and 414 days, respectively. The mean survival time for this cohort of dogs was 1697 days (95% confidence interval (CI) 935·5 to 2460·4), while the median survival time was not reached (Fig 1).

Euthanasia was performed because of the local tumour recurrence in three dogs. Two had not received chemotherapy treatment and one only went into partial remission with a COP protocol. Dog 7 underwent caudal laparotomy and midline pelvic osteotomy to resect the rectal mass, and local extension of the lymphoma to the mesentery was apparent during surgery. This patient developed wound dehiscence and was euthanased 15 days after diagnosis.

One dog was euthanased for respiratory problems (dog 3), one because of symptoms related to a vertebral body tumour of C2 (dog 2) and one was euthanased because of hepatic failure (dog 4). There was no palpable tumour recurrence on digital examination in any of these dogs.

Dogs that received chemotherapy lived significantly longer than the ones which did not receive chemotherapy [mean 2352 days (95% CI 1759·4 to 2945·6); median not reached versus mean 70 days (95% CI 0 to 170·3); median 28, 95% CI 7·2 to 48·8] (P=0·003)].

**DISCUSSION**

Previous studies have associated canine gastrointestinal lymphoma with short survival times. However, this small case series suggests that rectal lymphoma can have a more favourable prognosis. The overall median survival time in the present study was not reached, while the median follow-up time of 414 days is substantially longer than the survival time in previous studies on diffuse gastrointestinal lymphoma, which reported median survival times between 13 (Frank and others 2007) and 77 days (Rassnick and others 2009). Several such studies included individual cases with colorectal lymphoma, which had a prolonged remission time (Holt and Lucke 1985, Couto and others 1989, Miura and others 2004, Frank and others 2007). All but one of these long-term survivors could be localised to the rectum, although one study did not specify the anatomic location (Couto and others 1989). No dogs with macroscopic colonic involvement were included in our study, so these results are not applicable to dogs with colonic involvement.

Immunohistochemistry was performed in 10 of the 11 cases and all samples stained strongly with CD79a, a marker of B-cells. This is in contrast with most studies on canine gastrointestinal lymphoma (Coyle and Steinberg 2004, Miura and others 2004, Frank and others 2007, Rassnick and others 2009), which describe a T-cell lymphoma origin in 63 to 100% of the cases. Historically, B-cell lymphomas have been reported to be more likely to achieve complete remission, and are associated with longer remission and survival times than T-cell-derived lymphomas (Kiupel and others 1999, Dobson and others 2001, Simon and others 2006, Marconato and others 2011). One study on canine gastrointestinal lymphoma also reported a non-significant survival benefit for dogs with B-cell lymphoma (Rassnick and others 2009).
Marginal zone lymphoma is further divided into splenic, splenomegaly caused by lymphoma infiltration (Valli and others 2006). Marginal zone lymphomas are divided into marginal zone lymphoma, mantle cell lymphoma and follicular lymphoma. To our knowledge, all the dogs presented with a short clinical disease course and only two cases had a low mitotic rate, which is not consistent with the indolent disease course of low-grade B-cell lymphomas.

There are a number of limitations to this case series, largely caused by the retrospective nature of the study which resulted in incomplete data with respect to treatment, treatment-related side effects and follow-up. Two dogs suffered worsening gastrointestinal symptoms during the chemotherapy protocol. While repeat staging was not performed at the time, the symptoms resolved with symptomatic management, which is suggestive of a drug-related adverse effect rather than lymphoma progression.

The initial Veterinary Cooperative Oncology Group grading system on adverse effects of chemotherapy was first published in 2004 and reviewed in 2011 (VCOG 2004, 2011). A large number of these patients were diagnosed and treatment started before this time, and although chemotherapy adverse reactions were described, it was impossible to grade these retrospectively.

Three dogs were classified as “euthanased because of other reasons” and this was determined by the absence of abnormalities at the initial disease site on rectal examination and the absence of gastrointestinal symptoms. These dogs were euthanased 117, 936 and 2549 days after diagnosis. No post-mortem examination was performed in any of these cases, so it is possible that one or more of these dogs may have died because of lymphoma.

The retrospective nature and the size of the study did not lend itself to comparison of the different treatment modalities. The survival time of these patients varied widely, and this could have been caused by individual treatment differences, which depended on clinician preference. Although the log-rank test suggests a significant improvement in survival time with the addition of chemotherapy, it has to be remembered that the number of dogs is limited.

It is impossible to conclude from this study if patients that undergo surgical resection before chemotherapy have a better prognosis than those that receive chemotherapy alone. Nor can a preferred chemotherapy protocol be recommended, but this cohort of patients does suffer from a lymphoma subtype that is associated with a favourable prognosis. Further cytogenetic or histomorphological analysis of these cases might help in further defining prognostic factors in canine B-cell lymphoma.

**CONCLUSIONS**

This small retrospective study suggests that canine lymphoma of the rectum is associated with a good prognosis and long-term

It is unlikely that the prolonged survival time in these patients is attributed to low-grade or indolent lymphoma because of the incompatible histological description, morphological appearance and clinical disease course. Indolent forms of B-cell lymphoma are divided into marginal zone lymphoma, mantle cell lymphoma and follicular lymphoma. To our knowledge, all the dogs diagnosed with mantle cell lymphoma reported in the literature suffered from generalised lymphadenomegaly or marked, diffuse splenomegaly caused by lymphoma infiltration (Valli and others 2006). Marginal zone lymphoma is further divided into splenic, nodal and MALT (mucosa-associated lymphoid tissue) subtypes (Iaacson and others 2001, Flood-Knapik and others 2012). Only four confirmed canine cases of the MALT-type lymphoma were found in the literature (Ponce and others 2004). Marginal zone lymphocytes are small- to medium sized with a large, single central nucleus and a low mitotic index (<1/HPF) (Ponce and others 2004, Valli and others 2006), which is not consistent with the histological description of the cases in the present study. Follicular lymphoma has a typical nodular appearance, while all the current samples were classified as diffuse. In addition, most of the patients in this study presented with a short clinical disease course and only two cases had a low mitotic rate, which is not consistent with the indolent disease course of low-grade B-cell lymphomas.
survival if treated with chemotherapy. The ideal chemotherapy protocol and additional benefit of surgery to obtain best results need further investigation. Solitary lymphoma of the rectum was of B-cell origin in all cases in which immunophenotype was assessed.

**Conflict of interest**
None of the authors of this article has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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