Intestinal Small Cell Lymphoma: Are Dogs Big Cats?

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INTRODUCTION

Previously T-cell lymphomas of the gastrointestinal tract in human were classified as enteropathy-associated T-cell lymphoma (EATL) type I and type II. Type I is associated with celiac disease and characterized by large lymphocytes, whereas type II is not associated to enteropathies and characterized by small lymphocytes. In view of these differences, the nomenclature has been changed and EATL currently refers only to type I and type II has been renamed monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL).[1] EATL has an aggressive clinical course and tumor cells most commonly have an $\alpha\beta$ T-cell receptor phenotype. In comparison MEITL tumour cells express CD8, CD56, and megakaryocyte-associated tyrosine kinase.

T-cell lymphoproliferative disorder (TLPD) is another type of small cell lymphoma described in the intestinal tract. This lymphoma has typically an indolent clinical course and commonly express CD8 and is negative for CD4 and CD56,

Markers of T-cell lymphomas of the gastrointestinal tract have been much less extensively studied in cats and dogs and for this reason for the purpose of this lecture small cell lymphoma (SCL) will be used for neoplastic cells with nuclei smaller than 2 red blood cells in diameter and large cell lymphoma (LCL) for larger neoplastic cells.[2]

SCL characterized by infiltration of the intestinal mucosa by mature T-cells with variable epitheliotropism has been described for more than 10 years in cats. SCL has better outcome than other types of lymphoma in this species, with median survival times over 1.5 years.[3] Although criteria have been described in cats to diagnose SCL, these are not as well defined in dogs. However, several recent studies support that SCL is also present in dogs and the clinical findings and outcome will be described in this presentation.

CLINICAL PRESENTATION

There are currently only two studies reporting clinical signs in dogs with SCL in detail. The most reported clinical signs are summarised in table 1. Weight loss and diarrhoea are the most common, followed by vomiting and inappetence. Although 20 dogs were included in the Lane et al study, one dog diagnosed with B-cell lymphoma was excluded for this summary.

Overall clinical scores in several other studies have been reported to be higher in dogs with SCL than dogs with chronic enteropathy.

Table 1. Clinical signs reported in dogs diagnosed with SCL. The percentage of dogs with each sign is given.

	Lane, 2017[4] (n=19)	Couto, 2017[5] (n=17)
Weight loss	74	41
Diarrhoea	58	76
Vomiting	58	41
Inappetence	32	41

Some studies report male dogs to be more frequently diagnosed than female dogs, although no population comparison is available to confirm this finding, while other studies found no sex predisposition including the largest study from Matsumoto et al including 276 cases.[4–7,2]

Breed reported to have an increased risk of developing intestinal SCL in Japan include Shiba Inu, German shepherds dogs, Cairn terriers, Boston terriers, Papillons, Pugs and Maltese.[2]

DIAGNOSIS

Differentiating SCL from chronic enteropathy (CE) has proven challenging in cats and often requires a combination of intestinal histopathology, immunohistochemistry, and in some cases clonality testing by polymerase chain reaction (PCR) for antigen receptor rearrangement (PARR).[8] Similar criteria have been used in dogs as well to differentiate dogs with SCL from LCL. Typically, LCL is reported more frequently than SCL in dogs. For example, in a study assessing gastrointestinal lymphomas in dogs, out of 8 dogs diagnosed only two were SCL.[9] Figure 1 summarises the different diagnostic steps that can be considered to confirm a diagnosis of SCL.

Further complicating diagnosis, PARR clonality can be found in some inflammatory processes and some cases highly suggestive of SCL on immunohistology are PARR negative.[6] The latter can be explained in part because PARR sensitivity depends on the methodology used and will typically not detect all receptor rearrangements.[10] PARR testing should not be used as sole diagnostic test as healthy cats have been shown to have clonality in the absence of any detectable pathology and similar findings are likely to occur in dogs.[11]

One study reports the use of a squash-smear technique from endoscopic biopsies to differentiate between lympho-plasmacytic enteritis and SCL.[12] Although this method has the advantage of obtaining very fast results, the authors report a false positive result in 15% of dogs (i.e. small cell lymphoma on cytology and lympho-plasmacytic or eosinophilic enteritis on histology). For this reason, this method requires further refinement before being useful clinically.

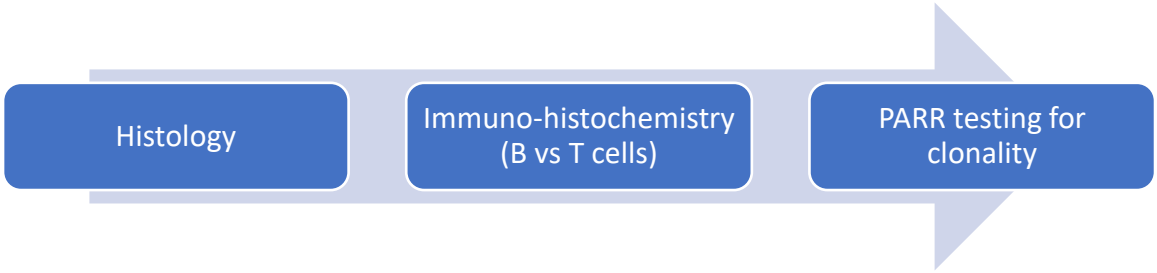

Figure 1. Steps that can be con considered to confirm a suspicion of SCL. If histology is suggestive of SCL, then additional tests can be pursued to further support the diagnosis. PARR: PCR for antigen receptor rearrangement.

LABORATORY ABNORMALITIES

A majority of dogs diagnosed with SCL present with hypoalbuminemia and up to 56% with hypocholesterolemia.[4,5] For this reason, SCL should be a differential in dogs presented with protein-losing enteropathy (PLE). There are currently no prospective studies assessing the number of dogs with SCL amongst dogs with PLE. However, a retrospective study from Nakashima et al assessing prognostic factors in dogs diagnosed with PLE reported a proportion of 21% of dogs diagnosed with SCL using the combination of suggestive histology and immunohistology as well as PARR clonality.[6] It is likely that we underdiagnose the proportion of dogs that develop PLE secondary to SCL, as reaching a diagnosis can be challenging and requires several diagnostic steps that may become unaffordable for owners.

Hypocobalaminemia is also commonly found and reported in 40 to 71% of dogs with SCL.

TREATMENT

There are currently no studies assessing different treatment strategies for dogs diagnosed with SCL. For this reason, there are no evidence-based recommendations that can be given. Based on previous experience in cats, these dogs are often treated with steroid and an alkylating agent (typically chlorambucil). Hypocobalaminemia is also treated if present.

Other considerations in dogs with PLE include an anti-thrombotic treatment to reduce the risk of thrombo-embolism. Some dogs are anecdotally reported to respond to multi-modal chemotherapy after escaping control with an alkylating agent, although no studies have been published yet.

One study comparing a treatment with azathioprine or chlorambucil combined with steroids in dogs with PLE reported a longer survival in dogs treated with chlorambucil. There was no suspicion of SCL in these dogs at time of diagnosis, but no further testing such as immunohistochemistry or PARR clonality were performed. The difference in treatment response raises the question if some of these dogs did indeed have an unrecognised SCL.[13]

OUTCOME

Similar to cats, prognosis is much better for dogs with SCL than LCL. Long remissions have been reported in dogs diagnosed with SCL and treated with a combination of steroid and an alkylating agent. Median survival times (MST) reported range from 424 to 628 days.[4,12,5,2] This is much longer than survival times reported for the more frequently diagnosed LCL in dogs, which has a poor prognosis.

Several negative prognostic factors have been reported including the presence of weight loss and anemia.[5] The same study reported that dogs treated with steroids and an alkylating agent had a significantly prolonged survival compared to dogs treated with steroids alone or no treatment (MST of 628 versus 127 versus 7 days). Survival of PLE dogs diagnosed with SCL is significantly longer than dogs diagnosed with LCL and shorter than dogs diagnosed with chronic enteropathy or lymphangiectasia (MST>1,000 days)

As mentioned earlier, PARR testing is suggestive for clonality in some dogs diagnosed where histology and immunohistochemistry supports a diagnosis of chronic enteropathy. Interestingly, PARR clonality alone was found to be significantly associated with a poorer outcome in two studies.[6,14] Although further studies are required to determine the reason for discrepancies between PARR testing and other testing, presence of clonality in dogs with clinical signs of CE might suggest a poorer outcome. The same finding has been reported in cats with clonality being significantly associated with poorer survival on multivariate survival analysis.[15]

CONCLUSION

In conclusion, SCL has now been described in dogs and a majority present with PLE. A definitive diagnosis is difficult to reach and will often requires a combination of histology, immunohistochemistry, and potentially PARR testing. A lack of gold standard diagnostic criteria makes a definitive diagnosis hard to reach and comparisons between methods difficult. For this reason, the clinical presentation dictates what diagnostic steps are required.

There are currently no studies assessing different treatment options, however, there is clear evidence that a majority of dogs will respond for more than a year when using a combination of steroid and an alkylating agent, similar to what is seen in cats.

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