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Research paper

Spirocerca lupi induced oesophageal neoplasia: Predictors of surgical outcome

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ABSTRACT

Canine spirocercosis is caused by the nematode *Spirocerca lupi*. Migration results in oesophageal fibro-inflammatory nodules that may undergo neoplastic transformation. No studies have assessed pre- or post-surgical prognostic indicators in dogs that undergo intervention for *S. lupi* induced oesophageal neoplasia.

This observational, multi-center study aimed to assess the outcome of dogs with *Spirocerca* induced sarcoma undergoing endoscopic-guided ablation (n = 12) or surgery (n = 18), and identify prognostic indicators. Parameters evaluated included: age, weight, gender, presenting complaints, duration of clinical signs, complete blood count, serum biochemistry, neoplasia size, placement of percutaneous endoscopically-placed gastrostomy tube, histopathological mitotic indices, days to discharge and chemotherapy administration.

Kaplan-Meier survival curves showed no difference in survival between ablation and surgery {(median: 73.5 days (range: 0–1511) vs. 108 days (range: 0–1550), respectively (p = 0.982)}. Reduced survival was documented in patients presenting with weight loss (P = 0.027), hypochromasia (MCHC < 33 g/dL, P = 0.023) or leucocytosis (> 15×10^9/L, P = 0.017) with a hazard ratio of 2.51 ($CI_{95\%}$ = 1.071–6.018, P = 0.034), 2.71 ($CI_{95\%}$ = 1.10–6.65, P = 0.03) and 4.39 ($CI_{95\%}$: 1.21–15.97, P = 0.025) respectively. In the dogs surviving more than 21 days, Ht < 36% and leucocytosis > 15.0×10^9/L at presentation were associated with reduced survival (p = 0.016, p = 0.021 respectively) and hazard ratio of 3.29 ($CI_{95\%}$ = 1.18–9.2, P = 0.023) and 3.81 ($CI_{95\%}$ = 1.15–12.55, P = 0.028) respectively. Intra-intervention-group survival analysis identified increased survival time in dogs receiving chemotherapy, but only within the surgical group (P = 0.02).The hospitalisation time of dogs undergoing ablation (median: 0 days, range: 0–4) was significantly shorter than dogs undergoing surgery (9 days, 1–21) (P < 0.001).

In this study, no clear benefit was identified for surgery, thus when ablation is technically possible it should be considered advantageous, as hospitalisation time is significantly shorter. Weight loss, hypochromasia and leucocytosis were identified as long-term prognostic indicators at presentation.

1. Introduction

Spirocercosis is caused by *Spirocerca lupi*, a spiurid nematode of carnivores, particularly Canidae. Spirocercosis is highly prevalent in dogs in the tropics and subtropics, including South Africa and Israel (Bailey, 1972; Mazaki-Tovi et al., 2002; Van der Merwe et al., 2008). Dogs become infected through ingestion of infected intermediate hosts (i.e., coprophagous beetles) or less commonly by preying on paratenic hosts. After ingestion, the infective (L3) larvae penetrate the gastric wall, migrate to the small gastric blood arterial vessels, travel in the gastric and celiac artery walls to the caudal thoracic aorta, and finally to the caudal thoracic oesophagus where it causes formation of fibro-inflammatory nodules (Krishna and Anantaraman, 1971). The latter, through uncharacterised mechanisms, may undergo neoplastic transformation to various types of sarcomas, in up to 25% of cases (Dvir et al., 2001; Dvir et al., 2010). Typical clinical signs relate to the presence of oesophageal nodules or neoplasia and include regurgitation, vomiting, dysphagia, weight loss, pyrexia and lethargy (Dvir et al., 2001; Mazaki-Tovi et al., 2002; Lavy et al., 2002).

Non-neoplastic nodules are responsive to avermectins (Lavy et al., 2002), however, treatment of dogs with neoplastic transformation is challenging. The tumour becomes progressively larger, eventually resulting in oesophageal obstruction (Dvir et al., 2001; Dvir et al., 2008). Histologically the neoplasms are typically classified as osteosarcoma,

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fibrosarcoma, or anaplastic sarcoma (Ranen et al., 2004a; Ranen et al., 2008). Oesophageal osteosarcoma, the most common form of sarcoma in spirocercosis, has been compared to appendicular osteosarcoma in which a number of prognostic indicators have been reported (Boerman et al., 2012; Romano et al., 2016). Comparing certain grading criteria of canine appendicular osteosarcoma, spirocercosis-induced sarcoma may be considered a more aggressive neoplasia (Kirpensteijn et al., 2002; Dvir et al., 2010). Although removal of the oesophageal neoplasia undoubtedly extends life expectancy, there are no studies that directly evaluate prognostic indicators in *Spirocerca* induced sarcoma.

Oesophageal neoplasia's are rare in areas not endemic to spirocercosis (Ridgway and Suter, 1979), making *Spirocerca* induced sarcoma a highly attractive model to study the prognosis and complications associated with oesophageal neoplasia and surgery. A review of dogs that underwent oesophageal surgery for various reasons found that the presence of a mass and mass size were significant independent prognostic factors for the development of delayed postoperative complications, but only seven dogs in the review had an oesophageal mass (Sutton et al., 2016).

The preferred surgical technique for *Spirocerca* induced sarcoma is a thoracotomy with a partial oesophagectomy (Ranen et al., 2004b), but the tumour is not always resectable due to infiltration into surrounding structures (Dvir et al., 2001). The procedure is considered invasive, costly, painful and is associated with prolonged hospitalisation. Recently, transendoscopic oesophageal mass ablation was described as a new mode of therapy (Yas et al., 2013; Shipov et al., 2015). Removal or debulking of the neoplasia was performed using a 9 mm video-endoscope and laser or electrocauterisation. The procedure is less invasive and can be performed on an outpatient basis (Shipov et al., 2015).

The aim of the current study was to evaluate the prognostic indicators of dogs diagnosed with *Spirocerca* induced sarcoma and to compare the outcome of the 2 validated removal techniques: transendoscopic ablation and partial oesophagectomy.

2. Material and methods

2.1. Animals

The medical records from 2007 to 2016 of Onderstepoort Veterinary Academic Hospital (Pretoria, South Africa) and The Hebrew University Koret School of Veterinary Medicine − Veterinary Teaching Hospital (Beit Dagan, Israel) were retrospectively reviewed for the following inclusion criteria: 1) any dog diagnosed with *Spirocerca* induced sarcoma, based on supportive clinical signs, typical cauliflower-ulcerated-necrotic appearance on endoscopy and confirmation with histopathology; 2) absence of macroscopic metastasis on radiographs or computed tomography (CT); 3) intervention with surgery (partial oesophagectomy) or endoscopic-ablation mass removal. Depending on the type of intervention, dogs were divided into the surgery or ablation group.

2.2. Procedures

Surgery was performed via thoracotomy with full thickness partial esophagectomy, ideally achieving 1 cm margins from the neoplasia borders as previously described (Ranen et al., 2004b). Transendoscopic oesophageal mass ablation was performed using a 9 mm video-endoscope and laser or electrocauterization as previously described (Shipov et al., 2015).

2.3. Data

The following clinical parameters were collected for all cases where available: age, gender, weight, presenting complaint and duration of clinical signs (based on the owner first noticing any sign attributable to spirocercosis). If weight loss was part of the presenting complaint, it was based on the owner's subjective perception of weight loss. The following clinical-pathological parameters were recorded and evaluated: haematocrit (Ht), mean corpuscular volume, mean corpuscular haemoglobin content (MCHC), total white cell count (WCC), total neutrophil, lymphocyte, monocyte, eosinophil and platelet counts; serum total protein, albumin, globulin, alanine aminotransferase, alkaline phosphatase (ALP), urea, creatinine, total calcium, amylase, glucose, phosphate, sodium, potassium and chloride. Additionally, the following parameters were recorded: the size of the mass on radiographs or CT and placement of percutaneous endoscopically placed gastrotomy (PEG) tube. Post-surgical parameters evaluated included histopathological mitotic indices (low, moderate or high), days to discharge, inclusion of chemotherapy and drug used as well as survival time after surgery.

2.4. Statistical analyses

All continuous variables were tested for normal distribution using a Shapiro-Wilks test. Values are reported as median (and range) unless specified otherwise. Difference in continuous variables between groups was analysed using the Mann-Whitney *U* test. The Kaplan-Meier method (log-rank test) was used to generate survival curves, and COX regression analysis used to generate hazard ratios (with 95% confidence interval ($CI_{95\%}$)) in all dogs, dogs surviving longer than 21 days after intervention (long-term survival group), as well as intragroup intervention analysis. Dogs that died < 21 days after intervention were classified as having a short-term survival. Dogs still alive at the time of analysis were censored. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS® 24.

3. Results

3.1. Animals

Thirty client-owned dogs met the inclusion criteria. Twelve dogs underwent endoscopic-guided laser ablation and 18 underwent surgery. One dog from Onderstepoort Veterinary Academic Hospital underwent ablation and fifteen underwent surgery, while eleven dogs from The Hebrew University Koret School of Veterinary Medicine underwent ablation and three underwent surgery. The age range was 3–12 years with a median of 6.5 years (mean 6.8 years). Twenty-one (70%) of the dogs were females (19 spayed), and 9 (30%) dogs were male (3 neutered). The median weight was 22.2 kg (range 4–40 kg; mean 20.3 kg). Breeds included 4 German shepherds, 3 Labrador retrievers, 2 Boxers, 2 Dachshund, 2 Siberian huskies, and one each of the following: Jack Russel Terrier, Fox terrier, Basset hound, Border Collie, Golden retriever, Pug, American Pitbull terrier and Cavalier King Charles spaniel and 9 mix-breeds. There was no significant difference between intervention groups regarding age, breed or sex.

3.2. Presenting complaint and duration of clinical signs

The most common presenting complaint of all dogs included gastrointestinal signs (26/30, 87%) and weight loss (10/30, 33%), with the following individual categories: regurgitation only (10/30, 33%); regurgitation and vomiting (4/30, 13%); regurgitation, vomiting and weight loss (4/30, 13%), regurgitation & weight loss (3/30, 10%), vomiting only (3/30, 10%), vomiting & weight loss (2/30, 7%), regurgitation and melena (1/30, 3%), weight loss only (3%), coughing only (3%) and melena only (3%). Survival analysis showed decreased survival times if a patient presented with weight loss ($P = 0.027$, Fig. 1.) with a hazard ratio of 2.51 ($CI_{95\%} = 1.071–6.018$, $P = 0.034$) compared to dogs without weight loss. Weight loss did not remain significant in the long-term survival group (dogs surviving > 21 days) ($P = 0.068$). The duration of clinical signs before presentation ranged from 1 to 170 days (median 23 days) and was not associated with survival ($P = 0.162$).