**REVIEW: CHALLENGES IN DIAGNOSIS AND TREATMENT OF CANINE SPIROCERCOSIS**

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*Spirocerca lupi* (*S. lupi*) is a nematode of worldwide distribution, most commonly found in tropical and subtropical areas (1). Dogs are the definitive hosts and become infested by ingesting the coprophagous beetle intermediate hosts (1) or various paratenic hosts, including poultry, wild birds, lizards, rodents, hedgehogs and rabbits (2). A previous study has revealed that *S. lupi* larvae-infected coprophagous beetles are small and feed within the feces, and dogs probably become infected through coprophagia rather than by catching the beetle (3). After ingestion, the larvae are liberated in the gastric lumen, migrate through the gastric mucosa via the gastric arteries, and reach the caudal thoracic aorta within 10 days. Later they migrate through the thoracic aortic wall to the caudal esophagus within 90 to 109 days (4). The *S. lupi* larvae settle within the esophageal wall, mature to adults and promote nodule formation (1, 2, 5). The nodules are usually incorrectly referred to as granulomas (1, 5). The early nodule is however composed predominantly of fibrocytes (amidst ample mature collagen), that with time (i.e. during nodule maturation), transform into actively dividing fibroblasts that are located between numerous immature capillaries, immediately peripheral to the worms and their migratory tracts (2, 6). The associated inflammatory reaction within the nodule is variable and is not characterized by the presence of macrophages, as in granulomatous inflammation (2, 5). Instead, the predominant infiltrate is lymphoplasmacytic in nature, with pockets of neutrophils specifically associated with the necrotic content of the worms’ migratory tract (6). Spirocercosis induces some pathognomonic lesions: aortic scarring with or without osseous metaplasia and/or dystrophic calcification as well as aneurysm formation, caudal thoracic vertebral spondylitis and a characteristic caudal esophageal nodule. The common clinical signs associated with spirocercosis are related to the presence of esophageal nodules and include regurgitation, vomiting and weight loss, with other non-specific signs such as pyrexia (7, 8).

Positive fecal flotation tests show numerous, characteristic, small (35 × 15 μm), thick-shelled, larvated eggs (Fig. 2). However, the sensitivity of fecal flotation is limited because eggs are shed intermittently by the female worms and the eggs are relatively heavy and may require special techniques and solutions such as sodium nitrate solution (specific gravity 1.36), supersaturated 33% zinc sulfate solution and supersaturated sugar solution (9). Recently, a copromicroscopic approach, the FLOTAC technique was reported to improve the sensitivity and increase the number of microscopically detected eggs (10). This method seems to be superior to the previously described techniques / solutions, however it only detected 10 out 31 cases (32%), detected by polymerase chain reaction (PCR), and required specific apparatus and centrifuge. Repeated fecal analysis was found to increase the sensitivity of the test (8). Recently a PCR assay was developed to detect fecal *S. lupi* (10). Such a test can maximize the sensitivity of fecal analysis but also depends on presence of egg-shedding female worms in a patent esophageal nodule. This proviso excludes cases with aberrant migration, extra-luminal nodules, early infestations and late disease with malignant transformation, where the worm is often no longer present.

The clinical diagnosis of spirocercosis largely depends on thoracic radiography, demonstrating a caudodorsal mediastinal mass, caudal thoracic vertebral spondylitis and aortic undulation due to aneurysm formation (with or without aortic mineralization) (7). A caudodorsal mediastinal mass on its own is highly suspicious for spirocercosis in endemic areas but if accompanied by spondylitis and/or aortic aneurysms the radiological changes are pathognomonic for spirocercosis. However, the clinical diagnosis of spirocercosis remains challenging due to several factors; Nodules may be small or atypically located and thus may not be visible on radiographs. Cases may present in early disease stages, prior to the formation of esophageal nodules. Differentiating between a *S. lupi*-induced benign nodule and a neoplastic tumor is sometimes difficult. Atypical cases due to disease related complications or aberrant migration are diagnostically challenging. These difficulties are discussed in this paper.

**Diagnosis of small or atypically located esophageal nodules**

Positive radiological diagnosis is very reliable, claiming 100% specificity in one study (11). However, the sensitivity of survey radiology is only about 84% (12), because small and atypically located esophageal nodules may not be detected by survey thoracic radiographs (7). Dorsoventral and right lateral recumbent radiographs are recommended to optimize
the masses and aortic aneurysms visibility (12). Small or atypical nodules may, however, readily be detected in contrast radiographic studies, especially pneuma-esophagograms (Fig. 1) (7). In the latter the air filled esophagus provides contrast to enhance the visibility of masses which otherwise tend to be effaced by the surrounding esophageal and mediastinal structures. Providing the esophagus is sufficiently distended with air the mural attachment location can usually also be seen allowing for better surgical planning. Additionally the extramural extent of the mass is also highlighted. Endoscopy is the most sensitive tool to detect and evaluate *Spirocerca*-induced intra-esophageal nodules (7, 8). It is the only tool that allows direct visualization of the nodules and its typical appearance contributes to the diagnosis substantially and it is also ideal to monitor response to treatment. Endoscopy does however also have its drawbacks as it provides no information on any other thoracic complications. Additionally the equipment is specialized and expensive and the procedure requires a full general anesthetic.

Computed tomography (CT) is emerging as a very effective tool for detecting small intraluminal nodules, mural and extraluminal nodules, atypically located nodules as well as dystrophic aortic mineralization (7). In CT the cross sectional images avoid superimposition of structures, as is seen on radiographs, enhancing mass detection. The greater sensitivity of CT to detect mineralization is also a great advantage, for example, aortic mineralization is seen in up to 50% of CT cases whereas on radiographs mineralization is rarely seen.

**Diagnosis of early infections when esophageal nodules are absent**

The detection of early cases of spirocercosis remains challenging. Computed tomography may detect early spondylitis and aortic mineralization as well as aberrant migration. Although CT will not be done routinely in every sick dog, our institution diagnoses about 8% of our confirmed cases of *S. lupi* incidentally when performing thoracic CT for other reasons. In endemic areas thoracic CT examinations should thus always include specific evaluation of the esophagus, aorta and the spine. Other diagnostic modalities such as endoscopy and fecal examination depend on the presence of an esophageal nodule or a viable egg laying passage respectively. Serology might prove to be a promising modality to detect early infection. Preliminary results of an immunofluorescent antibody test (using the mid-body region of the male worm as an antigen source) showed 100% sensitivity and 80% specificity for *S. lupi* at a titre of 1:640 (13). However, as yet nothing more has been published on this topic.

**Differentiating between *S. lupi*-induced esophageal nodules and neoplasms**

With time, esophageal nodules may undergo malignant transformation to sarcoma (5, 14). *Ante-mortem* differentiation between non-malignant and malignant cases is challenging yet clinically, therapeutically and prognostically very important. A few studies have tried to investigate criteria that might characterize dogs with *S. lupi*-induced malignant esophageal tumors (5, 14-16). Neoplasia occurs more frequently in older dogs, and in spayed females, while benign nodules are more common in young males, however there is a considerable age and sex overlap between groups. *Ante mortem* indicators of *S. lupi* esophageal neoplasia are non specific and insensitive (15). Hypertrophic osteopathy (HO) occurs in 40% of patients with *S. lupi* induced esophageal sarcoma (15) and is an indicator of neoplastic transformation. Spondylitis was more common and severe in malignant cases (15-17), but the prevalence of spondylitis in benign cases was 38% (15), indicating that spondylitis is initiated early in the disease process and is progressive. Anemia, leukocytosis, and thrombocytosis occur more commonly in malignancy (15), likely due to continuous esophageal irritation, inflammation and blood loss or they may have a paraneoplastic origin.

Radiology has been used to differentiate between esophageal malignancy and benign nodules. The length of esophageal masses was similar in both benign and malignant cases (15). This unexpected finding was probably due to the superimposition of smaller nodules (ranging 1-9) along the caudal length of the esophagus. In survey thoracic radiographs, the height and width of esophageal masses were significantly higher in neoplastic compared to benign masses (62.6 versus 43.4 mm and 73.9 versus 49.3 mm, respectively) and bronchial displacement was more common in the malignant group, probably secondary to the larger mass size (15). Radiographically detectable esophageal mass mineralization was observed in both neoplastic and non-neoplastic cases and could not be used to diagnose malignant transformation. In the non-neoplastic cases it was probably due to osseous metaplasia (15). False positive results may also occur due to entrapped mineralized ingesta. Assessment of esophageal mass mineralization as a differentiating characteristic between benign and malignant conditions using CT is currently being assessed at our institution. Macroscopically, the surface of malignant esophageal neoplasms tend to be cauliflower-like (2). Based on this characteristic appearance, Ranen and others (2004) reported that they were able to make a tentative diagnosis of *S. lupi*-induced sarcoma, using endoscopy, in all 15 cases examined. An ulcerative vegetative growth pattern with necrosis in deeper layers is common in malignancy (Fig. 3A), although malignant nodules may, on occasion, have a smooth surface. Benign nodules are typically small, smooth and rounded with a nipple-like protuberance (Fig. 3B), (7). Occasionally however, they may ulcerate and undergo necrosis and inflammation, and might be falsely diagnosed as neoplastic (15). Endoscopy-guided biopsy has limitations. Although highly specific, the procedure has very low sensitivity (7, 8, 16), because biopsies frequently include only the necrotic superficial layers of the tumor, rendering a definite diagnosis impossible. Thoracotomy and surgical resection of the mass
with histology of the entire mass has the highest sensitivity and specificity, but is invasive with increased risk of complications, can be cost-prohibitive and should be reserved for cases that show endoscopic evidence of neoplasia, HO, or mineralization on imaging. Computed tomography may aid in the planning of the surgical procedure (7). Where there is uncertainty about the diagnosis of neoplastic transformation, response to a medical therapy followed by repeated endoscopy might aid in the diagnosis, demonstrating nodule regression in non-neoplastic cases and further proliferation in neoplastic nodules.

Benign esophageal nodules regress with doramectin (Dectomax, Pfizer, France) treatment, 400 µg/kg SC at 2-week intervals (18). Pharmacokinetic studies of doramectin in dogs showed good absorption results for oral administration (19), suggesting that it could be an effective route of administration, but no clinical results have as yet confirmed this. The pharmacokinetics of doramectin and ivermectin in dogs are similar, rendering the latter a therapeutic option too, but clinical results are also necessary to confirm this (19). In avermectin susceptible breeds such as collies, milbemycin-specificity, but is invasive with increased risk of complications, should increase the oxime may be used (20).

In summary, female gender, anemia, leukocytosis, thrombocytosis, spondylitis and bronchial displacement, if found together in a spirocercosis case, should increase the index of suspicion for malignancy. In addition, according to our data, if HO is diagnosed, it is strongly indicative of neoplastic transformation of the esophageal nodule. Histologically, the malignant neoplasms are classified as osteosarcoma (most common), fibrosarcoma, or undifferentiated sarcoma (16). Osteosarcomas are defined by the presence of osteoid, produced by neoplastic pyriform osteoblasts (21), while fibrosarcomas are characterized by the presence of collagen matrix between interwoven neoplastic or anaplastic spindle shaped cells (22) and undifferentiated sarcomas lack distinctive architectural pattern, cell products / matrix as well as cytoplasmic and nuclear features (23). In areas where spirocercosis does not exist, malignant neoplasms of the esophagus are extremely rare (<0.5% of all malignant cases) (24), making spirocercosis the major cause of malignant esophageal neoplasms in the dog and certainly the primary cause of osteosarcoma, fibrosarcoma, or undifferentiated sarcoma at this site. Spirocercosis-induced sarcoma can metastasize to various locations, most commonly the lung (5, 7, 16). Based on the current knowledge, malignant esophageal neoplasms can only be treated by surgical excision. Advanced sessile tumors that require full circular esophageal resection carry a very poor prognosis, while small pedunculated tumors that require partial esophagectomies have a far better prognosis (16). Chemotherapies suggested for appendicular osteosarcoma, such as carboplatin and doxorubicin, can be used post-surgically, but thus far, their benefit is not clear (16). The average survival of esophagectomy plus doxorubicin was 267 days in one study in dogs with spirocercosis (16). A murine model of S. lupi-associated sarcoma showed doxorubicin and pegylated liposomal doxorubicin to be effective, but not carboplatin or cisplatin (25). Because it is less toxic than doxorubicin, pegylated liposomal doxorubicin is recommended for treatment of S. lupi-associated sarcoma.

Non-gastrointestinal clinical presentation in spirocercosis: disease-associated complications and aberrant S. lupi migration

Atypical clinical signs of spirocercosis can result from larval or adult worm migration, their presence in different organs and from inflammation. Respiratory signs are very common, occurring in 25%-50% of cases (2) and are due to airway tract compression by esophageal masses, aspiration pneumonia secondary to regurgitation, mediastinitis, pleuritis, pyothorax and pulmonary metastasis (7, 8, 26). Pyothorax occurs quite commonly due to esophageal perforation or aberrant migration (26). Although aortic lesions are extremely common in spirocercosis, aortic rupture with consequent hemothorax is observed less commonly, and is almost always fatal (27). Lameness is not uncommon (up to 25% in one report), and results from HO or secondary septic or immune-mediated arthritis (7). Paraparesis and back pain occur occasionally and have been attributed to the presence of spondylitis in the mid thoracic vertebrae (8). Hind quarter paralysis has been described in spirocercosis-associated aortic thromboembolism (28, 29).

Severe intractable dysphagia with firm mandibular salivary adenomegally has been documented in up to 8.5% patients presenting with spirocercosis with fox terriers and Jack Russell terriers over represented (30). The clinical history in these dogs was often prolonged and included retching, coughing, hypersialosis, gulping and choking, worsened with excitement and palpation of the pharyngeal area. No salivary gland biopsies were obtained, but fine-needle aspirate cytology in four cases showed hyperplasia with no evidence of inflammation. These dogs were all treated symptomatically and with doramectin and phenobarbitone (2 mg/kg q12h) and showed marked improvement within 48 hours from initiating phenobarbitone treatment (30). This response to phenobarbitone suggests an underlying central nervous system involvement, most likely continuous vagal stimulation, known as visceral epilepsy (31).

Aberrant migration of S. lupi is not uncommon, and has been reported in most thoracic organs including pleura, mediastinum, diaphragm, lung, trachea, bronchi, thymus and heart (32, 33). Non-thoracic aberrant migration was reported in the gastrointestinal and urinary tracts (34, 35) and subcutaneous tissue (33, 36). Recently, aberrant spinal S. lupi has been described in dogs (both extradural and intramedullary) (37, 38). Such migration can lead to paraparesis and paraplegia, clinically mimicking disc extrusion and fibrocartilaginous embolism (37). Intramedullary spinal cord migration presents a distinct neurological syndrome of an acute, progressive asymmetric, mostly painful paresis progressing to paralysis.
Neurological examination may suggest a focal spinal cord lesion between T3 and S1, but the pathological lesions might be far more extensive due to progressing larval spinal migration. Cerebrospinal fluid (CSF) neutrophilic and eosinophilic pleocytosis is commonly observed and differentiates such cases from fibrocortical embolism and disc disease. Extrudal spinal aberrant migration can be diagnosed by myelography. However, the diagnosis of intramedullary migration is far more challenging, because myelography or computed tomography are usually non-diagnostic (38, 39). Magnetic resonance imaging (MRI) can be used to demonstrate intraspinal parasitic lesions in humans (38), and has revealed abnormalities suggestive of myelitis and myelomalacia in two dogs with aberrant spinal intramedullary migration (39). When characteristic clinical signs of spirocercosis are present (e.g., regurgitation, vomiting, weight loss and dysphagia) and are supported by specific radiographic and endoscopic findings, a diagnosis of spirocercosis is fairly straightforward even if atypical clinical signs of aberrant migration or complications are concurrently present. However, in cases of aberrant migration or complications and in the absence of any of the typical abnormalities, the ante mortem diagnosis of spirocercosis is extremely difficult. Therefore, in endemic areas, spirocercosis should be included as a differential diagnosis in dogs presenting abnormal soft tissue masses, hypervasitisation with sialoadenomegaly, pyothorax, hemothorax, mediastinal effusion, asymmetric spinal cord neurological signs and aortic thromboembolism.

It is difficult to treat the aberrant migration cases and conventional doramectin treatment is not always effective in these cases. In dogs presenting with pyothorax, conservative medical treatment, including drainage and antibiotics together with doramectin treatment, was found relatively successful (26). In cases of extrudal spinal cord migration, removal of the worm was successful in only 1 of 3 cases (37), while in intramedullary spinal cord migration, the prognosis was always grave (38). In humans with spinal schistosomiasis, surgical removal of the worm and the surrounding damaged tissue was very successful (40). Such radical therapy was only attempted twice in dogs, so far without success (39). This review outlines challenging aspects pertaining to the diagnosis of spirocercosis. At present, the diagnosis of typical cases is routinely achieved. With advances made in diagnostic modalities and in identifying the clinical presentation of atypical spirocercosis such diagnostic challenges can be met.

REFERENCES
17. Brodey, R. S. Thomson, R. G. Sayer, P. D. and Eugster, B.:


Fig. 1
Collimated right lateral view of the caudodorsal thorax of a dog after pneumo-esophagography. An oval ventral esophageal nodule is highlighted by esophageal gas (arrow). This nodule could not be seen in survey radiographs.

Fig. 2
A typical, elongated, oval, thick-shelled *Spirocirca lupi* egg. The eggs are small (35 × 15 μm) and contain the first-stage larva.

Fig. 3
Esophageal endoscopic photos of a neoplastic mass (A) and three benign nodules (B) in two different dogs. The neoplastic mass is proliferative and lobulated and presents black discolouration due to ulceration and necrosis. This mass is large (15 centimetres in length) and occupies most of the esophageal lumen. The benign nodules have a smooth, round appearance and show a typical protuberance (operculum, arrow). The esophageal mucosa has a normal, healthy appearance. The nodules are small in relation to the oesophageal lumen.