Medical management of *Echinococcus multilocularis* infection mimicking a locally aggressive cavitary tumor with pulmonary metastases in a dog

Medicamenteuze behandeling van een Echinococcus multilocularis-*infectie die een lokaal agressieve cavitaire tumor met longmetastasen nabootst bij een hond*

[1]**J. Fritz**, [2]**M. Mahinc**, [1]**B. Rannou**, [1]**E. Cauvin**

[1]Azurvet referral center, Hippodrome, 2 boulevard Kennedy, 06800 Cagnes-sur-Mer, France
Clinique Vétérinaire du Lac, 4550 route d'Albertville, 74320 Sevrier, France

azurvet@orange.fr

ABSTRACT

A two-year-old Labrador retriever living in the French Alps was presented with abdominal distension, lethargy and weight loss but no other specific clinical signs. CT examination revealed a large, cavitary liver mass invading the caudal vena cava, associated with multiple hepatic lesions of similar appearance, lymphadenopathy and pulmonary nodules. The condition was initially mistaken for a malignant neoplasm. However, cytologic and histologic examinations of the largest liver mass were consistent with cestodiasis and PCR testing confirmed infection with *Echinococcus multilocularis*. Medical treatment with albendazole was initiated. The dog remained clinically well for ten months following the diagnosis, but had to be euthanized because the owners had to return to Great-Britain and the dog could not be legally imported. To the authors' knowledge, this is the first case report, in which long-term follow-up of *Echinococcus sp.* infection in a dog, managed medically, is described. This case also shows that medical management may be a viable option in case surgery is not feasible.

SAMENVATTING

Een twee jaar oude labrador retriever uit de Franse Alpen werd aangeboden omwille van een opgezet abdomen, lethargie en gewichtsverlies. Op computertomografisch onderzoek werd een grote, cavitaire levermassa vastgesteld die de vena cava caudalis in groeide en die geassocieerd was met multipele gelijkaardige laesies ter hoogte van de lever, alsook met longnodulen en lymfadenopathie. Initieel werd deze aandoening verkeerdelijk aanzien als een maligne neoplasie, maar cytologisch en histologisch onderzoek van de grootste levermassa was compatibel met een cestodeninfectie. Een PCR-test bevestigde een infestatie met *Echinococcus multilocularis*. Medicamenteuze therapie met albendazole werd opgestart. De hond bleef klinisch goed gedurende tien maanden na de diagnose, maar moest worden geëuthanaseerd omdat de eigenaars terug moesten keren naar Groot-Brittannië en ze niet legaal kon geïmporteerd worden. Volgens de auteurs is dit de eerste casereport waarin een langetermijnopvolging wordt beschreven van een *Echinococcus sp.*-infectie bij een hond, die medicamenteus behandeld werd. Dit geval toont ook aan dat medicamenteuze therapie een bruikbare optie is als chirurgie niet haalbaar is.

INTRODUCTION

Canidae are involved in the life cycle of *E. multilocularis* mainly as definitive hosts, ingestion of infected intermediate hosts causing intestinal infection. However, there have been occasional case reports describing dogs affected as aberrant intermediate hosts since the 1980's (Deplazes et al., 2001). In dogs, alveolar echinococcosis may develop through the ingestion of eggs shed by a definitive host or through autoinfection as a complication of intestinal infection. Although uncommon, cases of hepatic metacestode

infections in domestic dogs have been described in Switzerland (Haller et al., 1998 ; Scharf et al., 2004; Heier et al., 2007; Pezelet et al., 2013; Gendron et al., 2015), Germany (Geisel et al., 1990; Gwada et al., 2018), Belgium (Caron et al., 2017), Slovakia (Antolova et al., 2018), and Canada (Peregrine et al., 2012; Oscos-Snowball et al., 2015). In dogs, in which alveolar echinococcosis develop within the abdominal cavity (Geigy et al., 2013; Oscos-Snowball et al., 2015; Gwada et al., 2018), the most common clinical features include progressive abdominal enlargement, intermittent inappetence and vomiting. Imaging modalities are important steps in the diagnosis of alveolar echinococcosis, with abdominal radiography and ultrasonography being most commonly reported, while abdominal CT has only been described in two cases (Scharf et al., 2004; Gendron et al., 2015). *E. multilocularis* infection represents a major public health issue, considering the zoonotic implications of the disease.

CASE DESCRIPTION

A two-year-old, female, spayed Labrador retriever was presented with progressive abdominal distension associated with moderate lethargy but no other specific clinical signs. The dog was living in the French Alps but travelled regularly to the United Kingdom. The common vaccinations used in France and Great-Britain had been administered correctly, and the dog was given milbemycin oxime and praziquantel tablets (Milbemax®, Novartis, Switzerland) every three months as prophylactic treatment against endoparasites. Dosages were adequate for its body weight, according to the manufacturer's recommendations.

Upon clinical examination, the dog was in a poor body condition. A firm, voluminous cranial abdominal mass could be palpated. Complete blood count showed mild neutrophilia with a moderate left shift. Serum biochemistry including liver enzyme activity
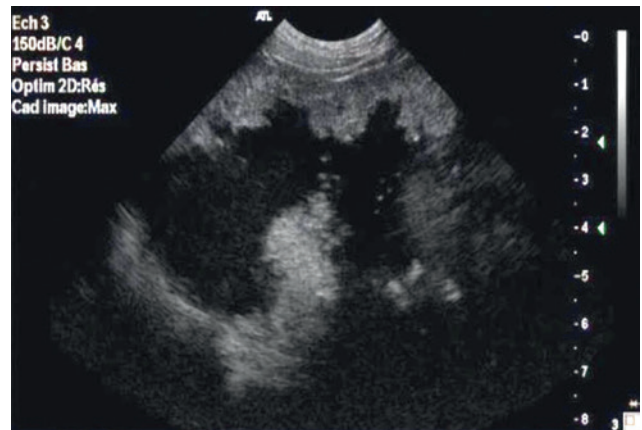

Figure 1. Ultrasonographic image of the largest hepatic cavitary lesion (image courtesy of Dr. M. Mahinc).

and bile acid measurement were within normal limits. Ultrasonographic abdominal examination performed by the referring veterinarian (HDI 5000 sonoCT, Philips Healthcare, France) confirmed the presence of a voluminous cranial abdominal mass, suspected to be originating from the liver (Figure 1). The large dimensions of the mass impaired comprehensive and detailed examination of the cranial abdominal region.

Computed tomography was performed at a second veterinary referral clinic (Les Hutins Veterinary Clinic, Saint-Julien-en-Genevois, France), using a 16-slice spiral CT (Brivo CT385, General Electric Healthcare, France). Precontrast helical acquisitions of the abdomen and thorax were first obtained with the lungs inflated (single breath-hold technique); CT angiographic examination of the abdomen was then performed by manually injecting 2 mg/kg iohexol (Omnipaque350®, Ge healthcare sas, France) followed by an early postcontrast acquisition, approximately ten seconds postinjection (portal phase). Delayed phase (four minute) postcontrast acquisitions of the thorax (thickness 1.25 mm, kV = 120, mA = 150) and abdomen (thickness 1.25 mm, kV = 120, mA = 160) were finally obtained. The CT images were re-
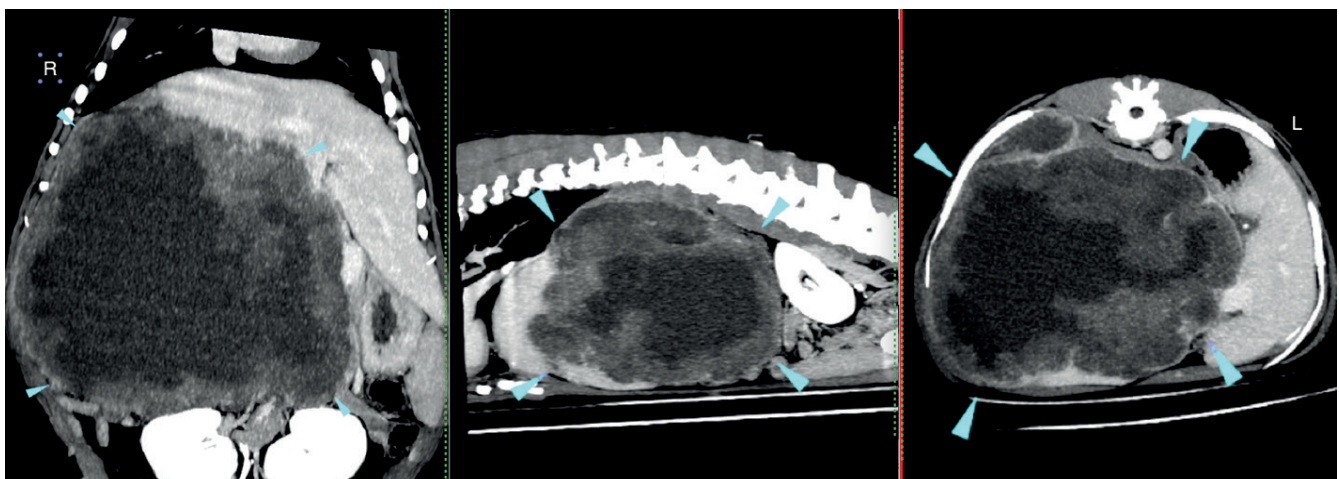

Figure 2. Multiple plane reconstruction (MPR) postcontrast image, using a soft tissue kernel showing a voluminous cavitary mass within the right liver lobes (arrowheads).
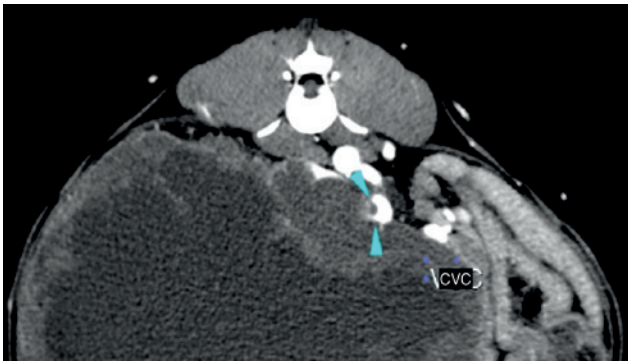
Figure 3. Transverse postcontrast reconstruction, using a soft tissue window at the level of the first lumbar vertebra showing mass effect on the caudal vena cava, left laterally displaced. A nick-shaped filling defect within the lumen (arrowheads), continuous with the mass, is noted within the lumen of the vena cava.
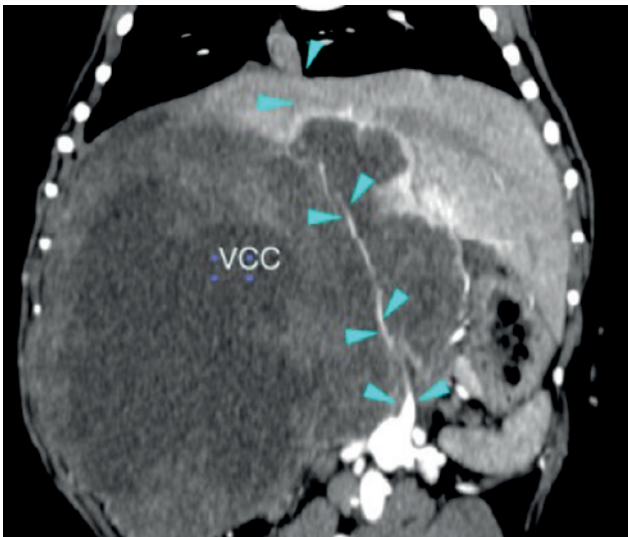

Figure 4. Dorsal plane MPR image with a soft tissue window, showing the caudal vena cava going through the mass, with severe narrowing of its luminal diameter (arrowheads).

viewed by a diagnostic imaging resident (JF) and a radiologist (EC).

A voluminous mass (20 cm craniocaudally, 22 cm laterally and 15 cm dorsoventrally) was present in the right cranial abdominal quadrant (Figure 2). The lesion was cavitary with a hypoattenuating center, unenhanced by the contrast medium (8 HU), and with a thick, heterogeneous tissue density (30 HU) periphery, which was very mildly and diffusely mineralized. This peripheral capsule was poorly enhanced by the contrast medium (30-40 HU). The mass displaced both kidneys caudally and to the left, the stomach laterally to the left, the duodenum ventrally and medially, and the portal vein ventrally and to the left. The mass was continuous with the parenchyma of the right liver and caused deviation of the intrahepatic portal vasculature.

The caudal vena cava was displaced dorsally and to the left. It was severely compressed and partially surrounded by the lesion. Although invasion of the venous wall was difficult to confirm, a focal, comma-shaped tissue density filling defect extended from the mass into the lumen of the caudal vena cava (Figures 3 and 4). The vein was moderately dilated caudal to the mass and barely visible immediately cranial to it. A hypoattenuating filling defect was also visible in the center of the portal vein lumen on postcontrast examinations. Two smaller cavitary nodules (measuring 3 mm and 7 mm, respectively), bearing the same appearance, were noted in the otherwise normal liver parenchyma. Hepatic, gastric and pancreaticoduodenal lymph nodes were moderately enlarged (8-10 mm). No peritoneal effusion was detected. The other abdominal structures were within normal limits. CT examination of the thorax revealed multiple, 3 to 7 mm-diameter nodules, distributed throughout the lung field, mostly in the periphery of the lobes (Figure 5). The pleural and mediastinal structures were within normal limits. Mediastinal and sternal lymph nodes were moderately enlarged (10 mm).

These features were consistent with a voluminous, locally aggressive cavitary hepatic mass lesion, with a high suspicion of invasion of the caudal vena cava and secondary thrombosis within the portal vein. Hepatic and pulmonary nodules and lymphadenopathy were identified. Based on these findings, including local aggressiveness and distant nodular lesions, a malignant neoplasm was considered most likely. The differential diagnoses included histiocytic sarcoma, hemangiosarcoma or, considering the young age of the dog, juvenile hepatocellular carcinoma. All these differentials were associated with a poor prognosis.

Fine-needle aspirates (Sterican® 23g, Braun, Germany) and needle biopsies (Trucut®, 14g, Merit Medical) were obtained under ultrasound guidance. Cytologic examination was consistent with granulomatous hepatitis associated with hyaline membrane-like structures, suggestive of alveolar echinococcosis (Figure 6A). Histologic examination confirmed the presence of numerous degenerated larvae (Figure 6B). Identification of *Echinococcus multilocularis* was confirmed by PCR testing (SEEpIAS LNR *Echinococcus multilocularis*).

The owners declined surgical treatment, considering the high risks involved with surgical removal of the mass, vascular implication and also the additional suspected parasitic masses in the liver and lungs. Medical treatment was therefore implemented, based on the daily oral administration of albendazole (Zentel 400®, GlaxoSmithKline) 10 mg/kg SID for life. Most of the fluid filling the main hepatic cavitary mass was aspirated in order to decrease abdominal pressure.

Considering the zoonotic risks associated with echinococcosis, a coproscopic examination was performed to ensure that the dog was not excreting any eggs, as this would have represented a significant threat to the owner's health. No *Echinococcus sp.* eggs were found.

The dog was re-examined eight months after the

initial presentation. She was presenting recurrence of abdominal distension, which, according to the owner, had progressively appeared. However, she was not lethargic and the owner reported that her behavior was normal and that there were no clinical signs. Follow-up CT examination was performed. The main hepatic cavitary mass had regained a volume similar to that in the initial scan (before complete aspiration of the fluid). The two smaller hepatic cavitary nodules had similar dimensions as previously. Pulmonary nodules were still present and yielded a similar size. Invasion of the caudal vena cava was more prominent and extended into the hepatic veins, to the point that the vena cava was barely visible within and cranial to the mass. Collateral drainage of the caudal portion of the caudal vena cava had developed via the deep circonflex iliac veins and dorsal subcutaneous veins, anastomosing with vertebral veins and the right azygos vein which appeared dilated. The cranial part of the liver still drained into the thoracic part of the caudal vena cava.

The fluid inside the largest cavitary hepatic mass was again aspirated in order to decrease abdominal pressure. The medical treatment was continued, as follow-up biochemistry and hemograms were within normal ranges (especially no neutropenia). The dog remained clinically stable for ten months after diagnosis. Unfortunately, she had to be euthanized, as her owners were moving back to Great-Britain, where she could no longer be legally imported. Necropsy was declined by the owners.

DISCUSSION

Echinococcus multilocularis is a small, zoonotic, tapeworm that occurs in central Europe, in much of northern, central and eastern Eurasia and parts of North America (Moro et al., 2009). In North America, some authors have reported an increasing incidence
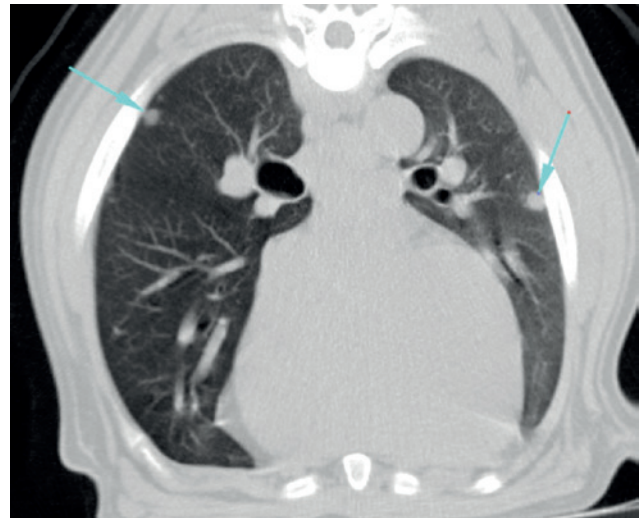

Figure 5. Transverse-plane image of the thorax using a lung parenchyma reconstruction kernel, showing two of the pulmonary nodules (arrows) at the periphery of the right and left cranial lung lobes.

of clinical echinococcosis in recent years (Peregrine et al., 2015). Adult parasites reside within the small intestine of definitive hosts, which primarily include wild canids (foxes, coyotes, wolves) and domestic dogs. Intestinal infection in the definitive hosts is usually asymptomatic. Following the ingestion of eggs by an intermediate host, most commonly arvicolidae but also occasionally other mammals including canids or man, the larval stage of the parasite (oncosphere) hatches, migrates to the liver and develops into alveolar echinococcosis (Oscos-Snowball et al., 2015). This larval stage of the parasite undergoes exogenous budding and behaves like an invasive tumor (Moro et al., 2009).

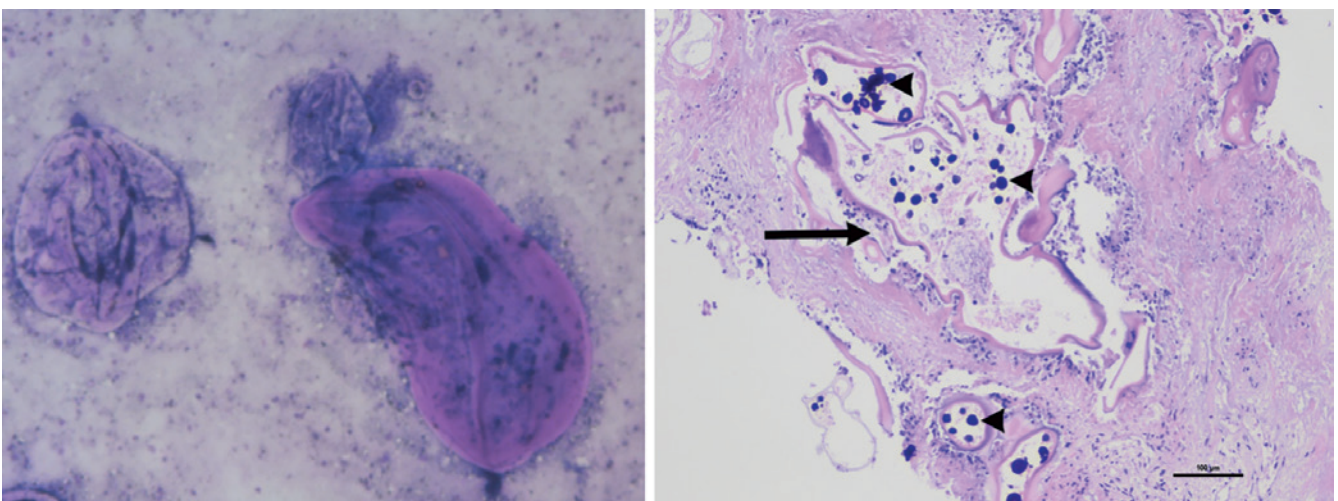The dog regularly travelled with her owners between the United Kingdom and France and was as

Figure 6. A. Cytology of a fine-needle liver aspirate, showing the presence of large, irregularly shaped, hyaline membrane-like structures (Wright-Giemsa, x100 magnification) (image courtesy of Dr. B. Rannou). B. Histologic slice of a liver biopsy, showing a degenerated cyst (arrows) containing calcareous corpuscles (arrowheads), consistent with degenerated protoscolisces (hematoxylin and eosin strain, the horizontal black line in bottom right corner represents 100 m) (image courtesy of Dr. A. Nicolier).

such regularly given prophylactic medication with milbemycin oxime and praziquantel (Milbemax®, Novartis, Switzerland). Although it cannot be ascertained where the dog had been infected, no known domestically acquired *E. multilocularis* infection in the United-Kingdom has been recorded (official U.K. government website, updated March 2019), but the French Alps are an endemic region (Umhang et al., 2017). It is therefore most likely that the dog became infected in France. The milbemycin oxime and praziquantel combination is not effective against the cyst stage forms of *Echinococcus* spp. and has no persistent activity (according to the summary of product characteristics), which may explain why the dog could develop larval disease.

The dog presented in this case report was a young (two-year-old) adult. Although there have only been very few cases reported in domestic dogs (Geisel et al.,1990; Haller et al., 1998) (Scharf et al., 2004; Heier et al., 2007; Peregrine et al., 2012; Pezelet et al., 2013 ; Gendron et al., 2015; Oscos-Snowball et al., 2015; Caron et al., 2017; Gwada et al., 2018), it seems that the condition mostly affects young adults (with the exception of an eleven-year-old, female Siberian Husky in Slovakia (Antolova et al., 2018). It is unclear whether this is due to immune pathophysiological considerations, behavioral patterns in younger dogs or to other causes. A possible bias may be a lack of further (microscopic) investigations performed in older dogs, in which the diagnosis of metastasized malignancy would have been presumed more easily. In one case report, in which a bitch was diagnosed with alveolar echinococcosis in the postpartum period, the authors suggested that gestation might have led to the progression of the disease (Gwada et al., 2018).

In the dog presented in this report, a large, cavitary hepatic mass was identified along with two additional, smaller nodules, both of which had a similar appearance. In a retrospective study of canine alveolar echinococcosis in eleven dogs by Scharf et al., (2004), all animals presented with a large liver mass on radiographs, 5/11 showing multifocal mineral opacities. CT examination was only performed in one dog in that study and yielded a large cavitary lesion with no contrast enhancement of the wall. This absence of contrast enhancement of the wall could have led the authors to consider a benign (including parasitic) lesion rather than a malignant liver tumor, despite local aggressiveness and distant lesions. The wall was partially mineralized, a feature considered typical of echinococcosis in children (Pohnan et al., 2017). In all the reported cases in the veterinary literature (Geisel et al., 1990; Deplazes et al., 2001; Scharf et al., 2004; Peregrine et al., 2012; Geigy et al., 2013; Gwada et al., 2018; Antolova et al., 2018), the most common ultrasonographic feature was a large cavitary mass within the liver. Color-flow Doppler imaging showed no visible blood flow within the lesion. In one case, a voluminous peritoneal effusion was detected, which

was not the case in the dog presented here (Gendron et al., 2015).

Although the present case shares many similarities with previously described alveolar echinococcosis liver lesions in dogs, only one other reported dog presented with metastatic spread to the lungs and signs of local aggressiveness (especially invasion of the caudal vena cava) (Gendron et al., 2015). These tomodensitometric features initially led to an erroneous diagnosis of malignant neoplasia in the present case. It is unclear whether invasion of the vena cava represented granulomatous invasion of the local vasculature draining into the caudal vena cava, possibly with secondary thrombus formation, or whether thrombus formation was due to focal compression, turbulent blood flow or coagulation disorder (coagulation tests were not performed).

Confusion between alveolar echinococcosis disease and neoplasia appears to be a major challenge in human medicine, in which alveolar echinococcosis may not be spontaneously included in the differential diagnoses in geographical areas where the disease is uncommon (Atanasov et al., 2013; Bansal et al., 2018). In a recent case report, hepatic *E. multilocularis* infection with pulmonary nodules was misdiagnosed as a cholangiocarcinoma with lung metastases in a 38-year-old woman from the Czech Republic living in Germany (Pohnan et al., 2017). The pulmonary nodules were resected and partial hepatectomy was performed. Histopathological examination revealed the presence of parasitic structures, subsequently identified as the larval stage of *E. multilocularis* in both liver and lungs.

In the only other reported dog with pulmonary metastatic nodules, the presence of the parasite was confirmed at necropsy (Gendron et al., 2015). In the present case, pulmonary nodules, in the absence of necropsy, could not be confirmed as parasitic granulomas. However, the peripheral distribution of those nodules in the pulmonary lung fields in combination with the confirmed hepatic *E. multilocularis* infection were highly suggestive of parasitic lung lesions.

Surgical treatment is usually recommended to treat liver echinococcosis in humans (Pohnan et al., 2017). In the present case, considering the risks due to the dimensions of the mass, the involvement of the caudal vena cava, and multifocal spread, the owners declined surgery. Medical treatment based on the daily administration of albendazole was therefore opted for, as based on previous recommendations and case reports (Haller et al., 1998; Caron et al., 2017). The most serious adverse effect associated with prolonged albendazole treatment in dogs is reversible bone marrow hypoplasia. This has been described to cause neutropenia (Meyer et al., 1998). However, this was not observed in the present case. The dog was found to be clinically stable after ten months of treatment.

While the metacestode stage in dogs does not theoretically carry an infectious risk for humans (De-

plazes et al., 2001; Rinaldi et al., 2014), both owner and dog might have been exposed to *E. multilocularis* eggs. Furthermore, dogs with alveolar echinococcosis may also harbor adult cestodes in their intestines. Eggs shed in their feces may be immediately infective for humans, who are at risk of developing alveolar echinococcosis (Deplazes et al., 2001). Considering the severity of the disease in humans and the potential therapeutic challenge, echinococcosis should be included in the differential diagnosis of cavitary liver nodules in dogs. Whenever there is a potential doubt as to the possibility of echinococcosis infection, coproscopic examination may be recommended to rule out a potential risk for the owners. In this dog, coproscopic examination was negative. Considering that coproscopic examination does not yield a 100% sensitivity, the dog was given milbemycin oxime and praziquantel tablets (Milbemax®, Novartis) every three months.

CONCLUSION

To the author's knowledge, this is the first report of canine vesicular *Echinococcus sp.* lesions medically managed for up to ten months. This shows that medical management may be a viable option when surgery cannot be envisaged, as was the case here due to vascular invasion and pulmonary metastases.

The authors suggest that echinococcosis should be included in the differential diagnosis of cavitary liver masses, even in the presence of lung nodules and local aggressiveness, such as vascular invasion, particularly in young dogs in endemic regions. Cytological and histological examinations are useful to confirm *Echinococcus sp.* infection and allow differentiation from malignant hepatic tumor. This is of particular importance, considering the potential health risk for the owners.

REFERENCES

Antolova D., Vichova B., Jarosova J., Gal V., Bajuzik B. (2018). Alveolar echinococcosis in a dog ; analysis of clinical and histological findings and molecular identification of Echinococcus multilocularis. *Acta Parasitologica 63(3)*, 486-494.

Atanasov G. (2013). Alveolar echinococcosis-spreading disease challenging clinicians: A case report and literature review. *World Journal of Gastroenterology 19(26),* 4257-4261.

Bansal N. (2018). A report on three patients with Echinococcus multilocularis: Lessons learned. *Indian Journal of Gastroenterology 37(4),* 353-358.

Caron Y., Losson B.J., Bayrou C. (2017). Cranial abdominal mass due to Echinococcus multilocularis in a two-year-old wirehaired dachshund in Wallonia (Belgium). *Veterinary Record Case Report.* 5:e000413. doi: 10.1136/vetreccr-2016-000413

Deplazes P. (2001). Veterinary aspects of alveolar echinococcosis - A zoonosis of public health significance. *Veterinary Parasitology 98,* 65-87.

Geigy H. (2013). Unusual presentation of alveolar echinococcosis as prostatic and paraprostatic cysts in a dog. *BMC Veterinary Research 9,* 159.

Geisel O, Barutzki D, Minkus G, Hermanns W, Löscher T. (1990). Hunde als Finnenträger (Intermediärwirt) von Echinococcus multilocularis. *Kleintierpraxis 35,* 275-280.

Gendron K. (2015). Pulmonary Echinococcus multilocularis metastasis in a dog. *Canadian Veterinary Journal 56,* 267-271.

Gwada N., Joekel DE. (2018). Postpartal clinically apparent alveolar echinococcosis in a female dog. *Tierärztliche Praxis Ausgabe Kleintiere Heimtiere 46(6)*, 403-409.

Haller M, Deplazes P, Guscetti F, Sardinas JC, Reichler I, Eckert J. (1998). Surgical and chemotherapeutic treatment of alveolar echinococcosis in a dog. *Journal of American Animal Hospital Association 34,* 309-314.

Heier A, Geissbühler U, Sennhauser D, Scharf G, Kühn N. (2007). A case of alveolar hydatid disease in a dog: Domestic animals as rare incidental intermediate hosts for Echinococcus multilocularis. *Schweizer Archiv für Tierheilkunde 149,* 123-127.

Meyer E.K. (1998). Adverse events associated with albendazole and other products used for treatment of giardiasis in dogs. *Journal of American Veterinary Medical Association 213*, 44-46.

Moro P., Schantz P. M. (2009). Echinococcosis: a review. *International Journal of Infectious Diseases 13,* 125-133.

Oscos-Snowball A. (2015). What is your diagnosis? Fluid aspirated from an abdominal mass in a dog. *Veterinary Clinical Pathology 44,* 167-168.

Pohnan R. (2017). Echinococcosis mimicking liver malignancy: A case report. *International Journal of Surgery Case Reports 36,* 55-58.

Peregrine A. S. (2012). Alveolar hydatid disease (Echinococcus multilocularis) in the liver of a Canadian dog in British Columbia, a newly endemic region. *Canadian Veterinary Journal 53,* 870-874.

Peregrine A. S. (2015). Alveolar echinococcosis in dogs: an emerging issue. *Veterinary Record 177*, 567.

Pezelet C. (2013). Échinococcose alvéolaire hépatique (Echinococcus multilocularis) chez un chien [hepatic alveolar echinococcosis (Echinococcus multilocularis) in a dog], *Pratique Médicale et Chirurgicale de l'Animal de Compagnie 4*, 44-48.

Rinaldi F. (2014). Cystic echinococcosis of the liver: A primer for hepatologists. *World Journal of Hepatology 6(5)*, 293-305.

Scharf G. (2004). Radiographic, ultrasonographic and computed tomographic appearance of alveolar echinococcosis in dogs. *Veterinary Radiology and Ultrasound 45(5)*, 411-418.

Umhang G. (2017). *Surveillance et Epidémiologie d'Echinococcus Multilocularis et d'Echinococcus Granulosus Sensu Lato*. Zootechnie. Université Paris-Est. p37-49.

Uit het verleden

HEEL VROEGE PAARDENJAGERS

De domesticatie door *Homo sapiens* van het paard is recent (ongeveer 4000 jaar v.C.), maar al veel vroeger, 500.000 jaar geleden, draafden er paarden van een groot type in het continent Eurazië rond. Ze werden bejaagd door de *Homo heidelbergensis*, een voorouder van de *Homo sapiens*. In de Duitse archeologische site Schöningen werden resten gevonden van de oudst bekende houten werpsperen samen met stenen werktuigen en resten van minstens tien paarden. Dat alles kwam er ca. 400.000 jaar geleden terecht. Nog 100.000 jaar ouder is een site in Sussex waar naast resten van gedode paarden ook beenderen van wolharige neushoorns en van *H. heidelbergensis* zelf gevonden werden. De gegevens wijzen er op dat deze 'mensen' (hominiden) jacht maakten op groot wild en slachtten. Gezien jagen in groep kennis, ervaring en samenwerking vereist, moet de *H. heidelbergensis* over niet onaanzienlijke cognitieve capaciteiten, communicatie- en sociale coöperatiemogelijkheden beschikt hebben.

Naar: Vanlerberghe, L. *Oorsprong en evolutie van de mens*. Amarant syllabus 2014, p. 44.

Luc Devriese