CASE REPORT

Salmon poisoning disease in dogs: clinical presentation, diagnosis and treatment

Doença da intoxicação por salmão em cães: apresentação clínica, diagnóstico e tratamento

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Abstract

Salmon poisoning disease (SPD) is caused by a rickettsial organism, *Neorickettsia helminthoeca,* that is carried by the trematode *Nanophyetus salmincola,* which encysts in freshwater fish, most commonly salmonids. We reported two dogs from the United States West Coast that had similar clinical signs, hematologic and biochemistry findings. They were both diagnosed with salmon poisoning disease. Lymph node cytology showed morula formation, suggestive of *N. helminthoeca* organisms in macrophages, while the parasitological fecal test found ova of *N. salmincola*. The dogs were treated early and showed complete remission of clinical signs within a few days. Lymph node cytology and fecal parasitology are quick and low-cost tests that can be performed whenever SPD is suspected. SPD should be considered as a differential diagnosis for a canine patient with clinical signs of vomiting, diarrhea, lethargy, and lymphadenomegaly; laboratory findings of thrombocytopenia and hypoalbuminemia; and potential exposure to raw fish from the West Coast of the US or Southern Brazil. The earlier the diagnosis and treatment, the greater the chance of survival.

Keywords: *Neorickettsia helminthoeca*, *Nanophyetus salmincola*, lymph node cytology, Rickettsia, morula.

Resumo

A doença da intoxicação por salmão (SPD) é causada por um organismo rickettsial, *Neorickettsia helminthoeca*, que é transportado pelo trematódeo *Nanophyetus salmincola*, que encista em peixes de água doce, mais comumente salmonídeos. Relatamos dois cães da Costa Oeste dos Estados Unidos que apresentaram sinais clínicos, achados hematológicos e bioquímicos semelhantes. Ambos foram diagnosticados com doença de envenenamento por salmão. A citologia de linfonodo evidenciou formação de mórula, sugestiva de organismos de *N. helminthoeca* em macrófagos, enquanto o exame parasitológico de fezes encontrou ovos de *N. salmincola*. Os cães foram tratados precocemente e apresentaram remissão completa dos sinais clínicos em poucos dias. A citologia de linfonodo e a parasitologia fecal são exames rápidos e de baixo custo que podem ser realizados sempre que houver suspeita de SPD. A SPD deve ser considerada como diagnóstico diferencial para um paciente canino com sinais clínicos de vômitos, diarreia, letargia e linfadenomegalia; achados laboratoriais de trombocitopenia e hipoalbuminemia; e exposição potencial ao peixe cru da costa oeste dos EUA ou sul do Brasil. Quanto mais precoce o diagnóstico e tratamento, maior a chance de sobrevivência.

Palavras-chave: *Neorickettsia helminthoeca*, *Nanophyetus salmincola*, citologia de linfonodo, Rickettsia, mórula.

Introduction

Salmon poisoning disease (SPD) has been reported along the western coast of North America, from northern California through Washington and Vancouver Island (Pastenkos et al., 2020). *Neorickettsia helminthoeca* was also diagnosed in dogs from Southern Brazil due to pathological findings comparable to those of SPD, this being the first description of this disease occurring outside the conventional area of *N. helminthoeca* (Headley et al., 2006). Definitive diagnosis of SPD in these Brazilian dogs was by molecular (Headley et al., 2006) and immunohistochemical diagnostic methods (Headley et al., 2009; Headley et al., 2020).

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SPD is caused by a rickettsial organism, *N. helminthoeca*, that belongs to the family Anaplasmataceae. *Neorickettsia helminthoeca* is carried within all stages of the trematode *Nanophyetus salmincola,* which encysts in freshwater fish, most commonly salmonids (Diniz, 2020). The Pacific giant salamander is also a known intermediate host. Most dogs become infected after ingestion of undercooked freshwater fish (Headley et al., 2011). However, dogs can also be infected by swimming in lakes and rivers with cercaria contamination (Diniz, 2020). An incubation period of 5-7 days follows the ingestion of parasitized salmon (Headley et al., 2011). After ingestion of the trematode-infested fish by a definitive host, the flukes mature and adhere to the intestine's mucosa, where the rickettsiae enter the epithelial cells of the intestinal villi (Greiman et al., 2016). The rickettsiae then disseminate via the lymphatic system, resulting in characteristic clinical signs of swollen lymph nodes, depression, anorexia, weight loss, dehydration, fever, vomiting, and diarrhea (Headley et al., 2011). *N. helminthoeca* replicates within macrophages. This results in the granulomatous inflammatory response within the stomach, lymph nodes, intestines, and spleen (Diniz, 2020).

Currently, serologic assays for *N. helminthoeca* are not available from commercial diagnostic laboratories (Diniz, 2020). Polymerase chain reaction (PCR) assays are available for the specific detection of *N. helminthoeca* DNA (Greiman et al., 2016). Due to the high mortality of SPF, clinicians should not wait for a PCR confirmation before starting appropriate antibiotic therapy (Sykes et al., 2010). Therefore, a definitive and quicker diagnosis of SPD usually is obtained via either cytologic identification of rickettsiae in lymph node aspirates or identification of trematode ova in feces (Headley et al., 2011; Johns et al., 2006; Pastenkos et al., 2020).

Survival is directly related to early diagnosis and appropriate antibiotic therapy and support care. If left untreated, the illness progresses quickly, which can cause severe hypotension, mucosal pallor, cardiac arrhythmias, and death. Most untreated animals die within 6–10 days of the onset of clinical signs. In contrast to other pathogens in the family Anaplasmataceae, infection with *N. helminthoeca* generates protective immunity against the same strain; however, alternate strains can still cause illness (Diniz, 2020; Headley et al., 2011; Sykes et al., 2010).

The aim of this study is to report clinical and laboratory changes in two dogs diagnosed, via lymph node cytology and fecal parasitological examination, with SPD. We present two successful cases, in which patients were diagnosed and treated early.

Case report

Two dogs from the same household were presented to the Small Animal Internal Medicine Service at Washington State University Veterinary Teaching Hospital (WSU-VTH) with a 1-week history of inappetence, listlessness, weakness, and lethargy. The dogs had a known history of eating raw salmon two weeks prior. Patient 1 is a 5-year-old female spayed Doberman Pinscher, and Patient 2 is a 4-year-old male castrated Standard Poodle. They both had similar clinical signs, hematologic and biochemistry findings. Clinical examination revealed mild cranial abdominal pain, 6% to 7% dehydration, and mild peripheral lymphadenomegaly. Patient 2 developed mixed bowel diarrhea as well. Initial laboratory findings revealed severe thrombocytopenia and moderate lymphopenia, elevated ALP, hyperglycemia, hypoalbuminemia, hyperbilirubinemia, hypocalcemia, hyponatremia, and hypochloremia (Table 1). Urinalysis showed hematuria, bilirubinuria, and mild proteinuria.

Fine needle aspiration (FNA) of right and left popliteal lymph nodes and right submandibular lymph node were performed in both patients and stained with Wright's-Giemsa (Harleco, EM Science, Gibbstown, NJ, USA). The cytology in both patients was similar. Representative photomicrographs of the lymph node cytology (Figure 1) are provided.

Microscopic evaluation revealed a moderate number of nucleated cells and erythrocytes against a lightly basophilic and variably vacuolated background with occasional cytoplasmic fragments. Large numbers of small lymphocytes with mild to moderate increases in intermediate and large lymphocytes were observed. The small lymphocytes had a round, eccentric nucleus, finely stippled chromatin, and a light rim of deeply basophilic cytoplasm. The intermediate and large lymphocytes had a round to indented, eccentric nucleus, finely stippled chromatin, 1-2 nucleoli, and a small to moderate amount of moderately basophilic cytoplasm that rarely contained clear cytoplasmic vacuoles. Occasional plasma cells and rare Mott cells were observed.

Table 1. Initial hematologic and biochemical values for each patient.

Parameter	Patient 1	Patient 2	Reference interval
	Result	Result	
HCT (%)	55	53	36 - 56
Hb (g/dl)	19.5	17.9	12 - 20
RBC (x10^6/ µl)	8.37	7.55	5.2 - 8.4
MCH (pg)	23	24	22 - 26
MCHC (g/dl)	35	34	34 - 38
MCV (fl)	66	70	62 - 73
WBC (x10^3/µl)	7.9	18.1	4.5 - 16
Segmented neutrophils (x10^3/µl)	6.952	16.109	2.8 - 13.4
Monocytes (x10^3/µl)	0.474	1.629	0 - 1.3
Lymphocytes (x10^3/µl)	0.395	0.362	0.9 - 4.0
Eosinophils (x10^3/µl)	0.079	0	0 - 1.2
PLT (x10^3/µl)	18	19	160 - 500
ALT (u/l)	25	50	0 - 100
ALP (u/l)	108	434	0 - 96
Glucose (mg/dl)	130	79	66 - 123
Total Protein (g/dl)	5.1	5.7	5.5 - 7.5
Albumin (g/dl)	2.3	2.4	2.9 - 3.8
Globulin (g/dl)	2.8	3.3	2.3 - 4.2
Calcium (mg/dl)	8.3	8.7	9 - 11.3
Bilirubin Total (mg/dl)	0.5	2.0	0 - 0.4
Sodium (mEq/l)	140	140	149 - 158
Chloride (mEq/l)	107	108	112 - 119

Abbreviations: Hb = hemoglobin; HCT = hematocrit; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean cell volume; PLT = platelets; RBC = red blood cells; WBC = white blood cells; ALT = alanine transaminase; ALP = alkaline phosphatase.

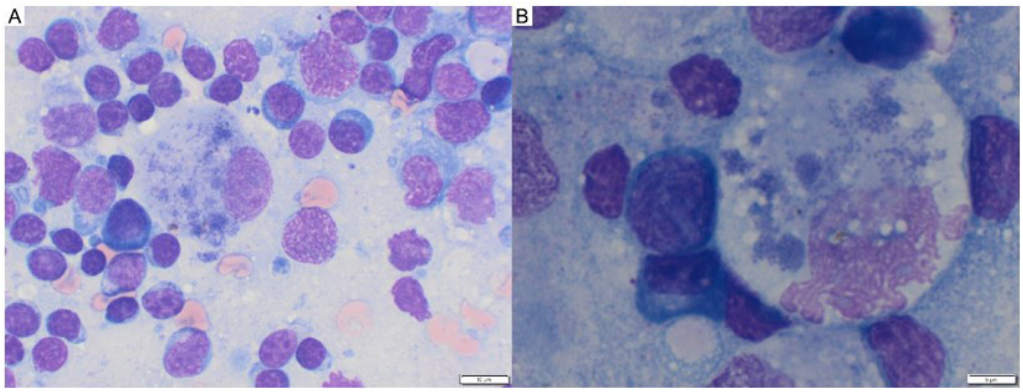

Figure 1. Fine-needle aspiration of lymph node showing macrophages containing deeply basophilic, round granules that often coalesce to form variably sized aggregates suggestive of *Neorickettsia helminthoeca*, Wright-Giemsa. 50× oil objective (A) and (B) 100× oil objective.

There were moderately increased numbers of macrophages, which had a round to irregularly ovoid to reniform, eccentric nucleus, coarsely stippled chromatin, and 1-3 variably sized and prominent nucleoli. These macrophages had a moderate amount of lightly basophilic cytoplasm

that occasionally contained variable numbers of discrete punctate vacuoles or fine magenta granules, and frequently contained deeply basophilic, round granules that often coalesced to form variably sized aggregates (Figure 1). Rare lymphophagocytosis was observed. Rare mast cells were observed.

The final cytologic Interpretation was histiocytic lymphadenitis with suspect of intracellular rickettsial organisms (*Neorickettsia helminthoeca*); moderate reactive lymphoid hyperplasia

Abdominal ultrasound was performed on Patient 1. The results showed mild mesenteric lymphadenopathy. Multiple mesenteric lymph nodes presented mildly hypoechoic and enlarged, associated with a scant peritoneal effusion.

Parasitology tests using the fecal flotation method performed at Washington Animal Disease Diagnostic Laboratory (WADDL) at Washington State University, found *Nanophyetus salmincola,* one egg per gram on Patient 1 and six eggs per gram on Patient 2.

Both patients were treated with doxycycline, praziquantel, maropitant, ondansetron, IV fluids, omeprazole, and sucralfate. Both patients responded well to treatment, showing improvement in their clinical signs within 48-72 hours, and were discharged from the hospital.

Discussion

Clinical signs of SPD are nonspecific and may vary from each patient. Inappetence and depression are usually the first findings, followed by progressive weight loss. Fever and peripheral lymphadenopathy are frequently seen during initial physical exams. Because of the multiplication of the pathogen in mesenteric and ileocecal lymph nodes, with consequent inflammation and tissue edema, vomiting, diarrhea, and dehydration are present in most cases. Melena, hematemesis, and abdominal pain may occur in one-third of cases. Although the patients, in this case, reported most of those signs, they did not present with fever, vomiting, and diarrhea developed only in one of them (Patient 2) about 2 weeks post-exposure.

The most consistent hematologic abnormalities are thrombocytopenia, followed by lymphopenia. Anemia and neutrophilia with a left shift are also common findings (Sykes et al., 2010). We found severe thrombocytopenia and moderate lymphopenia in both patients. Anemia and neutrophilia were not observed. Increased ALP activity, hypocalcemia, hypoalbuminemia, hyponatremia, and hypokalemia are frequent abnormalities in serum biochemistry (Sykes et al., 2010). Hypoalbuminemia may be due to decreased albumin production in the acute phase response, but gastrointestinal loss cannot be ruled out along with low-normal globulin levels. Hypocalcemia in the dogs of this report was likely the result of decreased protein-bound calcium secondary to hypoalbuminemia. We also noted hyperglycemia, hypochloremia, hyperbilirubinemia, and elevated ALP. Hypokalemia was not observed. A retrospective analysis confirmed cases of SPD had peripheral lymphadenopathy in most infected dogs, along with anorexia and depression (Diniz, 2020; Sykes et al., 2010). As observed in this report, urinalysis may reveal bilirubinuria, hematuria, and proteinuria. Other findings may be found as mild granular or hyaline cylindruria and glucosuria (Sykes et al., 2010).

SPD's clinical signs can be severe, particularly in the later stages of illness, but tend to be nonspecific. A history of exposure to fish helps raise clinical suspicion of SPD. A definitive SPD diagnosis is usually obtained via either cytologic identification of rickettsiae in lymph node aspirates or identification of trematode ova in feces (Diniz, 2020). *N. helminthoeca* is a coccoid to coccobacillus rickettsia approximately 0.3 μm in diameter or it can form pleomorphic rods of 2 μm in length that are sometimes bent into rings or crescents. The inclusions typically stain purple with Giemsa stains and may form morulae within cells. Individual organisms are commonly found enveloped within the host cell membrane. Many cases are associated with concurrent histiocytic lymphadenitis, as was observed in this case, which should raise clinical suspicion of SPD. The blue inclusions within the macrophages in lymph node aspirates from these dogs were often grouped in morulae, or are irregular clumps with occasional rod and crescent-shaped individual structures, consistent with *N. helminthoeca* (Johns et al., 2006; Pastenkos et al., 2020). Ova of *N. salmincola* can be found in feces by flotation, sedimentation, and direct-smear techniques. Although the fecal sedimentation test is often recommended over other methods to diagnose SPD, fecal flotation tests are often performed and yield the highest percentage of

positive results (Greiman et al., 2016). In these dogs, fluke ova were found in fecal flotation, even though the number of ova on Patient 1 was lower than on Patient 2.

However, eggs may not be detected in the feces of every infected dog, and serologic assays for *N. helminthoeca* are not available from commercial diagnostic laboratories. Polymerase chain reaction (PCR) assays are available for the specific detection of *N. helminthoeca* DNA from blood, aspirates of lymph nodes, spleen or liver, tissue samples, and feces. Because PCR assays can be specific and highly sensitive, they may aid SPD diagnosis if the laboratory has a short turnover time (Diniz, 2020). Due to the high mortality of SPF, clinicians should not wait for laboratory confirmation before starting appropriate antibiotic therapy (Sykes et al., 2010).

Tetracyclines are the antibiotic class of choice for a minimum of 7 days (Diniz, 2020; Johns et al., 2006; Sykes et al., 2010). Doxycycline is recommended at a dosage of 5 mg/kg every 12 hours, which was the dosage used in these patients. Trematode infection should be treated with praziquantel as well, as was done in these patients, to prevent reinfection. Prognosis is directly related to early diagnosis and the introduction of appropriate antibiotic therapy and supportive care. Most untreated animals die within 6–10 days of the onset of clinical signs. However, in treated patients, clinical improvement is seen within 24–72 hours after starting treatment (Diniz, 2020; Headley et al., 2011; Sykes et al., 2010).

Conclusion

Salmon poisoning disease is a rare cause of vomiting, diarrhea and lethargy, often severe, in dogs from regions endemic for SPD. Given the similarity of clinical signs to those of other more common disorders, SPD may not be considered as a differential diagnosis. The cytologic finding of morula-like inclusions within macrophages in lymph node aspirate smears and the finding of ova of *Nanophyetus salmincola* in the fecal parasitological test may be sufficient to confirm the clinical suspicion of Salmon poisoning disease in dogs. Early treatment is essential to increase the patient's chances of survival.

Ethics statement

All procedures were consented by the animal owner.

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None.

Conflict of interests

No conflict of interests declared concerning the publication of this article.

Authors' contributions

APF, HRC, AH, JW and CS - Writing, Review and Editing manuscript.

Availability of complementary results

All information is present in the paper, but if readers want any extra details, they can contact the corresponding author by email (furtadoap.vet@gmail.com).

The study was carried out at Veterinary Teaching Hospital, College of Veterinary Medicine, Washington State University, Pullman, WA, USA.

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