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## Uveitis and glaucoma associated with *Hepatozoon canis* infection: a case report¤

***Uveítis y glaucoma asociados a infección por Hepatozoon canis: reporte de un caso***

***Uveitis e glaucoma em um canino compatível com infecção por Hepatozoon canis: Reporte de um caso.***

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***Summary***

***We report the case of a five years old German Shepherd dog, who presented anterior uveitis in his left eye which then led him to glaucoma and corneal ulcer. Clinical examination found a patient with low body condition, muscle weakness, dull and brittle coat, and unspecific symptomatology. During both the cell blood count (CBC) and blood smears, gamonts of Hepatozoon canis were found in blood and aqueous humor. Diagnosis, treatment and progress are reported.***

**Key words:** *glaucoma, Hepatozoon canis, Rhipicephalus sanguineus, uveítis.*

***Resumen***

***Se expone el caso de un perro Pastor Alemán de cinco años y medio de edad, el cual presentó uveítis anterior en ojo izquierdo que luego le condujo a glaucoma y úlcera corneal. En el examen clínico se encontró un paciente con baja condición corporal, debilidad muscular, además de un pelaje opaco y***

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***quebradizo, con sintomatología inespecífica. Tanto en el hemograma como en los extendidos sanguíneos se encontraron gamontes de Hepatozoon canis en sangre y humor acuoso. Se discute su diagnóstico, tratamiento y evolución.***

**Palabras clave:** *glaucoma, Hepatozoon canis, Rhipicephalus sanguineus, uveítis.*

***Resumo***

***Expõe-se um caso de um cão Pastor Alemão de cinco anos de idade, o qual apresentou uveitis anterior no olho esquerdo e que levou à presencia de um glaucoma e uma úlcera de córnea. No exame clínico encontrou-se um paciente com baixa condição corporal, debilidade muscular e pelagem opaca e quebradiça, com sintomatologia inespecífica. No hemograma e nos estendidos sanguíneos encontraram-se gamontes de Hepatozoon canis no sangue e humor aquoso. Discute-se o seu diagnóstico, tratamento e evolução.***

**Palavras chave:** *glaucoma, Hepatozoon canis, Rhipicephalus sanguineus, uveitis.*

## Introduction

Hepatozoonosis in dogs is a worldwide disease, mostly prevalent in rural areas. The condition is caused by a protozoan of the phylum *Apicomplexa,* genus *Hepatozoon*, species *canis* (Aguiar *et al.,* 2004; Baneth et al., 2003; Stades *et al.,* 1999). Besides the dog, this protozoan infects other mammals such as fox, coyote, jackal, hyena, and leopard (Mateus *et al.*, 2007; Stades *et al.*, 1999).

*Hepatozoon canis* is transmitted through ingestion of ticks of the genus *Rhipicephalus sanguineus* contaminated with mature oocysts of *Hepatozoon canis*. There is no reported evidence regarding the transmission through the saliva of the tick (Aguiar *et al.*, 2004, Allen *et al.*, 2008). In dogs, the disease is often asymptomatic but can cause varying degrees of granulomatous inflammation in various organs, mainly in the muscles, which leads to anorexia, weight loss, weakness, diarrhea and eye discharge (Allen *et al.*, 2008, O'Dwyer *et al.*, 2006; Eiras *et al.*, 2007; Mundim *et al.*, 2008).

In this paper we describe the case of a canine patient who presented anterior uveitis in the left eye, and later developed glaucoma. The dog had clinical signs of infection with symptoms associated with Hepatozoon canis, a hemoparasite which was isolated from the blood and aqueous humor of the patient.

## Patient assessment

*Review*

Male German Shepherd dog, five years-old, weighing 31 kg, dewormed and vaccinated. During four years living in a farm located in the eastern region of Antioquia, Colombia.

*Anamnesis*

The owners took the patient for consultation when they noticed the dog had progressive vision loss in his left eye for about a week, along with purulent discharge and great pain. Gentamicin, dexamethasone and lidocaine-based eye drops were administered, but failed to improve the condition.

For several months he had lost weight, had a poor appetite, malaise and severe hair loss. A year ago, the patient had lost vision in his right eye after a trauma.

## Findings on physical examination

Clinical evaluation found a fearful patient, with marked anxiety, hyperemic ocular and oral mucous membranes, panting (50 breaths per minute, bpm), strong pulse (110 beats per minute, bpm), 39.5 ºC body temperature, 2 seconds capillary refill time, dull coat, low body condition (3/9), and difficulty to walk and to recognize objects and his environment (Table 1).

**Table 1.** Physiologic parameters at the initial evaluation.

| Parameter | Value | Reference | Values |
|---|---|---|---|
| Body temperature | 39.5 | 38.5-39.5 | °C |
| Heart rate | 110 | 80 to 100 | beats/min |
| Respiratory rate | 50 | 10 to 30 | breath/min |
| Weight | 31 | | kg |
| General Appearance | 3/9 | (low) | |
| Palpation | There is no evidence of a pathology | | |

Clinical neurological examination revealed no alterations. However, clinical ophthalmic examination found miotic pupil, a marked blepharospasm and eye pain, mucous-purulent secretion, corneal edema, chemosis and episcleritis (Figures 1 and 2). At the obstacles test, it hit everything and menace reflex showed negative.

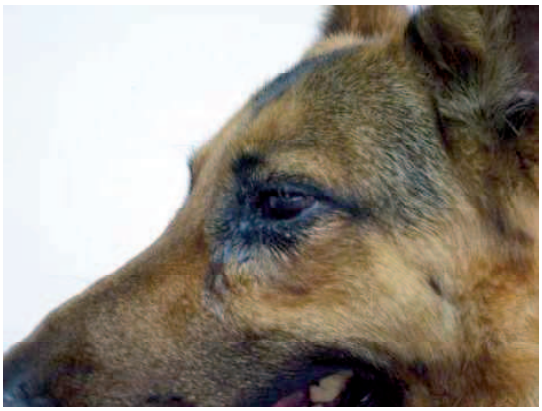

**Figure 1.** Notice the eye discharge in the left eye.

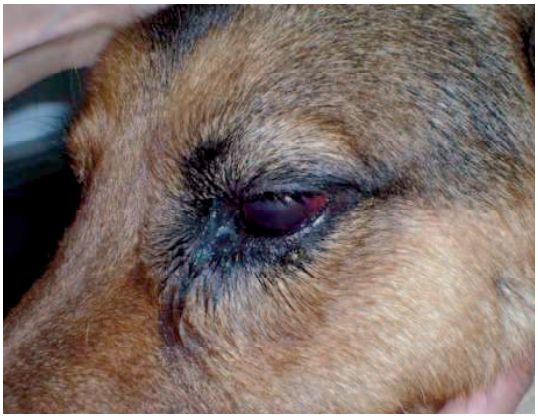

**Figure 2.** Generalized hyphema with corneal edema.

Buphthalmos was diagnosed in a second examination of the eye, four days after the first one. Intraocular pressure (IOP) was 67 mm Hg, which is a greatly increased value, considering that reference values fluctuate between 15 to 20 mm Hg for the Schiotz tonometer, confirming the glaucoma diagnosis. Furthermore, widespread hyphema and surface ulcer on the 50% of cornea was found.

### *Diagnostic aids*

Routine laboratory examinations were performed, such as hemogram (Table 2), creatinine, and ALT (Table 3), in addition to urinalysis (Table 4) to rule out a systemic disease which could be the cause of uveitis, including hypertension secondary to an acute renal failure, or vasculitis for blood parasites, such as *Ehrlichia canis,* bacteria such as Leptospira, or other parasites such as Onchocerca sp. The blood chemistry tests and urine analysis found no signs that might suggest some kind of alteration (Tables 1, 2 and 3). The hemogram showed a mild leukocytosis-lymphocytosis and moderate eosinophilia.

**Table 2.** Hemoleucogram results.

| Parameter | Units | Patient value | Reference Values |
|---|---|---|---|
| Hematocrit | % | 51.4 | 35.2 to 52.8 |
| Hemoglobin | % | 17 | 12.7 to 16.3 |
| Erythrocytes | Ery/ul | 7'280,000 | 5'300,000 to 8'600,000 |
| Leukocytes | Leu/ul | 18,800 | 8,300 to 17,500 |
| Neutrophils | % | 54 | 65 to 73 |
| Bands | % | 0 | 0 to 3 |
| Eosinophils | % | 10 | 1 to 8 |
| Lymphocytes | % | 36 | 9 to 26 |
| Monocytes | % | 0 | |
| Platelets | Plt/ul | 219,000 | 160,000 to 525,000 |
| Total protein | g/dl | 7.8 | |
| Comments: | *Hepatozoon canis* was found. | | |

**Table 3.** Blood chemistry tests.

| Parameter | Units | Patient value | Reference Values |
|---|---|---|---|
| Creatinine | mg% | 1.2 | 0.5 to 1.7 |
| ALT | U/l | 65 | 20 to 80 |

**Table 4**. Urinalysis results

| Parameter | Characteristic |
|---|---|
| Appearance | Cloudy |
| Color | Yellow |
| Ph | 8 |
| Density | 1030 |
| Gluc | Negative |
| Bile pigments | Negative |
| Proteins | + |
| Blood | Moderate |
| Urobilinogen | Normal |
| Leukocytes | 4 * AP |
| Epithelial cells | Not found |
| Cylinders | Not found |
| Bacteria | Not found |
| Crystals | Not found |
| Comments: | Oval fatty bodies are observed |

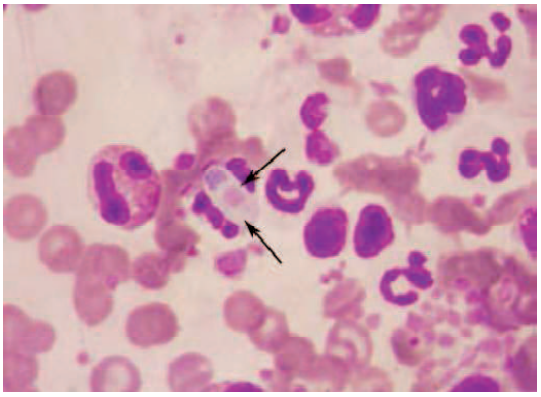

**Figure 3.** Arrows show a gamont of Hepatozoon canis in blood smear.

Three or more gamonts of *Hepatozoon canis* were found in every blood smear stained with Hemacolor (Figure 3), allowing us to relate the lesions observed with the parasite.

*Treatment*

At the time of consultation, while awaiting laboratory results, and given the severity of the lesions which could cause total blindness due to functional compromise of the other eye, an uveitis and corneal edema treatment was started based on topical NSAIDs (diclofenac sodium 1.0 mg drops), ophthalmic antibiotic (Ciprofloxacin 3.0 mg) and hypertonic saline 5% (Table 6) (Forlano *et al.*, 2007; Rubini *et al.*, 2006). Although there is no specific medical treatment for *Hepatozoon canis* (Aguiar *et al.*, 2004, Mateus *et al.*, 2007; Camacaro *et al.*, 1997), once the lab results were received and the parasite identified, the patient was medicated with Imidocarb dipropionate (12%) and Trimethoprim-sulfa 480 mg/5ml (Table 5), drugs commonly used in small animal medicine.

**Table 5**. Treatment recommended for *Hepatozoon canis.*

| Drug | Dose | Route | Frequency | Duration |
|---|---|---|---|---|
| Imidocarb dipropionate | 5 mg/kg | IM | | Days 1 and 14 |
| Trimethoprim-sulfa | 15 mg/kg | Orally | Every 12 hours 15 days | |

**Table 6.** Established treatment for uveitis.

| Drug | Dose | Route | Frequency | Duration |
|---|---|---|---|---|
| Diclofenac eye drops | 1 drop | Topically | Every 4 hours | 5 days |
| 3% ciprofloxacin drops | 1 drop | Topically | Every 4 hours | 5 days |
| Hypertonic saline solution | 1 drop | Ttopically | Every 4 hours | 5 days |
| Elizabethan collar | | | | |

Five days after the initial treatment started, the patient showed an increase in intraocular pressure to 67 mmHg, with pain and evidence of a superficial corneal ulcer compromising 75% of the corneal surface, making it necessary to try a new therapy (Figure 4). An anti-glaucomatous therapy with mannitol (20%) was started (Herrera, 2007). Given the seriousness of the problem and the risk of suffering *ptisis bulvi* because of increased intraocular pressure, 0.4 ml of aqueous humor were extracted through the iridiocorneal angle, under general anesthesia with propofol (5 mg/kg) and Diazepam (0.4 mg/kg), using a 26 gauge needle. The extracted fluid presented a bloody aspect.

The cytological analysis of the sample also resulted in the presence of *Hepatozoon canis* gamonts. After the extraction, intraocular pressure was closer to normal (52 mm/hg), preventing the loss of eye function and reducing the pain. Treatment also included ranitidine (2 mg/kg), Ampicillin-sulbactam (30 mg/kg, iv) and Tramadol (1mg/kg).

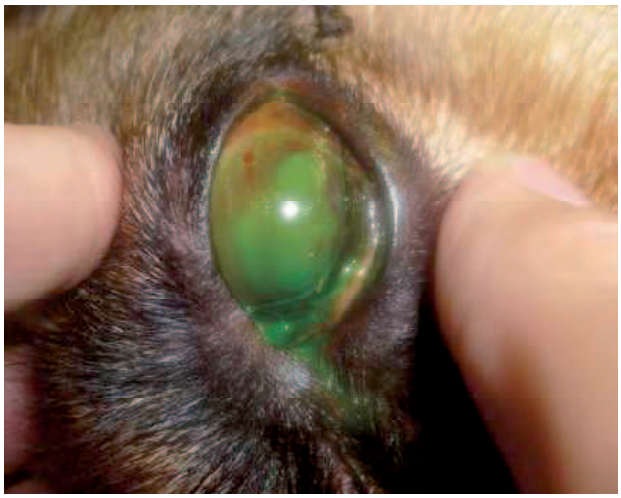

**Figure 4.** Ulcer compromising 75% of the cornea.

It was recommended to continue the treatment described in Table 4, and medical treatment for glaucoma (Table 7) and corneal ulcer (Table 8) was also started. It was also recommended the use of an Elizabethan collar, and to stop administering both diclofenac drops and saline.

**Table 7**. Established treatment for glaucoma.

| Drug | Dose | Route | Frequency | Duration |
|---|---|---|---|---|
| Tavaprost | 1 drop | Topical | Every 24 hours | 5 days |
| Topical dorzolamide | 1 drop | Topical | Every 24 hours | 5 days |
| 20% mannitol | 1 g/kg | I.V | Rapid infusion | 1 dose |
| Aqueous humor extraction | | | | |
| Elizabethan collar | | | | |

**Table 8.** Established treatment for corneal ulcer.

| Drug | Dose | Route | Frequency | Duration |
|---|---|---|---|---|
| 3% Ciprofloxacin drops | 1 drop | | | |
| Topically | Every 4 hours | 5 days | | |
| Carbomer | 1 drop | Topically | Every 4 hours | 5 days |
| Elizabethan collar | | | | |

The patient was examined again 10 days later, finding that glaucoma had improved. He also showed a significant reduction of pain and intraocular pressure, but vision loss was evident, which redirected diagnosis towards a possible retinal and optic nerve degeneration that could affect up to 100% vision.

Owners were advised to hospitalize the patient and not to move him back to the farm in order to keep him under observation. Unfortunately, despite all the possible treatments offered to them, they decided to take him to another clinic for euthanasia, arguing they were not willing to continue with medical therapy for economic reasons and because the animal could not fulfill the purpose for which they were keeping him.

## Discussion

Hepatozoonosis is a disease of difficult diagnosis (Johnson *et al.*, 2008, Li *et al.*, 2008; Swing *et al.*, 2003) because the clinical signs are diverse and nonspecific, resulting in nausea, malaise, uveitis, headaches and even mild to severe lameness for no apparent reason (Ettinger *et al.*, 2005). Routine laboratory examinations do not yield results that can guide to the diagnosis of the disease (Li *et al.*, 2008).

The routine laboratory method for the diagnosis of this condition is through blood smears using peripheral blood to try to visualize the gamonts (Mateus *et al.*, 2007). Nevertheless, it does not always work, because affected cells may be one or two per 1000 leukocytes (Aguiar *et al.*, 2004; Matjila *et al.*, 2008), which makes it extremely difficult to detect, generating many false negatives.

Because of this, the ideal diagnostic methods to confirm or exclude the disease include PCR, ELISA, indirect immunofluorescence or Western Blood (Aguiar *et al.*, 2004, Mateus *et al.*, 2007). But the high costs of such tests, combined with the unspecific signs, and the few reports of this condition, do not encourage their use in clinical practice (Matjila *et al.,* 2008). In our case, there was no possibility of performing these tests, because our laboratories do not have the required equipment.

What facilitated the accurate diagnosis in our case, was the direct visualization of *Hepatozoon canis* gamonts. It would be virtually impossible to diagnose the condition without visualizing the parasites, unless the patient had a very high parasite load.

In the case described, the parasite load was quite high, since there were three or more gamonts in each blood smear, which is very unusual and facilitated the correct diagnosis. It is important to highlight here the need of qualified laboratory personnel to properly identify the agent, avoiding false negatives.

The aqueous humor extract containing the protozoan is a very uncommon finding. No reports on *Hepatozoon canis* located in canine eyes have been found. This is difficult to explain case. For any biotic or abiotic material to go through the ocular blood-aqueous barrier it is necessary to pass through active or passive diffusion. The barrier has 40 Å pores and the gamonts of *Hepatozoon canis* measure 11 μm x 4 μm in average (Baneth *et al.*, 2003; Karagenc *et al.*, 2006), which makes it impossible for the transit of protozoan under normal conditions.

According to Maggs *et al.* (2008), the uvea is an immunologically competent tissue. When ocular antigens are processed at distant sites, the sensitized lymphocytes migrate toward the antigen, enter the uvea and deal with the formation of antibodies or cell-mediated immune reactions. Repeated exposure

to the same antigen results in a more rapid and potent response (anamnestic). This inflammation is evident because of the pain, vascular congestion and hyper-permeability. In summary the uvea acts as an accessory lymph node.

Autoimmune phenomena take place in the uvea. Any previous damage to the tissue (eg. a previous inflammation) releases specific uveal antigens normally located outside the patrol route of lymphocytes (intracellular location). These antigens promote an immune response in the uvea. It is possible that this is the mechanism participating in Canine recurrent uveitis, in which inflammatory stimulus may vary (eg, L*eptospira sp., Onchocerca sp*) (Maggs *et al.*, 2008).

A parasitic infectious process, like the one brought in this case, causes an acute inflammation which necessarily alters the structure of vascular endothelium and thus the permeability of uveal blood vessels, promoting hemoparasite transit to the anterior chamber with the local anatomical and physiological consequences previously described (Herrera, 2007; Peiffer *et al.*, 2002).

The anterior uveitis, initially manifested, produced glaucoma, since inflammation of the iris and ciliary bodies affected trabecular fibers, which together with the micro or particulate inflammatory exudates in the anterior chamber, sealed in the trabecular and ciliary cleft, favoring the accumulation of aqueous humor (Herrera, 2007).

Intraocular pressure is usually reduced during uveitis. The passage of aqueous humor can be mitigated by structural alterations that occur during uveitis, such as angle lock with inflammatory cells and debris, peripheral anterior synechia formation, cellular infiltration of the drainage angle, and pupillary blockage caused by occlusion of the pupil (Maggs *et al.* , 2008), resulting in glaucoma, secondary to anterior uveitis.

Several drugs have been used to treat hepatozoonosis. The most commonly used are trimethoprim sulfa and imidocarb dipropionate. Besides these, diminazene diaceturate, tetracyclines, primaquine phosphate, toltrazuril, clindamycin, or pyrimethamine in a combined therapy have been used with mixed results (Aguiar *et al.*, 2004; Baneth *et al.*, 2003; Mateus *et al.*, 2007). In general, these drugs do not give the expected result because the complete removal of protozoa has not been achieved (Baneth *et al.*, 2003).

In the case under discussion it was not possible to assess the patient's evolution, his response to the medical therapy, any changes in the number of gamonts, or the patient's recovery, given the owners premature decision to euthanize the patient. The autopsy would have been very helpful for understanding the pathology of the disease.

## Conclusions

Hepatozoonosis is a difficult to diagnose disease. Any animal that is taken to consultation with uveitis and glaucoma should be suspected of being infected with *Hepatozoon canis*, especially if the patient has no eye compromise and other diseases compatible with the clinical signs presented have been ruled out.

Considering the complexity of diagnosing the disease, when the diagnostic tests outlined above cannot be conducted, the clinician should perform blood smears asking the clinical laboratory to look for possible parasites in the sample submitted.

Given the diversity of clinical signs and the diagnostic limitations that have been discussed, it is imperative that the medical and clinical laboratory have the sufficient knowledge about this disease, so that the clinician can have a proper approach to its diagnosis. Therefore, it is important to establish protocols to determine the prevalence and incidence of hepatozoonosis, which may be underdiagnosed.

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