Abstract
Canine monocytic ehrlichiosis (CME) is a tick-borne disease caused by the rickettsia *Ehrlichia canis*. Ocular lesions are a common feature of the disease and can be present in all stages. The purpose of this retrospective study was to determine the prevalence, type and response to treatment of ocular lesions associated with monocytic ehrlichiosis in 46 affected dogs presented to the Autonomous University of Barcelona-Veterinary Teaching Hospital (UAB-VTH) from January 2000 to December 2002. Dogs were included in the study only if they had a positive serologic test for *E. canis* and information about the clinical outcome was available. Eighteen breeds were represented, with the German Shepherd dog (*n* = 6) being the most common. There were 25 intact and three castrated males, and 16 intact and two neutered females. Twenty dogs (43.4%) were between 5 and 10 years old. Seventeen dogs (37% of all cases of monocytic ehrlichiosis diagnosed during the study period) had ocular signs, and 11 dogs (64.7% of the ocular cases) had only ocular lesions without apparent systemic signs. Exudative retinal detachment was the most common ocular manifestation; other prevalent findings included anterior exudative uveitis and optic neuritis. Five of the 17 cases with ocular lesions (29.4%) had ocular bleeding disorders (hyphema or retinal hemorrhages). All the dogs with ocular disease presented with bilateral signs. Dogs with posterior segment disease had titers against *E. canis* that were ≥ 1:320, while lower titers were noted in dogs with anterior exudative uveitis. Two dogs presented with chronic autoimmune panuveitis after ehrlichiosis treatment. Canine ehrlichiosis should be considered in the differential diagnosis of exudative retinal detachment and anterior uveal inflammatory lesions.

Key Words: anterior uveitis, dog, ehrlichiosis, optic neuritis, retinal detachment

INTRODUCTION
Canine monocytic ehrlichiosis (CME) is a tick-borne disease caused by the rickettsia *Ehrlichia canis*, although other *Ehrlichia* species have been identified.1,2 The disease was first described in Algeria in 1935 by Donatien and Lestoquard.3 Since then, it has been reported worldwide, causing extensive morbidity and mortality among domestic dogs and other canids. In the United States it was reported for the first time in 1963, and subsequently it has been found in widely separated regions of the USA.4–11 At present, it is widely distributed around the world, particularly in tropical and subtropical areas.1,12 *Ehrlichia* spp. is an obligate intracellular bacterium with tropism for hematopoietic cells causing leukopenia and thrombocytopenia. *Ehrlichia canis* is transmitted primarily by the brown dog tick, *Rhipicephalus sanguineus*, and by the American dog tick, *Dermacentor variabilis*. CME is manifested by a wide variety of clinical signs that can be categorized into acute (1–3 weeks), subclinical (average 11 weeks) and chronic phases,1 although in endemically infected countries it is difficult to classify clinical cases into such distinct stages.11 The disease may be manifested by a wide variety of clinical signs of which depression, lethargy, weight loss, anorexia, pyrexia, lymphadenomegaly, splenomegaly, ocular signs and bleeding tendencies are the most common.13 The most important hematologic abnormalities described include thrombocytopenia, mild anemia and mild leukopenia during the acute stage, mild thrombocytopenia in the subclinical stage, and pancytopenia in the severe chronic stage.13 The main biochemical abnormalities reported include hypoalbuminemia, hyperglobulinemia, and hypergammaglobulinemia.13 Ocular lesions are a common feature of canine ehrlichiosis and can be present in all stages.14 The ocular signs may vary in severity and do not occur in every patient.14
monocytic ehrlichiosis requires visualization of morulae in peripheral blood smears or buffy coat smears, detection of *E. canis* antibodies, or PCR amplification. Doxycycline (5 mg/kg twice daily for 21 days) has become the standard drug for treating canine rickettsial infections.

Dogs with CME remain infected for their entire lives, even if they received antibiotic treatment with doxycycline. CME is a potentially fatal disease in dogs that requires rapid and accurate diagnosis in order to initiate appropriate therapy leading to a favorable prognosis.

The purpose of this retrospective study was to determine the prevalence, type and response to treatment of ocular lesions associated with monocytic ehrlichiosis in affected dogs presented to the Autonomous University of Barcelona-Veterinary Teaching Hospital (UAB-VTH) from January 2000 to December 2002.

**MATERIALS AND METHODS**

Medical records of all cases of confirmed CME at the UAB-VTH between January 2000 and December 2002 were reviewed. Dogs were included in the study only if clinical outcome information was available and the diagnosis was confirmed by serology. Serologic studies for *E. canis* were conducted with enzyme-linked immunosorbent assay (ELISA). The serologic cut-off titer for *E. canis* was < 1 : 40. A preliminary ophthalmic examination, which included inspection of the eyelids and globe with a focal light source, was performed on all cases, generally by the attending (internal medicine) clinician. If abnormalities were noted, a complete ophthalmic examination, including slit-lamp biomicroscopy, tonometry and indirect ophthalmoscopy, was performed by an ophthalmologist and ocular signs were recorded. Following a review of medical records, 56 cases of CME were identified. Only 46 of these fulfilled the criteria for inclusion. Dogs were considered to have systemic clinical signs if they had generalized lymphadenopathy, lethargy, anorexia, pyrexia, lameness, gastrointestinal signs (e.g. vomiting or diarrhea), nasal discharge, dyspnea, edema of the limbs or scrotum, hyperesthesia, muscle twitching or cranial nerve deficits. Anterior uveitis was defined as ocular changes involving several or all of the following signs: corneal edema, decreased intraocular pressure, aqueous flare, miosis, keratic precipitates, synchiae, hypopyon or hyphaema. Posterior uveitis was determined if one or more of the following signs were observed by ophthalmoscopy: white perivascular opacities, areas of grayish or brownish discoloration in the tapetal fundus, grayish to white lesions in the nontapetal area or opaque/translucent retina with subretinal exudates. Optic neuritis was defined as a swollen and edematous optic nerve head with blurring of the disc margins. In dogs with optic neuritis, a complete cerebrospinal fluid (CSF) analysis (cerebellomedular cisternal tap puncture), including cytologic evaluation, was performed to determine the specific cause of the optic nerve signs.

The affected dogs were treated with doxycycline (Vibracina 100 mg, Grupo Pfizer, Barcelona, Spain), orally at 5 mg/kg every 12 h for 21 days. In chronic or refractory cases, imidocarb dixipropionate (5 mg/kg IM; Imizol®, Schering-Plough Animal Health, Madrid, Spain) or doxycycline treatment of longer duration was used (2–3 months). Anterior segment ocular inflammatory lesions were treated with topical 0.1% dexamethasone solution (Maxidex®, Alcon Laboratories, Barcelona, Spain). Cycloplegia/mydriatic therapy was used for uveitis cases when appropriate. A variety of antihypertensive agents were prescribed when secondary glaucoma was present. Some dogs with anterior uveitis and all those with posterior segment disease received a short course of an anti-inflammatory dose of oral prednisone (0.5 mg/kg BID for 10 days, 0.5 mg/kg/day for 10 days and 0.5 mg/kg every other day for 10 days). The ocular response to the treatment was evaluated as follows; eyes that maintained vision were classified as having a good response and those that were blind, as poor. The follow-up period varied from 1 to 4 years.

**RESULTS**

Of the 46 dogs included in the study, 28 were males (25 intact and three castrated) and 18 females (16 intact and two neutered) and the mean age was 6.2 years (range: 7 months to 13 years). Twenty dogs (43.4%) were large breeds (> 20 kg) and the most common breed was German Shepherd dog (GSD) (n = 6).

Dogs with CME were most commonly presented for a variety of systemic signs including weight loss, depression, weakness, lethargy, fever, dermatologic disorders, neurologic signs, anorexia, renal failure, recurrent lameness, epistaxis, vomiting and diarrhea. However, in 17 dogs, abnormalities involving the eye were the presenting complaints (Table 1). Eleven of the 46 cases (23.9%) had only ocular lesions, without any other systemic sign.

When present, ocular lesions were bilateral in all dogs. In order of frequency, these included panuveitis with exudative retinal detachment in 11/17 cases (64.7%) (Fig. 1), anterior exudative uveitis in 5/17 cases (29.4%) (Figs 2 and 3) and optic neuritis in one case (5.8%). Five dogs with ocular involvement (29.4%) presented with hyphema and/or retinal hemorrhages (Fig. 4).

Concurrent diseases were detected in 12 dogs (26%). The most frequent was leishmaniasis in seven cases (15.2%). Other diagnosed diseases were anaplasmosis in one case (2.1%), hypothyroidism in one case (2.1%), hepatozoonosis in one case (2.1%), granulomatous meningoencephalomyelitis (GME) in one case (2.1%), and babesiosis in one case (2.1%). Only one dog with concomitant leishmaniasis presented with ocular signs. In this dog, leishmaniasis was diagnosed 1 year before ehrlichiosis and has been in treatment since then.

The results of CSF analysis of the dog with optic neuritis demonstrated mild, reduced glucose concentration (60 mg/dL; normal range 70–110 mg/dL) and mild increases in protein concentration and nucleated cells (protein concentration 40 mg/dL (normal < 25 mg/dL) and seven white blood cells/dL (WBC/dL; normal < 5 WBC/dL), with lymphocytes being the predominant cell type.

© 2005 American College of Veterinary Ophthalmologists, *Veterinary Ophthalmology*, 8, 387–393
Table 1  Cases of ocular canine monocytic herlichiosis

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Breed</th>
<th>Gender</th>
<th>Age</th>
<th>Ocular signs</th>
<th>Ocular bleeding disorders</th>
<th>Serologic titers E. canis</th>
<th>Concomitant diseases</th>
<th>Response to treatment</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Chow Chow</td>
<td>Male</td>
<td>9</td>
<td>Panuveitis OU (ERD)</td>
<td>Retinal hemorrhages</td>
<td>1 : 640</td>
<td>Leishmaniasis</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Mixed</td>
<td>Female</td>
<td>5</td>
<td>Panuveitis OU (ERD)</td>
<td>None</td>
<td>1 : 640</td>
<td>None</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>German Shepherd</td>
<td>Male</td>
<td>6</td>
<td>Panuveitis OU (ERD)</td>
<td>None</td>
<td>1 : 440</td>
<td>None</td>
<td>Poor</td>
<td>Autoimmune panuveitis OU (Retinal atrophy OU)</td>
</tr>
<tr>
<td>4</td>
<td>Mixed</td>
<td>Female</td>
<td>4</td>
<td>Panuveitis OU (ERD)</td>
<td>Vitreous hemorrhages</td>
<td>1 : 320</td>
<td>None</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Siberian Husky</td>
<td>Female</td>
<td>1</td>
<td>Anterior exudative uveitis OU</td>
<td>Hyphema</td>
<td>1 : 160</td>
<td>Babesiosis*</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Boxer</td>
<td>Female</td>
<td>7</td>
<td>Anterior exudative uveitis OU</td>
<td>None</td>
<td>1 : 320</td>
<td>None</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Beagle</td>
<td>Male</td>
<td>8</td>
<td>Panuveitis OU (ERD)</td>
<td>None</td>
<td>1 : 320</td>
<td>None</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Mixed</td>
<td>Male</td>
<td>3</td>
<td>Panuveitis OU (ERD)</td>
<td>None</td>
<td>1 : 320</td>
<td>None</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Rottweiller</td>
<td>Male</td>
<td>2</td>
<td>Anterior exudative uveitis OU</td>
<td>Iris hemorrhages</td>
<td>1 : 160</td>
<td>None</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Mixed</td>
<td>Male</td>
<td>3</td>
<td>Panuveitis OU (ERD)</td>
<td>None</td>
<td>1 : 640</td>
<td>None</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Mixed</td>
<td>Female</td>
<td>5</td>
<td>Panuveitis OU (ERD)</td>
<td>Retinal hemorrhages</td>
<td>1 : 320</td>
<td>None</td>
<td>Good OD, Poor OS</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Old English Sheepdog</td>
<td>Male</td>
<td>4</td>
<td>Panuveitis OU (ERD)</td>
<td>Subretinal hemorrhages</td>
<td>1 : 320</td>
<td>None</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Mixed</td>
<td>Female</td>
<td>8</td>
<td>Panuveitis OU (ERD)</td>
<td>None</td>
<td>1 : 320</td>
<td>GME</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Pyrenees Mountain dog</td>
<td>Male</td>
<td>5</td>
<td>Anterior exudative uveitis OU</td>
<td>None</td>
<td>1 : 160</td>
<td>None</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>German Shepherd</td>
<td>Male</td>
<td>7</td>
<td>Anterior exudative uveitis OU</td>
<td>None</td>
<td>1 : 80</td>
<td>None</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Mixed</td>
<td>Female</td>
<td>12</td>
<td>Panuveitis OU (ERD)</td>
<td>None</td>
<td>1 : 640</td>
<td>Thrombocytic canine ehrlichiosis</td>
<td>Good</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Mixed</td>
<td>Female</td>
<td>7</td>
<td>Optic neuritis OU</td>
<td>None</td>
<td>1 : 320</td>
<td>None</td>
<td>Poor</td>
<td></td>
</tr>
</tbody>
</table>

The diagnosis of CME was based on blood ELISA titers for *E. canis* (Table 1). All dogs with posterior ocular signs had ELISA titers ≥ 1:320, while dogs with anterior uveitis had lower titers. While all dogs with anterior uveitis had good ophthalmic results, ocular response to the treatment was poor for five eyes with panuveitis. In those cases, three eyes developed retinal atrophy and two developed phthisis bulbi. Two dogs presented with chronic panuveitis after 2–3 months of doxycycline treatment. Those two dogs had initial serologic titers for *E. canis* higher than 1:320, and no concomitant disease was detected. Despite appropriate antimicrobial and anti-inflammatory therapy and negative serologic titers (1 month after finishing doxycycline treatment), panuveitis recurred and long-term corticosteroids (1 mg/kg BID PO; Dacortín 30 mg®, Merck Pharma, Barcelona, Spain) treatment was required to control ocular signs. In one of the two dogs, other immunosuppressive therapy (azathioprine 1 mg/kg PO every 2 days, Imurel®, Medeva Pharma, Madrid, Spain) was needed for panuveitis control. CBCs and serologic tests were performed during the immunosuppressive therapy.
DISCUSSION

As has been previously reported, although all breeds can be infected with CME, the German Shepherd dog (GSD) seems to be more susceptible to CME than other breeds. Moreover, the disease in GSD is more severe and has a poorer prognosis than in other breeds. Results of this study suggest that this susceptibility for the disease could be possible although no assessments regarding the incidence of the disease in the total number of GSD visiting UAB-VTH were made. Differences in breed susceptibility can be attributed to breed differences in ability to mount adequate cellular and/or humoral immune responses. It has been documented that the cellular immune response against E. canis is depressed in GSD compared to Beagle dogs.

Slightly more male dogs than female dogs were affected in the current study. We believe that this difference may represent gender popularity rather than a true predisposition for CME. No predilection for age or sex has previously been observed.

Ocular tissues are commonly affected in dogs with CME, occurring in approximately 37% of confirmed cases of canine ehrlichiosis diagnosed at the authors’ institution over a 3-year period. This prevalence is higher than previously reported values in naturally occurring cases (10–15%). In one study 50% of experimentally infected dogs developed ocular lesions. For most of the 46 cases of CME diagnosed in our study, examination by an ophthalmologist was only performed if requested by the owner or by the attending clinician after they had noted evident ocular signs on a routine physical examination. As a result, mild, subclinical intraocular lesions may have gone undetected, and the prevalence of ocular signs may be underestimated.

Ocular signs caused by CME have been reported to occur in nearly every structure of the eye, and include conjunctivitis, conjunctival or iridial petechiae and ecchymoses, corneal edema, panuveitis, hyphema, secondary glaucoma, optic neuritis, retinal hemorrhages and detachment (either from massive subretinal hemorrhage or from exudates). In contrast to previous studies where anterior uveitis was the most prevalent ocular finding in CME, panuveitis with retinal detachment was the most frequent ocular lesion in the present study. The reasons for this difference are unclear but it may have resulted from an underestimation of mild ocular lesions by the attending or referring clinician, or from the fact that dogs are not usually presented for diagnosis to a reference hospital until CME is in the chronic stage. The most frequently reported ocular signs in CME are anterior uveitis (often with hyphema) and retinal lesions (including retinal vascular engorgement and tortuosity, perivascular cuffing, diffuse retinitis, retinal hemorrhage and detachment, and chorioretinal scarring). An unusual manifestation of canine ehrlichiosis is necrotizing scleritis associated with severe destruction of intraocular structures. Because of the extremely variable ocular signs of CME, it is necessary to consider the disease in the differential diagnosis of many ocular lesions. Importantly, in the current study, 11 out of the 46 cases (23.9%) had ocular lesions as the presenting complaint, and had no identifiable systemic signs assessed by physical and clinicopathologic examination. This finding suggests not only that ocular signs can be the unique identifiable systemic sign of CME, but also that the disease could be presented as subclinical. Therefore mild ocular signs can be detected. In this study all dogs with ocular signs presented with bilateral disease. It has previously been reported that systemic infectious diseases may result in seeding of the uveal tract and create varying degrees of intraocular inflammation. These ocular signs could be asymmetric depending on the degree of uveal involvement of each eye.

Of the dogs with ocular involvement, five (29.4%) presented with hyphema and/or retinal hemorrhages. Bleeding in cases of CME has traditionally been associated with thrombocytopenia, which is considered to be the most common and persistent hematologic abnormality observed in the disease. The fact that spontaneous bleeding in the anterior chamber or retina is not always related to platelet deficiency, suggests that other mechanisms can be involved in the pathogenesis of ocular bleeding. Blood hyperviscosity (secondary to monoclonal gammopathy), elevation in oncotic pressure, vasculitis and platelet dysfunction are all proposed to be important factors in the pathogenesis of ocular bleeding in CME. Serum hyperviscosity may further exacerbate the bleeding tendency via physical interference with platelets and blood clotting factors, damage to blood vessels’ endothelium and venostasis. Ocular effects of hyperviscosity include retinal blood vessel dilation and tortuosity, anterior and posterior segment bleeding and retinal detachment. Elevation in oncotic pressure, as well as ischemic changes secondary to hyperviscosity, may cause hypertensive retinopathy and hyphema. In the present retrospective study, the cause of the spontaneous ocular bleeding disorder was not studied. Vasculitis in CME is caused by deposition of immune complexes in the vascular walls (characterized by lymphoplasmacytic perivascular cuffing). Taking into account the serologic reference range (ELISA) for E. canis < 1:40, all the dogs with posterior ocular disease had titers ≥ 1:320, and dogs with anterior uveitis had lower titers. Because CME is characteristically associated with widespread immune complex formation and deposition, hyperglobulinemia from immune activation, and antinuclear antibody formation, it is possible that the CME-induced uveitis has an immunopathogenic basis. This might explain the relationship between serologic titers and severity of the ocular signs.

Canine leishmaniasis and babesiosis were two concurrent nonrickettial diseases diagnosed in dogs with ocular signs. Canine leishmaniasis (CL) is a chronic and sometimes fatal disease that is endemic along the Mediterranean shore. Ocular manifestations have often been described with CL, with or without systemic signs. The affected dog was diagnosed a year before the diagnosis of the ehrlichiosis, and had been under treatment since then without relapse of the systemic disease in the total number of GSD visiting UAB-VTH were made.
clinical signs attributable to CL. The serologic results for leishmaniasis (Leishmania infantum) had been slightly positive since the third month of treatment. Canine babesiosis (CB) was included in the differential diagnosis of canine hyphema because it can induce regenerative anemia and thrombocytopenia. In the affected dog the diagnosis of CB was made by means of serology. Indirect fluorescent antibody titer for Babesia canis was 1:80 (serologic cut-off titer ≥ 1:80) in the first evaluation. It has been previously reported that, because clinically normal dogs can be seropositive, serology alone should not be used to make a definitive diagnosis. A presumptive diagnosis of babesiosis should be based on historical findings, physical examination findings, test results and positive serology. Due to the doubtful babesia titer, the authors decided to treat ehrlichiosis and to repeat serology after 1 month (titer < 1:80).

The current treatment regimen for CME at our institution includes doxycycline for a minimum of 21 days. However, in chronic or refractory cases, imidocarb dipropionate or a longer doxycycline treatment is used, as it has been suggested in previous reports. In some dogs with ocular disease, prednisolone was added to the treatment. The use of prednisolone is limited to the first few days, until the ocular signs have regressed. Short-term anti-inflammatory or even immunosuppressive glucocorticoid therapy has been reported to be of value in some cases of canine ehrlichiosis where the immune-mediated lesions are important. Recurrence of ocular signs following treatment was seen in two dogs. These dogs presented with ocular signs with negative serologic tests and only responded to immunosuppressive therapy. Proposed mechanisms contributing to the development of autoimmune uveitis include abnormal induction of tolerance to autoantigens, release of normally sequestered autoantigens because of trauma and infection, molecular mimicry (homology between pathogens and host tissue antigens), and alteration of autoantigen structure caused by tissue injury or inflammation.

Ocular response to the treatment was good for 29 eyes (85.3%) and poor for five eyes (14.7%). All the dogs with poor ocular outcome had serologic titers higher than 1:320. Of these five eyes, three developed retinal atrophy and two developed phthisis bulbi. All the dogs with anterior uveitis had good ocular outcome. It must be taken into account that as the follow-up period varied from 1 to 4 years and some of these animals remain under treatment, the prognosis in a longer follow-up study could be lower.

In the present study one dog had optic neuritis due to CME. Other causes of optic neuritis were ruled out by CSF analysis and blood work. This presentation has been previously reported in humans and dogs. Experimental discrete perivascular infiltrates have been described during the subacute stage, but such infiltrates have not been described in clinical cases.

In summary, ocular signs are a common manifestation of CME, occurring in the present study in approximately 37% of the reported cases. Panuveitis with exudative retinal detachment was the most common finding. Dogs with posterior ocular disease had serologic titers for E. canis ≥ 1:320, and dogs with anterior uveitis had lower titers. CME should be considered in the differential diagnoses of anterior uveitis, panuveitis and retinal detachment in dogs from endemic areas or dogs travelling from these geographic regions.

REFERENCES