Review article

CANINE MONOCYTIC EHRLICHIOSIS: AN UPDATE ON DIAGNOSIS AND TREATMENT

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Canine monocytic ehrlichiosis (CME) is a tick-borne disease of worldwide distribution. The major causative agent is *Ehrlichia canis*, a gram-negative, obligate intracellular, pleomorphic bacterium of the genus *Ehrlichia*, which infects monocytes, macrophages and lymphocytes, forming intracytoplasmic, membrane-bound bacterial aggregates, called morulae. After an incubation period of 8-20 days, the course of *E. canis* infection, can be sequentially divided into acute, subclinical and chronic phases, although these phases can hardly be distinguished in the clinical setting. Clinical recovery is the typical outcome of acutely infected dogs, entering the subclinical phase, during which they show no or minimal clinical signs and/or mild hematological abnormalities. Immunocompetent dogs may eliminate the infection during the acute or subclinical phases, but an unpredictable proportion of dogs will eventually develop the chronic phase, characterized by aplastic pancytopenia and high mortality, due to septicemia and/or severe bleeding. This article outlines briefly the pathogenesis of CME due to *E. canis*, and more thoroughly reviews the recent scientific literature pertaining to the diagnosis and treatment of this devastating disease.

Key words: *Ehrlichia canis*, Canine, Dog, Tick-borne Diseases

INTRODUCTION

Canine ehrlichiosis is caused by gram-negative, obligate intracellular, pleomorphic bacteria of the genus *Ehrlichia* (order Rickettsiales, family Anaplasmataceae). *Ehrlichia* spp. infect primarily leukocytes, forming intracytoplasmic, membrane-bound bacterial aggregates, called morulae [1]. At least five tick-transmitted *Ehrlichia* species have been documented to infect dogs, potentially causing the clinical disease [1,2].

Ehrlichia canis was the first species recognized to infect dogs and is the principal cause of canine monocytic ehrlichiosis (CME) [1,3-4]. *Ehrlichia chaffeensis*, the cause of human monocytic ehrlichiosis, has recently emerged as an infrequent cause of clinical disease in the dog, indistinguishable from that caused by *E. canis* [5-7]. *Ehrlichia ewingii*,

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is the cause of canine granulocytic ehrlichiosis [5,8]. *Ehrlichia ruminantium*, the cause of heartwater in cattle, has been molecularly detected in the blood of healthy dogs or dogs presented with symptoms suggestive of ehrlichiosis, in the context of negative serological and molecular testing for *E. canis* [9]. *Ehrlichia muris*, has recently been identified in an ill dog from northern Minnesota that was seronegative to *E. canis* [10]. Recently, infection with Panola Mountain *Ehrlichia* sp. was documented in a clinically healthy dog with thrombocytopenia, atypical lymphocytes and T-cell expansion, which were resolved following doxycycline treatment [11].

Since the clinical importance and the bulk of scientific information pertaining to *E. canis* infection far outweigh those for the other canine ehrlichial infections, this article will briefly review the pathogenesis, and will emphasize on the diagnosis and treatment of *E. canis*-induced CME.

PATHOGENESIS OF CME

Ehrlichia canis is naturally transmitted transstadially and intrastadially, but not transovarially, by the tick *Rhipicephalus sanguineus* [1]. After an incubation period of 8-20 days, the course of *E. canis* infection, can be sequentially divided into acute (2-4 weeks), subclinical (several months to years) and chronic phases [2], but the distinction among these phases is not straightforward in the naturally-occurring disease. Clinical recovery is the typical outcome of acutely infected dogs, entering the subclinical phase, during which they show no or minimal clinical signs and/or mild hematological abnormalities [12-14]. Immunocompetent dogs may eliminate the infection during the acute or subclinical phases [5,12,15], but some will eventually develop the chronic phase, characterized by bone marrow (BM) aplasia, peripheral blood bi- or pancytopenia and high mortality due to septicemia and/or severe bleeding [16]. Occasionally, myelosuppression may develop soon after the recovery from the acute phase of the disease or without any prior signs of acute infection [16]. Therefore, the terms "non-myelosuppressive" and "myelosuppressive" CME, may better reflect the clinical severity of the disease, irrespective of its time progression [17]. The conditions that may precipitate the occurrence of myelosuppression have yet to be elucidated. Breed-specific susceptibility to the infection (German Shepherds seem to have higher morbidity and mortality compared to other breeds), coinfections with other vector-borne pathogens (e.g. *Leishmania infantum*, *Anaplasma* spp., *Babesia* spp., *Rickettsia* spp., *Bartonella* spp.), strain virulence or inoculum size variation, and the cytokine profile induced post-inoculation (i.e. high levels of INF-γ have been associated with mild disease, as opposed to elevated IL-1β and IL-8), may affect the clinicopathologic diversity and the outcome of CME [16-23]. While cellular immunity is pivotal for the protection against *E. canis*, the exuberant humoral response appears to confer no protection, and in fact may be detrimental to the host [24]. Several manifestations of the disease, including glomerulonephritis, uveitis, thrombocytopenia and anemia may have an immune-mediated pathogenetic component, as indicated by

the presence of circulating immune-complexes, lymphocytic-plasmacytic infiltration of many parenchymal organs, polyclonal hyperglobulinemia, antiplatelet antibodies and the splenectomy-associated clinical and hematological improvement [25-30]. Bleeding tendency, the clinical hallmark of CME, is associated with impaired primary hemostasis due to thrombocytopenia, thrombocytopathy and mild vasculitis [16,30-32]. Thrombocytopenia may be associated with immune-mediated platelet destruction, increased consumption secondary to mild vasculitis, splenic sequestration, over-expression of a platelet migration inhibition factor, BM failure in the myelosuppressive CME or a combination thereof [16,26,29,30,33].

DIAGNOSIS

Diagnosis of CME is based on the integrated interpretation of history (living in or traveling to endemic areas, evidence of tick infestation), clinical and clinicopathologic compatibility and the results of the *E. canis*-specific testing.

CLINICAL PRESENTATION

Ehrlichia canis-induced disease ranges from mild (non-myelosuppressive) to life-threatening (myelosuppressive) [30]. A percentage of experimentally-infected (and likely naturally infected dogs) will never exhibit clinical signs; on the other hand, in dogs living in endemic areas, coinfections with other vector-borne pathogens may complicate the diagnosis [5,6,22,34,35]. Fever (occasionally hypothermia in profoundly pancytopenic dogs), depression/lethargy, anorexia, lymphadenomegaly, splenomegaly, mucosal pallor, ocular abnormalities and bleeding tendency are typical clinical manifestations in the naturally-occurring disease [1,16,19,36-38]. Tick infestation may be seen, especially in the acute phase of the disease, while ulcerative stomatitis and necrotic glossitis, hind limb and/or scrotal edema, bacterial pyoderma, icterus and central nervous system signs such as seizures, ataxia, vestibular dysfunction and cervical pain, have been more frequently reported in chronic CME [16,38,39]. Bleeding diathesis is also more common and severe in the chronic phase of CME, and in those dogs with concurrent bleeding-predisposing conditions (e.g. infection with *L. infantum*, *A. platys* infection, von Willebrand's disease, drug-induced or uremic thrombocytopathy) [38,40]. It is manifested typically as cutaneous and mucosal petechiae and ecchymoses, hyphema, epistaxis, hematuria, melena, prolonged bleeding from venipuncture sites or intraoperative bleeding [16,19,40,41] (Figures 1-4). Ocular lesions are commonly seen in CME, and may be the sole presenting complaint. Anterior or posterior uveitis (Figure 3) is the most prevalent manifestation. Ocular discharge, blepharitis, conjunctivitis, corneal ulceration, painful necrotic scleritis, secondary glaucoma and retinal hemorrhage and/or detachment leading to blindness have also been reported [42-44]. Contrary to common belief, polyarthritis, manifested with lameness, joint swelling and stiff gait has yet to be documented in *E. canis* infection [45]. In subclinical

CME the clinical manifestations are absent or they are mild and may go unnoticed by the owners (e.g. splenomegaly, intermittent fever) [14].

Figure 1. Numerous petechiae and ecchymoses on the upper lip mucosa from a dog with acute CME.

Figure 2. Penile mucosal pallor, petechiae and ecchymoses in a dog with CME-associated aplastic pancytopenia.

Figure 3. Conjunctival hemorrhage and anterior uveitis in a dog with CME.

Figure 4. Scleral hemorrhage in a dog with CME.

HEMATOLOGY

Thrombocytopenia is the most frequent hematological abnormality in CME, appearing in more than 80% of the cases, regardless of the phase of the disease. However, CME

should not be ruled out solely on the basis of a normal platelet count [1,12,13,38]. A non-regenerative anemia, leukopenia, neutropenia (mild-to-moderate leukocytosis/ neutrophilia with or without a mild left shift may rarely be seen) and lymphopenia or mild lymphocytosis are additional abnormalities [32,46]. Granular lymphocytosis, with T-cell expansion in the blood and other tissues may occur in the subclinical and chronic phase of the disease, imitating lymphocytic leukemia (Figure 5) [11,47-50]. Thus, in endemic areas, CME should be a top differential for persistent lymphocytosis in the dog [49]. Aplastic pancytopenia typifies the myelosuppressive CME and the latter may be the major cause of canine pancytopenia in endemic areas [51]. Pancytopenia with normocellular BM may occur in acute CME, and is easily amenable to medical treatment [38]. A mild-to-moderate thrombocytopenia and/or anemia are the most consistent hematological findings in subclinical CME [13,52].
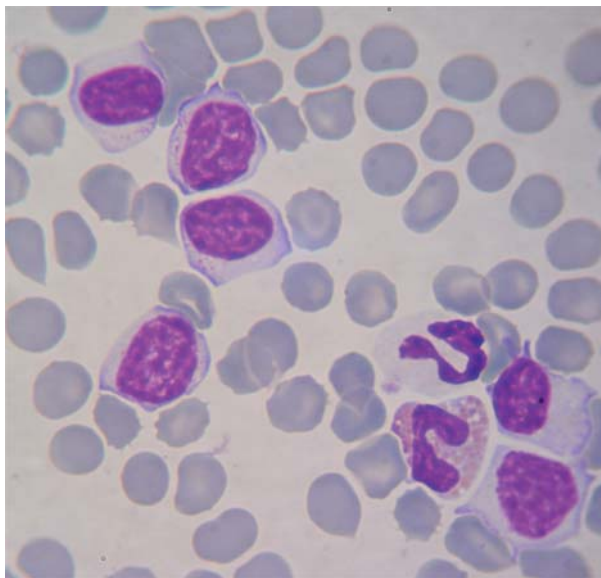

Figure 5. Blood smear from a dog with CME (Diff-Quik, objective 100x). The dog was presented with persistent mild lymphocytosis which resolved upon completion of the doxycycline treatment. Depicted are several granular lymphocytes and severe thrombocytopenia.

BLOOD SERUM BIOCHEMISTRY

Hyperproteinemia, hyperglobulinemia, hypoalbuminemia and mildly elevated alkaline phosphatase and alanin aminotransferase activities are common biochemical abnormalities in CME [13,36,38,53,54]. Hyperglobulinemia does not correlate with anti-*E. canis* IgG titers, and appears on serum electrophoresis to be caused by polyclonal or rarely, oligoclonal or monoclonal hypergammaglobulinemia [33,36,48,53]. Pancytopenic dogs tend to have lower total protein, total globulin and γ-globulin concentrations compared to their non-pancytopenic counterparts [53]. Liver disease may be primary or secondary to hypoxia, intrahepatic hemorrhage, or septicemia in the

myelosuppressive CME [25,32,54]. Creatinine concentration is elevated in some dogs while glomerular proteinuria may be present, attributable to glomerulonephritis with or without immune-complexes deposition in the chronic and acute CME, respectively [16,19,36].

Several reports indicate that in experimentally or naturally infected dogs, significant acute phase proteins and antioxidant responses may occur. C-reactive protein, haptoglobin, serum amyloid A, a1-acid glycoprotein and ferritin tend to increase (positive acute phase proteins), while albumin (negative acute phase protein) and paraoxonase-1 (oxidative stress indicator) tend to decrease [38,55-57] in dogs with acute and chronic, but not in the subclinical phase of the disease. However, the clinical relevance of these changes has yet to be fully appreciated. For instance, in a study with naturally occurring CME, the concentration of C-reactive protein, haptoglobin and serum amyloid A on admission were useful indicators of the clinical phase and severity of CME, but were not useful predictors of the clinical outcome [38]. In another study, they were of limited value as treatment response indicators in an experimental setting [57].

CYTOLOGY

Demonstration of *Ehrlichia* spp. morulae in monocytes, macrophages and lymphocytes (Figure 6) in Romanowsky-type stained smears from buffy coat and less frequently lymph node, BM, spleen, liver and cerebrospinal fluid smears, is helpful in establishing a definitive diagnosis of acute CME [2,54,58-62]. In a study with dogs naturally-infected by *E. canis* (presumptive acute CME), the diagnostic sensitivity of buffy coat (review of 1000 oil immersion fields, 100x objective lens), lymph node (500 oil immersion fields, 100x objective lens) or their combination was 66%, 61% and 74%, respectively [59]. In another study, diagnostic sensitivity of spleen cytology in dogs naturally infected by *E. canis* was 49% [60]. Cytology may also support the diagnosis of CME even before seroconversion in acutely infected dogs and is valuable in documenting coinfections (e.g. *Babesia* spp., *Hepatozoon canis*, *L. infantum*), which may have therapeutic and prognostic implications [54]. On the other hand, cytology is a labor-intensive examination even in the acute phase of the disease (less than 1% infected mononuclear cells), it is notoriously insensitive in the subclinical and chronic CME and its specificity is adversely affected by the inability to identify the involved ehrlichial species and the fact that extraneous material such as phagocytosed platelets or nuclear remnants and lymphocytic azurophilic granules may imitate morulae [16,59].

Bone marrow cytology is also useful to differentiate the non-myelosuppressive from the myelosuppressive CME, or to rule out other hematological syndromes causing pancytopenia (e.g. myelophthisis). Although BM histological biopsy is superior to cytology in appreciating the BM cellularity [63], review of at least 4 BM cytology smears correlates well with core biopsy in assessing BM cellularity in CME [64]. While in the acute CME BM appears to be normocellular, in the chronic CME a marked reduction

of hematopoietic tissue is noticed, occupying less than 25% of the marrow flecks and usually consists of adipocytes, endothelial and stromal cells [16]. Occasionally, mild-to-moderate mature mast cell and/or plasma cell hyperplasia may be seen and should not be confused with systemic mastocytosis or multiple myeloma, respectively [29].
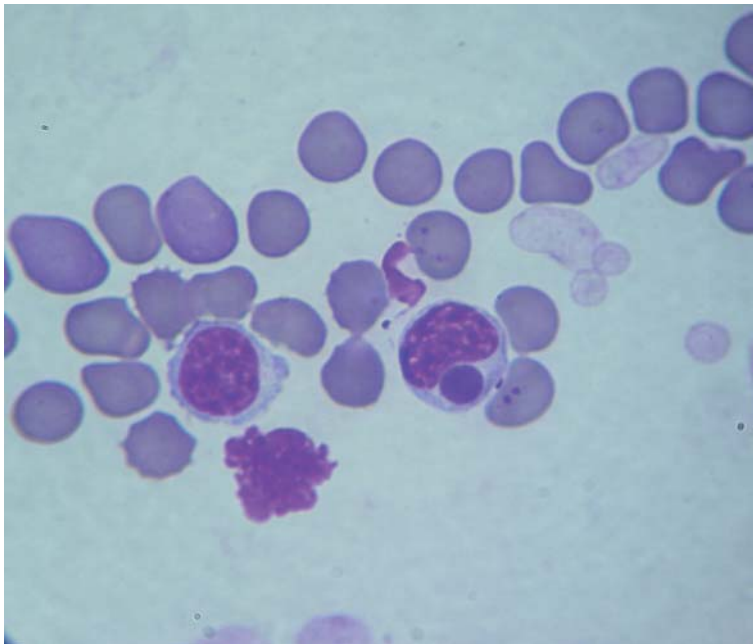

Figure 6. Buffy coat smear from a dog with experimental CME (Diff-Quik, objective 100x). An *Ehrlichia canis* morula is seen in a lymphocyte.

SEROLOGY

Serology is currently the mainstay for the confirmation of exposure to *E. canis* [62]. Indirect fluorescent antibody (IFA) testing is considered the "gold standard" for the detection and titration of anti-*E. canis* antibodies, although enzyme-linked immunosorbent assays (ELISA) are also used [65]. For most laboratories, an IgG titer equal to or greater than 1:80 is considered indicative of prior exposure to an *Ehrlichia* spp. Antibodies develop 7-35 days post-infection, and do not reliably correlate with the current carrier status, the duration of infection, or the presence and severity of clinical disease [4,62,66,67]. In experimental infections, IgG antibodies tend to increase earlier following intravenous (7-15 days) as compared to subcutaneous or intradermal inoculations (15-35 days) which may explain the variable intervals for seroconversion in the clinical setting [68,69]. Importantly, in acutely-infected dogs, clinical signs and hematological abnormalities may precede seroconversion [22,54,65, 66] and therefore, diagnosis of CME in an acutely ill patients should not be ruled out based on single time point serology alone. The demonstration of a four-fold seroconversion (IgG)

in paired serum samples obtained 2-3 weeks apart implies a recent infection [70]. Due to the prolonged subclinical phase and the persistent seropositivity following drug-mediated or self-eradication of the infection, the clinicians should be aware that seroreactivity to *E. canis*, especially in an endemic area, does not confirm that the clinical manifestations upon presentation are due to *E. canis* infection [70,71]. The kinetics of the IgM antibody titers is not predictable and it has currently limited clinical usefulness in CME [69]. The specificity of serology is also affected by the cross-reactivity that may occur among the same (i.e. *E. canis*, *E. chaffeensis* and *E. ewingii*), or, less likely, closely-related (i.e. *A. phagocytophilum*) genogroup species [62]. Although not routinely available, Western immunoblotting may distinguish between infections with *Ehrlichia* species that display cross-reactivity, while the chronicity of *E. canis* infection may be inferred based on immunoblot patterns [72,73]. Numerous in-house ELISA tests are commercially available for *E. canis* antibody testing. In general, these screening tests have been calibrated to become positive at an antibody level corresponding to an IFA titer of approximately 1:320 or higher; thus, a relatively low sensitivity may be anticipated, especially in acutely-infected dogs [62,65,74].

POLYMERASE CHAIN REACTION (PCR)

Polymerase chain reaction may overcome several diagnostic limitations of serology (confirmation of exposure rather than current infection) and cytology (overall low diagnostic sensitivity). It is a highly sensitive method for the early detection (usually 4-10 days post-inoculation), molecular characterization and quantification (real-time PCR) of the ehrlichial organisms [1,62,75,76]. Also, PCR is more useful than serology, for the documentation of concurrent infections with different ehrlichial species and the post-treatment monitoring [5,6,77,78]. Importantly, in dogs with profound aplastic pancytopenia the diagnostic sensitivity of PCR may be suboptimal [16]. Several assays have been developed targeting an array of genes, such as the 16S rRNA or the p30 genes, to specifically detect *E. canis* infections in the dog [62]. The p30-based nested PCR assay may be more sensitive than the 16S rRNA-based nested PCR assay [75].

Successful amplification of *Ehrlichia* DNA may be accomplished from several tissues, including whole blood, BM, spleen, lymph nodes, liver, kidney, lung, and cerebrospinal fluid. If blood or other tissues are not available, PCR can be applied in residual serum samples [79]. In the naturally-occurring CME, the diagnostic sensitivity and the optimal tissue for PCR testing in the untreated dog or in the post-treatment setting have yet to be clarified. Two previous studies indicated that spleen specimens were of higher sensitivity compared to BM or blood for the confirmation of subclinical CME [52] and the evaluation of the response to treatment [52,80]. However, other studies, have suggested that the spleen was inferior to other tissues [40,71,77,81].

TREATMENT

In a dog with clinical and clinicopathologic manifestations consistent with CME in conjunction with the serological evidence of exposure to, and/or molecular or cytological evidence of *E. canis* infection, the decision for treatment is straightforward. The decision to treat a clinically healthy, seropositive dog may be particularly challenging, especially in endemic areas. A positive PCR result justifies *E. canis*-specific treatment. However, if PCR is negative, the proper course of action should be decided on a case-by-case basis. The authors incline towards treating these seropositive dogs if they have compatible clinicopathologic abnormalities (e.g. thrombocytopenia, hyperglobulinemia) with no evidence of other potential causes of these abnormalities [1].

Historically, doxycycline, a semi-synthetic tetracycline, has been the first-line drug for the treatment of CME. The consensus dosing recommendations for doxycycline in CME is 5 mg/Kg, orally, twice daily, for at least 28 days [1,4]. Although doxycycline has been very effective in achieving clinical and/or clinicopathologic recovery in the vast majority of experimentally or naturally infected dogs experiencing acute or subclinical infections, it has not been invariably effective in eliminating *E. canis* infection [14,15,22,24,77,78,80,82-85]. For example, in a recent experimental study, the efficacy of the consensus doxycycline regimen was investigated during acute, subclinical and chronic CME. Despite the clinical and hematologic recovery of the dogs and the negative blood PCR in the majority of treated dogs, *R. sanguineus* ticks fed on the dogs after doxycycline treatment (xenodiagnosis) became PCR-positive for *E. canis* DNA, regardless of the phase treatment was instituted; similarly, most of the naïve dogs inoculated with pooled blood from the treated dogs became PCR positive [85]. These results may imply that *E. canis* infection may persist even following prolonged doxycycline treatment. Doxycycline is also ineffective in dogs with profound aplastic pancytopenia complicated with septicemia and severe bleeding [16]. Some dogs may experience nausea and vomiting with oral doxycycline, which may be mitigated by mixing the drug with food [86].

There is currently limited evidence-based justification for using other tetracyclines (minocycline, tetracycline, oxytetracycline) or chloramphenicol, while enrofloxacin, azithromycin and imidocarb dipropionate have been found ineffective in achieving clinical and hematologic remission or in clearing the infection [87-89]. Therefore, imidocarb dipropionate is no longer indicated in CME, except in dual infections with *Babesia canis* [1,88]. Rifampicin, an inhibitor of the B subunit of DNA-dependent RNA polymerase, has recently received attention as a potential alternative drug to doxycycline. In an *in vitro* study on antibiotic susceptibilities, rifampicin was as effective as doxycycline against *E. canis* [90]. When rifampicin was given (15 mg/kg/12 h orally for 7 days) to two subclinically infected, moderately pancytopenic dogs, pancytopenia was resolved and *E. canis* DNA was cleared from the blood, as documented by PCR [84]. The same rifampicin regimen, given to two asymptomatic *E. canis*-infected dogs

700 days post-inoculation, after an ineffective course with doxycycline, appeared to clear the infection in one of the two dogs, based on xenodiagnosis with ticks [85]. Finally, it was recently shown in an experimental setting that rifampicin (10 mg/Kg, once daily, orally, for 21 days) was partially effective in eliminating acute *E. canis* infection, but it objectively hastened hematologic recovery as opposed to infected untreated dogs [71]. Provided that the safety profile of rifampicin in the dog will be sufficiently refined [91], it might be a promising alternative to doxycycline in CME, as the clinical experience in human ehrlichiosis currently suggests [92,93].

A short-term glucocorticoid treatment (1-2 mg/Kg, daily, for one week), has been advocated in CME for attenuating the immune-mediated component of the disease manifestations. In the authors' opinion, this is very rarely needed, since rapid improvement is noticed soon after the institution of doxycycline treatment in acutely-infected dogs [22]; on the other hand, the administration of glucococorticoids in a profoundly leukopenic dog, may exacerbate the disease [37].

In dogs with CME-induced aplastic pancytopenia, supportive treatment is critically important if the limited chances for survival are to be pursued. It includes the administration of balanced crystalloid solutions and/or the periodic blood-typed and cross-matched packed red blood cells or whole blood transfusions, and prophylactic (asymptomatic dogs with moderate-to-severe neutropenia (neutrophil count <1,000/µl)) or therapeutic (symptomatic neutropenic dogs) use of bactericidal antibiotics [94].

POST-TREATMENT MONITORING

Post-treatment monitoring is particularly important in *E. canis* infections. Unlike the myelosuppressive CME which is refractory to treatment, acutely-infected dogs, experience a rapid clinical improvement within 24-48 hours from treatment initiation, while resolution of hematologic abnormalities takes 1-3 weeks [24,71,80]. Failure of the dog to respond in the aforementioned time frame should prompt the clinician to reconsider the diagnosis; on the other hand, clinical and hematologic recovery may precede the elimination of *E. canis*, thus, treatment should not be terminated based on the clinical and hematologic normalization alone [80]. Reappearance of thrombocytopenia 2-4 weeks after the cessation of doxycycline indicates treatment failure or re-infection [87]. Hyperglobulinemia tends to resolve 6-9 months after the initiation of treatment, and persistent hyperglobulinemia may indicate treatment failure or concurrent infectious or neoplastic conditions. The kinetics of IgG antibodies is unpredictable, frequently persisting several months to years following eradication of the organism, which minimizes the value of serology as a post-treatment monitoring tool [70,71,78,87]. In this respect, PCR applied in the blood, BM and spleen aspirates, 4-8 weeks after the completion of treatment, is the most reliable method in the clinical setting to prove the clearance of *E. canis* infection [14,35,71]. Prognosis is good to excellent in the acute or subclinical CME. Profound pancytopenia, severe leukopenia or neutropenia and severe anemia, herald a grave prognosis [38].

PREVENTION

Dogs that have recovered and cleared of the infection do not acquire permanent immunity and may become re-infected [24]. Therefore, tick control with careful manual removal or by applying appropriate acaricides on a year-round basis, is the single most important measure for the prevention of *E. canis* infection. Importantly, it was recently shown that *E. canis* transmission may start a few (3-8) hours after tick attachment [95]. Tick control products such as those containing phenylpyrazoles (pyriprol, fipronil), pyrethroids (permethrin, deltamethrin, tetramethrin, flumethrin), amitraz and isoxazolines (fluralaner, sarolaner, afoxolaner) have been shown to be very effective in reducing the incidence of *E. canis* infection and/or tick infestation, but the owners should be aware that no product can completely prevent the infection in all dogs, under all circumstances [96-98]. In highly endemic areas, when adequate tick control is hard to achieve, prophylactic daily use of low dose doxycycline during the tick season, reduces the risk of infection [99], although this practice may promote drug resistance. Incoming dogs in a non-endemic area should be serologically screened and treated accordingly.

Authors' contributions

MM was the main author of the manuscript. TK has helped to draft the manuscript. Both authors read and approved the final manuscript.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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MONOCITNA ERLIHIOZA PASA: AKTUELNOST U DIJAGNOSTICI I TRETMANU

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Monocitna erlihioza pasa (CME) je globalno rasprostranjeno obolenje koje prenose krpelji. Izazivač je Ehrlichia canis, gram-negativna, obligatno intracelularna, pleomorfna bakterija roda Ehrlichia, koja inficira monocite, makrofage i limfocite i pri tome formira morulu, tj. intracitoplazmatske agregate bakterija koji su okruženi membranom. Posle inkubacionog perioda koji traje od 8 do 20 dana, tok infekcije može da se podeli u akutnu, subkliničku i hroničnu fazu pri čemu se ove faze teško razlikuju samo na osnovu kliničkih ispitivanja. Tipično, ishod akutnog toka bolesti je ozdravljenje u kliničkom smislu pri čemu inficirana životinja ulazi u subkliničku fazu tokom koje nema simptoma ili su oni veoma slabo izraženi uz blage poremećaje hematoloških parametara. Imunokompetentni psi mogu da eliminišu uzročnika tokom akutne ili subakutne faze. Međutim, kod izvesnog broja pasa bolest prelazi u hroničan tok koji karakterišu aplastična pancitopenija i visok stepen mortaliteta usled septikemije i/ili krvarenja. U radu je ukratko opisana patogeneza monocitne erlihioze pasa uz detaljno opisana i analizirana najnovija saznanja koja se odnose na dijagnozu i tretman ovog ozbiljnog obolenja pasa.