

# *Rhipicephalus sanguineus* Infestation with Ehrlichiosis in Shitzu-Pomeranian Crossbred Dogs Treated using Red Fermented Rice: A Case Report

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## Abstract

This report aimed to provide information on the diagnosis, treatment, and therapeutic evaluation of Ehrlichiosis in crossbreed dogs treated using red fermented rice. A Shitzu-Pomeranian crossbreed was indicated with decreased appetite, weight loss, and the presence of high levels of pruritus due to suffering from blood parasites. Physical examination showed an infestation of *Rhipicephalus sanguineus* around the eyes and back area. A complete hematological examination and blood smear showed leukocytosis, lymphocytosis, thrombocytopenia, increased granulocytes, and the presence of intracytoplasmic bodies in monocytes. The results of the examination using the test kit showed that the sample was positive for Ehrlichiosis. Treatment using Doxycycline (5 mg/kg BW, for 28 days), Ivermectin 1% (0,2 ml SC), Diphenhydramine HCl 10 mg/kg (1,1 ml IM), Chlorpheniramine maleate (1 tablet/day for 14 days), Vitamin B12 (1 tablet/day for 28 days), and 5 ml of red fermented rice solution twice a day for 21 days. After 21 days, the whole treatment reported the appetite returned to normal, reduced infestation of *R. sanguineus*, and reduced frequency of pruritus.

Keywords: Ehrlichiosis, red fermented rice, *Rhipicephalus sanguineus*, thrombocytopenia

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## INTRODUCTION

Canines are household pets owned by people, and their uses range from house protection to other uses (Alfi *et al.*, 2015). It is very important to pay attention to the health management of dogs, even though they have been cared for intensively, dogs can be infected by various types of disease agents such as viruses, bacteria, and parasites. There are various diseases that can infect dogs, both infectious and non-infectious. Problems that are often found related to the health and welfare of dogs are parasitic infections, for example, flea and tick infestations which cause the entry of protozoa, viruses, and rickettsia (Rumlaklak *et al.*, 2018). Ticks are an important group of vectors in the phylum Arthropoda which play a role in the transmission and maintenance of several pathogens such as bacteria, worms, protozoa, and viruses that infect domestic animals and humans. Pathogens transmitted through tick bites that commonly attack dogs are Babesia, Ehrlichia, and

Anaplasma (The Center for Food Security and Public Health, 2013).

Ehrlichiosis is a zoonotic infection that can infect animals and humans and can be transmitted by ticks. Ehrlichiosis is an important disease in dogs caused by Gram-negative intracellular bacteria from the genus *Ehrlichia sp.* which belongs to the Anaplasmataceae family. Important species of the genus *Ehrlichia sp.* are *E. canis*, *E. ewingii*, and *E. chaffeensis* (Barman *et al.*, 2014). *Ehrlichia sp.* is a blood parasitic agent that often infects dogs. *Ehrlichia sp.* mainly infects white blood cells, forming intracytoplasmic aggregates called morulae (Mylonakis and Theodorou, 2017). *Ehrlichia sp.* can cause canine monocytic ehrlichiosis (CME), which is a fatal disease in dogs that requires rapid and accurate diagnosis to initiate appropriate therapy and is a very important tick-borne disease in dogs (Beall *et al.*, 2012). Ehrlichiosis in dogs is a disease transmitted by vectors called canine vector-borne diseases (CVBD). *Rhipicephalus*

*sanguineus* acts as a vector for Ehrlichiosis (Kurnia *et al.*, 2020; Nesti *et al.*, 2018).

The development cycle of *Ehrlichia sp.* starts when the larval stage of the tick sucks the blood of a dog suffering from Ehrlichiosis and then the pathogen enters and replicates in the tick's intestines. Tick larvae that are full from sucking blood will drop off and molt into nymphs, *Ehrlichia sp.* will remain in the tick's intestines and be carried along during the molting process. *Ehrlichia sp.* will migrate to the salivary glands when the tick nymphs are ready to suck blood (Putra *et al.*, 2015). Transfer of *Ehrlichia sp.* in ticks only occurs transtadially. When ticks suck blood, *Ehrlichia sp.* will enter the dog's body at the same time as the tick's saliva comes out. The saliva plays a role in anticoagulation of the host's blood. *Ehrlichia sp.* that has entered the host will go to the monocytes and replicate. Blood tests usually show thrombocytopenia, anemia, and leukopenia (Tsachev *et al.*, 2013). Thrombocytopenia is defined as a condition where the levels of platelets in the blood decrease to below normal. A decreased platelet value will decrease the condition of the circulatory system (Wijaya, 2018). One alternative to traditional medicine that can increase blood platelet levels is red fermented rice (Iryani and Soleha, 2016).

Red fermented rice is red-colored rice fermented from *Monascus purpureus* yeast. Red fermented rice is used in China, Taiwan, Philippines, Thailand, and Indonesia as a natural food coloring and as a food additive. The pigment and metabolite content of red fermented rice is believed to help the process of increasing blood platelet levels (Januardy, 2015). For health, red fermented rice can empirically treat digestive disorders, improve blood circulation, spleen and stomach protection, stop blood stasis, and increase the efficacy of medicines. Based on a study conducted by Mukherjee and Singh (2011), red fermented rice can inhibit the growth of *Bacillus mycoides*, *Bacillus subtilis*, and *Bacillus subtilis*. Several studies also show that platelet levels can be increased by administering red fermented rice (Prayoga, 2016).

Red fermented rice contains inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A

(HMG CoA) reductase which plays a role in the process of forming cholesterol and protein components, amino acids, lovastatin, saccharides, beta-sitosterol, campesterol, stigmasterol, isoflavones, saponins and various trace elements. Empirical experience reports that consuming red fermented rice can increase the number of platelets quickly using red fermented rice boiled water. Lovastatin in red fermented rice is believed to be a compound that plays a role in increasing blood platelet levels. The lovastatin content in red fermented rice can reduce LDL oxidation, thereby reducing barriers to the formation of monocyte and megakaryocyte chemotactic protein-1. This protein can stimulate the collection and migration of megakaryocytes in the endothelium space, thereby increasing platelet cell production. In addition, other secondary metabolites contained in red fermented rice dekokta are thought to have a synergistic effect in increasing blood platelet levels (Januardy *et al.*, 2015).

In this case study, a five-year-old crossbreed dog with Ehrlichiosis is treated with supportive therapy, which includes red fermented rice. This report sought to disseminate knowledge on the diagnosis, management, and therapeutic assessment of Ehrlichiosis with supportive therapy from traditional medicine.

## MATERIALS AND METHODS

### Study Location

This study was performed at the Laboratory of Internal Medicine, Animal Hospital, Udayana University, Sesetan, Denpasar, Bali in January 2023.

### Signals and Anamnesis

A Shitzu-Pomeranian crossbreed, 5-year-old female, weighing 11 kg, and white fur. Due to a significant tick infestation, the animal itched and scratched a lot for a year. Two weeks prior to the inspection, the animal's appetite had decreased, which caused it to lose weight. Information indicates that the owner of the animal had a severe infestation of ticks towards the end of 2019. At that time, the owner treated the animal with peditox and shaved its hair, but the ticks quickly

returned. The animal has had all recommended vaccinations and treatments to prevent deworming. The owner only has one pet, which he releases inside the house, but he frequently interacts with dogs in the neighborhood. Rice and boiling chicken are the foodstuffs fed to animals.

### Physical Examination

During the physical examination, the animal showed a weak condition and there was erythema, skin hyperpigmentation, there were wounds caused by scratching and tick bites accompanied by *R. sanguineus* infestation almost all over its body, in particular around the eyes and the back area (Figure 1). The limbs, digestion, nerves, urogenital, and lymph nodes were normal, but the skin was abnormal with the presence of erythema, crusts, and scales (Table 1).

Based on the American Kennel Club guidelines, a normal, healthy dog's skin appears supple and smooth, without scabs, growths, white flakes, or red areas. The limbs and musculoskeletal movements were normal. An abnormal nervous system will include changes in behavior, seizures, tremors, pain, numbness, lack of coordination, and leg paralysis. The effects of injury on sensory and motor function depend on its location and severity. Abnormal circulatory system disorders in dogs that can be observed include lethargy, weakness, fatigue, laziness in moving, weight loss, coughing, dyspnea, and polypnea. The normal urogenital system indicates if there is no disturbance in the flow of urine through the urinary tract system. Normal respiration is indicated by the absence of symptoms of difficulty breathing or panting in the animal. Normal digestion is if the animal does not have difficulty digesting and is able to absorb carbohydrates. Normal mucosa in animals is characterized by a pink color and smooth-shiny. The normal lymph nodes if a physical examination with palpation do not reveal any swelling.

### Clinical Examination

Based on heart rate and pulse examination showed that it was normal, the Capillary Refill

Time (CRT) showed normal results but the animal's respiration had decreased (Table 2).

### Supporting Examination

The supporting examination performed a complete hematology examination using a Hematology Analyzer machine (Licare CC-3200, PT. Aerocom Global Sejahtera, West Jakarta, Indonesia). The results of a complete hematological examination showed that the case dog had leukocytosis, lymphocytosis, thrombocytopenia, and an increase in granulocytes (Table 3). Test kit examination showed positive results for *Ehrlichia sp.* antibodies. Blood smear examination was carried out using Giemsa staining solution. The blood smear results of the case dog showed the presence of intracytoplasmic bodies in monocytes (Figure 2).

### Preparation of Red Fermented Rice Solution

Red fermented rice was preserved using *Monascus purpureus* yeast and distilled water. A total of 400 g of red fermented rice was mixed with 1 ml of distilled water and then boiled using a saucepan over medium heat. Red fermented rice was boiled and then kept the water at room temperature for further consumption.

### Diagnosis and Prognosis

Based on the history, physical examination results, clinical examination, and confirmed by the results of supporting examinations, the dog was diagnosed as having heavy tick infestation accompanied by Ehrlichiosis with a fausta prognosis.

### Therapy

The therapy was applied using Ivermectin 1% injection dose of 0,2 ml SC (Wormectin Injection, PT Medion Farma, Bandung, Indonesia), Diphenhydramine HCl injection 10 mg/ml dose of 1,1 ml IM (Vetadryl, PT. Global Multi Pharmed, Semarang, Indonesia). Administration of Doxycycline (Dohixat®, PT. IFARS Pharmaceutical Laboratories, Solo, Indonesia) dose of 5 mg/kg BW twice a day orally for 28 days. Supportive therapy was administered

using Vitamin B-complex (Livron B Plex, PT. Phapros, Semarang, Indonesia) once a day orally for 28 days. B-Complex vitamins play a role in energy metabolism in the body and increase appetite. Vitamin B12 also plays a role in forming platelets that suffer from thrombocytopenia and improves hyperpigmentation on the skin. Red fermented rice solution was administered twice a day, 5 ml for 21 days. The lovastatin content in red fermented rice is believed to increase blood platelet levels (Prayoga *et al.*, 2016).

## RESULTS AND DISCUSSION

After treatment for 21 days, the animals showed changes with reduced infestation of *R. sanguineus*, the improvisation on its appetite, and the frequency of scratching began to decrease (Figure 3). Routine hematology results showed that the levels of WBC, lymphocytes, and granulocytes which had previously increased had now reached normal limits, and platelets which had previously decreased had now reached normal limits (Table 3).

*R. sanguineus* can act as a vector for blood parasitic diseases including Ehrlichiosis (Koh *et al.*, 2016). This can occur in the case of dogs considering the way they are kept in cages and frequent contact with other animals, which can increase the risk of transmission of tick infections containing *Ehrlichia sp.* Based on a previous study, *Ehrlichia sp.* antibodies appear 7–14 days after the first infection and will become dormant in the body. Blood tests need to be carried out in cases suspected of being infected with parasitic agents.

In this study, the results of the hematological examination reported leukocytosis, lymphocytosis, increased granulocytes, and thrombocytopenia. This is in line with (Gonde *et al.*, 2016) which states that in cases of Ehrlichiosis blood tests such as leukocytosis, lymphocytosis, and thrombocytopenia are often found in dogs. The number of white blood cells is influenced by the dog's body's resistance to fighting infectious agents (Sudira *et al.*, 2018). Leukocytosis can indicate that the animal is under stress or acute inflammation is occurring (Paramita and

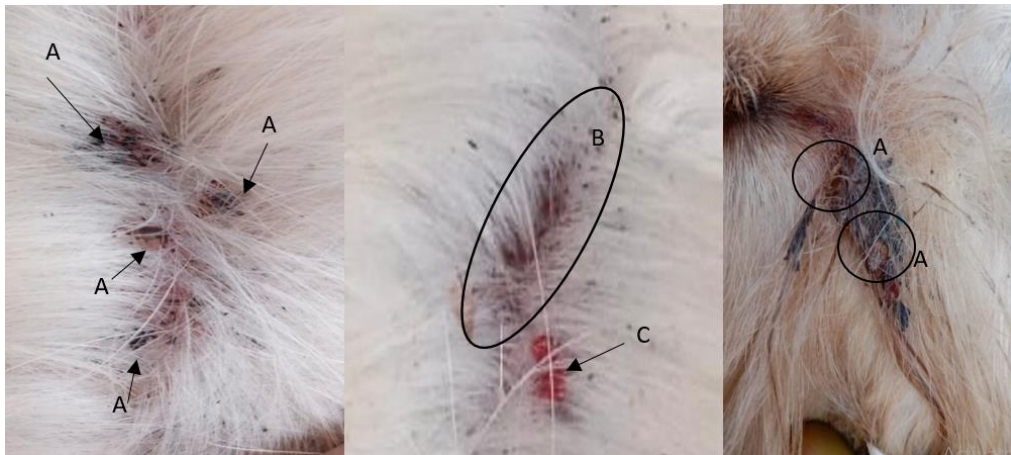
Widyastuti, 2019). In this case, the animal experiences stress and acute inflammation occurs due to the large number of ticks, as a result, the animal often scratches, resulting in wounds resulting from scratching which causes inflammation of the skin (Islami *et al.*, 2018). An increase in granulocytes is more indicative of an increase in neutrophils. In general, the increase occurs due to various factors, one of which is bacterial infection (Simarmata *et al.*, 2021).

The circulatory system is negatively impacted by thrombocytopenia. The normal observation in cases of Ehrlichiosis is that the animal has moderate to severe thrombocytopenia. There are numerous causes of thrombocytopenia, including illnesses like Ehrlichiosis. Because of the increased permeability caused by the inflammatory process in the blood vessel endothelium, more platelets are required to maintain hemostasis. Moderate to severe thrombocytopenia is a typical hematological finding in Ehrlichiosis cases (Erawan *et al.*, 2017).

In Ehrlichiosis patients, reduced platelet synthesis in the bone marrow can lead to thrombocytopenia. Animals with ehrlichiosis may have granulomas and morula of *Ehrlichia sp.* in their bone marrow, which will prevent the bone marrow from generating megakaryocytes, which are the progenitors to platelets. The *Ehrlichia sp.*-infected mononuclear cells that get localized in blood capillaries or migrate to the endothelial tissue, producing inflammation of the blood vessels during the acute phase, are the source of the thrombocytopenia that happened in the case dog. Due to autoreactive antibodies associated with platelets, infection by the parasite *Ehrlichia sp.* induces immune-mediated damage to platelets, potentially reducing their lifespan. According to estimates, platelets only live 8–11 days in circulating blood (Arsyitahlia *et al.*, 2021).

A blood smear examination was carried out to rule out differential diagnoses by looking for the presence of blood parasitic agents in the examination. Blood smear examination of the case dog revealed intracytoplasmic inclusions. The morulas discovery may indicate the presence





**Figure 1.** (A) *R. sanguineus* infestation on the back and around the eyes, (B) The skin was hyperpigmented, (C) There were wounds due to scratching and tick bites.

**Table 1.** Physical examination results

Parameter	Result
Integumentum	Abnormal
Locomotion system	Normal
Musculoskeletal	Normal
Nerve	Normal
Circulation	Normal
Urogenital	Normal
Respiration	Abnormal
Digestion	Normal
Mucosa	Normal
Lymph nodes	Normal

**Table 2.** Preasence status

Parameter	Result	Normal value	Information
Heart rate (x/minute)	100	90–120	Normal
Pulse (x/minute)	96	90–120	Normal
CRT (seconds)	< 2	< 2	Normal
Respiration (x/minute)	20	24–42	Decrease
Temperature (°C)	39,2	38,6–39,2°C	Normal

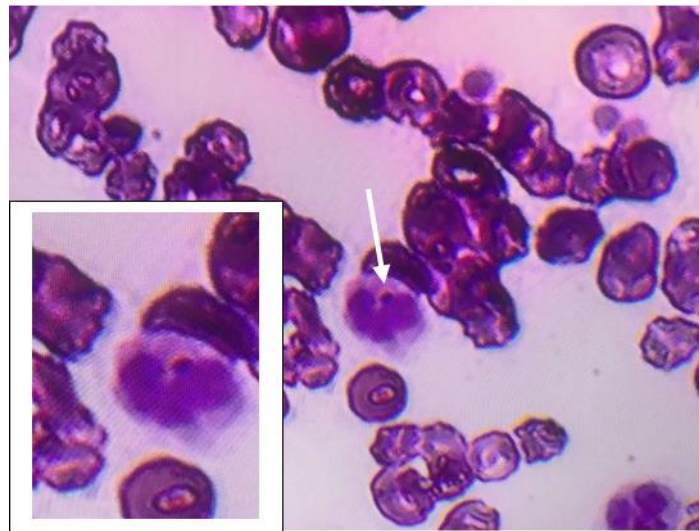
\*Reference: (Widodo *et al.*, 2017).

**Table 3.** Hematological evaluation

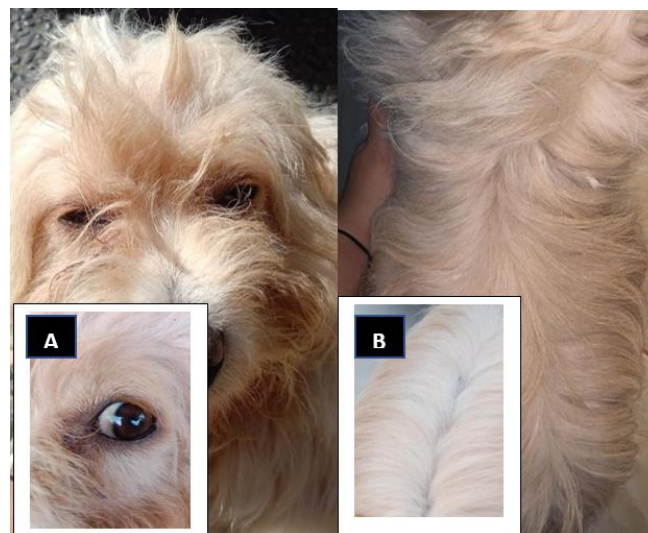
Parameter	Initial result	After 21-day	Reference*	Information
WBC (10 <sup>3</sup> /μL)	20,8	8,6	6–17	Increase
Lymphocytes (10 <sup>3</sup> /μL)	5,47	2,01	0,8–5,1	Increase
Granulocytes (10 <sup>3</sup> /μL)	14,1	6	4–12,6	Increase
RBC (10 <sup>6</sup> /μL)	5,91	6,28	5,5–8,5	Normal
Hemoglobin (g/dL)	12,2	13,1	11–19	Normal
Hematocrit (%)	44,9	39,6	39–56	Normal
MCHC (g/dL)	27,3	33	30–38	Decrease
MCV (fL)	76	63,1	62–72	Increase
Platelets (10 <sup>3</sup> /μL)	38	165	117–460	Decrease

WBC= White Blood Cell, RBC= Red Blood Cell, MCH= Mean Corpuscular Hemoglobin, MCV= Mean Corpuscular Volume, MCHC= Mean Corpuscular Hemoglobin Concentration.

\*Reference: (Weiss and Wadrop, 2010).



**Figure 2.** The presence of intracytoplasmic bodies in monocyte cells (white arrow) (400x).



**Figure 3.** Animal condition after 21 days of therapy showed reduced *R. sanguineus* infestation in (A) the eyes, and (B) the back area.

of Ehrlichiosis. This finding is in line with the report by Erawan *et al.*, (2018) which states that intracytoplasmic inclusions can support the diagnosis in acutely infected animals. Serological tests using a test kit are also useful for making a diagnosis because this test can detect antibodies to blood parasitic agents (Erawan *et al.*, 2017; Nesti *et al.*, 2018; Gallego *et al.*, 2016) and in dog cases, the results showed positive for *Ehrlichia sp.* antibodies.

In this case, the case dog was given causative therapy by injection dose of Ivermectin 1% at a dose of 0,2 ml SC and Doxycycline capsules. Ivermectin administration is able to bind to glutamate-activated chloride channels in the parasite's nerve or muscle cells with a specific and

high affinity, causing hyperpolarization of the nerve or muscle cells by increasing the permeability of chloride ions through the cell membrane, and as a result, the parasite will be paralyzed. Doxycycline is an effective antibiotic for treating infections with blood parasitic agents such as *Ehrlichia sp.* This antibiotic has a broad spectrum from the tetracycline group and has active intracellular penetration and bacteriostatic properties against *Ehrlichia sp.* Doxycycline is able to inhibit protein synthesis by interfering with the attachment of aminoacyl t-RNA to bacterial ribosomes (Mo *et al.*, 2019). In addition, this antibiotic has an inhibitory effect on apicomplexan protozoa by targeting the apicoplast which makes it impossible for the

protozoa to reproduce and causes death of the protozoa.

According to Fourie *et al.* (2015), the Doxycycline administration for 28 days was proven to be effective in eliminating morulae that infect dogs. Symptomatic therapy was administered by anti-histamine injection which works by blocking the histamine produced by the body during an allergic reaction in the form of Diphenhydramine HCl 10 mg/ml at a dose of 1,1 ml IM and Chlorpheniramine maleate 4 mg orally given one tablet a day for seven days (Wahyudi *et al.*, 2020). Red fermented rice solution and vitamin B complex are the supporting therapies administered. Because vitamin B12 is essential for blood production, the vitamin B complex is effective in meeting the body's needs for vitamins and minerals. Additionally, the vitamin B12 concentration of the complex helps to alleviate anemia symptoms. According to several studies, red fermented rice administration shows that it can increase platelet levels in the blood. Red fermented rice can convert starch substrates into several metabolite compounds such as alcohol, antibiotics, antihypertensives, enzymes, fatty acids, gamma amino butyric acid (GABA), several pigments, and vitamins. Red fermented rice contains inhibitors of the enzyme 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase which plays a role in the process of forming cholesterol and protein components, amino acids, lovastatin, saccharides, beta-sitosterol, campesterol, stigmasterol, isoflavones, saponins, and various trace elements. The lovastatin content in red fermented rice is believed to be a compound that plays a role in increasing blood platelet levels (Prayoga *et al.*, 2016; Purnomo *et al.*, 2022).

The lovastatin content in red fermented rice can reduce LDL oxidation, thereby reducing barriers to the formation of monocyte and megakaryocyte kinetic-stimulating proteins. This protein can stimulate the collection and migration of megakaryocytes in the endothelium space, thereby increasing platelet cell production. In addition, other secondary metabolites such as isoflavones and rubropunctatin contained in red fermented rice are thought to have a synergistic

effect in increasing blood platelet levels (Prayoga *et al.*, 2016).

## CONCLUSION

Based on the history, clinical examination, hematology examination, blood smear, and test kit, the dog was diagnosed as suffering from *R. sanguineus* infestation accompanied by Ehrlichiosis. Treatment using Ivermectin, Doxycycline, Diphenhydramine HCl, Chlorpheniramine maleate, Vitamin B-complex, and supportive therapy with red fermented rice solution reported an improvisation.

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