

Traditional Chinese Herbal Medicine *Fufang E'Jiao Jiang* as Supportive Treatment in Anaplasmosis Management of a British Shorthair CatPramita Rabiulfa^{1,a}, Palagan Senopati Sewoyo^{2,b*}, Made Santi Purwitasari^{2,c}, I Gede Soma^{3,d}, I Gusti Made Krisna Erawan^{4,e}¹Adilmart Ltd. Quality Control Veterinarian, Pontianak, Indonesia²Udayana University, Faculty of Veterinary Medicine, Postgraduate Program, Denpasar, Indonesia³Udayana University, Faculty of Veterinary Medicine, Department of Basic Sciences, Laboratory of Veterinary Physiology, Pharmacology and Pharmacy, Denpasar, Indonesia⁴Udayana University, Faculty of Veterinary Medicine, Department Clinics, Laboratory of Veterinary Internal Medicine, Denpasar, Indonesia^aORCID: 0009-0002-8017-8329; ^bORCID: 0000-0002-8713-7725; ^cORCID: 0009-0002-2546-1068;^dORCID: 0000-0002-0905-2400; ^eORCID: 0009-0003-7071-5108

*Corresponding Author

E-mail: palagansenopati@gmail.com

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Abstract

Anaplasmosis, caused by obligate gram-negative intracellular parasitic bacteria *Anaplasma* sp., is a serious disease affecting both domestic and wild animals. In summary, Anaplasmosis is a serious disease that requires prompt diagnosis and aggressive treatment. The presented case highlights the importance of a comprehensive treatment plan in managing the disease and the potential benefit of incorporating traditional Chinese herbal medicine into the treatment regimen. In this case, a female British Short Hair cat, weighing 2.29 kg and aged one year and eight months, presented with symptoms including lethargy, loss of appetite, and sneezing. Physical examination of the cat revealed several abnormalities including an increase in body temperature, capillary refill time of more than two seconds, slow skin turgor, pale eye mucosa and gums, and rales in breathing. Routine hematology examination results indicated the presence of hypochromic macrocytic anemia and thrombocytopenia, while blood biochemistry results revealed an increase in globulin and aspartate aminotransferase levels and a decrease in the albumin/globulin ratio. The examination of blood smear preparations showed intracytoplasmic inclusions (morula) of the blood parasite *Anaplasma* sp. The cat received a comprehensive treatment regimen including an infusion of 0.9% sodium chloride, doxycycline antibiotics, acetylcysteine mucolytic drugs, ornipural® hepatoprotector vitamin, and traditional Chinese herbal medicine *Fufang E'Jiao Jiang* (FEJ). Despite seven days of hospitalization, the cat's condition did not improve, and the hematocrit examination results continued to decline. As a result, a blood transfusion was performed, and the FEJ treatment was continued. After the transfusion, the cat's condition improved significantly, and on the 20th day, the cat was discharged from the hospital. Based on the results of the hematological examination which improved after blood transfusions, the supportive treatment with FEJ was quite promising. In addition, this study is a preliminary report and it is suggested to carry out large-scale clinical trials with various doses.

Keywords: Anaplasmosis, blood transfusion, cat, traditional Chinese herbal medicine, *fufang e'jiao jiang*.**INTRODUCTION**

Cats are a widely kept pet around the world, and their welfare demands attention, particularly in the area of health management. The presence of various infectious and non-infectious diseases in cats necessitates owners to take necessary precautions to ensure their pet's well-being. Among the infectious diseases that affect cats, Anaplasmosis, caused by *Anaplasma* sp., is one that requires attention (Savidge et al., 2015).

Anaplasma sp. is a gram-negative bacterium, first identified in Scottish sheep in 1932, that can affect various mammals, including cats, dogs, horses, camels, cattle, and humans (Heikkilä et al., 2010). The bacterium can be carried by ticks, particularly the *Ixodes* species, acting as a disease vector. Anaplasmosis in mammals is characterized by four stages: incubation, development, recovery, and carrier (Savidge et al., 2015).

Clinical signs of Anaplasmosis in cats are nonspecific, including lethargy, fever, anorexia, conjunctivitis,

dehydration, pale mucosa, respiratory symptoms, tachycardia, and weight loss. Thrombocytopenia and anemia are the most characteristic hematological abnormalities (Schäfer and Kohn, 2020). The diagnosis of anaplasmosis is established through various methods, including clinical symptoms, history of tick infestation, identification of morula in blood cells, positive serological results, PCR results, and response to treatment (Savidge et al., 2015).

Traditional Chinese herbal medicine has gained attention for its hematopoietic stimulating therapy, which is less expensive and has minimal side effects (Chan et al., 2011). One such traditional medicinal formula, *Fufang E'jiao Jiang* (FEJ), has been approved by the China Food and Drug Administration (CFDA). Its ingredients include *Colla corii Asini*, *Radix Codonopsis Pilosulae*, *Radix Ginseng Rubra*, *Fructus Crataegi*, and *Radix Rehmanniae Preparata* (Liu et al., 2014a). FEJ is primarily used to treat anemia and loss of appetite in humans (Chen et al., 2012),

and its use in veterinary medicine for treating anemia in cats is not well documented.

The presented case highlights the importance of a comprehensive treatment plan in managing the disease and the potential benefit of incorporating FEJ into the treatment regimen. By highlighting the use of FEJ in veterinary medicine, this case report adds to the body of knowledge on FEJ as supportive therapy.

CASE PRESENTATION

The case animal is a female British Short Hair cat, aged 1 year and 8 months, with a body weight of 2.29 kg. The animal presented to the Veterinary Clinic in Pontianak, Borneo, Indonesia with complaints of lethargy, loss of appetite, and sneezing that started two days prior to the examination (Figure 1). The cat was adopted by the owner one week before the examination and is kept indoors. The cat is fully vaccinated and regularly dewormed.



Figure 1. A 1-year-and-8-month-old female British Shorthair cat presented with lethargy, loss of appetite, and sneezing.

Physical examination

From the results of the present status examination, it was determined that the cat exhibited an increase in body temperature (39.6°C), heart rate of 92 bpm, pulse of 88 bpm, respiratory rate of 32x/min, capillary refill time (CRT) of more than two seconds, and decreased skin turgor. Cats commonly show signs of dehydration such as decreased skin turgor and dry mucous membranes. Based on the assessment of the degree of dehydration, the cat is 7% dehydrated. The cat appeared lethargic, with pale eye mucosa and gums, and rales were heard in the lungs upon examination of the respiratory system. The skin, nails, musculoskeletal, nervous system, cardiovascular, urogenital, and digestive systems were all determined to be in normal condition.

Ancillary Tests

Ancillary tests including x-ray, routine hematology, blood biochemistry, and blood smear examination were performed. X-ray findings indicated no abnormalities in

the respiratory system of the case cat (Figure 2). Results from routine hematology examination revealed macrocytic hypochromic anemia and thrombocytopenia in the case cat (Table 1). Blood biochemistry results showed an increase in the value of globulin and aspartate aminotransferase (AST), as well as a decrease in the albumin/globulin ratio (Table 2). Blood smear examination was conducted with Giemsa staining to confirm the diagnosis. Round dots were found in the erythrocytes upon examination of the blood smear preparations. These characteristics suggest that the round dots are intracytoplasmic inclusions (morula) of *Anaplasma* sp. (Figure 3).

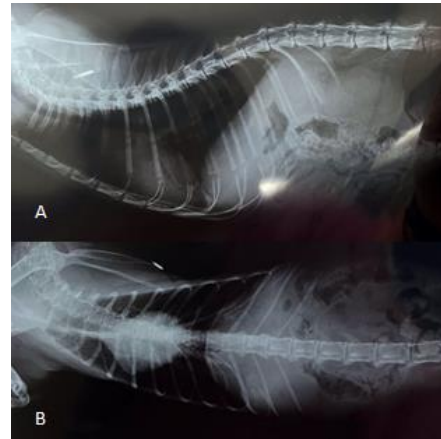


Figure 2. X-ray examination revealed no abnormalities in the cat's respiratory system in both lateral recumbency (A) and dorsoventral position (B).

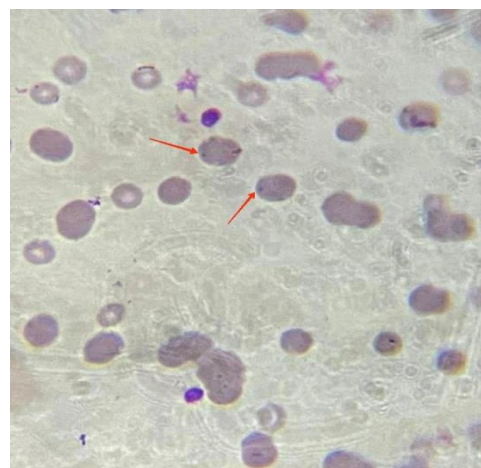


Figure 3. Upon examination of a blood smear using Giemsa stain at 400x magnification, *Anaplasma* sp. was observed in the erythrocytes of the cat, as indicated by the arrows.

Table 1. Results of the hematology examination of the cat during hospitalization are presented, with an emphasis on values related to anemia.

Parameter	Day-1	Day-4	Day-7	Day-10	Day-12	Day-15	Normal range ^a
WBC (10 ⁹ /L)	12.3	12.2	12.3	7.5	9.3	10.4	5.5-19.5
Lymphocyte (10 ⁹ /L)	2.5	2.1	2.1	1.3	1.2	1.4	0.8-7.0
Mid (10 ⁹ /L)	0.7	0.7	1.0	0.5	0.3	0.5	0.0-1.9
Granulocyte (10 ⁹ /L)	9.1	9.4	9.2	5.7	7.8	8.5	2.1-15.0
Lymphocyte (%)	20.4	17.5	17.3	17.2	12.6	13.4	12.0-45.0
Mid (%)	5.9	5.6	7.7	6.6	3.4	4.5	2.0-9.0
Granulocyte (%)	73.7	76.9	75.0	76.2	84.0	82.1	35.0-85.0
RBC (10¹²/L)	2.84	2.64	2.62	3.40	4.04	4.81	4.6-10
HGB (g/L)	34	32	34	43	54	67	93-153
HCT (%)	18.0	16.7	16.7	21.1	24.9	28.2	28-49
MCHC (g/L)	188	191	203	203	216	237	300-380
MCH (Pg)	11.9	12.1	12.9	12.6	13.3	13.9	13-21
MCV (fL)	63.7	63.3	63.8	62.1	61.7	58.7	39-52
RDWCV (%)	16.7	16.0	18.3	18.8	19.7	20.7	14-18
RDWSD (fL)	33.2	33.2	37.4	36.8	38.2	38.2	20-80
PLT (10 ⁹ /L)	41	35	4	30	31	63	100-514
MPV (fL)	9.3	10.1	10.9	8.7	9.4	7.7	5-11.8
PDW (fL)	7.1	8.8	12.1	7.8	8.4	8.0	5-20
PCT (fL)	0.038	0.035	0.004	0.026	0.029	0.048	0.100-0.500
P-LCR (%)	11	40.3	50.0	31.6	38.8	15.2	10-70

Note: The **bold** number is an important value for assessing anemia condition. The **dark blue**-colored number indicates an increase in value compared to the previous value, while the **red**-colored number indicates a decrease in value compared to the previous value. WBC = White Blood Cell; RBC = Red Blood Cell; HGB = Hemoglobin; MCHC = Mean Corpuscular Hemoglobin Concentration; MCH = Mean Corpuscular Hemoglobin; MCV = Mean Corpuscular Volume; RDWCV dan RDWSD = Red Blood Cell Distribution Width; HCT = Hematocrit; PLT = Platelet; MPV = Mean Platelet Volume; PDW = Platelet Distribution Width; PCT = Plateletcrit; P-LCR = Platelet Large Cell Ratio. ^aReference: Schalm, (2010).

Table 2. Results of blood biochemistry examination of case cat

Parameter	Result	Normal range ^a
Albumin (g/L)	19.7	18-36
Protein total (g/L)	88.7	60-94
Globulin (g/L)	69.0**	40-62
A/G ratio	0.29*	0.35-1.50
AST (U/L)	49**	0-48
ALT (U/L)	58	5-130
Amylum (U/L)	1218	500-1500
CK (U/L)	77	0-559
Creatinin (umol/L)	80.7	71-212
BUN (mmol/L)	9.61	4.0-12.9
BUN/Creatinin	119.124	27-182
Glucose (mmol/L)	7.89	4.11-8.83
TG (mmol/L)	1.00	0.00-1.13
Calcium (mmol/L)	2.75	1.95-2.83
Phosphorus (mmol/L)	1.64	1.00-2.42

Note: A/G Ratio = Albumin/Globulin Ratio; BUN = Blood Urea Nitrogen; AST = Aspartate Aminotransferase; ALT = Alanine Aminotransferase; CK = Creatine Kinase; TG = Triglyceride.

*Below reference range ** Above reference range. ^aReference: Schalm, (2010).

Diagnosis and Prognosis

Based on the findings from the anamnesis, physical examination which showed that the case cat was dehydrated, had a fever, pale eye mucosa, and gums, as well as ancillary tests including routine hematology which showed anemia and thrombocytopenia, blood biochemistry, and examination of blood smear

preparations which revealed the presence of *Anaplasma* sp. on erythrocytes, the case cat was diagnosed with Anaplasmosis with a guarded prognosis.

Treatment

The case cat was given fluid therapy using 0.9% sodium chloride solution for 7 days (with a 7% degree of dehydration). The case cat was treated with doxycycline antibiotics, given orally/PO twice a day at a dose of 9 mg/kg BW for 30 days, acetylcysteine mucolytic drug given PO twice a day at a dose of 10 mg/kg BW for 14 days, and 1 mL of Ornipur® hepatoprotector vitamin given twice a day subcutaneously as long as the animal was hospitalized. Additionally, the cat was given FEJ 2 mL twice a day PO for 30 days.

During the 7 days of hospitalization, the cat did not show any changes in its body condition. The results of the hematocrit examination continued to decrease (Table 1), and a decision was made to perform a blood transfusion. The blood transfusion was performed on the 9th day of hospitalization by collecting 25 mL of blood from the donor.

Before the blood transfusion, the cat's blood type was determined using a cat blood typing kit (Feline Blood Typing Kit, KABB Bio, South Korea), and it was found that the case cat had blood type A.

After the blood transfusion, the doxycycline was resumed according to the treatment plan. The injections of ornipur® hepatoprotector vitamin, as well as the FEJ, were also resumed. After the blood transfusion, the cat's condition began to improve. The cat's mucosa began to look pink, and the cat became more active. The results of supportive treatment with FEJ were quite promising, as seen from the results of the hematological examination which improved after blood transfusions (Table 1), so the cat was discharged from the hospital on the 20th day.

DISCUSSION AND CONCLUSION

Anaplasma species are intracellular pathogens that require cell penetration for effective treatment with antibiotics. The best treatment option for Anaplasmosis in dogs and cats is doxycycline (Schäfer et al., 2021). Transmission of *Anaplasma* species occurs through intermediary tick vectors, such as *Ixodes* species, and tick infestation is a common way for animals to become infected. The development cycle of *Anaplasma* species begins with the larval stage of the tick sucking the blood of an infected animal and the pathogen entering and replicating in the tick's intestine. *Anaplasma* species migrate to the tick's salivary glands when it is ready to suck blood. When ticks bite other animals, *Anaplasma* species simultaneously enter the animal's body with the release of tick saliva. They invade target cells through the process of endocytosis and binary fission, forming morula (Hermawan et al., 2021). Morula exits the cells (exocytosis) and destroys the cells, then repeats the infection to other target cells.

In the present case, the cat was suspected to have contracted the *Anaplasma* species during a previous tick infestation before being adopted. The blood biochemistry examination showed an increase in globulin and aspartate aminotransferase (AST) enzymes, as well as a decrease in the albumin/globulin ratio (A/G) (Table 2). An increased globulin level may indicate chronic infection, liver disease, or carcinoid syndrome (Hermawan and Restijono, 2021). A decrease in the A/G ratio may occur if the globulin level increases while the albumin level decreases or remains constant in the blood (Kaneko et al., 2008). Hyperglycemia is a common blood biochemical finding in cats with anaplasmosis (Schäfer and Kohn, 2020). The abnormal blood biochemical results observed in the present case may be due to a secondary infection or organ damage in the cat's body, requiring further observation.

The x-ray examination showed no abnormalities in the respiratory organs of the case cat. Although no abnormalities were observed in the x-ray, the present case exhibits rales sounds based on auscultation. However, as many as 9% of cats infected with Anaplasmosis have clinical symptoms of respiratory distress and abnormal lung sounds during auscultation (Schäfer and Kohn, 2020). Acetylcysteine was administered to the case cat to treat respiratory symptoms, which works as a mucolytic agent by breaking down mucopolysaccharide acid fibers to reduce mucus adhesion to the throat wall (Saito, 2010).

Target cells for *Anaplasma* sp. include erythrocytes, platelets, and leukocytes (Markey et al., 2013). This explains why affected animals with anaplasmosis often experience severe anemia and thrombocytopenia. Anemia occurs due to hemolysis caused by the binary fission of *Anaplasma* sp. on erythrocytes, with the release of morula leading to cell lysis. Meanwhile, thrombocytopenia is caused by the high consumption of platelets due to inflammation of the vascular endothelium caused by infection with this intracellular obligate parasite.

The combination of *Colla corii Asini*, *Radix Rehmanniae Preparata*, and *Fructus Crataegi* in FEJ is traditionally used to nourish the blood, increase blood volume and benefit the bone marrow, and refresh the spleen, respectively. Studies have reported that each component of FEJ can enhance the body's blood production function (Zhao, 2011; Raghavendran et al., 2013). In particular, *Colla corii Asini*, the most important ingredient in FEJ, and its enzyme-digested fraction have been extensively studied for their hematopoietic effects in

a mouse model of chemotherapy-induced anemia and leukopenia (Wu et al., 2007; Fu et al., 2010).

In Zhang et al., (2019) study, FEJ was administered to mouse models with chemotherapy-induced myelosuppression, resulting in the promotion of hematopoietic stem cell proliferation and hematopoietic progenitor cell differentiation. This case report reveals that anemia was regenerated, as evidenced by the macrocytic size of red blood cells, indicating the presence of immature blood cells in peripheral blood vessels. Hence, it is plausible that FEJ stimulates red blood cell production in the bone marrow.

The 2 mL dose of FEJ in this present case is based on Liu et al., (2014b) study that used rats with renal anemia. In humans, the standard FEJ dose is 20 mL. Since clinical trials have not been conducted on animals, particularly cats, the safest approach is to administer a low dose. However, conducting large-scale clinical trials with various doses in the future is necessary to determine the optimal and maximum safe dose for FEJ. The underlying mechanism also requires further investigation. Consequently, FEJ could be deemed a useful supplement for enhancing blood production in animals afflicted with *Anaplasma* sp-induced anemia.

In addition to causative therapy, proper attention must also be given to the general health status of the animal, including its hematological profile, in the treatment of anaplasmosis. Supportive therapy may be required to address hematological disorders such as anemia and thrombocytopenia. The use of traditional Chinese medicine FEJ, in this case, showed promising results in the treatment of such disorders following blood transfusion. Nevertheless, it is important to note that further large-scale clinical trials are necessary to substantiate the efficacy of this herbal medicine. This study is a preliminary report and it is suggested to carry out large-scale clinical trials with various doses.

Conflict of Interest

The authors declared that there is no conflict of interest.

Authorship contributions

Concept: P.R., Design: I.S., I.E., Data Collection or Processing: P.R., P.S., Analysis or Interpretation: M.P., I.E., Literature Search: P.S., I.S., M.P., Writing: P.R., P.S.

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