Successful Management of Immune-Mediated Hemolytic Anemia Secondary to Infection with *Cytauxzoon felis* and Feline Immunodeficiency Virus

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Abstract : *Cytauxzoonosis* is caused by *Cytauxzoon felis* (*C. felis*) in wild and domestic cats. However, cytauxzoonosis is uncommon in Asia. Additionally, clinical reports of *C. felis* infection along with associated complications are rare. A seven-year-old neutered male Maine Coon cat was presented with acute dyspnea and lethargy despite the absence of a history of overseas travel. Mild regenerative anemia and autoagglutination were detected in hematological investigations. The parasitic and viral PCR assays revealed infection with *C. felis* and feline immunodeficiency virus (FIV). Thoracic radiographs showed pleural effusion with secondary bacterial infection. Ultimately, a diagnosis of infection-induced secondary immune-mediated hemolytic anemia (IMHA) and pyothorax was established. The cat was treated with a combination of atovaquone, prednisolone, and cyclosporine over 6 months and the final treatment was completed 8 months after initiation of therapy. This is the first report of its kind demonstrating successful management of feline IMHA and fatal pyothorax induced by FIV and *C. felis* in South Korea.

Key words : anemia, atovaquone, *Cytauxzoon felis*, FIV, IMHA.

Introduction

Cytauxzoonosis is an emerging tick-borne feline disease caused by *Cytauxzoon felis* affecting wild and domestic felids (9). For many years, cytauxzoonosis in domestic cats was reported only in North and South America (8) and the species in European cases differ from *C. felis*, which causes infection and disease in the United States (13). *Dermacentor variabilis* and *Amblyomma americanum* have been shown to be the tick vectors for *C. felis* (21). Recent studies have shown that domestic cats can harbor subclinical infections and may act as reservoirs (8,12). In domestic cats, natural and experimental infections have led to a rapid course of illness and death, typically in fewer than 5 days (9,21). Information regarding the epidemiological distribution, clinical presentation, genetics, and pathogenicity of infection by *C. felis* in Asia is scant. The cat in the present case had no history of traveling abroad to known epidemic areas. We report the first *C. felis* infection case in South Korea.

Case Presentation

A 7-year-old neutered male Maine Coon cat was presented with a history of acute onset of dyspnea, lethargy, and anorexia. The cat was born and raised in South Korea and had never travelled abroad. No health issues had previously been diagnosed, and its past history was unremarkable. At physical examination, the patient was tachypneic and dys-

pneic with a mildly pale mucous membrane. Capillary refill time was approximately 2 sec. Moderate hypochromic anemia with mild neutrophilic leukocytosis was noted (Table 1). Abnormality of serum biochemistry was detected only decreased levels of albumin (2.1 g/dL; reference range: 2.2-4.0).

Thoracic radiographs verified the cause of dyspnea to be pleural effusion (Fig 1), which was sampled by therapeutic thoracocentesis for cytology and bacterial culture. The fluid was revealed to be an exudate containing degenerative neutrophils with phagocytized bacteria and sensitivity test was submitted (Fig 2).

The cat was hospitalized and oxygen therapy was started. Additionally, intravenous (IV) crystalloid fluid therapy was administered to correct the dehydration and provide fluid therapy maintenance. Antibiotic treatment with cefotaxime (50 mg/kg, IV, b.i.d.) and metronidazole (15 mg/kg, IV, s.i.d.) was started, and furosemide (4 mg/kg, IV, b.i.d.) and dexamethasone (0.5 mg/cat, IV, s.i.d.) were administered to treat the pleural effusion. After intensive care, the clinical signs improved, and then cardiac problems were ruled out by echocardiography.

The patient was discharged and CBC on day 10 showed more severe anemia (HCT: 20.6%; reference range: 30.3-52.3). A blood smear test for anemia revealed small inclusions within erythrocytes (Fig 3). The inclusions were annular, suggesting the possibility of small piroplasmid parasite infection. Marked agglutination of erythrocytes was also noted with saline dilution on microscope. A real-time polymerase chain reaction (PCR) panel (Anemia RealPCR™ Panel; IDEXX Reference Laboratories, Westbrook, ME, USA) confirmed *C. felis* and FIV (subtype-b) infection. Ultimately, *C. felis* and FIV infection-induced secondary IMHA

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Table 1. Summary of blood cell counts follow-ups from the presentation

Parameter (unit)	Day 0	2 weeks	1 month	2 months	8 months	Reference range
RBC (M/ μ L)	4.76	6.92	7.34	7.39	8.15	6.54-12.2
Hematocrit (%)	26.5	34.8	38.9	35.2	39.1	30.3-52.3
RETIC (K/ μ L)	120.4	9.7	29.3	14.0	11.6	3-50
Hemoglobin (g/dL)	8.1	11.5	12.8	11.6	13.2	9.8-16.2
MCV (fL)	55.7	50.3	53.0	47.6	48.0	35.9-53.1
MCHC (g/dL)	30.6	33.0	32.9	33.0	33.8	28.1-35.8
WBC (K/ μ L)	51.12	10.69	11.06	13.67	11.46	2.87-17.02
Neutrophils (K/ μ L)	3.38	9.95	5.87	10.80	5.01	1.48-10.29
Eosinophils (K/ μ L)	0.50	0.11	1.80	0.87	1.39	0.17-1.57
Monocytes (K/ μ L)	13.23	0.21	0.48	0.43	0.55	0.05-0.67
Lymphocytes (K/ μ L)	33.86	0.42	2.83	1.55	4.47	0.92-6.88
Platelets (K/ μ L)	244	471	319	341	277	151-600

RBC: red blood cells count; RETIC: reticulocytes; MCV: mean corpuscular volume; MCHC: mean corpuscular hemoglobin concentration; WBC: white blood cells count.

Fig 1. (A) Right lateral thoracic radiograph of a cat with fluid opacity in the pleural space. (B) Decreased pleural effusion and pulmonary edema 36 h after treatment.

Fig 2. Hematoxylin and eosin (H&E) stain of the pleural fluid, revealing large amounts of bacteria and degenerated neutrophils and macrophages ($\times 1,000$ magnitude).

Fig 3. Blood smear with H&E staining showing *Cytauxzoon felis* piroplasms (arrow) in erythrocytes ($\times 1,000$).

and pyothorax were diagnosed.

Treatment included oral atovaquone (15 mg/kg, p.o., t.i.d., Glaxo Wellcome, London, UK), azithromycin (10 mg/kg, p.o., s.i.d., Pfizer, NY, USA), prednisolone (2 mg/kg, p.o.,

b.i.d., Lloyd Inc, Shenandoah, USA), and cyclosporine (5 mg/kg, p.o., b.i.d., Chong Kun Dang, Seoul, South Korea) for *C. felis* infection-induced IMHA and doxycycline (5 mg/

kg, p.o., b.i.d., Parsippany-Troy Hills, NJ, USA) and metronidazole (10 mg/kg, p.o., b.i.d., Pfizer, NY, USA) for pyothorax. Two weeks after treatment, the patient exhibited excellent health, appetite was good, and parasitemia was absent according to a blood smear microscopic examination. Anemia was resolved (HCT: 34.8%; reference range: 30.3-52.3), and real-time PCR test yielded negative results. However, 3 weeks after treatment, the cat was presented with a new episode of vomiting twice a week. A feline pancreatic lipase immunoreactivity assay (SNAP fPLI kit; IDEXX Reference Laboratories) yielded abnormal results. Supportive therapy consisted of intravenous fluids, antiemetic drugs, and fresh frozen plasma to treat pancreatitis, which recovered rapidly without other clinical signs. Abnormalities revealed by blood work gradually resolved (Table 1). Blood work, including slide smear tests and complete blood count (CBC), was regularly checked (2 weeks, 1 month, 2 months, and 8 months later). No definitive organisms were observed on the smears and no protozoans were detected using real-time PCR test (IDEXX Reference Laboratories).

Clinical presentation, blood tests, morphological and molecular investigation confirm the presence of *C. felis* in cats. More specific and sensitive methods, such as PCR, can also be adopted for confirmation (4). In the present case, hemolytic anemia with intraerythrocytic inclusions and real-time PCR results indicated *C. felis* infection. The organism is an arthropod-borne organism, which may be one of the causes of secondary IMHA (8,9). Secondary IMHA in cats is relatively common compared to dogs and can be caused by infections (e.g., blood parasites and viruses), inflammations, drugs, and neoplasia (8,10,16,19). The present case was in emergency, because pyothorax occurred with dyspnea and severe respiratory distress in the cat. Pyothorax may be caused by immunosuppressive conditions. The cat needed aggressive antibiotic therapy based on a sensitivity test with the removal of pleural effusion. Secondary IMHA caused by immunosuppressive agents and anemia caused by infectious parasites were also treated at the same time. The urgent and emergency status was managed effectively and the patient became stable.

Discussion

Cytauxzoon sp. infection has been reported to be significantly related to FIV infection (7,15), which frequently causes immune suppression in infected cats. Clinical signs of FIV infection can arise from direct viral effects or other infections secondary to the development of immunodeficiency (15,17). In this case, immune suppression caused by FIV may be a factor for susceptibility to *C. felis* and bacterial pleural infection, or FIV could directly cause IMHA through simultaneous infection with *C. felis*. Therefore, both infectious agents could exert effects on systemic immunity. Chronic infections or infections caused by opportunistic pathogens such as FIV can trigger monocytosis and lymphocytosis in some cats (14). In this case, blood work revealed monocytosis and lymphocytosis. However, additional diagnostic approaches may identify treatable etiologies because, in many cases, the clinical signs associated with FIV can be caused by opportu-

nistic infections.

Cytauxzoonosis caused by *C. felis* has been considered a fatal disease, with mortality approaching 90% among infected cats (3). Treatment for *C. felis* can be problematic because the infection is not typically resolved by standard cytauxzoonosis therapies. The cat in this case was treated with atovaquone and azithromycin, and the response was favorable. A recent study demonstrated that therapy combining atovaquone and azithromycin is a safe and effective treatment for cytauxzoonosis in cats (2). Thirty-two of 53 domestic cats (60%) treated with atovaquone and azithromycin survived to discharge, whereas only 26% of domestic cats (7 of 27 cats) treated with imidocarb survived (5). Atovaquone targets *C. felis* cytochrome *b*, and azithromycin targets the mitochondrial ribosomes of the parasite (11). However, atovaquone remains an expensive drug, and few reports have described its side effects (6). In this case, 3 weeks after therapy with atovaquone, the cat was diagnosed with acute pancreatitis. In human medicine, atovaquone has been reported to induce pancreatitis (1). Another recent study also reported a potential association between pancreatitis and IMHA in cats (22).

Conclusion

In conclusion, this case report is the first to describe *C. felis* infection with FIV and the subsequent occurrence of secondary IMHA in a domestic cat in South Korea. The fatal systemic complications caused by infectious agents were successfully managed with anti-parasitic drugs, antibiotics, and immunosuppressive agents. The transmission epidemiology of *C. felis* infection in South Korea remains unclear and additional studies are needed.

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Conflict of Interest

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

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