

Rapid Resolution of severe feline infectious peritonitis using natural products

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Short report

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Abstract

This is the first report of a successful treatment of a severe feline infectious peritonitis (FIP) case using Lianhuaqingwen (LH) capsule, a Chinese patent medicine “natural products” and it has been used for the treatment of coronavirus disease 2019. A 1-year-old cat was diagnosed FIP and presented with severe ascites, aphagia, inflammation, breathing difficulties and weight loss. Within 22 days of LH capsule treatment, all indicators of the cat eventually returned to normal, and the ascites gradually disappeared. This case report is the first description of the clinical recovery features of a cat with a systemic FCoV infection using LH capsules.

Background

Feline coronavirus (FCoV), a RNA alpha coronavirus, is a highly infectious enteric virus which is a member of the Coronaviridae family of the order Nidovirales^[1,2] from the epidemiological point of view, FCoV can infect cats of all ages. Most cases occurred in cats aged 1-2 years and older than 11 years. It can lurk in the intestines for a long time, and caused feline infectious peritonitis (FIP) in a weakened immune or stressed state^[3], which known as an “incurable disease” for cats with nearly 100% death rate.

Although FIP treatment using new therapies have previously been reported^[4], but the efficacy and safety of broad-spectrum antiviral drugs targeting FCoV need further investigation. The GS441524 shows great promise for the treatment of cats with feline infectious peritonitis^[5] but is not currently approved by the FDA. What’s more, the treatment expense of FIP cost \$5,000 to \$9,000, it is a financial burden for most of ordinary family. LH capsule, one of natural product, was a manufactured product of the TCM prescription marketed in China that could significantly inhibit SARS-CoV-2 replication^[6]. LH capsule exerts its anti-influenza activity by regulating the immune response to interfere with both viral and host reactions^[7]. The LH capsule has been endorsed by the National Health Commission for treatment of Covid-19, the prospective randomized study including 284 patients conducted in multicenter settings suggest that the treatment with LH capsules for 14 days markedly improved the rate of symptom recovery^[8].

Case Report

"Big tangerine" is a 1-year-old male neutered Chinese garden Cat (*Felis catus*) from a household of four cats (2 *Felis catus*, 2 British Shorthairs). "Big tangerine" was found appetite and weight loss for several weeks. But other cats are normal. On November 15, 2020, he was taken to Guaiguai Pet Hospital (Tianjin, China). A large amount of ascites was found by abdominocentesis. FCoV was detected by RT-PCR in ascites and the FIP was diagnosed. The symptoms include aphagia, diarrhea, abdominal distension (ascites), lethargy, emaciation and breathing difficulties (**Fig.1**)

The RT-PCR of ascites indicated a high viral load of FCoV (Ct value 21.73). The laboratory testing results reflected elevated levels of white blood cells (WBC) and neutrophile granulocyte (Neu), indicating severe inflammation of the cat (**Table 1**). In addition, there were alteration in immune function measures: levels

of lymphocyte rate (Lym%) significantly decreased, which indicated that the lymphocytes depletion caused by the virus. Given the cat's diarrhea and breathing difficulties, the SAA (markers of inflammation and tissue injury) was tested (**Fig 2A**). The patient received supportive care, including normal saline and protein for nutrition. Given the severe clinical presentation, the veterinarian recommends euthanasia or experimental drug GS-441524 for the cat. In consideration of the high price of the treatment with GS-441524, cat guardians have to seek to other therapies.

The guardian turned to look for help from traditional Chinese medicine. Given the cat's coronavirus infection and breathing difficulties, the LH capsule was recommended, which has been prescribed in treating disease of respiratory system and endorsed by the National Health Commission for treatment of covid-19. The FCoV and SARS-CoV-2 share partly RNA sequence identity, therefore, drug targeting viral of SARS-CoV-2 are likely to be effective for FCoV.

On November 17, 2020, the Cat "Big tangerine" was given LH capsule (**table 2**) three times a day, 4 capsules at a time (0.35 g per capsule) combined with antipyretics, no adverse events were observed. 24 hours later (Nov, 18, day 1), his shortness of breath relieved. He just received liquid food during these times for his continued anorexia and diarrhea. 48 hours after taking medicine (Nov, 19, day 2), the patient's condition remained largely stable, and his first loose stools was reported; meanwhile his mental state is a bit better. He could sit licking his hair, instead of lying on the ground and panting just like a few days before. 3 days after taking the medicine (Nov, 20th), he was observed to feed himself (though in small amounts). Within the next 7 days of treatment, his appetite improved and ascites gradually decreased. His stools have been loose during this time. At the beginning of December, he was given a palpation examination, which showed the ascites almost completely disappeared. As shown in **Fig.1**, with the disappearance of ascites, he was estimated to be about 1.5 kg lighter, which was the lightest weight during the whole process. On Dec, 2nd, all symptoms have resolved. He began to run and play with the other cats.

Outcome and Follow-up

The patient continues to take LH capsule medication daily until on Dec.9th. The medication period lasted for 3 weeks and the symptoms did not recur after the drug withdrawal. He was taken to Guaiguai Pet Hospital on Jan, 3rd and his blood counts and SAA level lie within the normal range, apart from total protein (8.2g/dL, Normal 5.4-8.2) and blood urea nitrogen (42mg/dL, Normal 10-30). (**table 3 & Fig. 2**). His specimens later tested negative by FCoV RT-PCR which meant the FCoV viral load was lower than the limit of detection. The symptoms did not recur until the report submission (Mar.17th).

Discussion

FIP is a fatal disease in cats caused by FCoV, which is lurking in the intestinal system. FIP is still a terminal disease with a variable time of death, over 95% of cats died in days to months after diagnosis^[9]. The symptoms of FIP in cats comes in two forms: dry and wet^[10]. The most prominent

symptom of wet FIP is large effusion in the chest and abdomen^[11]. The glucocorticoids such as prednisolone are used to attenuate symptoms. While once FIP ascites is diagnosed, veterinarian may generally recommend euthanasia, as there are few successful cure cases.

At present, some effective therapies have been evaluated. For instance, the successful treatment of FIP using GS441^[12], GC376^[13], or oral adenosine nucleoside analogue^[14] was reported recently. GS441 combined with antibiotic therapy, recommended by many veterinarians, have shown good therapeutic effect. GS441 is the precursor of remdesivir, which is previously used in the COVID-19 treatment. The course of GS441 treatment takes 1–3 months, which may spend about \$5,000 to \$9,000 in China. Unfortunately, because of price and access channel (GS441 is not officially listed yet), many cat guardians give up this proven effective treatment.

In this case, the veterinarian fears it's hard to survive a week without using GS441. Hence the cat guardians hoped to seek other therapies. LH Capsule, a Chinese patent medicine composed of 13 herbs is a commonly used broad-spectrum antiviral medicine developed from traditional Chinese medicine formula^[15]. It has been used to treat a series of influenza viruses such as viral cold, pneumonia and so on^[16, 17]. Pharmacological and clinical trials showed that it can significantly relieve the inflammatory response by inhibiting virus replication and reducing the cytokine release from host cells^[17]. And is also recommended as one of the COVID-19 adjuvant therapy drugs^[6, 18, 19]. Hence, we initially tried to use this medicine to alleviate the inflammatory response and symptoms caused by FIP. Surprisingly, within the first week of treatment, there was a significant improvement on a daily basis. Therefore, we reported this case in detail for the reference of researchers.

It is worthy to mention several strengths of this case report. First, it is cheap and easily available for the cat guardians, which can benefit more animals. Especially in China, where pet populations have skyrocketed in the last decade, while the existing pet hospitals are inadequate to meet the needs of pet medical care. Meanwhile, many pets have to face euthanasia since their guardians cannot afford the expensive drugs. Second, LH takes effect within a week and heals FIP in about a month. While the recommended duration of administration of GS-441524 was 84 days.

Although a decision to administer LH for compassionate use was based on the case cat's worsening clinical status and an optimistic result obtained, we should treat it with caution. Further study are needed to determine the safety and efficacy of LH for treatment of cat's with feline infection. It is notable that although the specimens were negative for FCoV, the TP and BUN is a little higher than the normal value. We cannot yet be sure it's due to LH capsules or the virus. According to the previous clinical studies, we did not find that LH capsule has the side effect of causing liver injury in human. But obviously, more cases and BUN levels in future cases following this FIP treatment protocol require further investigation. In order to avoid the special reaction, we extended the trial to 3 cats, and all of them recovered in about a month. Due to incomplete test data of some cats, we could only put them in supplementary materials for reference.

Conclusions

To our knowledge, this is the first case of nature products being used to remit (or clinical cure) a cat of FIP. More cases following this FIP treatment protocol require further investigation.

Abbreviations

FCoV: Feline coronavirus ;

FIP : Feline infectious peritonitis

LH capsule: Lianhuaqingwen capsule

TCM: Traditional Chinese medicine

Declarations

Ethics approval and consent to participate

The animal medication was approved by the Committee of Ethics of Animal Experimentation of the Beijing University of Chinese Medicine.

Consent for publication

All the co-authors were aware of this submission and approve for publication.

Availability of data and materials

Data sharing is applicable to this article.

Competing interests

The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Authors' contributions

Clinical Data was obtained by Fang Lu and Xin Zhao. Lili Zhu and Xin Du served as medical advisor. Manuscript was Prepared by Yue Zhang, Yuanfeng Zhang and edited by Tao Lu. All authors read and

approved the final manuscript.

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Tables

Table 1. Laboratory data pertinent to FIP treatment monitoring

Test item	Day0	Day 30	Reference ranges	Units
White Blood Cells (WBC)	44.8	13.85	5.5-19.5	%
Neutrophile granulocyte rate (Neu%)	94.1	76.2	38-80	%
lymphocyte rate (Lym%)	2.2	17.2	12-45	%
Monocyte rate (Mon%)	2.3	2.6	1.00-8.00	%
Eosinophilic granulocyte rate (Eos%)	1.4	3.9	1.00-11.00	%
Basicyte rate (Bas%)	0	0.1	0.00-1.20	%
Neutrophile granulocyte count (Neu#)	42.16	10.56	3.12-12.58	10 ⁹ /L
Lymphocyte count (LYM#)	0.98	2.38	0.73-7.86	10 ⁹ /L
Monocyte count (Mon#)	1.04	0.36	0.07-1.36	10 ⁹ /L
eosinophilic granulocyte count (Eos#)	0.62	0.54	0.06-1.93	10 ⁹ /L
Basicyte count (Bas#)	0	0.01	0.00-0.12	10 ⁹ /L
Red blood cell (RBC)	5.83	7.23	4.62-10.20	10 ¹² /L
Hemoglobin (HGB)	85	117	85.0-153.0	g/L
Hematocrit (HCT)	24.8	34.6	26.00-47.00	%
Mean Corpuscular Volume (MCV)	42.5	47.9	38.00-54.00	fL
Mean Corpuscular Hemoglobin (MCH)	14.6	16.1	11.89-18.00	pg
Mean Corpuscular Hemoglobin Concentration (MCHC)	342	337	290.0-360.0	g/L
Coefficient of variation of red blood cell distribution width (RDW-CV)	20.6	16	6.50-23.00	%
red blood cell distribution width (RDW-SD)	40.5	35.5	19.30-43.10	fL
Platelets (PLT)	187	333	100.0-518.0	10 ⁹ /L
Mean Platelet Volume (MPV)	11	11.7	9.90-16.30	fL
Platelet Distribution Width (PDW)	10.2	14.7	12.00-17.50	
Plateletocrit (PTC)	0.21	0.39	0.09-0.70	%

Table 2 Formulation of Lianhuaqingwen capsule Granule

Ingredient *	Components	%
<i>Forsythia suspensa</i>	Dried Fruit	12.7
<i>Lonicera japonica</i>	Dried flower bud or opening flower	12.7
<i>Ephedra sinica</i>	Dried herbaceous stem	4.2
<i>Isatis indigotica</i>	Dried root	12.7
<i>Pogostemon cablin</i>	Dried aerial part	4.2
<i>Rheum palmatum</i>	Dried root and rhizome	2.5
<i>Glycyrrhiza uralensis</i>	Dried root and rhizome	4.2
<i>Dryopteris crassirhizoma</i>	Dried rhizome and frond bases	12.7
<i>Rhodiola crenulata</i>	Dried root and rhizome	4.2
<i>Houttuynia cordata</i>	Dried aerial part	12.7
<i>Prunus sibirica</i>	Dried ripe seed	4.2
gypsum	CaSO ₄ ·2H ₂ O	12.7
1-menthol	C ₁₀ H ₂₀ O	0.4

* LH capsules were manufactured based on The Pharmacopeia of People's Republic of China.

Table 3. Laboratory data pertinent to FIP treatment monitoring

Test item	Day 30	Reference ranges	Units
Albumin ALB	4	2.2-4.0	g/dL
Alkaline phosphatase ALP	38	10-90	U/L
Alanine aminotransferase ALT	60	20-100	U/L
Amylase AMY	1082	300-1100	U/L
Total bilirubin TBIL	0.5	0.1-0.6	mg/dL
Blood urea nitrogen BUN	42	10.0-30.0	mg/dL
Calcium CA	11.7	8.0-11.8	mg/dL
Phosphate PHOS	4.5	3.4-8.5	mg/dL
Creatinine CRE	1.5	0.3-2.1	mg/dL
Glucose GLU	101	70-150	mg/dL
NA+	146	142-164	mmol/L
K+	4	3.7-5.8	mmol/L
Total protein TP	8.2	5.4-8.2	g/dL
Globulin GLOB	4.2	1.5-5.7	g/dL

Figures

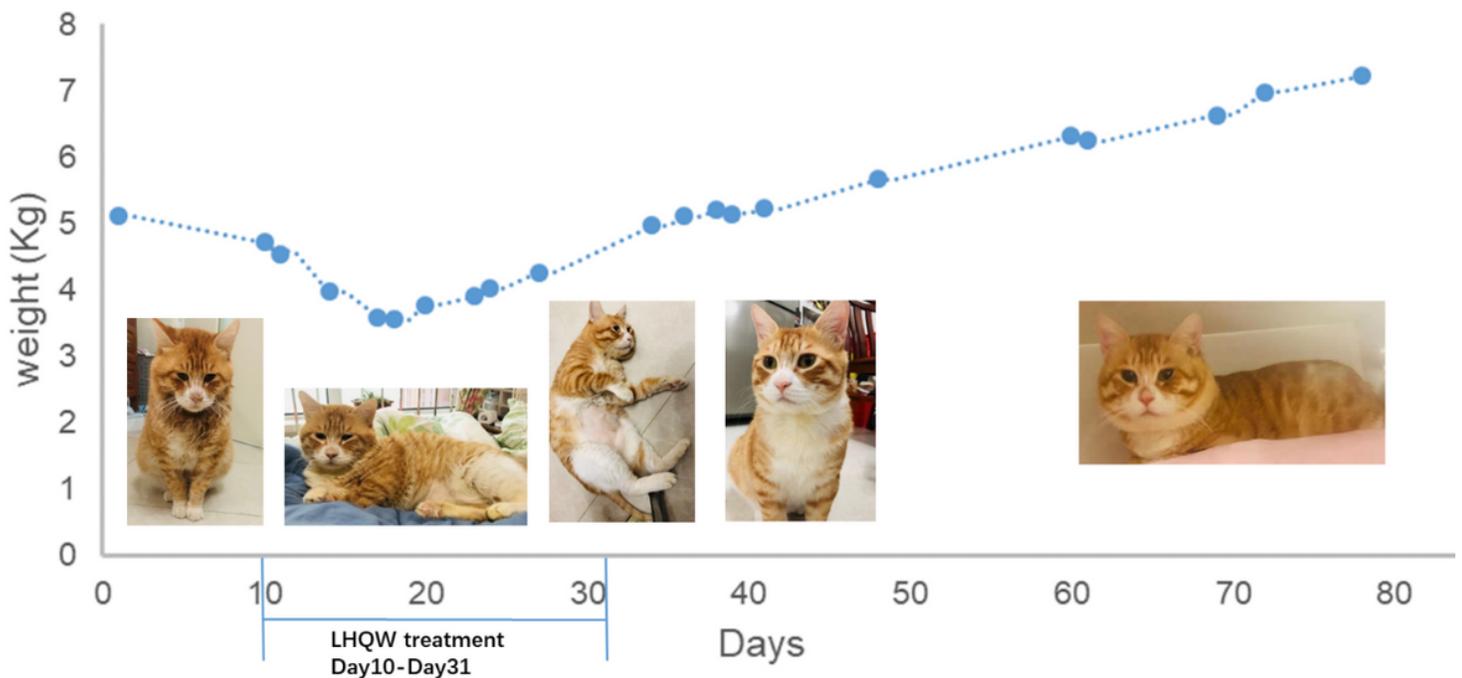


Figure 1

Body weight of the cat before, during and after recovery from FIP and the timeline. The cat's weight is shown on the graph above: Day 0 represents FIP diagnosis at the clinic. LH treatment was given between Days 1 to 22. The cat lost 1.5 kg of weight during drain ascites treatment using LH (Day 1 to 15). The cat's weight rapidly increased following the body returning to normal, and continually increased after the treatment stopped, until leveled out at around 7.2 kg now.

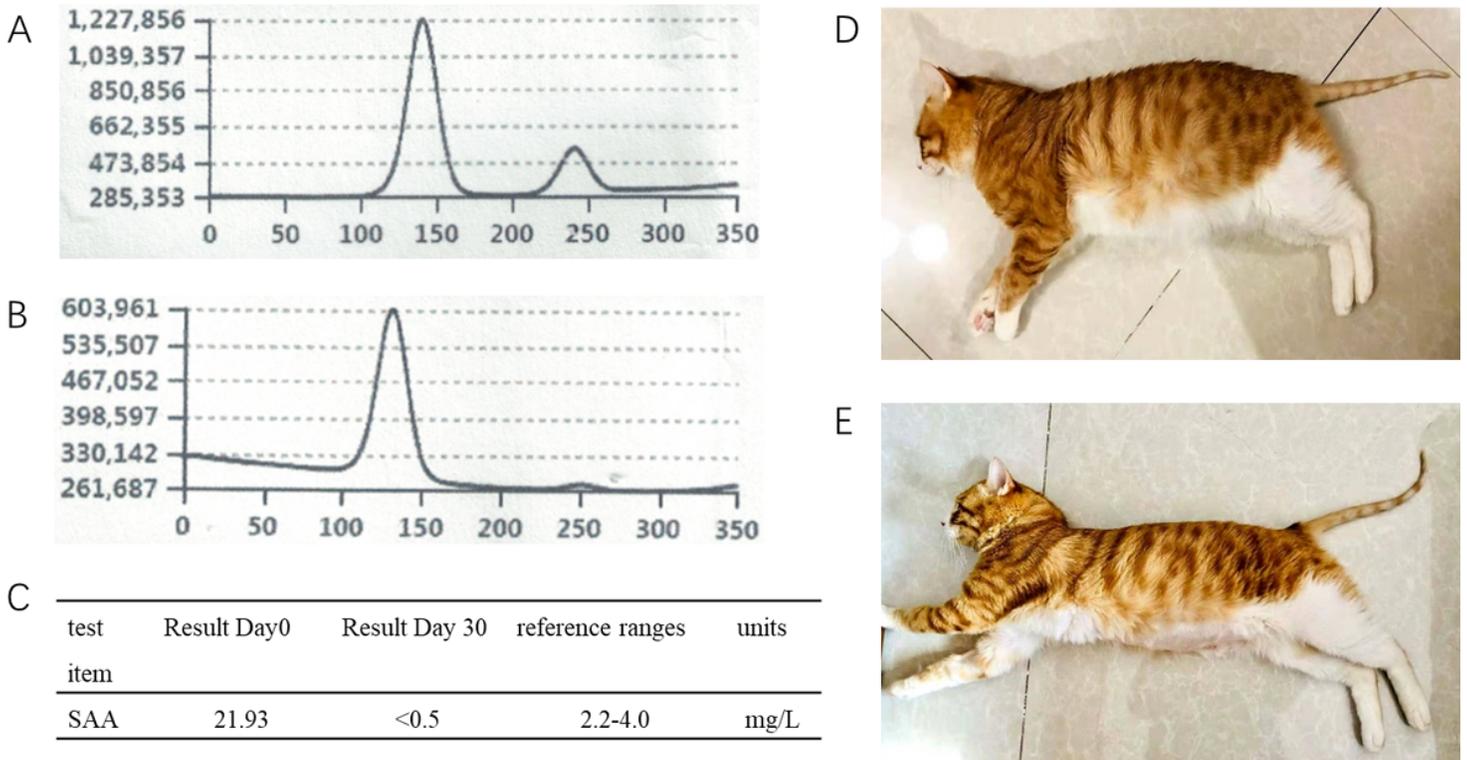


Figure 2

A, B, C SAA value in Day 0 is 21.93 mg/L and <0.5 mg/L in Day 30. D, The swollen abdomen and ascites in Day 0. E, Ascites disappeared in Day 21.