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Effect of Polyprenyl Immunostimulant on the survival times of three cats with the dry form of feline infectious peritonitis

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Feline infectious peritonitis (FIP) is considered a fatal disease. Three cats with dry form FIP were treated with Polyprenyl Immunostimulant. Two of the three cats are still on treatment and are alive and well 2 years after diagnosis. The third cat survived 14 months but was treated for only 4.5 months. Further studies are necessary to assess the potential of the Polyprenyl Immunostimulant.

Feline infectious peritonitis (FIP) is a devastating disease seen more frequently in young cats. It is due to a mutated form of feline coronavirus that induces a pyogranulomatous perivascular reaction on serosal surfaces of the abdomen and thorax. The large amounts of exudate produced from these lesions result in the 'wet' form of FIP. The 'dry' or non-effusive form is characterized by a pyogranulomatous infiltration in lymph nodes, kidneys, liver, eyes, and brain that produces inflammatory masses in the organs. The dry form is considered a less aggressive form of the disease in which there is some immune control of the inflammatory process.[1]

FIP has long been considered an incurable disease. The only report of long-term control is a non-placebo controlled study done by Dr Ishida[2] using glucocorticoids and recombinant feline interferon-omega. This treatment produced 2-year remissions in 4/12 cats with FIP. In a placebo controlled, double blind study of 37 cats with mainly the effusive form FIP treated with steroids, amoxicillin/clavulanic acid and +/− recombinant feline interferon-omega; there was no difference between the placebo group and the group treated with recombinant feline interferon.[3] Median survival time for all cats was 9 days with the longest surviving cat living for 200 days. The cat that survived 200 days was in the treatment group. Feline interferon is not available in the United States.

The objective of this study was to assess the effect of the Polyprenyl Immunostimulant on survival time in cats with the dry form of FIP.

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Materials and methods

Treatment

Polyprenyl Immunostimulant is an investigational veterinary biologic manufactured by Sass & Sass, Inc comprising a mixture of phosphorylated, linear polyisoprenols. The agent has low toxicity and is orally absorbed.[4] The substance was shown to upregulate biosynthesis of mRNA of Th-1 cytokines[4,5] and was used for treatment of a number of viral diseases.[6] The substance was administered to the cats in a concentration of 2–4 mg/ml; administration routes and frequencies are described for each case study.

Signalment and selection criteria

Cats were considered eligible for this initial study if there was histologic/histopathologic evidence of lesions compatible with FIP. Adequate supportive tests such as coronavirus antibody titers and polyclonal gammopathy were required as well as tests that excluded other disease processes.

Results

Cat 1

An 11-month-old, 1.8 kg, female domestic shorthair cat from a multiple cat household was brought to the University of Tennessee Veterinary Teaching Hospital on July 29, 1999 because of an abdominal masses found during ovariohysterectomy (OHE). The masses bled easily when touched, and the OHE was aborted. The

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cat had been less active than normal for several months. The largest of the abdominal masses was approximately 5 × 7 cm. On examination at the Veterinary Teaching Hospital, the cat was depressed but responsive. The cat had a hematocrit of 21% (normal range 27.7–46.8), a neutrophilia of 15,930 cells/μl (normal range 3000–13,400) and a lymphopenia of 880 cells/μl (normal 2000–7200). The cat was negative for feline leukemia virus and had a coronavirus antibody titer of 1:5120. Significant changes on plasma chemistry panel were hyperglobulinemia of 5.9 g/dl (normal 2.9–5.1), hypoalbuminemia of 1.9 g/dl (normal 2.5–4.5) and a total bilirubin of 1.7 mg/dl (normal of 0–0.2). Abdominal ultrasonography localized the masses to the area of the mesenteric lymph nodes. The masses incorporated several loops of small intestine. Cytology obtained by needle aspirates of the masses was designated as granulomatous lymphadenitis. A clinical diagnosis of FIP was made. A poor prognosis was given the owners, and the cat was started the treatment on August 2, 1999 at a dose of 1 mg/kg twice a day of Polyprenyl Immunostimulant diluted to 3 ml with saline and given subcutaneously. Over the next 2.5 months, the cat improved and was eating well. Body weight increased to 2.0 kg. The abdominal masses were unchanged as assessed by abdominal palpation. The coronavirus antibody titer dropped from 1:5120 to less than 1:40. The globulin levels continued to increase reaching 9.4 g/dl. The cat was spayed and the masses were biopsied. Biopsy was assessed as marked pyogranulamatous inflammation highly suggestive of FIP. The cat was continued on the Polyprenyl Immunostimulant for another 2.5 months and did well. The treatment was discontinued because family problems precluded returning the cat to the University of Tennessee for re-evaluation. The cat was returned for re-evaluation 14 months after initial evaluation. She had been off the Polyprenyl Immunostimulant for 9 months. The cat started getting ataxic the month before re-evaluation. The cat had lost 0.5 kg over the last 11 months and had diarrhea. The Polyprenyl Immunostimulant was restarted 3 weeks before re-evaluation but no improvement was noted. Euthanasia was performed. At necropsy, there was 15 ml of clear fluid in the abdomen and the small intestine was markedly thickened. There was a severe lymphoplasmacytic infiltrate with lesser numbers of macrophages and neutrophils. A similar infiltrate was found in the meninges. The final diagnosis was FIP. The cat survived over 14 months from the start of treatment.

Cat 2

A 3-year-old, 4.3 kg, male-castrated domestic shorthair cat was seen on April 28, 2006 for a 0.7 kg weight loss over the previous 2 weeks. The cat had a scruffy appearance and a 4 cm in diameter mid-abdominal mass was palpated. The cat had an increase in plasma proteins of 9.3 g/dl (normal range 5.2–8.8) with an albumin of 2.7 g/dl (normal 2.5–3.9) and a plasma globulin concentration of 6.6 g/dl (normal 2.3–5.3). The initial coronavirus antibody titers were <1:40. An exploratory surgery on May 11 identified the mass as a greatly enlarged mesenteric lymph node. The mass was characterized as a severe chronic-active pyogranulomatous necrotizing lymphadenitis. The pathologist commented that the changes are fairly typical of FIP virus infection. Special stains and bacterial cultures did not identify fungal, mycobacterial or bacterial infection. The tissue was positive for coronavirus antigen by immunohistochemistry. A clinical diagnosis of FIP was made, and the cat was treated with Polyprenyl Immunostimulant at a dose of 3 mg/kg given orally twice a week starting on June 7. Before starting therapy, a repeat serum coronavirus antibody titer was positive at 1:1600. A serum protein electrophoresis had a broad based polyclonal gammopathy 2.98 g/dl (normal 0.5–1.9) and an increase in α-2 globulins of 2.22 g/dl (normal 0.2–1.5). On re-examination 3 months after starting the Polyprenyl Immunostimulant treatment, the mass was smaller (approximately 2.5 cm in diameter) and the gammaglobulin concentration had decreased to a normal level at 1.85 g/dl and the α-2 globulin was 1.82 g/dl. The cat was continued on the Polyprenyl Immunostimulant. In February 2007, the cat was clinically normal. The plasma globulin concentration was normal at 4.0 g/dl and the coronavirus antibody titer was positive at 1:1600. The cat has been continued on the Polyprenyl Immunostimulant treatment, and at the last conversation with the cat's veterinarian in July 2008 the cat appeared normal and is doing well.

Cat 3

A 2-year-old male-castrated, 3.7 kg, Abyssinian cat was seen on February 6, 2006 for a routine evaluation to be considered as a blood donor. The cat had neutrophilia of 17,380 cells/μl (normal range 3000–13,400 cells/μl), hyperproteinemia of 10.1 g/dl (normal 6.7–8.5), a globulin of 7.6 g/dl (normal 2.9–5.5) and hypoalbuminemia of 2.5 g/dl (normal 2.9–4.3). A mid-abdominal mass was palpated and identified on radiographs and ultrasonographic imaging as involving mid-abdominal lymph nodes. The mass was 23-mm in the longest diameter. Cytology of aspirates of the mass indicated a suppurative or pyogranulomatous lymphadenitis. The eyes were normal. The cat was started on azithromycin for 10 days awaiting results of pending tests. The cat did not have feline leukemia virus antigen on an enzyme-linked immunosorbent assay (ELISA) test and the feline immunodeficiency virus antibody titers were negative. The increase in globulins was due to a polyclonal gammopathy with a concurrent increase in α-2 globulins. The serum coronavirus antibody titer was greater than 1:2560. A clinical diagnosis of dry form FIP was made. On February 28, 2006 the cat was started on Polyprenyl Immunostimulant given orally at a dose of 3 mg/kg twice a week. The frequency was increased to three times a week in June 2006 because the mass

was bigger on palpation and gammaglobulin concentration had increased from 3.9 to 6.3 g/dl (normal 0.5–2.3). Coronavirus antibody titers have remained greater than 1:2560 and the globulin concentrations have slowly but steadily increased. The electrophoresis done on January 17, 2008 had a gammaglobulin concentration of 6.8 g/dl. In March 2008, the cat had an episode of retinopathy and uveitis that was consistent with FIP. The eye changes responded to topical steroid therapy. The cat was clinically normal on June 2, 2008 over 27 months since the initial diagnosis and the start of Polyprenyl Immunostimulant in spite of persistent neutrophilia, hypergammaglobulinemia and a coronavirus antibody titer of $\geq$1:2560.

Discussion

It is generally accepted that FIP is a fatal disease. A 2008 review article on treatment of cats with FIP states that 'there is currently no effective therapeutic regime for control of FIP'.[7] When a treatment affects the expected course of the disease process, the initial consideration is that an incorrect diagnosis was made. We believe that the clinical findings in these three cats strongly support the diagnosis of FIP.

Making a definitive diagnosis of the dry form of FIP is difficult. The diagnostic work-up for the three cats was somewhat different but cytologic or histologic findings consistent with FIP were found in each cat. After the initial diagnostic period, the cats were only treated with the Polyprenyl Immunostimulant. If other pyogranulomatous diseases were present, signs of other conditions should have appeared over the years of treatment. A polyclonal gammopathy was noted in all three cats. In cat 1, the diagnosis was confirmed at necropsy and the lymph node biopsy was assessed as FIP. In cat 2, the histologic changes were consistent with FIP and coronavirus antigen was found in the granulomatous lesions. In cat 3, the pyogranulomatous lymphadenitis, the persistently increased coronavirus antibody titers and the polyclonal gammopathy strongly support the diagnosis of FIP. Demonstration of coronavirus antigen on cytology would have enhanced the certainty of the diagnosis. All cats tolerated the treatment well and no adverse effects were attributed to the Polyprenyl Immunostimulant.

There are no experimental models for dry form FIP, therefore, the studies must be undertaken in naturally occurring disease. Our experience in the treatment of wet form FIP with Polyprenyl Immunostimulant has been dismal probably because the rapid progression of the disease process does not allow time for an immune response to modify the course of the disease. Survival times for cats with FIP are generally short. In the study of interferon-omega treatment of FIP the median survival times was 9 days with the longest surviving cat living 200 days.[3] Most of the cats in this study had the effusive form of FIP. It is difficult to predict the survival times for cats with dry form FIP but Addie and Jarett[1] state that 'cats with non-effusive FIP can survive many weeks or months'.[1] The survival times in our study cats is longer than would be expected from our experience and from the veterinary literature but there was not a placebo control group.

Polyprenyl Immunostimulant appears to control the disease process in cats with the dry form of FIP. Further studies are needed to assess this treatment. Currently, Polyprenyl Immunostimulant is an investigational veterinary biologic and is not commercially available but can be obtained by contacting Dr Al Legendre at alegendr@utk.edu, or the manufacturer (Sass & Sass, Inc, info@sassandsass.com). Only cats with well documented dry form FIP will be considered for inclusion into a subsequent study.

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References

1. Addie D, Jarett O. Feline coronavirus infections. In: Greene CE, ed. Infectious diseases of the dog and cat. St Louis Missouri: Saunders-Elsevier, 2006: 88–102.
2. Ishida T, Shibanai A, Tanaka S, et al. Use of recombinant feline interferon and glucocorticoids in the treatment of feline infectious peritonitis. *J Feline Med Surg* 2004; **6**: 107–9.
3. Ritz S, Egberink H, Hartman K. Effect of feline interferon-omega on the survival time and quality of life of cats with feline infectious peritonitis. *J Vet Intern Med* 2007; **21**: 1193–7.
4. Danilov LL, Deeva AA, Kuritz T, et al. Therapeutic composition and methods. US Patent 6,525,035, 2003.
5. Narovlianskiy AN, Ershov FI, Kuritz T. Cytokine mRNA profile in cell line MG-63 with and without induction with phosprenyl and kagotsel. *Abstr Eur Cytokine Netw* 1998; **9**: 515.
6. Deeva AV, Ozherelkov SV, Novikov AY, et al. Phosprenyl – an antiviral substance with a broad spectrum of action. *Veterinar (In Russian)* 1998; **3**: 15–21.
7. Hartman K, Ritz S. Treatment of cats with feline infectious peritonitis. *Vet Immunol Immunopathol* 2008; **123**: 172–5.