Every Cat is a Herpes Candidate FHV-1: Can One Virus Cause all Those Diseases?

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Feline herpes virus- 1 (fhv-1)

FHV-1 is a virus with an affinity for sensory nerves and epithelial tissue. Transmission is primarily by ocular and oronasal secretions of infected queen to kitten or infected cat to naïve cat or kitten. The virus may also be transmitted by fomites such as human hands. The virus can live in a moist environment for up to 18 hours but is easily killed by hand washing and soap and disinfectants.

FHV-1 is the most common infectious disease in cats. FHV-1 directly or indirectly accounts or over 90% of the feline corneal and conjunctival diseases. Therefore it is of major importance in feline ocular diseases. The diseases directly related to the active viral infection include ophthalmia neonatorum, rhinotracheitis (with bilateral keratoconjunctivitis), acute conjunctivitis, periocular dermatitis, anterior uveitis, and ulcerative keratitis. There are sequelae due to prior or concurrent infections. These include eosinophilic keratitis, corneal sequestration, keratoconjunctivitis sicca (KCS), conjunctival cysts, symblepharon, and Mycoplasma spp., resulting in keratomalacia. Clinical signs begin 2-9 days after inoculation. Overt clinical disease may last 10-14 days or the disease may become subclinical. It is estimated that 80% of the exposed cats become latently infected as the inactive virus resides in the trigeminal ganglion and corneal stroma. Of these cats, 45% will have spontaneous reactivation of the virus sometime during their life. They may develop overt clinical signs or be asymptomatic shedders of the virus. Reactivation is caused by emotional, physical, or drug induced stressors. It has been reported that as high as 70% of the initially affected animals will shed virus in the face of corticosteroid therapy. Many of these surely will have recurrence of clinical signs.

Feline herpetic keratitis

There are three forms of ulcerative keratitis seen in the adult cat. All three forms may be unilateral or bilateral. The cat may be presented with severe blepharospasms, conjunctival hyperemia, or serous to seromucoid ocular discharge. When the cornea is closely examined, small linear punctate or branching ulcers termed dendritic ulcers may be found without associated corneal vascularization or edema. Unstained, these ulcers will have a ground glass appearance. Early cases may have only the pain and severe conjunctival involvement without corneal ulcers. Some cases may have only corneal epithelial erosions. Only outer epithelial layers are lost, therefore these cases would be fluorescein negative. The necrotic and damaged epithelial layers would stain with a vital stain such as rose bengal. Cases may also present with no subjective signs of pain, little to no conjunctival hyperemia yet multiple linear and punctate superficial ulcers and/or erosions.

In a more chronic form of the disease, the ulcers may coalesce, forming larger superficial ulcers termed geographic ulcers. In this form, superficial blood vessels and mild corneal edema may be present.

In severe cases, the corneal stroma is involved. In this form, interstitial edema may be severe, preventing visualization of the anterior chamber. Corneal ulcers extend into the stromal layers and deep limbal vascularization is present. This form may involve not only herpes virus infection but also an immune reaction or the rare secondary bacterial infection.

In all three forms of the disease, tear production may be decreased. Secondary anterior uveitis may be present especially with the stromal form of the disease.

Testing

Diagnostic tests are available. Some tests are lengthy and expensive while other tests have a high incidence of false negative results. The different tests include conjunctival smears for cytology and indirect fluorescent antibody tests, virus isolation, and serologic tests for serum neutralizing antibodies procedures have proven to be the most reliable. It is more sensitive and has fewer false negative results then the IFA test. Its drawbacks include the fact that few laboratories do the test and false negatives are still possible. By far the most reliable test for FHV-1 involves polymerase chain reaction procedures. Refined PCR testing protocols have been developed with reported 100% specificity and very high sensitivity. But, keep in mind the high percentage of asymptomatic carriers and that the test is for the virus and not the “disease”.

Response to therapy and clinical signs may be the best diagnostic test. If the condition worsens with topical corticosteroids, a herpes infection is frequently indicated. Topical antibiotics may either result in no improvement or worsen the condition. With specific antiviral drugs, response to therapy is usually rapid. Within 48 hours, hyperemia and blepharospasms will reduce.

Treatment

Topical medications are available with specific antiviral activity: adenosine arabinoside (Vira A®, Parke-Davis-often unavailable), trifluridine (Viroptic®, Monarch Pharmacy), trifluridine generic, idoxuridine (IDU) solution and ointment generic, cidofovir (0.5% formulated), and ganciclovir (Zirgan Bausch & Lomb) . Topical interferon alpha 2b is available from formulating pharmacies.

Interferons although still used have questionable efficacy and are seldom used. Gancilovir is the most commercially available drug, but is very expensive. The newest topical drug being used is the nucleoside analogue cidofovir. This is formulated as a .5% solution from an intravenous preparation. The drug is less expensive than ganciclovir and now has shown to have a shelf life of 6 months. Its advantage is the reported efficacy at twice daily treatment. ALL other topical medications must be administered every 4-6 hours minimal.

Unfortunately, all antiviral drugs can cause local irritation manifested by increased blepharospasms, hyperemia of the conjunctiva and lid margin hyperemia and depigmentation. Due to the frequent incidence of adverse reactions to other drugs, i.e. atropine and antibiotics, minimal drugs should be used. I do not use any additional topical medication for at least 72 hours unless severe keratomalacia is also present. In cases of severe adverse reaction the topical medication must be discontinued for 48-72 hours. I will try to re-institute the medication immediately following a topical gel tear replacement. If the irritation recurs, the topical antiviral must be changed.

Epithelialization should be complete within seven days. Topical corticosteroids can then be added to the treatment regime if corneal edema or vascularization is present. The antiviral drug should be continued for at least two weeks following remission of all clinical signs.

Recurrence rate is high and the client should be so advised. Cases of recurrent attacks, or severe stromal involvement should be evaluated for FeLV and F.I.V. In some cases, antiviral medication is continued throughout life at once daily or every second day to prevent recurrence.

There are three oral medications currently used to treat FHV-1. Famciclovir (Famvir®), interferon, and L-lysine have all been effective for both active cases and to prevent recurrence.

Purine nucleoside analogues have used in man for their inhibitory activity against several human herpes viruses. Several investigators have questioned their efficacy in feline herpes. Neutropenia and renal disease have been reported as adverse side effects with drugs previously used in this class. Most recently, famciclovir (Famvir®, 125mg, 250mg) has been used at a wide range of doses from ¼ of a 125mg tablet bid, to a dosage of 90mg/kg t.i.d! Even at the higher levels, no side effects have been reported. I use this drug for nonresponsive recurring cases with good clinical results at a dose of 125mg b.i.d. or t.i.d. Studies have shown 40mm/kg t.i.d. to be as affective as higher dosages.

Interferon (Roferon-A® Roche Laboratories) has also been used in several cases that are refractory to routine therapy or show a high incidence of recurrence. In theory, it should be inhibitory to virus growth. The stock product of Roferon A® is diluted to 30 IU/ml and dosed at 1 ml orally daily or daily on alternate weeks. The efficacy is difficult to prove and, as with the topical preparation, the oral use has fallen out of favor.

L-lysine is viral-static as the amino acid lysine replaces arginine in the replicating virus. The amino acid L-lysine has been used at a dose of 500mg b.i.d. This is readily available at pharmacies and health food stores. There are several products that have been developed for cats with presumed herpes. The side effects are rare (gastritis). In spite recent papers to the contrary I still use L-lysine in all cases as an effective, inexpensive, and safe drug to prevent recurrence. Table 1 list the majority of the drugs available as L-lysine supplements with a comparative but outdated cost. Presently my personal preference is manufactured by Aventix and distributed by MWI as Optixcare chews. The 500mg treat is very palatable and at the current cost is $160.00 yearly.

Sequelae

Corneal sequestration

This disease is unique to cats. All breeds are susceptible; however, the incidence is highest in the Persian and Siamese. Etiology is unknown, but the disease appears to be caused by any chronic irritation to the cornea. Trichiasis, entropion and K.C.S. have all been incriminated. The exophthalmia and lagophthalmos may be the cause of irritation in the Persian since most cases in this breed have axial or central corneal involvement. Herpes virus may be the source of chronic irritation in some cases, but not all respond to antiviral therapy. Cases of "classical" herpes virus keratitis have been treated that develop into corneal sequestration. Perhaps the sequestration is part of an immune complex disease. In most cases, a definitive cause is never found. Corneal sequestration has been submitted for P.C.R. tests with positive results for herpes virus. Cases have also been treated with classical ulcers and sequestrum in the same or opposite eye.

The black or brown plaque found on the cornea is composed of desiccated and degenerative stroma. Two forms may be found. The discoloration may be diffuse and poorly delineated within the stroma, or the borders may be well delineated and the dark plaque even elevated above the surrounding cornea. There is most frequently associated superficial vascularization and corneal edema. The epithelium over the sequestrum is often incomplete and a perilesional ulcer may be present. Subjective signs of pain may be mild to severe.

Treatment is aimed first at identifying the primary source of irritation if possible. If there are no corneal ulcers, and the animal is comfortable, topical corticosteroids may be used to control associated pannus. In severe cases with corneal ulcerations, edema and severe pain, topical antibiotics, hypertonic saline ointment (multiple generic forms; Muro 128®, Alcon), and atropine are used. Many

of these cases will have anterior uveitis resulting in more pain. If herpes virus is suspected, Viroptic® is also added to the treatment regime. It is important to keep in mind the high incidence of topical drug reaction.

Once the cat is comfortable, you have the options of continual medical treatment or a lamellar keratectomy. It is possible for the sequestrum to spontaneously slough; however this process may take months. In some cases of elevated sequestrums, a third eyelid flap may hasten the sloughing process.

If the cat is not made comfortable with medication or if the sequestrum does not slough given reasonable time, surgery is indicated. This would be a lamellar keratectomy and/or a third eyelid flap. Care should be taken with the keratectomy because many sequestrums extend deep into the stroma, even to Descemet's membrane. In severe cases, a conjunctival flap or corneal graft may be needed. If the majority of the sequestrum can be removed, the epithelium tends to cover the defect resulting in a comfortable eye. Following the keratectomy, a temporary tarsorrhaphy is used to protect the cornea and topical antibiotics are administered until epithelialization is complete. The resulting pannus is cleared with topical corticosteroids. L-Lysine has been used after surgery if herpes is believed to be the inciting cause.

Eosinophilic keratitis

Eosinophilic keratitis is an inflammatory disease found in cats. It has also been referred to as chronic keratoconjunctivitis and proliferative keratitis. The disease may be unilateral or bilateral. All breeds may be affected and it has been identified in cats from one year to 14 years of age. The majority of the cats, however, are less than four years of age.

Cats are frequently presented with a history of chronic irritation to the eyes including ulceration for up to six months prior to their current condition. Affected cats may show subjective signs of pain manifested by squinting and prolapsed nictitans. Although the corneal lesion may be found anywhere on the cornea, most lesions are at the temporal limbus the next most common site is the nasal limbus. In advanced cases the entire cornea may be involved.

Lesions appear as superficial vascularization that progresses to a thick granulation bed. The corneal surface will appear rough or irregular. When stained with fluorescein, geographic and linear defects in the epithelium may become evident. White gray plaques of a cheese-like consistency loosely adhering to the corneal surface are found in the majority of cases and should be considered pathognomonic for the disease. These same white plaques can be found on the temporal bulbar conjunctiva. Thickening of the nictitans has been noted in some cases.

No relationship between eosinophilic keratitis and the eosinophilic granuloma complex of cats has been noted. A significant number of cats have demonstrated a peripheral eosinophilia.

Diagnosis is based on clinical findings and cytology of corneal scrapings. The white plaques consist of amorphous eosinophilic material and occasionally intact eosinophils. Scrapings in other areas may also demonstrate mast cells. Corneal biopsies (not necessary for diagnosis)show an inflammatory infiltrate consisting primarily of plasma cells and lymphocytes with mast cells, eosinophils and histiocytes less frequently.

Treatment consists of megestrol acetate (Ovaban®, Schering Corp.; Megestrol Acetate, USP, Par Pharmaceutical, Inc.) at a dose of 5mg daily for one week then on alternate days. As the lesion regresses, the dose is reduced to weekly or even monthly to prevent recurrence. Clearing of the cornea is usually remarkable during the first week. If response is not as anticipated, topical prednisolone acetate or dexamethasone is added to the regime B.I.D. to T.I.D. "Cures" are not achieved. Cases that have been taken off of treatment by the owners have exacerbated months to years following the initial episode.

Of the many side effects of megestrol acetate that have been described (polyphagia, personality changes, hair loss, diabetes mellitus, mammary hyperplasia and neoplasia, and pyometra), only weight gains and mellowing of aggressive cats have been reported by owners. The only cats that I have had with induced diabetes have been older cats. In all cases but one the diabetes was transient following discontinuation of megestrol acetate. The fact that megestrol acetate is reported to have marked adrenal cortical suppression and is metabolized almost entirely by the liver should be kept in mind.

The etiology of eosinophilic keratitis has not been proven. Corneal biopsies and special staining techniques have failed to demonstrate any infectious organisms. The type of cellular infiltrate and peripheral eosinophilia would suggest an allergic or immune mediated reaction; however the antigen has not been identified.

Cases have been presented with classical eosinophilic keratitis in one eye and classical herpetic keratitis in the other eye. Cases of herpetic keratitis have been treated, responded to treatment and then developed eosinophilic keratitis. The history of many cases of eosinophilic keratitis having chronic corneal irritations including ulcers is compatible with herpetic keratitis. It is possible that the herpes virus is the antigen or that the virus alters the cornea resulting in the cellular infiltrate seen. Positive P.C.R. test for FHV-1 results have been obtained from corneal scraping of cats with eosinophilic keratitis.

Topical corticosteroids and cyclosporine have also been recommended for treatment. But if the disease is related to FHV-1 the chance of recurrence of active herpes keratitis is high.

Mycoplasma

Mycoplasma spp was first described as a pleuropneumonia-like organism in 1932. By 1956, 15 species of this organism were identified and the genus *Mycoplasma* was assigned. Today, *Mycoplasma felis* is one of over 150 different species of *Mycoplasma* that has been identified. The organism is believed to be part of the normal flora in the upper airway in cats and other species. *Mycoplasma felis* has also been found in the conjunctiva in asymptomatic cats.

In one study, it was difficult to reproduce the infection without prior immunosuppression i.e. corticosteroids. Many consider *Mycoplasma felis* to be an opportunistic organism, secondary to feline herpes virus. *Mycoplasma* involves the lower respiratory tract only in animals with additional underlying diseases.

Mycoplasma felis has been cultured from the cornea in cats with deep stromal ulcers and/or keratomalacia. Although possibly not the primary microorganism in these cases, it is believed to be the greatest threat to vision.

In the past, over a dozen cases of deep stromal ulcerative keratitis and malacia have yielded a positive culture for *Mycoplasma*. The cats ranged in age from 7 weeks to 15 years. There was no breed or sex predisposition. Unilateral and bilateral cases have been identified. One cat 15 years of age was on chemotherapy drugs at the time of presentation. Additional cats had recently received systemic or topical corticosteroids prior to presentation. Most cats had a history of recent feline herpetic keratitis or concurrent corneal ulceration typical of feline herpetic keratitis. All cats had prior treatment with either topical or systemic antibiotics which would be ineffective for *Mycoplasma*. Other cats have been presented with acute stromal ulcers and/or keratomalacia. However, *Mycoplasma* has never been cultured from the cornea of a case that did not have a history of topical treatment for an ocular disease.

All cases have been treated with topical erythromycin or fluoroquinolones and systemic doxycycline or azithromycin. If indicated, they were treated also for feline herpetic keratitis with topical and/or systemic anti-viral medication. Response to therapy has been excellent in all cases.

Symblepharon & conjunctival inclusion cyst

These usually originate from neonatal infection or severe keratoconjunctivitis in juvenile individuals. Conjunctival erosions and large superficial corneal ulceration result in abnormal adhesion and involution of the conjunctiva. When present they always indicate prior FHV-1 infection. They can present as mild limbal conjunctival vessels, prominent nictitans, epiphora to blindness. It all depends on the location and extent of involvement. Surgical correction may not be warranted and could prove to be problematic if needed.

Table One L-Lysine B.I.D. Annual Cost to Veterinarian of 500mg