Feline herpes dermatitis treated with interferon omega

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What is known about the topic of your paper
- A good pathology service is important.
- Make sure that the treatment induced reveals the effect expected.

What your paper adds to the field of veterinary dermatology
- Treatment of feline herpes virus (FHV)-1 with feline interferon omega.
- Clinical description of FHV-1 infection causing feline herpes dermatitis (there are not many described).

Abstract

This case report describes the diagnosis, demonstration and treatment of feline herpes virus-induced facial dermatitis in a cat. The cat was successfully treated with interferon omega (IFN-ω).

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Introduction

Feline herpes virus type 1 (FHV-1), is a double-stranded DNA virus that replicates in the nucleus of host cells producing intranuclear inclusion bodies.[1] FHV-1 is one of the major causes of feline upper respiratory tract disease. In addition to the classical rhinotracheitis, these viral infections may also induce chronic conjunctivitis and keratitis, chronic sinusitis, glossitis, neonatal disease and abortion.[2] Rarely, cases of ulcerative and crusting dermatitis in cats[3–7] and cheetahs[8] have been described. In reported cases of feline herpes dermatitis the lesional skin is histologically characterized by a severe eosinophil-rich necrosis and epidermal ulceration with extension of necrosis into hair follicles and underlying dermis. Intranuclear inclusion bodies in the surface epithelia and adnexal epithelia can be found within the lesions.[7,9] Misdiagnosis as eosinophilic granuloma may occur, if inclusion bodies are missed.[6,7] Currently, limited information exists on therapy, clinical course, and outcome of feline herpes dermatitis. Thus, the purpose of this case report is to describe a case of feline herpes dermatitis successfully treated with interferon omega (IFN-ω).

Case report

Case history and treatment

A 14-year-old neutered Abyssinian-mix female in- and outdoor cat was presented for dermatological examination of a progressive lesion on the left lateral muzzle. The cat had no health problems except for a 3 years' duration of hypertrophic cardiomyopathy treated since with 6 mg Atenolon (Tenormin Submite®, AstraZeneca, Zug, Switzerland) daily. A single episode of vomiting unrelated to the treatment was observed. Three months before referral the cat was presented to the referring veterinarian with an exudative lesion on the left latero-rostral muzzle. There was no previous history of rhinotracheitis and/or conjunctivitis. As the lesion did not respond to either antibiotics or prednisolone, the referring veterinarian took a skin biopsy and submitted it to the dermatopathology service of the Institute of Animal Pathology (Vetsuisse Faculty University of Berne, Berne, Switzerland). Histologically, a diagnosis of eosinophilic granuloma was made. Upon diagnosis, the cat, weighing 3.5 kg, was further treated with oral prednisolone, 5 mg day^{-1} for 6 weeks and with oral clindamycin (Antirobe®, Pfizer Animal Health, Zürich, Switzerland), 25 mg twice daily for 6 weeks. The lesions did not show any response to therapy. Dermatophyte culture was negative. Two months after the biopsy, the cat developed a new lesion on the right nasal ala. The cat was then referred to the dermatology service. At presentation, the cat had two lesions. The lesion on the left side of the muzzle bordering on the nasal planum and lip margin was 1.5×3 cm, firm on palpation with thickening of the lip. The lesion was erythematous, alopecic, had a shiny appearance and had several erosions and small crusts. Some whiskers remained. A second small, ulcerated lesion with a thin crust was present on the right ala of the nose (Fig. 1). The lip margin itself and the oral cavity were not affected. Physical examination revealed no other abnormalities. Treatment with oral cephalexin 20 mg kg^{-1} twice daily for 3 weeks was started in order to reduce possible secondary bacterial infection to obtain a good quality biopsy. To limit a possible corticosteroid influence on histology, a recheck was scheduled after 3 weeks to biopsy the lesions. Clinical differential diagnoses consisted of feline herpes dermatitis, mosquito bite hypersensitivity, mast cell tumour, and dermatophytosis. At re-evaluation of the histological sections of the skin biopsies taken by the referring veterinarian, intranuclear inclusion bodies were detected and a presumptive diagnosis of infection

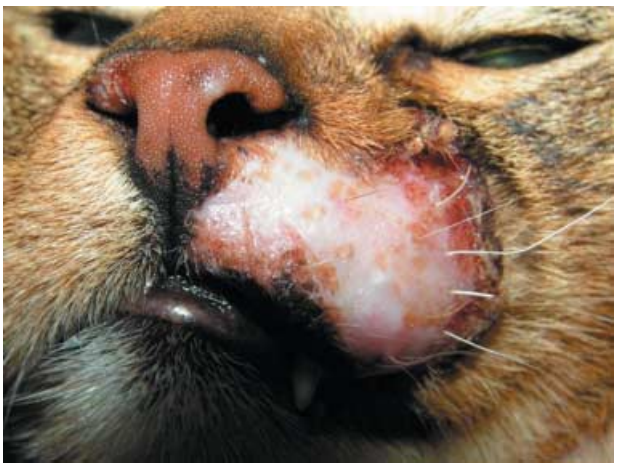

Figure 1. The cat at first presentation. A plaque–like lesion on the muzzle with alopecia and some erosions and crusts. A small erosive lesion on the right ala of the nose is visible.

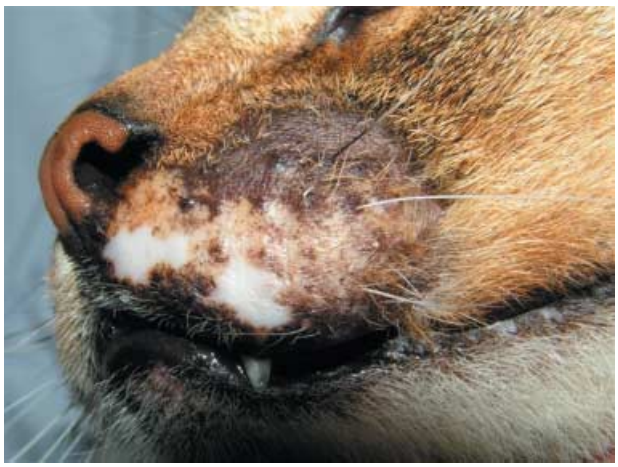

Figure 2. The lesion 6 weeks after the last rFeIFN-ω injection. Erosions and crusts have disappeared, the lesion is less raised and hairs are regrowing at the margin of the lesion.

with FHV-1 was made. During the second visit a conjunctival swab was taken to confirm and assess the actual FHV-1 status of the cat by polymerase chain reaction (PCR). Detection limits of PCR techniques vary widely and they do not discriminate between viable cultivable virions and immature, immunologically inactivated DNA.[10] For ethical reasons, the planned skin biopsies were not taken. PCR for detection of FHV-1 was performed at the Institute of Virology (Vetsuisse Faculty Zürich, University of Zürich, Switzerland), following an established protocol for real time TaqMan PCR,[11] which confirmed the diagnosis of a FHV-1 infection. After obtaining the owner's consent and discussion with a representative of Virbac Switzerland, the following treatment schedule with recombinant interferon omega (rFeIFN-ω) (Virbagen omega®, Virbac SA, Carros, France) was started. Day 0: injection of 1.5 million units (MU) kg^{-1} of rFeIFN-ω, half of which was injected perilesionally and intradermally and the other half subcutaneously on the lateral thorax while the cat was sedated with propofol (Propofol®1% Fresenius, Fresenius AG, Bad Homburg, Germany), as needed (2–5 mg kg^{-1}). The lesion on the nose regressed very rapidly, showing a clear improvement at day 2 already.

Day 2 and day 9: 1.5 MU kg^{-1} of rFeIFN-ω was injected subcutaneously on the lateral thorax and 10 days later, the cat was re-examined. The lesion on the right nasal ala had disappeared completely and the lesion on the muzzle was less swollen and ulcerations had healed.

On days 19, 21, and 23 again 0.75 MU kg^{-1} of rFeIFN-ω was injected perilesionally and intradermally as well as 0.75 MU kg^{-1} subcutaneously on the lateral thorax. The cat was sedated as described above.

Six weeks after the last injection of rFeIFN-ω examination revealed that the swelling was markedly reduced, no crusts or erosions were present and hair regrowth was noted at the lesion margin. Only a few whiskers had regrown in the centre of the lesion (Fig. 2).

As the lesion seemed quiescent and to cause minimal stress to the cat, treatment was not continued. The owner was instructed to inform the dermatology service of any changes. Two months after the last examination (e.g. 4 months after the last treatment), the cat presented for the evaluation of a small crust at the lateral edge of the lesion, on the muzzle (Fig. 3). The original lesion itself, however, had decreased in size since the initial presentation. The cat was in good clinical health and the cardiomyopathy was well controlled. Biopsies were taken to verify the cause of the crust and a conjunctival swab was taken for FHV-PCR. By taking biopsies, the entire crust was removed. At the moment of writing, 4 months later, the lesion on the muzzle has further regressed.

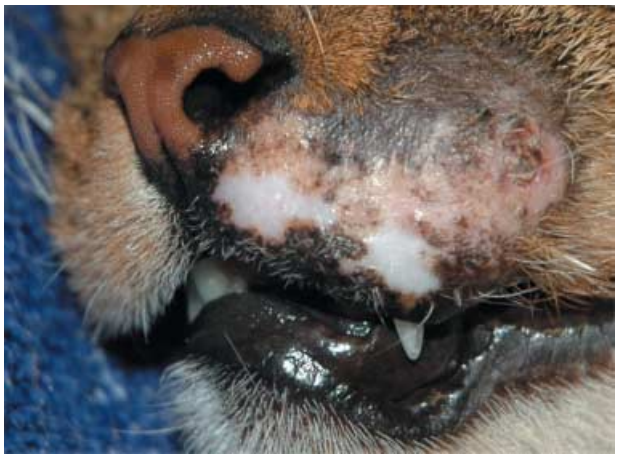

Figure 3. Skin lesion 2 months after the first presentation. Small crusts are present at the lateral edge of the initial lesion.

Histological findings, immunohistochemistry and PCR results

Histological findings before rFeIFN-ω therapy

The histopathological re-examination of haematoxylin and eosin-stained sections of the biopsy taken by the referring veterinarian showed a focal extensive ulceration of the epidermis, covered by a thick serocellular crust containing degenerate eosinophils and neutrophils and rare bacterial colonies. Focally, the necrosis extended into the follicular infundibulum and into the underlying superficial dermis (Fig. 4). The necrotic surface and infundibular epithelial

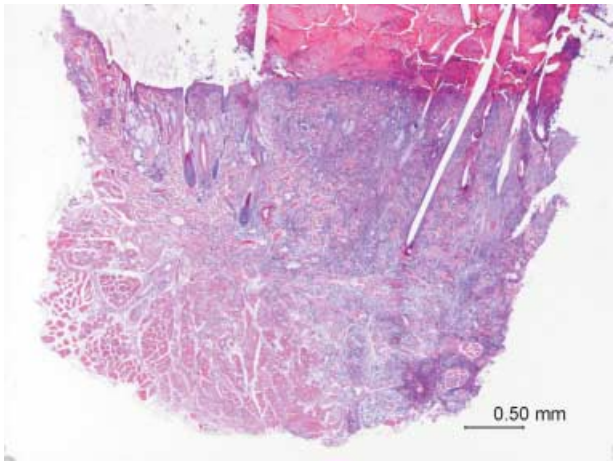

Figure 4. Overview of the histology section of the biopsy taken by the referring veterinarian: A large serocellular crust with severe ulceration of the epidermis is present in association with an inflammatory infiltrate that extends into the deep dermis. Haematoxylin and eosin. Bar = 500 μm.

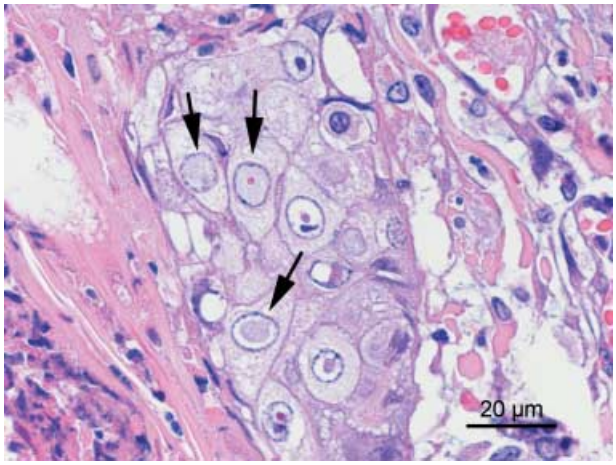

Figure 5. Hair follicle infundibulum: Multiple keratinocytes show swollen and pale cytoplasm and intranuclear eosinophilic inclusion bodies (arrow) with a peripheral halo and margination of the nuclear chromatin.Haematoxylin and eosin. Bar = 20 μm.

cells had shrunken and had pyknotic nuclei, whereas the adjacent, still viable cells were occasionally swollen.

Infundibular epithelium in one section contained a small group of keratinocytes with round, eosinophilic to amphophilic, intranuclear inclusion bodies, 4–7 μm in diameter, with marginated nuclear chromatin and a peripheral halo (Cowdry type A) (Fig. 5). The residual follicular epithelium was infiltrated with numerous eosinophils with focal, partial destruction of the follicular wall. Occasionally, complete destruction of the follicle resulted in a furunculosis, and free hairs were surrounded by a severe eosinophilic infiltration. In the adjacent dermis a severe perivascular to interstitial, superficial to deep infiltration with numerous eosinophils, fewer mast cells and rare lymphocytes and macrophages was noted, in association with a moderate to severe interstitial oedema. Based on the histological findings a presumptive diagnosis of infection with FHV-1 was made.

Histological findings after rFeIFN-ω therapy (biopsy was taken 2 months after the last injection with rFeIFN-ω)
On histological examination the epidermis showed a diffuse, moderate, irregular hyperplasia with a mild, compact, orthokeratotic hyperkeratosis. A serocellular crust was present and the underlying epidermis showed multifocal hydropic degeneration of the keratinocytes with spongiosis and lymphocytic exocytosis. Focally the stratum basale and to a lesser extent the stratum spinosum was characterized by increased eosinophilia with a fine fibrillar structure, suggestive of trans-epithelial collagen elimination, intermixed with cellular debris. Scattered apoptotic cells were also found in the basal layer of the entire epidermis. A mild to moderate perivascular to interstitial infiltrate composed of numerous plasma cells and lymphocytes with fewer macrophages and mast cells and rare eosinophils and neutrophils was present in the superficial dermis. Occasionally, the inflammatory infiltrate was centred around hair follicles. The wall of the infundibular portion of a few hair follicles was infiltrated by a small number of lymphocytes. A focal accumulation of epithelioid macrophages with rare giant cells was found surrounding the fragments of birefringent foreign material. Inclusion bodies were not observed and therefore these histological findings did not suggest an active herpes infection.

PCR results

PCR for FHV of a conjunctival swab was positive at first presentation and negative after rFeIFN-ω therapy. PCR for FHV using skin tissue was only performed on skin after rFeIFN-ω therapy and the result was positive. There was not sufficient material left of the first skin biopsy to perform PCR analysis.

Immunohistochemistry

Immunohistochemistry (IHC) was performed on skin before and after the rFeIFN-ω therapy. A monoclonal anti-FHV-1 antibody (type 4A1 R) was used according to the method described by Suchy *et al.*[6] This antibody specifically stains viral protein appearing in nuclei as well as in cytoplasm. A skin sample from the case presented in the mentioned paper served as positive control. Numerous foci of positive cells were present in the biopsy taken prior to the rFeIFN-ω therapy (Fig. 6). IHC of skin biopsies taken after treatment was negative (Fig. 7).

Discussion

In this case report, a cat diagnosed with herpes virus-induced facial dermatitis was successfully treated with IFN-ω. Reports on treatment and prognosis of feline herpes dermatitis are lacking. Cats with herpes dermatitis have been managed with antibiotics and oral human IFN-α, surgical excision and acyclovir.[1,7,8] Acyclovir, however, is known to have a relatively poor *in vitro* efficacy against FHV-1[12] and a poor bioavailability in cats.[13] Oral supplementation with L-lysine has been shown to be effective *in vitro* and *in vivo* in cats with latent infections with FHV-1.[14] The presumed mechanism is based on the known antagonism of the growth-promoting effects of arginine, which is an essential amino acid for herpes simplex virus type 1 (HSV-1) of humans, which shows a comparable biological behaviour to FHV-1.[15,16] Oral administration of human

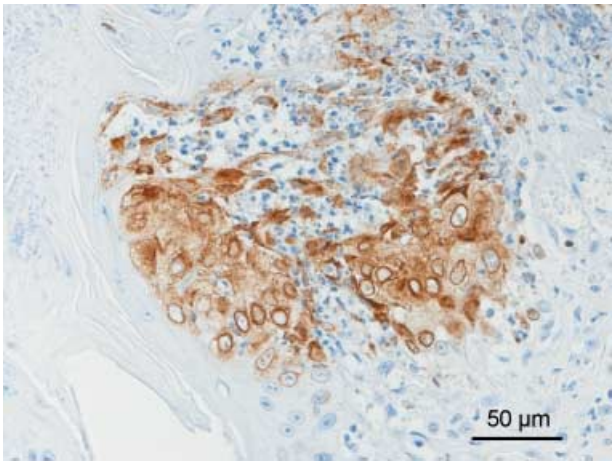

Figure 6. Immunohistochemical stain for FHV-1 of the skin biopsy taken before treatment. Positive nuclear and cytoplasmic immunoreactivity is present in the epithelial cells at the margins of necrotic areas. Scattered fine granular reactivity is visible within the necrotic debris. Avidin-biotin-peroxidase-complex (brown). Bar = 50 µm.

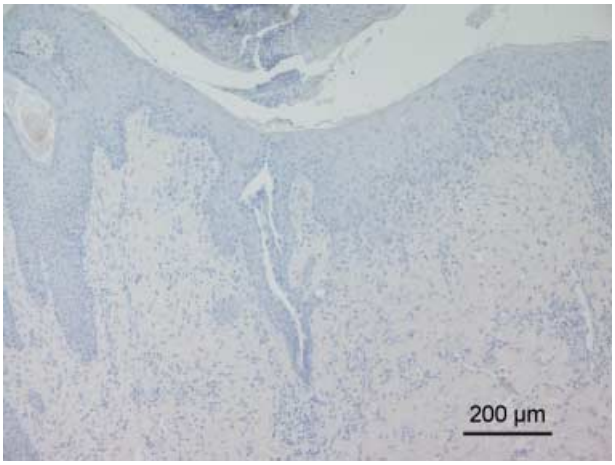

Figure 7. Immunohistochemical stain for FHV-1 of the skin biopsy taken 2 months after treatment. There is no immunoreactivity visible neither in the epidermal and follicular epithelium nor in the serocellular crust. Avidin-biotin-peroxidase-complex (brown). Bar = 200 µm.

IFN-α has been reported in several studies in cats with FeLV infection showing different efficacies.[17–19]

Recombinant feline IFN-ω (rFeIFN) is a type I IFN and has a similar mode of action as IFN-α. Type I IFNs bind to α/β receptors on host cells and have multiple antiviral, antiproliferative and immunomodulatory activities.[20] IFNs can inhibit cell growth and thereby prevent replication of some viruses. IFNs induce apoptosis in virus-infected cells and enhance expression of major histocompatibility complex (MHC) class I proteins and thereby promote CD8+ T-cell responses and stimulate cytotoxicity of natural killer cells.[20,21] IFN also induces a form of nitric oxide synthase ($iNOS_2$) and MHC class I and II proteins, all of which play important roles in immune responses to infections.[21] rFeIFN-ω has a dose-dependent inhibitory effect on the replication of FHV-1 *in vitro*.[22] Other studies have shown an antiviral effect of rFeIFN-ω in the treatment of herpes keratitis,[23,24] FeLV and FIV infection,[25] canine parvoviral enteritis[26–28] and gingivo-stomatitis.[29] rFeIFN-ω showed efficacy *in vitro* against canine parvovirus, feline panleucopeniavirus, FHV-1, feline calicivirus and feline coronavirus.[30] The treatment schedule was chosen after discussion with the manufacturer and was based on experience with treatment of other diseases using rFeIFN-ω such as feline infectious peritonitis and feline calicivirus infection. Generally, rFeIFN-ω is injected subcutaneously on days 0, 2 and 4 and a second series is repeated after 1–2 weeks. Because the cat showed marked improvement after the perilesional injection, suggesting a strong local effect of the IFN, the perilesional application was chosen for the second treatment course.

Feline herpes virus is considered to be a rare cause of ulcerative and crusting facial dermatitis in cats. However, when the often rare viral inclusions are overlooked, the histological changes can be easily misdiagnosed as eosinophilic plaque, mosquito bite hypersensitivity and eosinophilic ulcer.[9] At present, limited information exists on the natural course of herpes dermatitis in cats and the influence of corticosteroids. This cat had received corticosteroids after developing the lesion, which may have delayed spontaneous healing. In theory, cessation of the corticosteroids may have influenced spontaneous regression of the lesion. However, the marked quick initial response to rFeIFN-ω therapy, combined with the results of the histology, IHC and PCR analysis, strongly suggests a direct or at least additional treatment effect.

PCR for FHV-1 of skin tissue remained positive after the treatment. However, the clinical relevance of this finding is not clear. Potentially, PCR is a more sensitive method to detect FHV compared to IHC, which was shown in humans with herpes simplex virus (HSV)-1.[31] However, Weigler and coworkers showed that after replication at sites of initial inoculation, FHV retracts along the facial nerves and establishes latent infections in trigeminal ganglia, optic nerves, optic chiasma, the olfactory bulb and cornea, but is not expected to remain in the skin.[32] In cats with disease, detection of virus may indicate coincidence, consequential infection, or true causation with respect to the primary disease. Viral DNA detected by PCR assays in samples of healthy cats may represent avirulent virus or viral DNA fragments remaining after resolution of infection.[10]

The finding of trans-epidermal collagen elimination was unexpected. Treatment of the trans-epidermal collagen elimination with halofuginone was discussed. Halofuginone is a collagen alpha 1 inhibitor[33] and was shown to be effective as a topical treatment of one cat diagnosed with reactive perforating collagenosis.[34] Unfortunately, halofuginone is not available in Switzerland, and as the cat did not develop new lesions, this type of treatment was not pursued.

In conclusion, this case report illustrates that a correct histological diagnosis is essential for the treatment of feline herpes dermatitis and that treatment with rFeIFN-ω can be a safe and efficacious therapy. Further investigations into the treatment protocol and its efficacy are warranted.

Acknowledgements

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Résumé Ce cas clinique décrit le diagnostic, la mise en évidence et le traitement d'une dermatite faciale à herpès virus chez un chat en utilisant l'interféron oméga (IFN-ω).

Resumen Este artículo describe el diagnóstico, demostración y tratamiento de la dermatitis facial felina producida por la infección con herpes virus en un gato. El gato se trato con éxito con interferón omega (IFN-ω).

Zusammenfassung Dieser Fallbericht beschreibt die Diagnose, Demonstration und die Behandlung einer felinen Herpesvirus-induzierten Dermatitis des Gesichts bei einer Katze. Die Katze wurde erfolgreich mit Interferon Omega (IFN-ω) behandelt.