How I Treat Refractory Feline Chronic Gingivostomatitis

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Chronic gingivostomatitis (CGS) refers to a clinical syndrome in which severe, ulcerative, and/or proliferative inflammation is widespread throughout the oral cavity. The term oral mucositis, with a qualifying reference as to location (eg, alveolar, buccal, labial, caudal), has recently been adopted by the American Veterinary Dental College to more specifically describe oropharyngeal inflammation. For example, caudal mucositis refers to mucosal inflammation that involves tissue caudal to the dental arches including the soft palate dorsally, the buccal mucosa laterally, and the palatoglossal folds caudally. Caudal mucositis and widespread buccal mucositis are key clinical features of CGS in cats, in that mucosal inflammation extends well beyond the immediate vicinity of the teeth. In contrast, periodontal disease and tooth resorption affect individual teeth, so inflammation associated with those diseases tends to be localized to the alveolar mucosa and occasionally the buccal mucosa. CGS, periodontal disease, and tooth resorption can all be present in a single patient.

Clinical Signs
☑ Evaluate for clinical signs of disease (ie, weight loss, excessive salivation, reluctance to yawn, failure to groom, dropping food; often accompanied by vocalizing)

Beyond widespread inflammation of the oral cavity, cats affected with CGS show pain if their mouth is opened (eg, examination, oral medication). Clients frequently describe that their cat is reluctant to eat, or that their cat will attempt to eat but then may vocalize and drop the food or run away from the food. Weight loss, excessive salivation, reluctance to yawn, failure to groom, and oral malodor are also common.

Diagnosis
☑ Assess for signs of CGS; clinical signs of inflammation extend beyond the immediate vicinity of the teeth
☑ Evaluate for hyperglobulinemia, which affected cats frequently demonstrate

The cause of CGS, currently unknown, may be multifactorial, although the majority of cats with CGS have been shown to be actively shedding feline calicivirus (FCV).2,3 FCV, a nonenveloped RNA virus, has a hypervariable region on its capsid protein that can readily mutate within an individual patient.4 This rapid mutation may be partly responsible for the inability to consistently reproduce CGS in healthy control cats after inoculation with an FCV isolate from a CGS–affected cat.5 Irrespective of the inciting

CGS = chronic gingivostomatitis, FCV = feline calicivirus

How I Treat Refractory CGS

☐ Unless confirmed as edentulous, perform a full-mouth, intraoral radiographic survey of dentition and associated osseous structures to ensure no dental tissue remains.

☐ Perform a thorough examination to record and photograph the extent of inflammation.

☐ Initiate immunosuppressive therapy and appropriate pain management (not per os unless the patient accepts medication added to food).

☐ Avoid repeated injections of long-acting corticosteroids because of increased risk for inducing diabetes mellitus; recommend oral or transdermal steroids.

☐ Slowly taper immunosuppressive medications (25% reduction every 30 days to alternate day therapy and ultimate discontinuation) once the patient is comfortable and inflammation is reduced.

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cause(s), cats with CGS have increased mRNA expression of numerous inflammatory cytokines compared with age-matched, healthy controls. Hyperglobulinemia is common on routine serum chemistry panels, and increased numbers of lymphocytes and plasma cells are seen on histopathology from biopsies from representative lesions. A recently published online survey of veterinarians categorized the oral health status of 5179 cats relative to ELISA test results for feline immunodeficiency virus (FIV) and feline leukemia virus (FeLV). Of that population, 203 cats (3.9%) were reported to have stomatitis, of which 162 (79.8%) were retrovirus-seronegative and 41 (20.2%) were retrovirus-seropositive.

Know Science Behind the Diagnosis

✔️ Understand that feline calicivirus is associated with CGS
✔️ Remember that CGS is a disease of overzealous immune targeting of oral microorganisms
✔️ Realize that periodontitis and/or tooth resorption can also be present in cases of CGS

In health, immune system tolerance permits hundreds of different microbial species to exist in the oral cavity without inducing an inflammatory response. The indigenous symbiotic microorganisms are referred to as the microbiome, which is defined as the aggregate genetic material of all microorganisms living in or on a defined habitat. Some bacterial species have been identified by standard culture methods, but many more have only been identified by their unique ribosomal RNA (16S rRNA) gene sequences. The majority of microbial species exist together within a self-produced matrix referred to as a biofilm, which typically adheres to the surfaces of oral mucous membranes or teeth. The sheer multitude of different microbial species and their presence within a biofilm explains why systemic antibiotic treatment is generally ineffective against oral disease in general, and CGS in particular.

Commensal colonization factors produced by symbiotic bacterial species are able to modulate CD4+ T-cell function by inducing anti-inflammatory cytokines that permit commensal organisms to coexist without inducing immune targeting. In other words, commensal organisms are tolerated because they suppress immune activation. Disease develops when the local environment is altered, resulting in microbiome disruption (dysbiosis) such that cytokine expression shifts from immune tolerance to inflammation. In CGS, immune system tolerance to the oral microbiota appears to become down-regulated, and an inappropriate hypersensitivity develops in response to ordinarily tolerated microorganisms.

In experiments designed to investigate the frequency of asthma in adult humans infected with respiratory syncytial virus (RSV) during childhood, female mice were exposed to an antigen (ovalbumin), which conveyed ovalbumin immune tolerance to puppies through nursing. Diminished immune tolerance likely occurred because RSV infection altered T-cell phenotype and function. It seems plausible that infection by certain strains...
of FCV could similarly result in decreased immune tolerance to the oral microbiome that typically does not illicit immune system targeting and inflammation.

Treatment

- Extract all teeth and roots
- Confirm complete extraction with radiographs
- For refractory cases, begin immunosuppressive therapy

The biofilm attached to the surface of oral mucous membranes has a relatively short-lived adhesion because of the continuous shedding of surface cells from tongue movements, salivary flow, abrasion by food and other objects, and swallowing. In contrast, biofilm attachment to dental surfaces is not as readily displaced or shed. The teeth, especially when covered by dental calculus, provide an extremely large surface area for biofilm attachment. This helps explain why removal of all or the majority of teeth in cats with CGS has been associated with the greatest degree (80%–85%) of clinical improvement in affected cats. Although full-mouth extraction does not alleviate the hypersensitivity, removal of teeth significantly reduces the attachment sites, so overall oral microbiota are reduced. Anecdotally, many cats continue to experience pain and inflammation until every root of every tooth has been surgically removed and removal has been confirmed radiographically.

Refractory CGS Treatment

Refractory CGS will be defined here as those patients that continue to exhibit clinical signs of oral pain despite radiographic confirmation that every tooth has been removed. For such refractory cases, immunosuppressive therapy by means of medications such as cyclosporine or corticosteroids has been helpful in resolving the chronic inflammation.

Cyclosporine

- Discuss risks and monetary cost with clients
- Test for Toxoplasma gondii and assess cyclosporine absorption
- Consider oral cyclosporine solution

Cyclosporine, a potent immunosuppressive agent, blocks transcription of genes necessary to produce proinflammatory cytokines by T cells in response to antigenic stimulation. Inhibited cytokine production prevents clonal expansion of activated T cells, which additionally interferes with activation and proliferation of B cells. Cyclosporine use has expanded to include treatment for a variety of immune-mediated and inflammatory diseases in humans and other animals. At low doses, cyclosporine is generally regarded as safe; however, there have been numerous reports of de novo malignant tumor development and fatal infections in humans and other animals receiving cyclosporine therapy.

An oral solution of cyclosporine (Atopica, atopica.com) has been approved by the FDA for the treatment of allergic skin disease in cats. The package insert includes the following warning: Owners should be informed of the risks of increased susceptibility to infection and the development of neoplasia, and they should be provided advice on how to avoid exposure of their cat to Toxoplasma gondii infection. Absorption and metabolism of cyclosporine is highly variable, so cyclosporine blood levels should be measured. In a recent clinical study, cats with refractory stomatitis received 2.5 mg/kg of an oral compounded formulation of cyclosporine once daily, yet trough whole blood levels in treated cats ranged from 32.1 ng/mL to 1,576.2 ng/mL. Low absorption of oral cyclosporine was correlated with continued oral pain and inflammation. Given the recommended testing before cyclosporine treatment, and the requisite blood testing to determine the ability to absorb the medication, the financial investment could be considerable. Full disclosure of the risks and monetary costs should be discussed before therapy is initiated.

Corticosteroids

- Select immunosuppressive doses
- After 3–4 weeks, taper dose
- Watch for development of diabetes mellitus

In veterinary patients, dosing regimens for corticosteroids (eg, prednisolone) have been described as being either antiinflammatory (1–2 mg/kg q24h) or immunosuppressive (3–4 mg/kg q24h). The author’s approach is to manage cats with refractory CGS in a manner similar to treating cats with immune-mediated hemolytic anemia, in that immunosuppressive doses of corticosteroids are administered. For the average 4.5-kg cat with refractory CGS, a dose of 10 mg of prednisolone q12h is administered either orally or transdermally for 3–4 weeks before beginning a slow taper of 25% of the dose every month, provided inflammation is controlled and comfort is maintained.

Direct comparisons of immunosuppressive treatments for managing cats with refractory CGS have been confounded by the failure to restrict study populations to only cats without teeth
Another Option: Interferon

In Europe, recombinant feline interferon-omega (rFeIFN-ω), a drug licensed to treat refractory infections, has been used to treat refractory CGS. Interferons are host cytokines which interfere with viral replication. In a comparison between cats receiving oral–mucosal application of rFeIFN-ω and cats receiving antiinflammatory doses of prednisolone (1 mg/kg q24h), approximately 55% of both groups were moderately to markedly improved over the study period, a difference that was not statistically significant.29

References