Lymphoplasmacytic keratitis in a ferret with lymphoma

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- Unilateral lymphoplasmacytic keratitis was believed to be associated with multicentric lymphoma in a ferret.
- Plasmacytosis (Aleutian disease) should be considered in any ferret with lymphoplasmacytic infiltration of any organ.
- Ferrets with antibodies to the parvovirus causing plasmacytosis are believed to be more susceptible to concurrent disease because of immunosuppression.

A 2-year-old 1.5-kg male neutered fitch ferret (Mustela putorius furo) was referred for evaluation of an infiltrative lesion of the right cornea. The owner reported noticing a nonprogressive corneal opacity 3 weeks earlier at which time the referring veterinarian began treatment with gentamicin/betamethasone solution (1 drop, q 12 h). Response to treatment was not observed.

Complete ophthalmologic examination revealed a white infiltrative lesion of the right temporal portion of the cornea, 3 × 4 mm, extending axially from the 8 o’clock to the 11 o’clock positions. Biomicroscopy of the cornea revealed the lesion to involve the anterior half of the corneal stroma. The cornea did not retain fluorescein stain, and binocular indirect ophthalmoscopy failed to reveal fundic abnormalities. Clinical signs of ocular pain or vision loss were not evident. The left eye was normal. Initial scraping of the corneal lesion failed to provide enough cells from which a diagnosis could be made. The ferret was released and the owner was instructed to apply gentamicin solution (1 drop, q 12 h) because of the epithelial defects caused by the corneal scraping.

Three weeks later, the size of the lesion was determined to be unchanged; however, deep corneal neovascularization of the infiltrate was evident. Differential diagnoses of vascular corneal opacities included nodular granulomatous episclerokeratitis, chronic superficial keratitis (pannus), eosinophilic keratitis, squamous cell carcinoma, lymphoma, and amelanotic melanoma. However, to our knowledge, there are no reports of these diseases in the cornea of ferrets.

Superficial lamellar keratectomy and beta radiation (strontium 90) of the lesion were performed because of the presumptive diagnosis of inflammatory or neoplastic corneal disease. At surgery, the anterior half of the right cornea was removed, and the remaining, posterior half of the cornea was irradiated, using a strontium 90 probe delivering 6,000 rad/10 mm². Postoperative medication consisted of atropine sulfate 1% ointment (q 24 h) and bacitracin/neomycin/polyoxin ointment (q 8 h).

Histologically, fragments of the cornea had various degrees of inflammation, with subepithelial infiltrates of lymphocytes mixed with a few plasma cells (Fig 1). The morphologic diagnosis was chronic subepithelial lymphoplasmacytic keratitis of unknown cause.

Seven weeks after surgery, the ferret was re-admitted for evaluation of a firm, smooth, well-delineated mass measuring 1.5 × 1.5 × 1.0 cm in the right temporomandibular region. The right submandibular lymph node was approximately 3 times the size of the left submandibular lymph node.

Figure 1—Photomicrograph of a section of the anterior half of the right cornea of a ferret with lymphoplasmacytic keratitis. Notice cellular density of the corneal stroma, consisting of primarily lymphocytes and plasma cells. H&E stain; bar = 0.05 mm.

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node. Abdominal palpation revealed the spleen to be larger than normal. Ocular examination the right cornea did not reveal scarring or an infiltrate.

Fine needle aspirates of the right submandibular lymph node and the right temporomandibular mass were not diagnostic cytologically. Histologic examination of a wedge biopsy specimen of the right temporomandibular mass revealed extremely anaplastic lymphoid cells and a few areas of inflammation. A diagnosis of multicentric lymphoma was supported by results of examination of impression smears of the biopsy specimen. The smears contained primarily large, round, mononuclear cells with eccentric ovoid to round nuclei and moderate amounts of deeply basophilic cytoplasm. Some cells contained prominent nucleoli and mitotic figures.

Abnormal laboratory results obtained prior to the initiation of chemotherapy for lymphoma included anemia (PCV 25%; 4.6 x 10^6 RBC/μL), hyperproteinemia (plasma protein concentration, 8.6 g/dL), and leukopenia (4,900 WBC/μL; 2,010 neutrophils/μL). In addition, the ferret was hypoalbuminemic (2.5 g/dL) and hyperglobulinemic (6.3 g/dL). Thoracic and abdominal radiography revealed splenomegaly.

A modification of Cotter’s chemotherapeutic protocol for cats with lymphoproliferative disorders was used. Vincristine was administered IV at the rate of 0.75 mg/m^2 weekly for 4 weeks (days 1, 8, 15, and 22). Cyclophosphamide was given at the rate of 50 mg/m^2 PO on day 4 and 18. Prednisone was given PO at 40 mg/m^2/d.

After 1 week of treatment, the mass in the right temporomandibular region was no longer palpable and the right submandibular lymph node had decreased in size, although it was still twice as large as the left submandibular lymph node. On palpation, the spleen was decreased in size but still large. A CBC performed at this time revealed an absolute neutropenia and low platelet cell count.

On reevaluation at week 4, the owner believed the ferret was tolerating the treatment well because there was no decrease in appetite or change in attitude. At this time, the right temporomandibular mass was not detected and palpation of the submandibular, prescapular, and popliteal lymph nodes determined that they were of normal size. Splenic size was normal via palpation. On the basis of these results, it was believed that remission status was complete. A maintenance chemotherapeutic protocol consisting of cyclophosphamide at a dosage of 50 mg/m^2, PO, once per month and prednisone at a dosage of 40 mg/m^2, PO, every 48 hours was instituted.

At 8 weeks after the initiation of chemotherapy, the ferret was reexamined because of redevelopment of the right temporomandibular mass and an enlarged right submandibular lymph node. Examination of a fine needle aspirate of the temporomandibular mass confirmed the redevelopment of multicentric lymphoma. An induction chemotherapeutic protocol similar to the one described was instituted. However, after 1 week of treatment, the ferret became severely neutropenic and thrombocytopenic, probably as a result of cyclophosphamide-induced myelotoxicosis. The dosage of cyclophosphamide was reduced by 25%, but the ferret’s health continued to decline, and it died 2 weeks later. A request for necropsy was denied by the owner.

Lymphoid tumors are common neoplasms in most domestic animals, but however, reports of lymphoma and lymphoid leukemia in ferrets are rare. In dogs, the reported prevalence of ocular involvement with multicentric lymphoma is between 33 and 37%. 5,6 Most cases have bilateral involvement, with anterior uveitis being the most common sign. Other commonly observed signs are interstitial keratitis, conjunctival infiltrates, intraretinal and subretinal hemorrhages, and glaucoma. The keratitis is unique in that it begins with corneal edema and vascularization followed by perilimbic corneal infiltrates of neoplastic lymphocytes. 21

Although the lymphocytes infiltrating the cornea in the ferret of this case did not appear to be neoplastic, the possibility of the interstitial keratitis being part of the multicentric lymphoma could not be excluded. The infiltrating lymphocytes in this ferret’s cornea did not appear neoplastic, and when exposed to glucocorticoids topically, there was no evidence of cell lysis in the corneal biopsy. Glucocorticoids have been shown to induce cell lysis of neoplastic lymphocytes, as evidenced by free nuclei and cellular debris. 22

In any ferret with a lymphoplasmacytic infiltration of an organ, the possibility of plasmacytosis (Aelutian disease) must be considered. Plasmacytosis is an immune complex-mediated disease caused by infection with a specific parvovirus. 23 In mink with experimentally-induced Aelutian disease, uveitis characterized by infiltrates of lymphocytes and plasma cells within the iris and ciliary body was the principal ocular lesion. Cellular infiltration of the limbus with the same population of cells was identified in about 20% of 122 mink, yet except for a few neutrophils in the corneal stroma of 2 ferrets, the cornea was generally unaffected. 24 The lymphoplasmacytic corneal infiltrate in the ferret of this report closely resembled the inflammatory infiltrates seen in this population of mink.

Ferrets with clinical plasmacytosis commonly have signs of chronic progressive wasting, anorexia, melena, and hypergammaglobulinemia. 25-27 In the ferret of this report, hyperglobulinemia (6.3 g/dL) was detected, but serum immunoelectrophoresis was not performed to determine whether a hypergammaglobulinemia (se-
rum gammaglobulins exceeding 20% of total serum protein) was the cause. Even though most of these clinical signs were not apparent in the ferret of this report, the diagnosis of plasmacytosis cannot be excluded, as all disease processes can be associated with variability in clinical signs. In retrospect, serum could have been examined by counterimmunoelectrophoresis for virus antibody to obtain a definitive diagnosis. Several investigators have postulated that ferrets with antibodies to the parvovirus causing plasmacytosis are more susceptible to concurrent disease because of immunosuppression and, therefore, are more likely to develop diseases such as lymphoma.13,28