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Infectious crystalline keratopathy in dogs and cats: clinical, *in vivo* confocal microscopic, histopathologic, and microbiologic features of eight cases

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Abstract

Objective To describe clinical, *in vivo* confocal microscopic, histopathologic, and microbiologic features of canine and feline cases of infectious crystalline keratopathy (ICK).

Animals studied Six dogs and two cats with naturally acquired ICK.

Procedures Medical records of dogs and cats with a clinical diagnosis of ICK were reviewed. Signalment, medical history, clinical findings, and diagnostic evaluations were retrieved, including corneal cytology, histopathology, *in vivo* confocal microscopy, and microbiology results.

Results All animals presented with fine, needle-like, and branching white crystalline anterior stromal opacities emanating from corneal facets or corneal epithelial defects. Mild conjunctival hyperemia and anterior uveitis were frequently present. Concurrent ocular and systemic diseases were common, including keratoconjunctivitis sicca, corneal sequestrum, diabetes mellitus, hyperadrenocorticism, and malignant neoplasia. Bacteria, with minimal or absent leukocytes, were identified by cytology and histopathology. Histopathologically, the crystalline corneal opacities corresponded with dense accumulations of bacteria present in the interlamellar stromal spaces and forming cord-like projections within the stroma. *In vivo* confocal microscopy demonstrated deposits of reflective crystalline or amorphous structures within the stroma with a paucity of associated inflammatory changes. The most frequently cultured bacteria were alpha-hemolytic *Streptococcus* and *Staphylococcus* species. Resolution of clinical lesions was achieved in most cases with long-term medical or surgical therapy; however, the initiation of medical treatment was associated with an acute, dramatic onset of severe keratitis and anterior uveitis in some animals.

Conclusions Infectious crystalline keratopathy in dogs and cats shares many features with this condition in human patients. Prolonged medical therapy, or surgical intervention, is required for resolution.

Key Words: bacterial keratitis, cat, cornea, dog, *in vivo* confocal microscopy, infectious crystalline keratopathy

INTRODUCTION

Infectious crystalline keratopathy (ICK) is a distinct corneal infection first described in human patients during the early 1980s.[1,2] Clinically, ICK is characterized by slowly progressive, branching, white, crystalline opacities in the corneal stroma with minimal or absent associated inflammation and a frequently intact corneal epithelium.[3] Alpha-hemolytic streptococci of the viridans group are the most frequent etiologies of this condition, but other microorganisms, generally of low corneal virulence, can be isolated.[4,5] The term 'crystalline' is used to describe the appearance of the ICK lesion, but true crystals are not deposited in the cornea during this infection. Chronic colonization of the interlamellar stromal spaces by populations of bacteria produces the distinct crystalline clinical appearance.[6]

In human patients, ICK occurs most frequently after corneal surgery, particularly penetrating keratoplasty, but

may also be associated with other causes of corneal epithelial damage including *Acanthamoeba* keratitis, bullous keratopathy, contact lens wear, herpetic keratitis, neurotrophic keratitis, and other ocular surface diseases.[7–12] The onset of clinically detectable ICK may be several months after the presumed initiating event.[13] Long-term use of topical corticosteroids and antimicrobials are additional risk factors for the development of ICK.[9–11]

A previous abstract described a single dog with a bacterial corneal infection clinically resembling ICK, but additional details were not provided.[14] The objectives of the present report are to describe the clinical, *in vivo* confocal microscopic, histopathologic, and microbiologic features of canine and feline cases of ICK.

METHODS

Medical records review and case selection

Medical records of dogs and cats with a diagnosis of ICK evaluated by the ophthalmology service at the Cornell University Hospital for Animals between January 1, 2006, and December 31, 2015 were reviewed. Inclusion criteria included a clinical diagnosis of ICK and supportive diagnostic assay results. The clinical diagnosis of ICK was based on the presence of otherwise unexplained, progressive, white, crystalline opacities in the corneal stroma that emanated from corneal facets or ulcers and were associated with minimal or absent keratitis. Information obtained from the medical record included signalment, date of initial evaluation, previous clinical history, concurrent ocular and systemic diseases, clinical examination findings, therapy administered, treatment response, and clinical outcome. Additionally, results of corneal cytology, histopathology, *in vivo* confocal microscopy, and microbiologic cultures were recorded.

Clinical examination and diagnostic evaluation

A complete ophthalmic examination was performed on each dog and cat, including slit-lamp biomicroscopy, indirect ophthalmoscopy, Schirmer I tear testing, applanation tonometry, and corneal application of fluorescein stain. *In vivo* confocal microscopic examination of the cornea was performed with a Heidelberg Retina Tomograph II and Rostock Cornea Module (Heidelberg Engineering, Dossenheim, Germany) as previously described.[15] Corneal samples for cytologic, histopathologic, and microbiologic assessment were obtained from corneal scrapings performed with a Kimura platinum spatula and surgical anterior lamellar keratectomy specimens. Corneal scrapings were collected in conscious animals after application of topical anesthetic and keratectomies were performed on anesthetized animals. All diagnostic specimens were obtained by directly sampling the crystalline corneal lesions, which included removal of the overlying epithelium for some corneal scrapings.

Routine diagnostic sample processing, cytologic stains (i.e., Wright's and Gram stains), and histopathologic stains (i.e., hematoxylin & eosin, Gram, and von Kossa stains) were employed. Microorganism identifications and antimicrobial susceptibility determinations by the broth microdilution method were performed by use of an automated system (Sensititre, Trek Diagnostic Systems Inc, Cleveland, OH) supplemented with bacterial phenotypic tests and PCR speciation to confirm identifications when necessary.

Statistical analysis

Signalment, historical, clinical, and diagnostic characteristics were analyzed with descriptive statistics. Distribution of specific study data (i.e., age, duration of historical ocular disease, and duration of treatment until clinical resolution of corneal disease) was assessed with a Shapiro–Wilk test. Median and range values were determined for nonparametric data, including age, duration of historical ocular disease prior to presentation, and duration of treatment with medications until clinical resolution of corneal disease.

RESULTS

Six dogs and two cats were identified that met the study inclusion criteria (Table 1). The median age of dogs was 106.5 months (range, 78–179 months). There were four spayed-female and two castrated-male dogs. Breeds represented included single dogs of the following: Beagle, Cavalier King Charles Spaniel, Dachshund, Golden Retriever, Lhasa Apso, and Maltese. Four dogs were affected in the right eye, and two dogs were affected in the left eye. The median age of cats was 16.5 months (range, 9–24 months). Both cats were castrated-male Persians. One cat was affected in the right eye and one in the left eye.

Five dogs were referred by primary veterinarians or presented by clients for one or more ocular abnormalities that were determined to potentially be a direct result of the ICK, including epiphora or ocular discharge ($n = 3$ dogs), enlarging white corneal opacity ($n = 2$ dogs), conjunctival hyperemia ($n = 2$ dogs), and intermittent blepharospasm ($n = 1$ dog). In these dogs, clinical abnormalities were present for a median of 21 days (range: 2–56 days) prior to initial examination. The remaining dog was presented for elective phacoemulsification evaluation and both cats for assessment of enlarging corneal sequestrum.

Concurrent ocular conditions identified on presentation in the eyes with ICK included keratoconjunctivitis sicca ($n = 4$ dogs), corneal sequestrum ($n = 2$ cats), hypermature cataract with lens-induced uveitis ($n = 1$ dog), inferior eyelid entropion ($n = 1$ cat), progressive retinal atrophy ($n = 1$ dog), pseudophakia ($n = 1$ dog), and uveal lymphoma ($n = 1$ dog). No animals had a known history of

Table 1. Signalment, concurrent ocular conditions, concurrent systemic diseases, prior ophthalmic anti-inflammatory medications, bacterial isolates, treatment, and therapeutic outcome for six dogs and two cats with ICK

Case and Signalment	Ocular Conditions	Systemic Disease	Prior Ophthalmic Medications	Bacterial Isolates	Treatment	Outcome
1. 97-month-old FS Golden Retriever	None	None	None	*Staphylococcus epidermidis*	MT	Resolved
2. 133-month-old FS Lhasa Apso	KCS, pseudophakia	DM, HAC	Flurbiprofen	*Staphylococcus pseudintermedius*, *Streptococcus* spp.	ALK, CPG	Resolved
3. 179-month-old FS Dachshund	KCS, uveal lymphoma	Lymphoma, HAC	CSA, PA	*Enterococcus faecalis*, *Streptococcus parasanguinis*	MT	Euthanized
4. 116-month-old MC Beagle Hound	KCS, PRA	Osteosarcoma	CSA, NPD	*Staphylococcus schleiferi*, *Streptococcus gallolyticus*	MT	Resolved
5. 97-month-old FS Maltese	Cataract, LIU	DM	CSA	*Staphylococcus epidermidis*, *Streptococcus salivarius*	MT	Resolved
6. 78-month-old MC Cavalier King Charles	KCS	None	None	*Pseudomonas aeruginosa*	ALK, CPG	Resolved
7. 9-month-old MC Persian	Sequestrum	None	None	*Sphingobacterium multivorum*	ALK, CCT	Resolved
8. 24-month-old MC Persian	Sequestrum, entropion	None	None	*Pseudomonas aeruginosa*	ALK, CCT	Resolved

ALK = Anterior lamellar keratectomy; CCT = Corneoconjunctival transposition; CPG = Conjunctival pedicle graft; CSA = Cyclosporine solution; DM = Diabetes mellitus; FS = Female spayed; HAC = Hyperadrenocorticism; KCS = Keratoconjunctivitis sicca; LIU = Lens-induced uveitis; MC = Male castrated; MT = Medical therapy only; NPD = neomycin–polymyxin B-dexamethasone solution; PA = Prednisolone acetate solution; PRA = Progressive retinal atrophy.

external corneal trauma. Ophthalmic medications being administered on presentation to the eyes with ICK included cyclosporine solution ($n = 3$ dogs), gentamicin solution or ointment ($n = 1$ dog, $n = 1$ cat), artificial tear gel ($n = 1$ dog), atropine ointment ($n = 1$ cat), erythromycin ointment ($n = 1$ cat), flurbiprofen solution ($n = 1$ dog), idoxuridine solution ($n = 1$ cat), neomycin–polymyxin B-bacitracin ointment ($n = 1$ dog), neomycin–polymyxin B-dexamethasone solution ($n = 1$ dog), and prednisolone acetate solution ($n = 1$ dog). With the exception of a single dog, all dogs and cats were being administered at least one ophthalmic medication at the time of presentation.

Concurrent systemic conditions included diabetes mellitus ($n = 2$ dogs), hyperadrenocorticism ($n = 2$ dogs), generalized lymphoma ($n = 1$ dog), and osteosarcoma ($n = 1$ dog). Systemic medications being administered on presentation included insulin ($n = 2$ dogs), antineoplastic chemotherapy ($n = 1$ dog; lymphoma protocol which included asparaginase, cyclophosphamide, doxorubicin, prednisone, and vincristine), L-lysine ($n = 1$ cat), selegiline ($n = 1$ dog), and trimethoprim–sulfamethoxazole ($n = 1$ dog).

During ophthalmic examination, all animals had fine, needle-like, branching, white crystalline anterior stromal opacities emanating from the peripheral borders of corneal facets ($n = 5$ dogs), corneal sequestra ($n = 2$ cats), or a focal corneal epithelial defect ($n = 1$ dogs; Fig. 1). When viewed by slit-lamp biomicroscopy, the crystalline structures were isolated to single lamellar planes and typically localized to the immediate subepithelial stroma. All corneal lesions were fluorescein negative with the exception of the single dog with a focal, superficial corneal ulcer and the two cats each with a ring of superficial ulceration surrounding corneal sequestra. The crystalline lesions were located in the axial or paraxial cornea in all animals. Mild peripheral corneal vascularization, not spatially associated with the more centrally located crystalline opacities, was detected in four dogs and in both cats. Additional findings during the initial ophthalmic examination potentially related to the ICK included mild conjunctival hyperemia ($n = 6$ dogs), anterior chamber reaction (trace aqueous flare or cell; $n = 5$ dogs), clinical signs of mild-to-moderate ocular discomfort (blepharospasm or ocular rubbing; $n = 5$ dogs, $n = 2$ cats), and miosis ($n = 2$ dogs).

The diagnosis of ICK was confirmed by a combination of diagnostic evaluations of corneal samples performed on initial presentation in three dogs and both cats. In the other three dogs, corneal samples were collected for diagnostic evaluation during recheck examinations. In each of these dogs, progressive expansion of the crystalline stromal opacities was observed with persistent ocular discomfort, conjunctival hyperemia, or anterior uveitis despite treatment with anti-inflammatory or supportive medical therapies (i.e., topical cyclosporine, edetate disodium, or nonsteroidal anti-inflammatory medications). Diagnostic evaluations in these dogs were performed on the first recheck evaluation ($n = 1$ dog) or second recheck evaluation ($n = 2$ dogs) of the corneal lesions. The diagnostic evaluations were performed a median of 21 days (range 10–35) after the initial ophthalmic examination.

Corneal cytology was performed in five dogs and one cat. Gram-positive cocci (n = 4 dogs, n = 1 cat) or gram-negative bacilli (n = 1 dog) with few or no neutrophils were identified in all cases. Corneal histopathology was performed in two dogs and two cats. The crystalline corneal opacities histopathologically corresponded with dense accumulations of bacteria (gram-positive cocci) in the interlamellar stromal spaces that formed cord-like projections or pockets within the stroma (Fig. 2). The interlamellar spaces appeared distended and separated by the bacterial accumulations, but stromal microstructure was otherwise well preserved. Corneal mineral or lipid deposits were not identified. There was a distinct paucity of inflammatory cells in the stromal regions immediately surrounding the bacteria.

In vivo confocal microscopy of the cornea was performed in four dogs and two cats. In all cases, numerous moderately to highly reflective stromal deposits were found in the region of the clinically visible crystalline structures. The deposits most commonly appeared as fine, needle-like, branching, crystalline structures that often assumed stellate patterns (Fig. 3a). Less commonly, the deposits were larger and assumed the appearance of thick linear branching structures, random geometrical shapes, or they were amorphous (Figs 3b and c). Both deposit types were present in all corneas examined, and each cornea was further characterized by a distinct lack of keratocyte nuclei, nerves, vessels, and leukocytes in the corneal region in the immediate vicinity of the lesions. Keratocyte nuclei, nerves, vessels, and leukocytes were common confocal microscopic findings in corneal regions remote from the ICK regions.

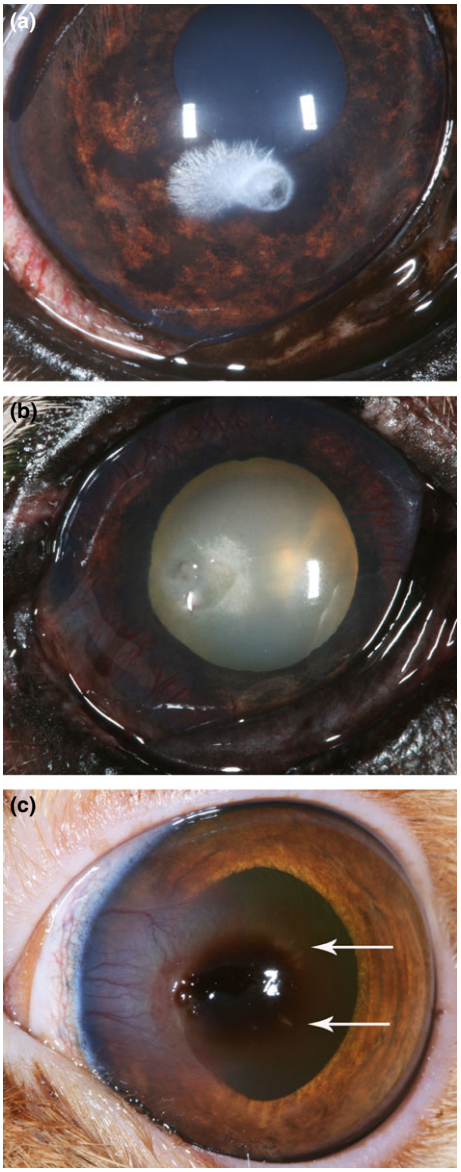

Figure 1. Clinical photographs of infectious crystalline keratopathy in two dogs (a,b) and a cat (c): fine, needle-like, branching, white crystalline anterior stromal opacities (arrows) emanate from the peripheral borders of corneal facets (a,b) or a corneal sequestrum (c).

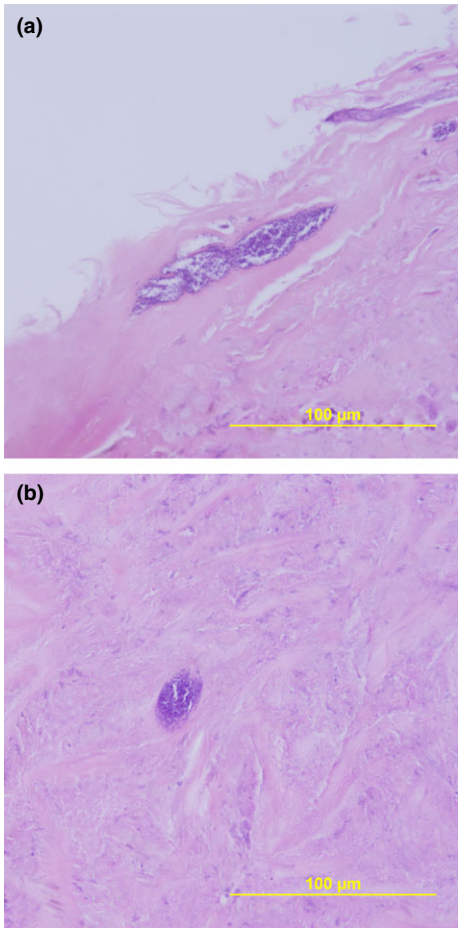

Figure 2. Histopathologic photomicrographs of anterior lamellar keratectomy specimens stained with H&E from a dog (a) and cat (b) with infectious crystalline keratopathy: interlamellar spaces are distended by pockets of bacterial cocci with a paucity of inflammatory cells in the stromal regions immediately surrounding the bacteria.

Aerobic bacterial culture of corneal specimens was performed for all cases, anaerobic bacterial culture in six cases, fungal culture in two cases, and virus isolation in one case. One or more aerobic bacteria were isolated from the corneal samples in all animals (Table 2). In the dogs, *Staphylococcus epidermidis* (n = 2 isolates) and single isolates of *Enterococcus faecalis*, *Staphylococcus pseudintermedius*, *Staphylococcus schleiferi*, *Streptococcus gallolyticus*, *Streptococcus salivarius*, *Streptococcus parasanguinis*, *Pseudomonas aeruginosa*, and an unidentified nonhemolytic *Streptococcus* species were identified. In the cats, *Pseudomonas aeruginosa* and *Sphingobacterium multivorum* were identified. Results of all anaerobic bacterial, fungal, and viral cultures were negative.

Initial therapy in all six dogs included medical treatment only. Antimicrobial therapy was based upon bacterial culture and susceptibility test results (Table 2). Topical antimicrobials used, often in combination, included ciprofloxacin solution (n = 3 dogs), gatifloxacin solution (n = 3), cefazolin solution (n = 2), and neomycin–polymyxin B-bacitracin ointment (n = 2). Systemic antimicrobial therapy included amoxicillin–clavulanic acid (n = 2 dogs) and enrofloxacin (n = 2 dogs). Supportive therapies, including topical atropine (n = 3 dogs), topical diclofenac (n = 2), and oral meloxicam (n = 2), were administered as required to control uveitis and discomfort. Topical cyclosporine therapy was continued during the course of therapy for the three dogs who were being administered this medication on presentation. All other ophthalmic medications being administered on presentation, including corticosteroids, were discontinued during ICK therapy.

Five dogs were successfully treated with resolution of the keratopathy and retention of vision. The response to medical therapy varied markedly between dogs. In the three dogs that responded to medical therapy alone, the white crystalline stromal opacities slowly regressed, the corneal lesions progressively vascularized, and the conjunctival hyperemia and anterior uveitis resolved (Fig. 4a). In each of these dogs, partial regression of the crystalline lesions occurred prior to the vessels reaching the region of ICK; however, lesion infiltration with vessels was followed by a rapid disappearance of the crystalline structures. In these dogs, the median duration of medical therapy until keratopathy resolution was 35 days (range: 28–196 days). In two dogs, initiation of medical therapy was associated with an acute (i.e., <7 days), dramatic onset of keratitis and uveitis (Figs 4b and c). Both dogs developed corneal leukocyte infiltrates, diffuse corneal edema, and stromal ulcers (one progressing to a descemetocele) in the region of the crystalline keratopathy. Keratitis in the dogs was associated with severe anterior uveitis (miosis, marked aqueous flare, and hypopyon). Both dogs with decompensated corneal lesions were treated with an anterior lamellar keratectomy, to remove residual crystalline stromal opacities, and a conjunctival pedicle graft. Both dogs had unremarkable surgical recoveries. The final dog was treated medically for 77 days with progressive improvement, but was euthanized prior to keratopathy resolution due to complications associated with generalized lymphoma.

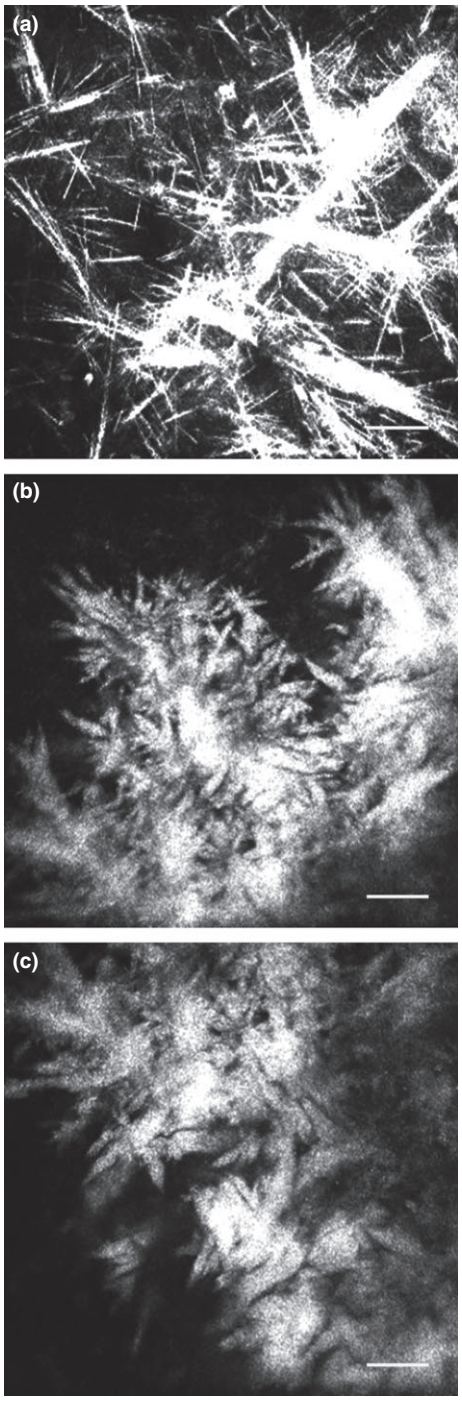

Figure 3. *In vivo* corneal confocal photomicrographs of infectious crystalline keratopathy in two dogs (a,b) and a cat (c): numerous, moderately to highly reflective stromal deposits that appear as needle-like branching structures, random geometrical shapes, or amorphous structures are present in the regions of the clinical keratopathy. Leukocytes and normal corneal anatomic structures are not present in the immediate vicinity of the keratopathy lesions. Bars: 50 μm.

Table 2. Selected *in vitro* ophthalmic antimicrobial susceptibility determinations and mean inhibitory concentrations (μg/mL) for 12 bacterial isolates from dogs and cats with infectious crystalline keratopathy

Bacterial Isolates	Species	AMK ≤ 32.0	BAC ≤ 2.0	CEF ≤ 2.0	CIP ≤ 2.0	ERY ≤ 4.0	GEN ≤ 8.0	NEO ≤ 8.0	OXY ≤ 8.0	TOB ≤ 8.0
Enterococcus faecalis	Dog	R	R	R	S	R	R	R	R	R
Pseudomonas aeruginosa	Dog	S	R	n/a	S	R	R	S	R	S
Staphylococcus epidermidis	Dog	S	R	S	S	S	S	R	S	S
Staphylococcus epidermidis	Dog	S	R	S	S	S	S	S	R	S
Staphylococcus pseudintermedius	Dog	S	R	n/a	S	S	S	S	R	S
Staphylococcus schleiferi	Dog	S	R	S	S	S	S	S	S	S
Streptococcus gallolyticus	Dog	S	S	n/a	S	n/a	S	S	S	S
Streptococcus parasanguinis	Dog	S	R	n/a	S	R	S	R	R	S
Streptococcus salivarius	Dog	S	R	n/a	S	n/a	R	R	S	S
Streptococcus spp.	Dog	R	R	n/a	S	R	S	S	R	S
Pseudomonas aeruginosa	Cat	S	R	n/a	R	R	S	S	R	S
Sphingobacterium multivorum	Cat	R	R	n/a	S	S	S	S	S	R

AMK = Amikacin; BAC = Bacitracin; CEF = Cefazolin; CIP = Ciprofloxacin; ERY = Erythromycin; GEN = Gentamicin; NEO = Neomycin; OXY = Oxytetracycline; R = Resistant; S = Susceptible; TOB = Tobramycin.

Both feline cases were complicated by the concurrent presence of corneal sequestrum and were initially treated with anterior lamellar keratectomy and corneoconjunctival transposition. Keratectomy was performed to remove the sequestrum and all visible crystalline stromal opacities. Following surgery, both cats were administered topical ciprofloxacin and atropine. One cat also received oral amoxicillin-clavulanic acid. Recovery after surgery was unremarkable in both cats.

DISCUSSION

The proposed pathophysiology of ICK begins with an epithelial defect (surgical or associated with other ocular surface diseases) that allows invasion of the corneal stroma by relatively low virulence microorganisms. Under these suboptimal growth conditions, the microorganisms slowly replicate along lamellar planes, with glycocalyx deposition, unhindered by host immunity or inflammation.[16] The crystalline appearance and growth pattern of the clinical lesion are a result of intracorneal glycocalyx deposition and the lamellar compact nature of the corneal architecture.[17] Biofilm production, low virulence organisms with slow growth rates, and local immunosuppression are all theorized to contribute to the absence of corneal inflammation. Of these, local ocular immunosuppression appears especially critical to the development of ICK in humans as the majority of reported cases were receiving topical ophthalmic corticosteroid therapy.[9–11] Additionally, intrastromal corneal inoculation with viridans streptococci in rabbits only results in crystalline opacities with the concurrent administration of corticosteroids.[18] Specific bacterial factors may also contribute to the pathogenesis of ICK as only some specific bacterial strains and serotypes can produce this corneal lesion in experimental animal models.[19,20]

Only two of the dogs in the present report were being administered a topical ophthalmic corticosteroid when the ICK developed; however, three additional dogs had received long-term ophthalmic cyclosporine therapy. In clinical situations that require continued maintenance of ocular immunosuppression during the treatment of ICK, cyclosporine is recommended as a relatively safe alternative to corticosteroids in human patients; however, apparently contradicting this recommendation are reported human cases of ICK that developed in individuals using topical cyclosporine to prevent corneal graft rejection.[21,22] The role of cyclosporine in the development of ICK requires further investigation; however, it is plausible that this medication contributed to the local immunosuppressed state that permitted development of ICK in the dogs of this report. Atypical corneal infections are previously described in dogs during cyclosporine therapy.[23] Some of the dogs described in this series were also affected by immunosuppressive systemic diseases or receiving immunosuppressive systemic therapeutics. Infectious

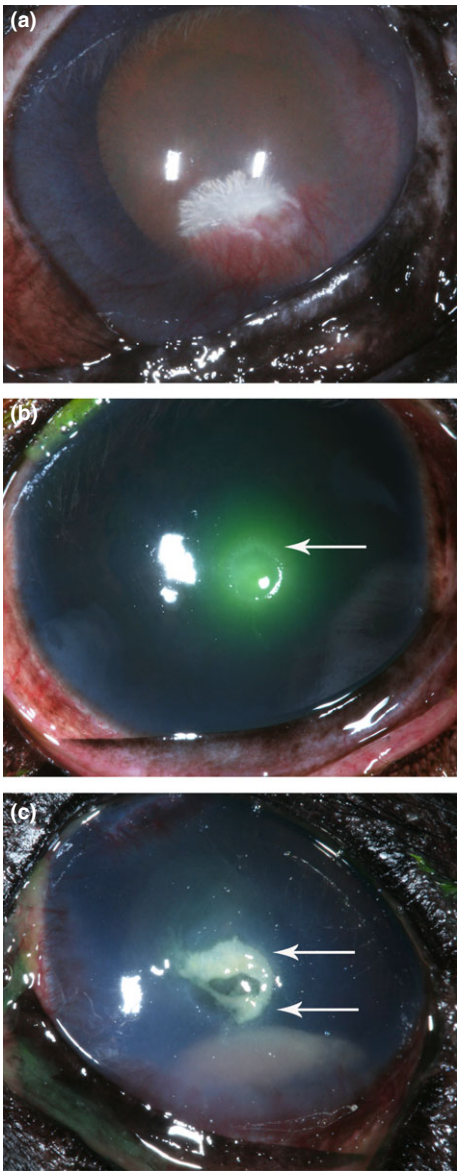

Figure 4. Clinical photographs of dogs with infectious crystalline keratopathy after the initiation of medical therapy. In most treated dogs (a), the white crystalline stromal opacities slowly regressed and the corneal lesions progressively vascularized. Two dogs (b,c) developed an acute onset of fulminant keratitis and anterior uveitis after the initiation of medical therapy. Crystalline stromal deposits remain visible in the corneas (arrows), but both dogs have perilesional corneal leukocyte infiltrates, diffuse corneal edema, and corneal stromal loss. Severe anterior uveitis, characterized by miosis and marked aqueous flare (b), or hypopyon (c), are also present.

crystalline keratopathy is reported in systemically immunosuppressed humans, including individuals not receiving topical ophthalmic corticosteroids, and these conditions and medications may be additional risk factors for development of ICK in dogs.[24–26] In contrast to the described dogs, the only risk factor identified for ICK in the brachycephalic cats of this report were chronic corneal epithelial defects associated with corneal sequestrum.

In human cases, ICK is most commonly associated with infection by streptococci of the viridans group.[3] Viridans group streptococci are a large and diverse group of commensal bacteria that are abundant in various human and animal microfloras (e.g., oropharyngeal, gastrointestinal, and genitourinary) and are generally considered infrequent pathogens of low virulence.[27,28] In dogs, there are uncommon descriptions of nonocular infections with viridans streptococci and rare reports of the isolation of unidentified viridans *Streptococcus* species from the conjunctiva of clinically normal dogs and dogs with ulcerative keratitis.[29–32] The etiological significance of the viridans streptococci in the reported dogs with keratitis was not established or clear in the prior reports.[31,32] Two species of viridans streptococci (i.e., *Streptococcus salivarius* and *Streptococcus parasanguis*) were isolated and conclusively identified from corneal samples of two dogs with ICK in this report. The majority of the other aerobic bacteria isolated from the dogs and cats in the present series are less frequently reported etiologies of ICK in humans. Microorganisms less commonly associated with human ICK include other gram-positive aerobic bacteria (i.e., *Abiotrophia*, *Actinomyces*, *Corynebacterium*, *Enterococcus*, *Gemella*, *Staphylococcus*, and other nonviridans *Streptococcus* spp.), gram-negative aerobic bacteria (i.e., *Acinetobacter*, *Citrobacter*, *Enterobacter*, *Haemophilus*, *Klebsiella*, *Pseudomonas*, *Serratia*, and *Stenotrophomonas* spp.), anaerobes (i.e., *Peptostreptococcus* and *Propionibacterium* spp.), fungi (i.e., *Alternaria*, *Candida*, and *Fusarium* spp.), nontuberculous mycobacterium, and spirochetes (i.e., *Borrelia garinii*).[33–42]

The treatment of ICK in human patients generally necessitates aggressive and long-term topical antimicrobial therapy combined with discontinuation of topical corticosteroids.[43] Medical therapy often fails to clear the bacterial infection with satisfactory visual results, necessitating lamellar keratectomy or penetrating keratoplasty.[3,43] Failure to respond to medical therapy might occur as a result of antimicrobial resistance, biofilm-associated reduction in antimicrobial penetration, or the slow replication rate of the bacteria impairing the effectiveness of certain types of antimicrobials.[44,45] Additional adjunctive treatments described in human cases include intrastromal antimicrobial injection following keratectomy and Nd:YAG or excimer laser photodisruption of the crystalline keratopathy, which is postulated to disrupt the protective biofilms, enhance leukocyte access, and improve antimicrobial penetration.[46–49] Similar to human ICK, prolonged medical therapy or surgical intervention was required in the described dogs and cats to clinically resolve the ICK. Prolonged medical therapy included a dog that required >6 months of therapy to clear the keratopathy. Medical therapy was also associated with a rapid clinical deterioration in two dogs of the present report. A similar finding is described in human patients, typically associated with initiation of antimicrobial therapy and the discontinuation of

topical corticosteroids. In these patients, the crystalline stromal opacities rapidly disappear, suppuration and stromal loss occur, uveitis develops, and corneal perforation or endophthalmitis may ultimately result.[33,44,50,51]

Two basic and distinct lesion patterns are described by *in vivo* confocal microscopy in human ICK.[52,53] The first consists of distinct needle-like or crystalline opacities within the corneal stroma that vary in size, orientation, distribution, and reflectivity. Alternatively, amorphous stromal deposits may be observed by *in vivo* confocal microscopy. These confocal microscopy findings are not considered pathognomonic for ICK and bacteria are not directly visible. The regression of these confocal microscopic abnormalities may be followed by serial examination to guide therapy.[54] *In vivo* confocal microscopy of the cornea was performed in most of the dogs and cats of this report and all had numerous, reflective, crystalline, or amorphous structures within the corneal stroma corresponding to the region of the keratopathy. This is in contrast to human cases that typically displayed only one of the two distinct confocal microscopic lesion patterns. Dogs and cats with ICK displayed a greater range of lesions that included both needle-like and amorphous structures within the same cornea.[52,53] Additional research is required to determine the role of *in vivo* confocal microscopy as a diagnostic evaluation for canine and feline ICK.

Based upon this report, clinical differentiation of ICK from other corneal lesions with a crystalline appearance (e.g., corneal dystrophy, lipid keratopathy, corneal degeneration, pharmaceutical deposits) can be challenging without additional diagnostic assays.[55–57] Infectious crystalline keratopathy in dogs and cats appears to be most commonly unilateral, progressive, not initially associated with perilesional corneal vessels, and isolated to a single lamellar plane when viewed by biomicroscopy. The ICK lesions in dogs and cats are often secondary to other corneal insults (e.g., corneal facets, corneal sequestra, or corneal epithelial defects) and accompanied by otherwise unexplainable ocular discomfort, mild conjunctival hyperemia, and mild anterior uveitis. The mild anterior uveitis observed in cases of ICK may represent a neurogenic reflex uveitis. Cases meeting these clinical criteria should be considered for additional diagnostic evaluations to determine if ICK is present.

Infectious crystalline keratopathy in dogs and cats appears to share many features with this condition in humans, including clinical appearance, histopathologic findings, *in vivo* confocal microscopic abnormalities, etiological bacterial agents, and apparent clinical risk factors. Prolonged medical therapy, or surgical intervention, is required for resolution. Diligent clinical monitoring is recommended at the onset of therapy, as the initiation of aggressive antimicrobial treatment may be associated with an acute, dramatic onset of severe keratitis and uveitis.

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