OPPORTUNISTIC INFECTIONS ASSOCIATED WITH LONG-TERM TOPICAL IMMUNE SUPPRESSION IN DOGS

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Purpose

• To describe eight dogs that developed corneal and conjunctival infections, often nodular in appearance, following treatment with topical immune suppression or modulation

• **Background** - An observation at the COPLOW linking opportunistic infections to long term treatment with topical immune suppressants
Methods

• We searched the database for canine opportunistic and protozoal corneal or conjunctival infections

• Opportunistic:
  – Unusual inflammatory response
  – Unusual organism

• 9 cases were identified, 1 was misclassified

• All other 8 cases received topical tacrolimus 0.03% or cyclosporine 0.2%
Study population

- 8 dogs
- Sex- 3 MN, 5 FS
- Age- Median 10 years (range 5-15 years)
- Breeds
  - 2 Pugs and 1 each: Shih Tzu, Havanese, Cavalier King Charles Spaniel, Yorkshire Terrier, German Shepherd cross, Terrier cross
- Clinically, SCC was on top of the differential list
<table>
<thead>
<tr>
<th>Eye</th>
<th>Preexisting ocular disease</th>
<th>Clinical presentation</th>
<th>Duration of treatment</th>
<th>Microorganism</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OU KCS + Pigmentary keratitis</td>
<td>Pink limbal mass</td>
<td>6 years</td>
<td>Toxoplasma</td>
</tr>
<tr>
<td>2</td>
<td>OU Pigmentary keratitis</td>
<td>Fleshy Corneal mass</td>
<td>8 months</td>
<td>Neospora? Leishmania</td>
</tr>
<tr>
<td>3</td>
<td>OU Pyogranulomatous meibomitis</td>
<td>Raised fleshy conjunctival masses</td>
<td>&gt;2 years</td>
<td>Toxoplasma?</td>
</tr>
<tr>
<td>4</td>
<td>OD KCS</td>
<td>Pink corneal mass</td>
<td>&gt;2 years</td>
<td>Protozoa</td>
</tr>
<tr>
<td>5</td>
<td>OD KCS</td>
<td>Pink corneal mass</td>
<td>4 months</td>
<td>Amoeba</td>
</tr>
<tr>
<td>6</td>
<td>OS KCS</td>
<td>Fleshy corneal mass</td>
<td>Long-term</td>
<td>Amoeba</td>
</tr>
<tr>
<td>7</td>
<td>OD (Pannus) CSK</td>
<td>Fleshy corneal mass</td>
<td>Years</td>
<td>Gram + Bacteria</td>
</tr>
<tr>
<td>8</td>
<td>OD KCS</td>
<td>Devitalized ulcerating cornea</td>
<td>4 months</td>
<td>Candida Parapsilosis</td>
</tr>
</tbody>
</table>
Phenotyping infections

- Histology- HE, PAS, GMS, Gram
- IHC- toxoplasma (n=3), neospora (n=3), cryptosporidium (n=1)
- EM- 2 cases
- PCR- sarcocystis, toxoplasma, piroplasm, and trichomonas were all negative (n=2), for one case t. cruzi negative and leishmania positive
- Culture- Mycology positive in one case
- Serology – neospora and toxoplasma (N=3)- negative
Case 1- KCS, pigmentary keratitis
years of topical immunosuppression

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CASE REPORT

Keratoconjunctivitis associated with Toxoplasma gondii in a dog

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Figure 1. Photograph OD 7 weeks following superficial keratectomy and cryosurgery for a corneal mass. Note the dorsomedial 10 mm yellow/tan perilimbal bulbar conjunctival mass and associated diffuse conjunctival chemosis and hyperemia. Additionally, dense pigmented keratitis affects the entire corneal surface.

Figure 2. Photomicrographs of the conjunctival biopsy from the mass shown in Figure 1. There is extensive tissue edema, lymphoplasmacytic and supplicative inflammatory infiltrate, and dilated blood vessels. Clusters of T. gondii tachyzoites are noted by the arrow.

Figure 4. Immunohistochemical staining of the conjunctival biopsy in Figure 3. Toxoplasma gondii antigens are labeled red.
Repeat IHC

Toxoplasma

Neospora
Case 2- Pigmentary Keratitis
8m tacrolimus

Courtesy Dr. Sturgeon
Histology- suspicious of toxoplasma
IHC- suspicious of neospora

Neospora

Toxoplasma
EM (Case 2)

- This case was suspected as toxoplasma by histology
- Was positive by IHC for Neospora
- EM showed a kinetoplast
- Positive PCR band for leishmania, negative T. Cruzi.
- 2 infections?
Case 3- Pyogranulomatous meibomitis (>2 years systemic and topical immunosuppression)

Courtesy Dr. Gittelman
Cytology- suspect neospora/toxoplasma/leishmania
Histology suspected toxoplasmosis or neospora
Outcome
Case 4- KCS (>2 years tacrolimus)

- Pink fleshy mass
- Histology, suspect protozoa
- Crypto IHC negative
- Improved after keratectomy and tacrolimus was continued d/t severe dry eye
Case 5- Amoeba keratitis 1
KCS (4 months tacrolimus)

Suspected SCC clinically
Improved after keratectomy and d/c tacrolimus
Case 6- Amoeba keratitis 2 (years)
Case 7- Bacteria
CSK (years CSA and tacrolimus)

- Gram positive
- Impossible to differentiate by histology
- Culture recommended not performed
- Histologically deemed opportunistic due to lack of immune response
- A mass lesion was removed and recurred after 3 weeks
- Tacrolimus was d/c and the mass resolved

Courtesy Dr. Hacker
Case 8- Yeast
KCS (4 month tacrolimus)

• Impossible to differentiate by histology
• Candida was suspected
• Candida parapsilosis identified by culture
• Resolved with keratectomy and conj. graft
• Common in immune compromised patients
• Not reported in veterinary medicine
• The only case that did not present a mass lesion

Courtesy Dr. Burling
Literature

• In people long term CSA was associated with ocular papillomatosis (Manzouri 2013), and in canines systemic CSA was associated with dermal papillomatosis (Seibel 1989)

• In canines steroids were associated with reactivation of herpetic keratitis (Ledbetter 2010), but in mice CSA was associated with improvement of HSK (Yoon 2008)

• Systemic immunosuppression was associated with dermal neosporosis in dogs (La Perle 2001)

• Fungal keratitis was more common in dogs receiving topical steroids and CSA, and pre-existing corneal disease (Scott 2014)
Association with Therapy

- Treatment was initiated due to KCS, Pigmentary keratitis, CSK and pyogranulomatous meibomitis.
- All but 1 dog had an ocular surface disorder, likely playing a major role in the occurrence of these infections.
- Treatment ranged from 4 months to 6 years.
- In most cases the immune suppressor was d/c after an infectious agent was diagnosed and specific therapy was initiated.
- Excision seems to be helpful.
Conclusions and discussion

- Corneal and conjunctival opportunistic infections are rare
- Within our database, protozoal infections were only found in immune suppressed patients
- We often get idiopathic lesions in similar patients, however we cannot term them infections without a recognizable organism
- Finding the organisms is challenging
- Identifying the organism presents further challenges
- When an unusual lesion is seen, fungal and bacterial cultures as well as biopsies are needed
- Negative serology does not rule out a diagnosis
Thank you for your attention!