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Human Eye Infections

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Glossary

Blepharoconjunctivitis Inflammation of the eyelid and conjunctiva.
Dacryoadenitis Inflammation of the lacrimal gland.
Iridocyclitis Inflammation of the iris and ciliary body.
Meibomian gland Modified sebaceous glands lining the eyelid margin that provide the lipid layer of the preocular tear film.
Retinochoroiditis Inflammation of the retina and choroid (uveal) layers of the eye.

Introduction

The eye contains diverse tissues intricately linked to subserve visual function (Figure 1). The ocular adnexae – periorbita, eyelids and lashes, lacrimal and meibomian glands – produce, spread, and drain the preocular tear film, physically protect the sensitive ocular mucosa, and cushion the globe. The redundant conjunctiva with its low-viscosity tear film allows rapid multidirectional eye movements. Lymphoid tissues within the conjunctiva and lacrimal glands furnish acquired immune defense. The cornea and its tear film fashion the major refractive surface of the eye. The sclera forms the wall of the globe and scaffolds the intraocular tissues. The eye's lens provides additional refractive power and filters ultraviolet light. The iris diaphragm dynamically regulates the amount of light incident upon the retina, and together with the choroid and optic nerve head provides immune effector cells to the interior of the eye. The retina transduces light energy into neural signals; retinal function is requisite for vision. The vascular choroid nourishes the outer layers of the retina. The anterior (aqueous) and posterior (vitreous) humors provide internal pressure sufficient for maintenance of normal anatomic relationships, nourish the interior ocular tissues, provide immunosuppressive factors necessary to the maintenance of immune deviation, and during infection act as conduits for the distribution of inflammatory cells derived from the iris, ciliary body, and optic nerve head.

Eye infection by viruses most often follows direct contact with virus externally, either from infected secretions in the birth canal (herpes simplex virus, human papillomavirus), on fomites (adenovirus), or airborne particles (rhinovirus), or is acquired during viremia (human cytomegalovirus, measles virus). Other mechanisms of ocular viral infection include extension from contiguous adnexal disease (herpes simplex virus), spread from the upper respiratory tract via the nasolacrimal duct (rhinovirus), and transplacental passage of infectious virus (rubella virus). Rarely, ocular infection may disseminate elsewhere (enterovirus 70).

Acute viral infection produces stereotypic changes in ocular target tissues. Infection of the eyelid skin induces the formation of vesicles and ulcers. Viral infection of the conjunctiva results in vasodilatation, serous discharge, hyperplasia of conjunctival lymphoid follicles, and enlargement of the corresponding draining lymph nodes. Severe conjunctival infection can cause permanent scarring of the globe to the eyelids and turning in of the eyelashes against the eye. Viral infection of the corneal epithelium induces punctate epithelial cytopathic effect evident biomicroscopically as isolated swollen epithelial cells (punctate epithelial keratitis) and loss of individual epithelial cells (punctate epithelial erosions). When extensive, the punctate erosions may coalesce to form confluent epithelial ulcers with dendritic, dendritiform, or geographic morphology. With herpetic infection, corneal anesthesia can ensue, and in the absence of epitheliotropic neural growth factors, corneal epithelial integrity is impaired. Reduced corneal clarity and progressive sterile ulceration may result. Corneal stromal infection induces white blood cell recruitment; subsequent corneal scarring, vascularization, and lipid deposition may permanently reduce vision. Intraocular infection manifests in inflammatory cell deposits on the posterior surface of the cornea and on the vitreous scaffold, and in free-floating leukocytes and biomicroscopically visible protein spillage into the normally cell-free and protein-poor aqueous humor. Iridocorneal and iridolenticular adhesions may develop and lead to glaucoma and cataract. Retinal infection concludes with necrosis and lost function. Viral encephalitis and meningitis can result in cranial nerve inflammation and secondary dysfunction of vision and extraocular motility.

Classical viral pathogenic mechanisms of latency, reactivation, and carcinogenesis all can be demonstrated in the eye. Herpes simplex virus causes recurrent lytic epithelial keratitis when viral reactivation within sensory ganglia of the first division of the fifth cranial nerve gives rise to virus in the preocular tear film. Necrotizing herpes stromal keratitis follows viral reactivation within the cornea stroma. Intraepithelial neoplasia and invasive squamous cell carcinoma of the conjunctiva and cornea

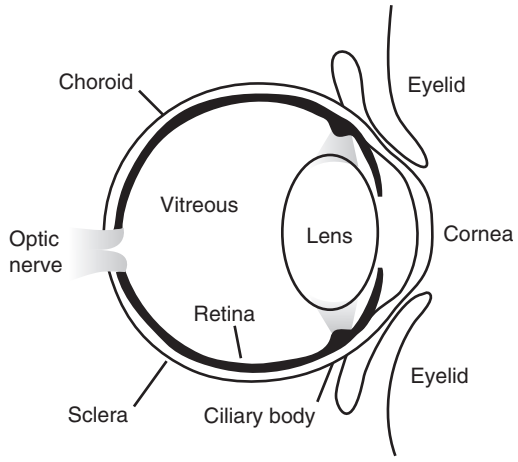

Figure 1 Cross section of the human eye.

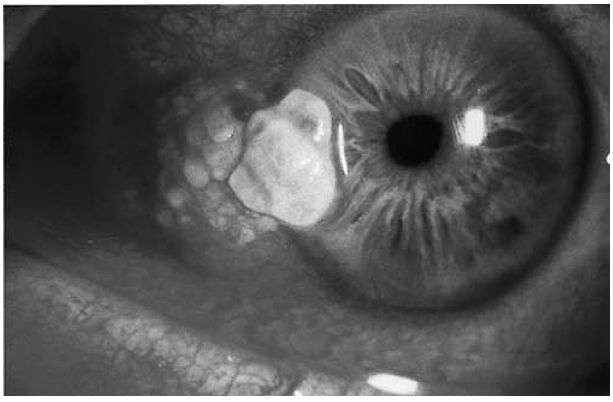

Figure 2 Squamous cell carcinoma of the corneal limbus is associated with infection by human papilloma virus types 16 and 18.

(Figure 2) have been associated with human papilloma virus types 16 and 18. When infected with oncogenic human papillomaviruses, corneal limbal stem cells can provide a persistent source of dysplastic ocular surface epithelium. Molecular mimicry has also been demonstrated as an immunopathogenic mechanism in ocular disease. Systemic infection with hepatitis C virus is associated with autoimmunity against a corneal stromal antigen and peripheral ulcerative keratitis. In a murine model of herpes simplex infection, non-necrotizing stromal keratitis accompanies T-cell reactivity against a corneal protein antigenically similar to a herpes simplex coat protein.

Ocular Immunology of Relevance to Viral Infection

Tissue diversity within the eye and adnexa compel varied means of innate immune defense. The eye's external surfaces (conjunctiva and cornea) encounter viruses by both airborne and contact routes. The eyelids, an intermittent barrier, periodically wipe the eye's surface free of debris and spread and drain the preocular tear film. The ability of the tear film to nonspecifically impede primary infection by viruses is unknown, although such mechanisms are well established for bacterial pathogens. An inhibitory effect of goblet cell-derived and intrinsic mucins and meibomian gland-derived lipids on viral adsorption to the ocular surface is speculative. Early in infection, aqueous tears from the main and accessory lacrimal glands furnish proinflammatory cytokines, and the conjunctival blood vessels provide both soluble and cellular components of innate immunity. After viral infection is established, aqueous tears carry lacrimal gland-derived monospecific secretory immunoglobulin A.

The constitutive defense armaments of the cornea and conjunctiva differ. The normal cornea is considered an immune-privileged site due to the high success rate of corneal transplantation; it lacks blood vessels, lymphatics, resident lymphoid cells, and Langerhans cells, expresses Fas ligand on its surface epithelium, and demonstrates reduced delayed hypersensitivity responses. Because corneal inflammation and subsequent scar reduce vision, corneal function is best served by its reduced immunologic responsiveness, also known as immune deviation. Necrotizing inflammation presupposes infection beneath the surface epithelium, and follows chemokine synthesis by infected corneal stromal fibroblasts. In contrast to the cornea, the conjunctiva is well endowed with blood and lymphatic channels, lymphoid cells, and Langerhans cells, and demonstrates classical delayed hypersensitivity responses. The immunology of the interior eye is less well established, but immune deviation appears to extend beyond the cornea to the aqueous and vitreous humors and to the central retina.

Ocular Disease Caused by RNA Viruses

Conjunctivitis is probably the most common viral ocular syndrome, and typically accompanies upper respiratory infections due to RNA viruses (Table 1). Rhinovirus, influenzavirus, respiratory syncytial virus, and parainfluenzavirus conjunctivitis typically are mild and self-limited, and most patients do not seek medical attention. More serious are the keratitis, uveitis, and retinitis caused by some RNA viruses. For example, influenzavirus infection of the respiratory tract, usually associated with a mild and short-lived conjunctivitis, less commonly causes inflammation in the lacrimal gland, cornea, iris, retina, optic and other cranial nerves.

Like influenzavirus, other RNA viruses can infect virtually every ocular tissue. For instance, rubella virus when acquired *in utero* may have devastating consequences for the eye. Characteristic features include

Table 1 Ocular targets of human RNA viruses

Virus	*Family*	*Subfamily/genus*	*Nuc. acid*	*Env.*	*Ocular target*
Rift Valley fever virus	*Bunyaviridae*	*Phlebovirus*	ss (−)	+	Conjunctiva Retina
Human coronavirus	*Coronaviridae*	*Coronavirus*	ss (+)	+	Conjunctiva
Dengue virus	*Flaviviridae*	*Flavivirus*	ss (+)	+	Conjunctiva
Hepatitis C virus	*Flaviviridae*	*Hepatitis C virus*	ss (+)	+	Cornea Lacrimal Glands Retina
West Nile virus	*Flaviviridae*	*Flavivirus*	ss (+)	+	Retina Uvea Optic nerve Cranial nerves
Yellow fever virus	*Flaviviridae*	*Flavivirus*	ss (+)	+	Conjunctiva
Influenzavirus	*Orthomyxoviridae*	*Influenzavirus* (A, B, C)	ss (−)	+	Lacrimal gland Conjunctiva Episclera Cornea Uvea Retina Optic nerve Cranial nerves
Measles (rubeola) virus	*Paramyxoviridae*	*Morbillivirus*	ss (−)	+	Conjunctiva Cornea Uvea Retina Optic nerve Cranial nerves
Mumps virus	*Paramyxoviridae*	*Paramyxovirus*	ss (−)	+	Lacrimal gland Conjunctiva Sclera Cornea Trabecular meshwork Uvea Optic nerve Cranial nerves
Newcastle disease virus	*Paramyxoviridae*	*Paramyxovirus*	ss (−)	+	Conjunctiva Cornea
Parainfluenza virus(es)	*Paramyxoviridae*	*Paramyxovirus*	ss (−)	+	Conjunctiva
Respiratory syncitial virus	*Paramyxoviridae*	*Pneumovirus*	ss (−)	+	Conjunctiva
Enterovirus(es): (includes poliovirus, coxsackievirus, echovirus, enterovirus)	*Picornaviridae*	*Enterovirus*	ss (+)	−	Conjunctiva Cornea Cranial nerves
Rhinovirus	*Picornaviridae*	*Rhinovirus*	ss (+)	−	Conjunctiva
Colorado tick fever virus	*Reoviridae*	*Coltivirus*	ds (+/−)	−	(?: reported to cause photophobia, retro-ocular pain)
Human T-cell lymphotropic virus-1	*Retroviridae*	*Deltaretrovirus*	ss (+)	+	Cornea Uvea
Human immunodeficiency virus	*Retroviridae*	*Lentivirus*	ss (+)	+	Lacrimal gland Retina
Rabies virus	*Rhabdoviridae*	*Lyssavirus*	ss (−)	+	(Transmission via corneal button)
Rubella virus	*Togaviridae*	*Rubivirus*	ss (+)	+	Cornea Uvea Lens Trabecular meshwork Retina Globe

+, Enveloped; −, nonenveloped; ss, single stranded; ds, double stranded; (+), positive-sense RNA genome; (−), negative-sense RNA genome.

Table 2 Ocular targets of human DNA viruses

Virus	*Family*	*Subfamily/genus*	*Nuc. acid*	*Env.*	*Ocular target*
Adenovirus	*Adenoviridae*	*Mastadenovirus*	ds	−	Conjunctiva Cornea
Herpes simplex virus, type 1 (HHV1)	*Herpesviridae*	*Alphaherpesvirinae/Simplexvirus*	ds	+	Eyelid Conjunctiva Cornea Trabecular meshwork Uvea Retina
Herpes simplex virus, type 2 (HHV2)	*Herpesviridae*	*Alphaherpesvirinae/Simplexvirus*	ds	+	Eyelid Conjunctiva Cornea Trabecular meshwork Uvea Retina
Varicella zoster virus (HHV3)	*Herpesviridae*	*Alphaherpesvirinae/Varicellovirus*	ds	+	Eyelid Conjunctiva Cornea Trabecular meshwork Uvea Retina Optic nerve
Epstein–Barr virus (HHV4)	*Herpesviridae*	*Gammaherpesvirinae/ Lymphocryptovirus*	ds	+	Lacrimal gland Conjunctiva Cornea Uvea Retina Optic nerve
Human cytomegalovirus (HHV5)	*Herpesviridae*	*Betaherpesvirinae/Cytomegalovirus*	ds	+	Retina Optic nerve
Human herpes virus 6 (HHV6)	*Herpesviridae*	*Betaherpesvirinae/Roseolovirus*	ds	+	Retina
Human herpes virus 8 (HHV8)	*Herpesviridae*	*Gammaherpesvirinae*	ds	+	Conjunctiva (Kaposi sarcoma)
Human papillomavirus	*Papovaviridae*	*Papillomavirus*	ds	−	Eyelid Conjunctiva Cornea
Molluscum contagiosum virus	*Poxviridae*	*Molluscipoxvirus*	ds	+	Eyelid Conjunctiva Cornea
Orf virus	*Poxviridae*	*Parapoxvirus*	ds	+	Eyelid
Smallpox (variola) virus	*Poxviridae*	*Orthopoxvirus*	ds	+	Eyelid Conjunctiva Cornea Uvea Optic nerve
Vaccinia virus	*Poxviridae*	*Orthopoxvirus*	ds	+	Eyelid Conjunctiva Cornea

ds, Double stranded; +, enveloped; −, nonenveloped; HHV, human herpes virus.

microphthalmos, corneal haze, cataracts, iris hypoplasia, iridocyclitis, glaucoma, and 'salt-and-pepper' pigmentary retinopathy. Rubella virus can be cultured from the lens of infected neonates at the time of cataract extraction. Congenital ocular abnormalities due to rubella, like those in other organ systems, are much worse when maternal infection ensues earliest in pregnancy.

In contrast to rubella virus, measles (rubeola) virus infection *in utero* rarely causes significant ocular disease. The classic triad of postnatally acquired measles – cough, coryza, and follicular conjunctivitis – can be accompanied by Koplik spots on the conjunctiva and a mild epithelial keratitis. Less common are optic neuritis, retinal vascular occlusion, and pigmentary retinopathy. Measles

keratopathy, a major source of blindness in the nonindustrialized world, typically presents as corneal ulceration in a malnourished child. A rare and fatal complication of measles virus infection, subacute sclerosing panencephalitis (SSPE), occurs in about 1 per 100 000 cases, and often years after clinically apparent measles. Along with devastating central nervous system damage, ocular abnormalities occur commonly in SSPE, including central retinal (macular) hyperpigmentation and inflammation, optic nerve atrophy, peripheral retinitis, and ocular motility disorders. Cortical blindness can occur in the absence of ocular involvement.

The most common ocular complication of mumps virus infection is dacryoadenitis, and this may occur concurrently with parotid gland involvement. Aseptic meningitis, associated oculomotor palsy, and optic neuritis also occurs. Follicular conjunctivitis, epithelial and stromal keratitis, iritis, trabeculitis, and scleritis have all been reported within the first 2 weeks after onset of parotitis.

Acute hemorrhagic conjunctivitis (AHC), caused predominantly by enterovirus type 70 and coxsackievirus A24 variant, but also by adenovirus type 11, is one of the most dramatic ocular viral syndromes. Sudden onset of follicular conjunctivitis associated with multiple petechial conjunctival hemorrhages characterizes AHC. The hemorrhages may become confluent and appear post-traumatic. In approximately 1 out of every 10 000 cases due to enterovirus type 70, a polio-like paralysis can ensue. Neurologic deficits are permanent in up to one-third of the affected individuals.

Human immunodeficiency virus (HIV) is the etiologic agent of the acquired immune deficiency syndrome (AIDS). Although HIV can be cultured from the retinas of individuals with AIDS, and has been shown to be present in the donated corneas of deceased AIDS patients, a direct relationship between local viral infection and ocular disease remains to be established. One example is the dry eye so common in AIDS patients. It is not known whether primary HIV infection of the lacrimal gland, immune deficit-induced potentiation of another virus such as Epstein–Barr virus within the lacrimal gland, or a putative HIV-induced neuro-immune-endocrine defect can account for AIDS-related dry eye. However, the severe immunosuppression of AIDS results in a host of other ocular diseases (discussed below).

Ocular Disease Caused by DNA Viruses

DNA viruses (**Table 2**) are responsible for most significant ocular viral infections in the industrialized world. Even the protean ocular manifestations of the HIV, an RNA virus, result largely from reduced immunity to DNA viruses.

Adenovirus is probably the most common DNA virus to cause eye disease. Three common ocular syndromes have been identified. Simple follicular conjunctivitis occurs with infection by many adenovirus types and may be subclinical. Pharyngoconjunctival fever typically follows infection with adenovirus types 3, 4, and 7. As the name implies, patients have pharyngitis, conjunctivitis, and fever, and may be misdiagnosed as having influenza. Epidemic keratoconjunctivitis, most often caused by adenovirus types 8, 19, and 37, is a highly contagious syndrome with significant morbidity. The conjunctivitis can be severe (**Figure 3**); associated inflammatory conjunctival membranes can permanently scar the eyelids to the globe. Corneal involvement begins as a punctate epithelial keratitis and may proceed to a large central epithelial ulcer. Stromal keratitis presents about 2 weeks after the conjunctivitis as multifocal subepithelial corneal infiltrates, and causes both foreign body sensation and reduced vision. The stromal infiltrates may resolve spontaneously, but can become chronic, require long-term treatment with corticosteroids, and cause persistent visual morbidity. A fourth ocular syndrome occasionally associated with adenovirus infection, AHC (discussed above), may be caused by adenovirus type 11. Interestingly, adenovirus type 11 also causes acute hemorrhagic cystitis. Follicular conjunctivitis (clinically indistinguishable from adenovirus conjunctivitis) can also be caused by Newcastle disease virus, an RNA virus that gives rise to fatal epidemics in poultry and infects the birds' human handlers.

The human herpes viruses are preeminent among DNA viruses in eye disease with at least seven of the eight known human herpes viruses associated with ocular disorders. Herpes simplex virus type 1 (HSV-1) is the most common herpes virus to cause eye disease, and herpes simplex keratitis is the most common cause of infectious blindness in the industrialized world. HSV-1 causes self-limited and relatively benign infections of the

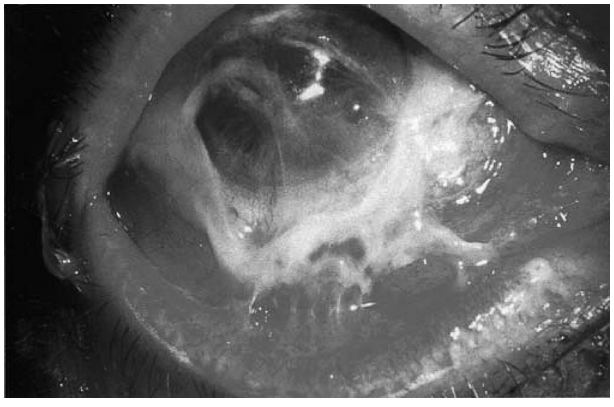

Figure 3 Epidemic keratoconjunctivitis. Infection with adenovirus serotype 19 has resulted in severe ocular surface inflammation.

eyelids, the conjunctiva, and the corneal epithelium, but infections of the corneal stroma, uvea, and retina may result in chronic or recurrent blinding stromal keratitis, uveitis, and retinal necrosis, respectively. Elevation of intraocular pressure due to involvement of the trabecular meshwork is not uncommon and may help to differentiate herpetic uveitis from noninfectious causes. Postnatally acquired HSV-2 ocular infection, less common than HSV-1, causes disease similar in most respects to HSV-1. Neonatal herpes simplex infection, acquired during transit through the birth canal and usually due to HSV-2, commonly causes vesicular blepharitis and conjunctivitis, but can also cause permanent visual loss due to keratitis, chorioretinitis, optic neuritis, and encephalitis of the visual cortex.

Varicella zoster virus, the etiologic agent of chickenpox and shingles, rarely causes keratouveitis with primary infection (chickenpox). However, vision-threatening keratitis, uveitis, and, less commonly, retinal necrosis are complications of varicella zoster virus reactivation in the distribution of the fifth cranial nerve (zoster ophthalmicus). Lid ulceration with frank tissue loss or lid malposition leads to corneal exposure and ulceration. Optic neuritis and cranial nerve paresis can accompany onset of the zoster rash. Sectoral iris atrophy is pathognomonic for zoster ophthalmicus. Postinfectious corneal anesthesia and secondary sterile corneal ulceration may follow herpes simplex types 1 and 2, but are most severe in zoster ophthalmicus. Chronic scleritis, keratitis, uveitis, and glaucoma may ultimately limit the visual acuity.

Acute systemic infection with Epstein–Barr virus may cause conjunctivitis and epithelial keratitis. Stromal keratitis occurs but is difficult to differentiate clinically from herpes simplex keratitis, and the true incidence of Epstein–Barr viral keratitis is unknown. Reports of uveitis and retinochoroiditis are unconfirmed. Delayed-onset optic neuritis following infectious mononucleosis is not uncommon.

Human cytomegalovirus (CMV) typically causes infectious retinitis (**Figure 4**) in immunocompromised patients with $CD4^+$ T-cell counts of less than 50 cells ml^{-1}. Although not the most common ocular complication of AIDS, CMV retinitis is the most common cause of blindness in AIDS patients. CMV retinitis in AIDS patients can be controlled but not cured. In contrast, congenital CMV infection in an otherwise normal fetus results in various degrees of retinochoroiditis, but is not progressive postnatally.

Human papillomavirus (HPV) causes a range of conjunctival tumors ranging from venereally acquired benign papillomas (HPV types 6 and 11) to invasive squamous cell carcinoma (**Figure 2**) (HPV types 16 and 18). Venereal papillomas are clinically similar to those of the larynx and anogenital tract. Ocular surface squamous neoplasia (conjunctival intraepithelial neoplasia and invasive squamous cell carcinoma) are most similar to dysplastic intraepithelial and invasive squamous lesions of the uterine cervix. Papillomatous eyelid neoplasms due to HPV also occur, and can be benign or malignant.

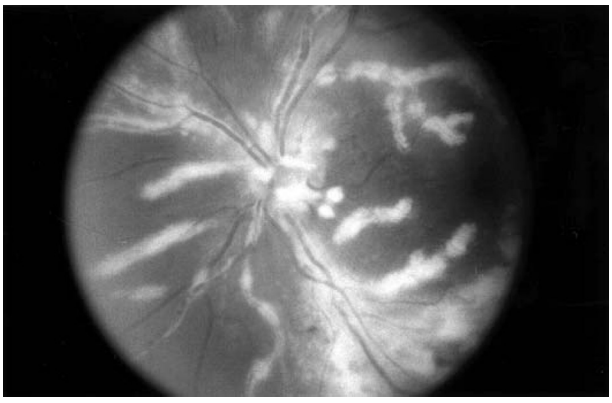

Figure 4 Cytomegalovirus retinitis. Discrete areas of perivascular necrosis and hemorrhage are typical.

Molluscum contagiosum virus is a poxvirus that may infect the eyelid skin or less commonly the conjunctiva. Skin lesions typically appear as elevated nodules with umbilicated centers, and may be multiple and quite large in HIV-infected patients. Molluscum lesions of the eyelid are fairly common in children, and can be associated with a follicular conjunctivitis that resolves with incisional or excisional biopsy of the lid lesion.

Prior to eradication, smallpox virus infection was associated with pustular blepharoconjunctivitis, secondary lid scarring, and stromal keratitis. In nonindustrialized nations, secondary bacterial infection of smallpox keratitis was a major source of blindness. Vaccination against smallpox virus with vaccinia virus was occasionally complicated by inadvertent autoinoculation of vaccinia into the eye, with potential for a severe blepharoconjunctivitis, keratitis, and globe perforation.

Ocular Complications of AIDS

Tay-Kearney and Jabs (1996) classified the ocular complications of HIV infection into five broad categories: (1) HIV retinopathy, (2) opportunistic ocular infections, (3) ocular adnexal neoplasms, (4) neuro-ophthalmic lesions, and (5) drug-induced manifestations.

HIV retinopathy is seen in over half of AIDS patients; cotton wool patches, or multifocal infarcts of the retinal nerve fiber layer, are the most common ocular sign of AIDS. Intraretinal hemorrhages occur less often. HIV can

be cultured from the retina of AIDS patients, but a direct relationship between retinal infection and AIDS retinopathy has not been established.

Some ocular infections, including CMV retinitis (**Figure 4**), *Pneumocystis carinii*, fungal, and mycobacterial choroiditis, and microsporidial keratoconjunctivitis are seen almost exclusively in AIDS. CMV retinitis is a major cause of morbidity in AIDS patients. Other infections, such as toxoplasmosis retinochoroiditis, ocular syphilis, herpes zoster ophthalmicus, and molluscum contagiosum of the eyelids are seen in immunocompetent as well as immunosuppressed individuals, but may be more severe and leave more profound deficits in HIV-infected patients. Herpes zoster ophthalmicus in young patients may be the first clinical clue to HIV infection. Acute retinal necrosis due to herpes simplex virus types 1 or 2, or varicella zoster virus, occurs more commonly in HIV-infected than in otherwise normal patients and can result in unilateral or bilateral blindness despite antiviral therapy.

Kaposi sarcoma of the eyelids or conjunctiva, associated with human herpes virus 8 infection, is exceedingly uncommon in immunocompetent individuals, but is probably the most common adnexal tumor in AIDS patients. Non-Hodgkin's lymphomas of the orbit, although rare overall, occur more frequently in AIDS patients than in the general population. Recently, squamous cell carcinoma of the ocular surface (conjunctiva and cornea) has been suggested as a marker for AIDS, but whether HIV infection potentiates HPV-induced carcinogenesis in the eye remains speculative.

Neuro-ophthalmic lesions in AIDS may occur directly due to HIV infection of the central nervous system, but most commonly are caused by cryptococcal meningitis or other opportunistic infections. Retinitis and uveitis due to anti-HIV medications can be confused with opportunistic intraocular infections.

Conclusion

Diverse ocular tissues act in concert to create vision. All of the tissues and structures within the eye are susceptible to viral infection, with consequences ranging from mild discomfort to severe pain and blindness, and almost all known human viruses cause ocular disease. Often, the same virus can infect widely disparate tissues within an eye. Classical viral pathogenic mechanisms are readily demonstrated in the eye, but the fine functions of ocular tissues within the visual axis (cornea, anterior chamber, lens, vitreous, and macula) compel altered immune responsiveness. The eye is uniquely affected by viral infection and provides an exceptional model for studies of viral pathogenesis and immunity.

Acknowledgments

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See also: Equine Infectious Anemia Virus; Feline Leukemia and Sarcoma Viruses.

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