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A Glimpse into Uveitis in the Aging Eye

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Abstract

Uveitis describes a group of inflammatory conditions of the eye that have various underlying causes and clinical presentations. Susceptibilities to uveitis in the elderly may be attributed to age-related risk factors such as immunosenescence, increased immunological inflammatory mediators, and autoimmunity. Overall anterior uveitis is more common than posterior and panuveitis in the general population and also in the elderly. Some causes of uveitis in the elderly are herpes simplex virus (HSV), ocular ischemic syndrome, sarcoidosis, and central nervous system lymphoma and these will be discussed in detail herein. Eye care professionals need to consider the wide differential for uveitis, obtain the appropriate history, conduct a detailed clinical examination, and tailor management to the clinical presentation and underlying cause of disease. The challenges of polypharmacy and nonadherence in the elderly impact patient outcomes and must be taken into consideration when considering treatment.

1. Introduction

Uveitis is a common cause of legal blindness in both the United States (US) and developing countries, comprising 10% and 25% of cases respectively.¹ Though it most typically affects patients ages 20 to 60 years, there are subtypes of uveitis that are more common in older individuals. In addition, developed countries such as the US have a higher mean percentile of uveitis in comparison to developing countries among the older population (18% versus 7% respectively)¹, likely due to the larger elderly population with more access to healthcare in developed countries.

Uveitis is characterized by inflammatory processes that affect the iris, ciliary body, retina, and/or choroid. The inflammation has several possible etiologies that include autoimmunity, infections, neoplasms, and toxins.² Based on the Standardization of Uveitis Nomenclature (SUN) criteria, uveitis is subtyped by the primary site of inflammation (anterior, intermediate, posterior, pan-uveitis).³ Structural changes caused by inflammatory processes (e.g. macular edema and/or neovascularization) are often seen with differing frequency depending on the uveitis sub-type.

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The major site of anterior uveitis is the iris and/or ciliary body, which is common in both younger and middle-aged groups.⁴ It is also the most common subtype of uveitis in the elderly population.¹ Anterior uveitis can be associated with autoimmune disorders as well as infectious diseases. Intermediate uveitis has most of its inflammation in the vitreous. This subtype is more common in younger populations and is associated with sarcoidosis and multiple sclerosis.⁵ Posterior uveitis involves the retina, choroid, blood vessels, and optic nerve. Panuveitis has no predominant site of inflammation and affects all layers of the eye.

Uveitis is further divided by time course. In general, uveitis is characterized as acute if its time course is less than 3 months; furthermore, once the inflammation is resolved, the individual is able to stop all medications without a recurrence within a 3 month time frame. Uveitis is characterized as chronic if its time course is greater than 3 months, and if once inflammation is controlled and medications are stopped, a recurrence occurs within 3 months.

2. Pathophysiology of uveitis in the elderly

2.1. Immunosenescence

There are several reasons why the elderly may be susceptible to certain forms of uveitis. Immunosenescence is a process where numerous key players of the immune system are either decreased or negatively altered with age, increasing the elderly's susceptibility to infection. For example, hematopoietic stem cells (HSCs), found in bone marrow and responsible for differentiating into white blood cells, have a decreased ability to differentiate.^{6,7} This may occur both because of intrinsic changes in HSCs and because of changes in the bone marrow environment.⁶ Regarding the latter, with age there is a reduction of osteoblasts, cells responsible for secreting osteopontin, a matrix glycoprotein.⁸ After exposing HSCs to bone marrow stroma that lacked osteopontin, a mice study found that HSCs had decreased functional abilities.⁸

White blood cells are primarily divided into innate and adaptive components and both are affected with aging.⁹ The innate immune system is the first to act during an infection and involves macrophages, neutrophils, dendritic cells, and natural killer cells. Although the innate immune system is quick to respond, it does so in a nonspecific manner.⁹ Components of the innate immune system become less effective with age. Macrophages secrete pro-inflammatory cytokines that help fight extracellular pathogens (e.g. bacteria). With increasing age, monocyte numbers (macrophage precursors) are reduced and macrophage function is decreased.⁹ While the number of neutrophils remains relatively constant with age, their CD16 Fc-gamma receptor, which facilitates the destruction of extracellular pathogens, is impaired.⁹ In a similar manner, natural killer cell numbers also remain stable with age, but their production of interleukin-2 (IL-2), which helps recruit lymphocytes that destroy intracellular organisms, decreases.⁹ Dendritic cells, antigen-presenting cells (APC) which present possible harmful material to lymphocytes for destruction, acquire mitochondrial dysfunction with age. The latter dysfunction leads to oxidative stress that can cause deoxyribonucleic acid (DNA) and protein damage, impairing function.¹⁰ Furthermore, several organs such as the skin, mucosa (respiratory and gastrointestinal lining), and hair are

important members of the innate immune system as they provide barriers to infection. These structures often deteriorate (skin thins with age¹¹) or are lost (i.e. hair) with age.⁹

The adaptive immune system is slower to respond but is more specific and effective in ridding the body of pathogens, especially intracellular organisms (e.g. viruses). It is composed of lymphocytes (B and T cells) whose proliferative abilities wane with age.¹² After being produced in the bone marrow, T cells mature and multiply into 2 main subsets in the thymus: CD4+ cells which include both helper T cells that facilitate immune cell recruitment and regulatory T cells that suppress the immune system and CD8+ which are cytotoxic and help destroy cells affected by intracellular pathogens. CD4+ and CD8+ T cells that have not encountered a pathogen are called *naïve*. The population of naïve T cells declines with age (partly due to shrinkage of the thymus), and they are less able to differentiate into effector cells.⁹ T cells are also less able to produce cytokines such as the immune signaling molecule IL-2 with age.^{9,13} Short-lived effector T cells either die or differentiate into memory cells after they have completed their role in an infection.^{14,15} IL-2 helps prevent cell death, promoting memory cell differentiation.^{14,16} Long-lived memory T cells provide “memory” of the infection so that the body can mount a stronger and quicker response when it encounters a similar infection again.¹⁵ Decreased IL-2 secretion leads to a less robust memory T cell response, contributing to the increased susceptibility of infection reactivation (such as herpes virus) seen in the elderly.¹⁶

Memory T cells also differentiate directly from naïve T cells.^{14,15} To compensate for the decline in naïve T cell populations, naïve T cells live for longer periods of time in the peripheral tissues with increasing age.^{17,18} This increased survival in the periphery allows naïve T cells to acquire multiple intrinsic defects over time, interfering with their protective role.¹⁷ One mice study found that memory T cells that differentiated from naïve CD4+ T cells in aged mice had worse memory function than naïve CD4+ T cells differentiated from young mice.¹⁹ Interestingly, although there is general decline of the naïve T cell population with age, T regulatory cell numbers have been found to increase. These findings also likely contribute to the elderly’s susceptibility to infection, particularly to reactivation of a chronic infection.⁹

B cells are the second type of lymphocytes that play an important role in adaptive immunity. They are APCs that present foreign material (or antigens) to T cells. Plasma cells (activated B cells) also produce antibodies. Antibodies (or immunoglobulins) are large Y-shaped proteins that have 5 subtypes: IgM, IgD, IgE, IgA, IgG. These subtypes are used to neutralize pathogens during an infection, and certain types are used depending on the type of infection. For example, IgA plays a critical role in mucosal immunity.⁹ Antibodies provide protection from both extracellular and intracellular pathogens.²⁰ Overall, with age, there is a reduced population of plasma cells in the bone marrow, leading to decreased antibody production, and increased vulnerability to infection.¹² However, the antibodies that are produced are more frequently autoreactive (as discussed below).^{21,22}

The elderly are also more susceptible to infections and cancer because of the accumulation of reactive oxygen species (ROS)/free radicals. Apoptosis is a programmed way for cells to shut down in the event of an uncontrollable accumulation of DNA errors. ROS damage the

DNA reparative and restorative processes of cells.⁹ As such, increased ROS make cells more resistant to apoptosis and results in mutated and dysfunctional cells.⁹

2.2. Inflammaging

While some cytokine levels are reduced with age (e.g. IL-2), others are increased including the pro-inflammatory cytokines IL-6, IL-1, and tumor necrosis factor (TNF).²³ An imbalance between players that inhibit the immune system and those that mediate inflammation is thought to contribute to the pathophysiology of non-infectious uveitis in the elderly. While increasing levels of IL-6, IL-1, and TNF promote chronic inflammation, the eye has regulatory molecules and processes that dampen inflammation, such as transforming factor- beta 2, alpha-melanocyte stimulating hormone, vasoactive intestinal peptide, and Fas ligand (FasL).^{24,25} When pro-inflammatory cytokines overwhelm the anti-inflammatory responses of the eye, the extent of inflammatory damage from an immune response becomes unchecked and can manifest as uveitis.

This upregulation of pro-inflammatory cytokines results in what is termed *inflammaging*, which describes the non-infectious, “chronic, low-grade, and systemic inflammation” that occurs during the aging process and is responsible for many age-related conditions and diseases, like decreased muscle mass, osteoporosis, Alzheimer’s disease, vascular disorders, cognitive decline, and vascular dementia.^{23,26}

Senescent cells that increasingly accumulate in adipose tissue with age and secrete pro-inflammatory markers are thought to underlie inflammaging.^{23,27} Senescent cells are cells that no longer divide or proliferate because of damage or dysfunction.^{23,27} They accumulate because the body has a decreased ability to clear them with age.^{23,27} Another source of inflammaging is an accumulation of debris that occurs from damaged/dysfunctional cells or metabolites such as urate crystals (observed in gout²⁸), which can trigger an inflammatory immune response.²³ If the debris resembles the molecular patterns of foreign antigens (molecular mimicry), these *neo-self antigens* induce an autoimmune response.²⁹ Like senescent cells, self-antigens are cleared less quickly from the body with age and can cause chronic inflammation.²³

As one ages, the immune system is also less able to distinguish between antigens that are “self” versus “foreign,” which is theorized to lead to a paradoxical overproduction of autoreactive antibodies in the presence of a declining population of plasma cells.^{21,22} In a baboon study, levels of circulating autoantibodies increased from younger to older baboons, even in the absence of immune pathology.²² The increase in autoreactive antibodies in the elderly is proposed to result partly from reactivation of memory B cells and accumulation of neo-self antigens as discussed above.²⁹

Increased antibodies leads to increased autoreactive autoantibody-antigen complexes.^{22,29} When these complexes accumulate at a faster rate than they can be cleared by mononuclear phagocytes, they start depositing in highly vascular tissues such as the ciliary body or choroidal plexus of the eye.³⁰ These complexes can block vascular flow and activate the complement system with subsequent inflammation.³⁰

Mitochondria also play a critical role in inflammaging.²³ Mitochondrial components (e.g. cardiolipin) resemble foreign pathogens, activating the innate immune system and the pro-inflammatory signaling pathway called the Nlpr3 inflammasome.²³ While its role in uveitis is unclear, this latter pathway is involved in other eye diseases such as age-related macular degeneration (AMD).³¹ Overall, many of the studies above described aging changes that occur in animal models which is not directly translatable to human disease. However, these ideas provide insight on the pathogenesis of uveitis in the elderly.

3. Symptoms and course

Patients with uveitis can experience visual disturbances such as blurred vision, floaters, eye redness, and spontaneous and evoked pain (such as to light). Symptoms profiles vary by uveitis subtype. For example, individuals with acute anterior uveitis typically report eye redness and pain, while central vision loss is more common with posterior uveitis.⁴ Floaters are often the presenting complaint in intermediate uveitis. Uveitis can be described as acute (lasting < 3 months), persistent (lasting > 3 months), or recurrent (episodes occurring after periods of inactivity, without treatment for at least 3 months).³ Chronic uveitis is characterized as persistent with relapses within 3 months after cessation of treatment.

4. Uveitis evaluation

In evaluating a patient for uveitis, ophthalmologists perform an eye exam that includes visual acuity assessment, intraocular pressure measurement, slit lamp examination, and fundoscopy. Specifically, ophthalmologists grade the presence of anterior chamber cells and flare, vitreous cell, vitreous haze (based on clarity of retinal vessels and optic nerve) as well as document the involvement of posterior structures. The doctor may also note any redness of the eyes and its location. For instance, redness at the limbus (between the region of the cornea and the sclera) is characteristic of anterior uveitis. A thorough review of systems is needed to look for systemic manifestations of inflammation or infection. A review of the medical history and medication list is essential as well. Additional testing is determined by the clinical presentation and review of systems. For example, individuals with anterior uveitis are usually tested for the HLA-B27 gene, syphilis (with specific and non-specific treponema serologies), and lung pathology (with a chest x-ray or computed tomography (CT) to evaluate for sarcoidosis, tuberculosis, ect.). In intermediate uveitis, focus is also given to the presence of neurologic symptoms that could suggest multiple sclerosis and prompt an MRI. Additional testing in posterior uveitis depends on the presentation (retinitis, choroiditis, retinochoroiditis, vasculitis) as each of these entities has its own differential diagnosis.

5. Discussion of some causes of uveitis in the elderly

The most common type of uveitis in the elderly, as it is in the general population, is anterior uveitis, followed by panuveitis and posterior uveitis.¹ One review article summarized the most common causes of uveitis in the elderly derived from 10 studies conducted in 8 countries (Table 1).¹ This article will discuss two of the most common diagnoses found in the latter review (herpes simplex virus (HSV) and sarcoidosis) along with other causes of

uveitis (ocular ischemic syndrome and CNS lymphoma) that should be considered in the elderly. Although uveitis can first occur after 60 years of age, it is possible that the inflammatory process may have begun at an earlier time, continuing after the age of 60. Other etiologies, including HLA-B27 associated disease and other common causes of uveitis, may be the underlying causes of inflammation. A wide differential must thus be entertained when evaluating a patient with uveitis, regardless of age.

3.1 Anterior uveitis in the elderly

Anterior chamber inflammation is the most common location for uveitis in the elderly,^{1,32} with acute anterior uveitis being the most common sub-type (as opposed to chronic anterior uveitis). Two notable causes of anterior uveitis in the elderly population are herpetic uveitis and ocular ischemia.

A. Herpetic uveitis—Herpetic uveitis can affect all layers of the eye but most commonly presents with anterior uveitis. Herpetic disease is the most common cause of infectious uveitis, the top culprits being herpes simplex virus (HSV) and varicella-zoster virus (VZV). Herpetic uveitis makes up 90% of infectious uveitis cases seen by community ophthalmologists, often affecting patients of working age.³³ At autopsy, HSV is found in the trigeminal ganglion in almost 100% of individuals over age 60 years and is the most frequent cause of herpetic uveitis.³⁴ HSV is a double stranded DNA virus, categorized into 2 groups based on specific viral antigens (HSV I and II). HSV I most often affects the oropharyngeal region while HSV II most often affects the genital region; however, they can overlap. The primary manifestation of HSV in the eye is a blepharoconjunctivitis. Herpetic uveitis is thought to result from disruption of latency after which the virus travels up sensory axons and reactivates in the eye. Reported risk factors for viral reactivation are immunosuppression, stress, and sunlight.³⁵

Patients with herpetic uveitis may complain of blurry vision due to concomitant corneal disease (scarring/edema), photophobia, eye pain, and/or headache. Some individuals with recurrent episodes of HSV do not report pain due to virally-mediated trigeminal nerve damage. Iritis associated with HSV is usually unilateral and may or may not have corneal involvement, such as keratitis or corneal edema. Multiple studies have reported iris atrophy and a distorted pupil in many patients (Figure 1).³⁶ Herpetic uveitis is commonly accompanied by high intra-ocular pressure (IOP). The elevated IOP can occur from inflammation of the trabecular meshwork, posterior synechiae (the adherence of the iris to either the cornea or lens), and/or sensitivity to topical steroids. The keratic precipitates associated with herpetic uveitis are often pigmented and located inferiorly on the cornea.³⁷

Herpetic uveitis is primarily treated with topical corticosteroids as the pathophysiology is believed to be an immune-mediated response to the virus. The Herpetic Eye Disease Study (HEDS) assessed the benefit of adding oral acyclovir to a regimen of topical prednisolone phosphate and trifluridine for the treatment HSV uveitis. This was a multi-centered trial that randomly assigned patients to a 10-week course of oral acyclovir 400 milligrams 5 times daily or oral placebo in conjunction with topical trifluridine and a topical corticosteroid. Treatment failure was defined as a persistence or worsening of ocular inflammation,

withdrawal of medication because of toxicity, or a request by the patient to withdraw from the trial for any reason. Treatment failure occurred in 11 (50%) of 22 patients in the acyclovir group and in 19 (68%) of 28 patients in the placebo group. While this difference did not reach statistical significance, there was a trend that suggested a benefit of oral acyclovir.³⁸ In reality, topical antivirals are not used to treat individuals with HSV uveitis without active keratitis; systemic antivirals are often used concomitantly with topical corticosteroids. Uveitis complications also need to be treated, and IOP lowering medications are often needed either acutely or chronically. Fortunately, treatment of inflammation typically leads to a decrease in IOP in these patients.

Herpetic disease can also manifest in the retina as acute retinal necrosis (ARN). This entity is more commonly seen the elderly compared to younger individuals.³⁹ HSV I and varicella-zoster virus (VZV) more common causes of ARN in the older populations, while HSV2 is more common in younger populations.³⁹ ARN can masquerade as an anterior uveitis, and it is thus important to perform a detailed dilated fundus examination in all patients with uveitis. Unlike HSV anterior uveitis, ARN presents bilaterally in about 66% of patients.³⁹ Symptoms of ARN include ocular pain, decreased visual acuity, floaters, and photophobia.³⁹ ARN progresses quickly and rapid diagnosis and treatment are needed. Even with prompt treatment, patients are at risk for retinal detachment arising from areas of retinal atrophy.³⁹ Treatment involves intravitreal, oral, and/or intravenous antivirals; corticosteroids are often used concomitantly to treat inflammation.³⁹

B. Ocular ischemic syndrome (OIS)—Ocular ischemia can lead to anterior and posterior-segment ischemia, and one of its manifestations can be anterior uveitis.⁴⁰ Ocular ischemia is a condition caused by stenosis or blockage of either the common or internal carotid artery. The ophthalmic artery, a branch of the internal carotid artery, supplies the orbital structures of the eye. Any type of occlusion of the carotid arteries can result in decreased blood supply to the orbital structures which can lead to visual loss. A complete occlusion of the carotid artery is seen in about 50% of all patients with ocular ischemic syndrome.⁴¹ More men are affected by ocular ischemia than women, partially explained by the higher rates of atherosclerosis in men.⁴¹ Pre-existing ipsilateral carotid stenosis can be found in more than 90% of patients with OIS.⁴² This condition usually occurs in patients over 65 years of age, and it is uncommon in patients under 50. It should always be suspected in elderly patients with asymmetric anterior uveitis, hypotony, neovascularization, cataract, and retinopathy.

The most common manifestation of OIS is transient or permanent vision loss. A mild anterior uveitis (trace cell and flare) is present in approximately 20% of affected individuals.⁴¹ The presence of ocular ischemia is an indicator of systemic ischemic disease and treatment includes systemic management of vascular risk factors. A carotid ultrasound should be performed in these patients and based on the findings, endarterectomy (removing the blockage in the artery) or carotid stenting can be considered. Locally, topical corticosteroids can be used to decrease anterior segment inflammation, as needed. Iris neovascularization is also seen in OIS and should be evaluated and treated, since 90% or more of patient who develop neovascular glaucoma become legally blind.⁴² Posterior segment ischemic findings are present in almost all patients and include narrowing of the

retinal arteries and dilated retinal veins. Midperipheral intraretinal hemorrhages are present in about 80% of the patients (Figure 2).

3.2 Posterior and panuveitis in the elderly

One common cause of posterior and panuveitis in the elderly is ocular sarcoidosis. Central nervous system lymphoma, while not common, must be considered in older individuals as it can masquerade as a posterior and panuveitis.

A. Ocular sarcoidosis—Sarcoidosis is a leading cause of ocular inflammation and non-caseating granulomas can affect all parts of the eye as well as other organs. Specifically, sarcoidosis can present in the eye as a conjunctivitis, scleritis, uveitis, and/or orbital inflammation. The most common presentation is a bilateral granulomatous uveitis seen in 20%–60% of individuals with sarcoidosis.^{43–45} The HLA-DRB1 locus was found to be a significant risk factor for sarcoidosis, and the allele HLA-DRB1*0401 was associated with ocular involvement in both blacks and whites (odds ratio 3.49).^{43,46} Sarcoidosis has a bimodal peak age of presentation of 20 to 30 years and 50 to 60 years.⁴³ Blacks are more likely to develop the disease at a younger age than whites (35 to 44 vs. 43 to 52 years).⁴³ Women are more frequently affected than men.⁴³ The pathophysiology of sarcoidosis involves the interplay of macrophages, dendritic cells, B cells, and T-helper cells, particularly Th1.⁴⁷ Th1 cells release cytokines like IFN γ that promote macrophage accumulation which are responsible for the formation of granulomas.⁴⁷

Ocular sarcoidosis can present with findings both in the anterior (cornea, iris, ciliary body, and/or lens) and posterior (vitreous humor, retina, choroid, and/or optic nerve) segments of the eye. Anterior chamber inflammation is a common finding in sarcoid uveitis (91% in one study⁴⁸) both with and without posterior segment findings.⁴³ Mutton-fat keratic precipitates, iris nodules or both are present in about 46%.⁴⁴ Vitritis (Figure 3A) with snowballs or string of pearls can be found in approximately 50% of patients. Posterior uveitis in sarcoidosis is usually bilateral and typically manifests with choroidal inflammation.⁴³ Choroidal granulomas can present as unifocal or multifocal spots, and centrally or peripherally.⁴⁴ Many times, punched out choroidal lesions are seen representing inactive choroidal disease (Figure 3B). Perivascular exudates along retinal veins can be seen in severe forms and have been described as “candle-wax drippings.”⁴⁹ Leakage is often seen on fluorescein angiography from midperipheral vessels typically without vascular occlusion.⁴³

Sarcoid uveitis is typically a chronic condition; and ocular complications such as cystoid macular edema, vitreous opacities, and glaucoma are well-recognized complications of sarcoid uveitis, with the former two being major causes of vision decrease in patients with sarcoid intermediate uveitis.⁴³ Currently there is no definitive diagnostic test for sarcoidosis other than a biopsy. The advancement of imaging technology has allowed for useful non-invasive imaging of the choroid and retina in cross-section, offering insights into the underlying diagnosis and helping to differentiate between an autoimmune granulomatous disease like sarcoidosis from an infectious granulomatous uveitis like tuberculosis. Sattler’s medium-sized vessel choroidal layer appears disproportionately enlarged in sarcoid compared with tuberculous uveitis on enhanced depth optical coherence tomography imaging.⁵⁰

Management of ocular sarcoidosis depends on the area of the eye affected and the severity of inflammation. Systemically, anti-tumor necrosis factor alpha (TNF- α) agents (e.g. adalimumab (Humira™, AbbVie, Mettawa, Illinois)) have become first line agents for the disease.⁵¹ Locally, anterior uveitis can be managed with topical corticosteroids, while intermediate and posterior uveitis can be treated with intravitreal corticosteroid injections or longer acting depot, as needed. Typically, a combination of systemic and local therapy is used to manage inflammation with the goal being total control of inflammation and minimal side effects (local and systemic) from therapy. Imaging can be used to monitor response to treatment since the choroid appears to be thicker in active granulomatous uveitis. Imaging can also be used to demonstrate resolution of the lesions.⁵⁰

B. Central nervous system (CNS) lymphoma—CNS lymphoma can masquerade as a bilateral intermediate, posterior, and pan- uveitis. It is most commonly caused by high-grade non-Hodgkin lymphoma, with the tumor arising from B cells.^{52,53} Major risk factors for this disease are immunodeficiency and advancing age.⁵⁴ The age of peak incidence for this lymphoma is around 75 to 84 years.⁵² Asians are more likely to be affected than blacks and whites. Though incidence is higher among men than women, women are more likely to present with intraocular involvement compared to men.^{52,53,55} Fifteen to twenty five percent of individuals diagnosed with CNS lymphoma have intraocular involvement, approximately half of which had eye involvement as the presenting feature of the disease.^{56,57}

The typical clinical profile is an elderly patient with treatment refractory uveitis. The posterior segment of the eye, particularly the vitreous and the uvea, are common sites of involvement.⁵⁶ On examination, findings are typically bilateral but can be asymmetric. Circulating tumor cells can appear in the anterior chamber in as many as 75% of patients and occasionally settle into a pseudo-hypopyon formation. The keratic precipitates in PCNSL typically have a branching appearance, and the vitritis appears as coarse, clumped cells which are a mix of reactive lymphocytes and malignant lymphocytes.⁵⁸ The most distinct feature of PCNSL is low-lying, yellow-whitish lesions deep in the sensory retina (Figure 4). They can be single, multiple, confluent, or discrete. Subretinal pigment epithelium infiltrates due to the accumulation of atypical lymphocytes are found beneath the RPE and optic nerve. These atypical lymphocytes can also accumulate within or around retinal vessels, compromising vasculature and giving a clinical aspect of an ischemic retinopathy or viral retinitis.

The optimal management of CNS lymphoma with intraocular involvement remains controversial. It is often systemic, as sub-clinical CNS disease is suspected even in patients with isolated ocular manifestations. Locally, therapies that have been described include external beam radiation⁵⁹ and intravitreal chemotherapy.⁶⁰

6. Challenges in treating the elderly

6.1 Polypharmacy in elderly

Treatment of the different types of uveitis can include both local and systemic medications. The elderly are a special population because they are often on multiple medications, including “aspirin, anti-hypertensives, and statins”⁶¹ in addition to systemic medications

they may be using to treat uveitis. Therefore, there is a need to consider the resulting multi-drug interactions that occur in the elderly.

Along with an increased number of total medications, there are also changes in drug pharmacokinetics (the movement of a drug throughout the body) and pharmacodynamics (effects of a drug on the body) with age. Regarding pharmacokinetics, with age, blood flow to the liver decreases. There is decreased liver mass, with a subsequent decrease in the amount of drug that can be metabolized.⁶¹ Drug metabolism is important because it not only helps prevent drug toxicity, but also marks harmful substances for renal excretion. Unfortunately, renal clearance also decreases with age⁶¹; and drugs stay in the bloodstream longer and may accumulate if inappropriate dosing is given. Regarding pharmacodynamics, drugs may be more effective in the elderly because of lessened regulatory functions (e.g. risk of postural hypotension after taking anti-hypertensives).⁶¹ Eye care professionals must take into consideration the challenges of polypharmacy in the elderly and ensure that the doses for systemic medications result in benefit with the least amount of harm.

6.2 Adherence

Nonadherence is another challenge faced by health professionals. One explanation for nonadherence is a lack of or inadequate health literacy.⁶² Adherence can be improved by taking time to ensure that the patient understands why they are using medications as well as clear instructions on how to use them. Another barrier to adherence is cognitive, hearing, and/or vision impairment which is common in the elderly.⁶² Health professionals should ask whether individuals need someone to assist them in taking medication. Another challenge comes from side effects or adverse reactions.⁶² If nonadherence is an issue, it is imperative that health professionals inquire about the reasons for nonadherence. This discussion may lead to alternative therapies that are more acceptable and/or comfortable for the patient.

Conclusions

Uveitis is a group of inflammatory conditions of the eye that have various underlying causes and various clinical manifestations. Certain types of uveitis are more common in the elderly and this may be attributed to age-related risk factors such as immunosenescence (predisposing the elderly to infectious uveitis and cancer) and inflammaging (predisposing the elderly to non-infectious uveitis). Eye care professionals should approach all patients with uveitis with a wide differential, obtaining the appropriate history and clinical examination to arrive at the correct diagnosis. Management of uveitis varies based on the underlying etiology, disease manifestations, and structural complications. Treatment options for uveitis include systemic drugs, which raise challenges regarding drug interactions in a population that is likely on multiple medications already. Eye care professionals must work with their patients as partners to increase education, manage side effects, and examine possible reasons for nonadherence to help achieve optimal patient outcomes.

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Key Points

- Uveitis is an inflammatory condition that can present in different locations in the eye and can have various etiologies.
- A decline in effective immunological function that occurs with aging (e.g. decreased ability to fight infection, imbalance of inflammatory mediators) likely contributes to the elderly's susceptibility to uveitis.
- Eye doctors need to consider the epidemiology and the different clinical profiles of uveitis in their differential diagnoses as well as take into consideration the challenges of polypharmacy and nonadherence when determining treatment.

Figure 1.
Slit lamp photograph depicting iris atrophy in an individual with herpes simplex virus associated chronic iritis.

Figure 2.
Fundus photograph depicting mid-peripheral hemorrhages and narrowed arteries in an individual with ocular ischemic syndrome.

Figure 3. Fundus photograph depicting (A) vitreous haze (arrow) in the setting of vitritis in an individual with sarcoidosis and (B) punched out peripheral choroidal lesions representing inactive disease.

Figure 4. Fundus photograph depicting multifocal, creamy, sub-retinal lesions (arrow) in an individual with primary central nervous system lymphoma.

Table

Summary of studies evaluating the most common diagnoses of uveitis in the elderly, reproduced from Abdulaal 2015.

Study	Most Common	Second Most Common	Third Most Common
Lebanon 2014	Idiopathic uveitis (5/18)	Herpes simplex virus (5/18)	Tuberculosis (3/18)
Colombia 2019	Toxoplasmosis (10/55)	Idiopathic uveitis (9/55)	Herpes Simplex virus (5/55)
Saudi Arabia 2009	Acute anterior uveitis (14/51)	Herpes simplex virus (8/51)	Tuberculosis (7/15)
Turkey 2005	Idiopathic uveitis (34/50)	Herpes simplex virus (3/50)	Sarcoidosis (2/50)
Japan 2005	Idiopathic uveitis (53/82)	Sarcoidosis (9/82)	Herpes simplex virus (7/82)
France 2003	Idiopathic uveitis (40/80)	Herpes simplex virus/Varicella zoster virus (10/80)	Birdshot (10/80)
Saudi Arabia 2002	Acute anterior uveitis (5/18)	Tuberculosis (5/18)	Herpes simplex virus (3/18)
France 2002	Idiopathic uveitis (5/19)	Sarcoidosis (3/19)	Lymphoma (2/19)
United States 1998	Idiopathic uveitis (43/138)	HSV (16/138)	Sarcoidosis (11/138)
Finland 1994	Acute anterior uveitis (118/191)	Idiopathic uveitis (21/191)	Sarcoidosis (2/191)
United Kingdom 1994	Idiopathic uveitis (55/71)	Insulin dependent diabetes mellitus (5/71)	Sarcoidosis (3/71)