Uveitis: Etiology, clinical manifestations, and diagnosis

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INTRODUCTION

Uveitis, the process of intraocular inflammation, may result from many causes. Referral to an ophthalmology specialist is indicated for the diagnosis and management of most patients with symptoms suggesting uveal tract inflammation.

The definition of uveitis and its subsets; causes of uveitis and differential diagnosis of underlying conditions; clinical manifestations, diagnosis, and differential diagnosis of uveitis; and the role of the non-ophthalmologist in the diagnostic evaluation of patients with uveitis are described here. The treatment of uveitis is presented separately. (See "Uveitis: Treatment".)

DEFINITIONS

Uveitis is characterized by inflammation of the uvea, which is the middle portion of the eye; the anterior portion of the uvea includes the iris and ciliary body, and the posterior portion of the uvea is known as the choroid (figure 1). The term "uvea" derives from the Latin word for "grape," since anatomists once thought that the peeling of the outside of the eye left a grape-like structure beneath.

- Inflammation of the anterior uveal tract, characterized by the presence of leukocytes in the anterior chamber of the eye, is called anterior uveitis and is synonymous with iritis. When the adjacent ciliary body is also inflamed, the process is known as iridocyclitis [1].

- The presence of leukocytes in the vitreous humor and evidence of active chorioretinal inflammation are diagnostic of intermediate uveitis and posterior uveitis, respectively. Terms used to describe forms of uveitis posterior to the lens include vitritis, intermediate uveitis, pars planitis, choroiditis, retinitis, chorioretinitis, and retinochoroiditis [1].

- Panuveitis is defined as simultaneous inflammation in the anterior chamber, vitreous humor, and retina or choroid.

ETIOLOGY

Uveitis frequently occurs in association with other systemic medical conditions, especially infections and inflammatory diseases, but may occur as an isolated process. Individual forms of uveitis may be distinguished on the basis of location within the eye (see 'Definitions' above); onset, symmetry and continuity of inflammation; associated complications (see 'Complications' below); and distribution of cells along the corneal endothelium. The latter changes are known as keratic precipitates (picture 1). Both the size and distribution of keratic precipitates are helpful in the differential diagnosis of the underlying cause. The diversity of keratic precipitates is especially appreciated by magnified images obtained with confocal microscopy [2].

Uveitis may be divided into four major subsets based upon the etiology of the inflammation (table 1A-C):

- Infections (see 'Infectious causes' below)

- Systemic immune-mediated disease, including:

  - Systemic inflammatory diseases (see 'Systemic inflammatory diseases' below)
  - Other immune-related conditions (see 'Drugs and hypersensitivity reactions' below)

- Syndromes usually confined to the eye (see 'Uveitis syndromes usually restricted to the eye' below)

- Masquerade syndromes such as lymphoma, leukemia, or retinal degeneration that result in a leukocyte response that can easily be mistaken for inflammation (table 2) (see 'Differential diagnosis' below)

Approximately 40 percent of patients have uveitis associated with a systemic immune-mediated disease in the author's referral population; the proportion of patients with each type of uveitis in an unselected general population is uncertain and varies between populations. Approximately 30 percent of patients with uveitis do not fit into any well-defined diagnostic

category and are usually labeled as having idiopathic uveitis. Other alternative terms for idiopathic uveitis include undifferentiated and unclassifiable uveitis.

A genetic predisposition may contribute to the development of uveitis. For example, birdshot chorioretinitis is strongly associated with human leukocyte antigen (HLA)-A29, and acute anterior uveitis is associated with HLA-B27 Epidemiologic data have also shown differences in incidence among different ethnicities, further supporting a role for genetic factors [3]. A few studies have also suggested that cigarette smoking may be associated with an increased risk of uveitis and with increased severity [4,5].

Infectious causes — The infectious causes of uveitis include bacterial and spirochetal diseases, viral diseases, fungal infections, and parasitic infections (table 1A). These infections generally have distinctive presentations and are likely to affect different populations. In addition, broad-spectrum amplification of pathogen ribonucleic acid (RNA) or deoxyribonucleic acid (DNA) using ocular fluid has implicated an infectious cause of uveitis in nearly 10 percent of patients for whom no other cause was found [6].

- **Herpes virus** – Both herpes simplex and herpes zoster can cause a keratouveitis, which is usually unilateral. Keratouveitis is an inflammation of the cornea along with uveitis that is primarily anterior. The presence of cutaneous vesicles, characteristic corneal changes, reduced corneal sensation, elevated intraocular pressure, and iris atrophy may be clues to the diagnosis. Both herpes simplex and zoster can also cause a retinitis known as acute retinal necrosis. This is a rare but treatable cause of visual loss. (See "Epidemiology, clinical manifestations, and diagnosis of herpes simplex virus type 1 infection", section on 'Ocular manifestations' and "Epidemiology, clinical manifestations, and diagnosis of herpes zoster", section on 'Herpes zoster ophthalmicus'.)

- **Cytomegalovirus** – Cytomegalovirus (CMV) as a cause for posterior uveitis in adults is found almost exclusively in the immunocompromised host, especially patients with human immunodeficiency virus (HIV) infection and extremely low CD4 counts (picture 2). Uveitis (CMV retinitis) is the most common serious ocular complication of the acquired immunodeficiency syndrome (AIDS) and is discussed in detail elsewhere. (See "Pathogenesis, clinical manifestations, and diagnosis of AIDS-related cytomegalovirus retinitis".)

  CMV infection is also an uncommon cause of anterior uveitis in patients in North America or Europe. It is much more common in southeast Asia, where it occurs in patients who are not immunocompromised and who often present with ocular hypertension [7]. (See

"Epidemiology, clinical manifestations, and treatment of cytomegalovirus infection in immunocompetent adults", section on 'Ocular manifestations'.)

- **Toxoplasmosis** – Toxoplasmosis is a surprisingly common cause of uveitis in the normal host. In many instances, it is presumed to be a reactivation of a congenitally acquired infection. It is suspected on the basis of a typical chorioretinal lesion (picture 3); the diagnosis is supported by serology. Serologic evidence for previous infection by toxoplasmosis is extremely common in the healthy United States population [8]. Most chorioretinal scarring from toxoplasmosis is due to infection during gestation, but scarring is increasingly recognized as a result of recent infection [9]. (See "Toxoplasmosis in patients with HIV" and "Toxoplasmosis: Ocular disease".)

  Ocular toxoplasmosis can affect both normal and immunocompromised hosts but is far more common in immunocompetent patients, in contrast to central nervous system toxoplasmosis, which is seen almost exclusively in the immune-compromised.

- **Syphilis** – Syphilis accounts for less than 1 percent of patients with uveitis in most large series. It may present in a variety of forms, including posterior uveitis, such as a chorioretinitis or retinal vasculitis (picture 4) [10]. It is critical to recognize syphilis because of its important therapeutic implications. (See "Neurosyphilis".)

- **Tuberculosis** – Tuberculosis is an uncommon cause of uveitis in North American referral centers. It should be considered in the differential diagnosis when the uveitis worsens despite glucocorticoid therapy. Additional factors that raise suspicion for this diagnosis are active tuberculosis elsewhere in the body, cachexia, homelessness, a history of incarceration, a granulomatous appearance for the ocular inflammation, or immunosuppression. In some geographic areas such as Saudi Arabia, tuberculosis is considered a common cause of uveitis. (See "Tuberculosis and the eye".)

- **Cat-scratch disease** – Cat scratch disease is increasingly recognized as a cause of uveitis that is typically unilateral. Although the uveitis associated with cat scratch disease can have a variable presentation, a macular star and optic nerve edema are especially characteristic (picture 5) [11]. (See "Microbiology, epidemiology, clinical manifestations, and diagnosis of cat scratch disease".)

- **West Nile virus** – West Nile viral infection can cause chorioretinitis in association with a retinal vasculitis. Uveitis is a common feature of this viral disease and may be asymptomatic. (See "Clinical manifestations and diagnosis of West Nile virus infection", section on 'Ocular manifestations'.)

- **Ebola virus disease** – The occurrence of uveitis during the convalescent phase of Ebola virus disease has been reported in four patients in one case series [12], as well as another patient in a separate case report in which viable virus was obtained from the aqueous humor of the affected eye nine weeks after clearance of viremia [13]. In a study of 277 survivors of Ebola in Sierra Leone, 60 percent had new ocular symptoms and 18 percent were diagnosed with uveitis [14]. (See "Clinical manifestations and diagnosis of Ebola virus disease", section on 'Signs and symptoms' and "Clinical manifestations and diagnosis of Ebola virus disease", section on 'Convalescence' and "Epidemiology and pathogenesis of Ebola virus disease", section on 'Risk of transmission through different body fluids'.)

- **Zika virus disease** – The Zika virus appears to be another infectious cause of uveitis, including both presumed congenital disease and uveitis in adults with active infection. In 2015, during an epidemic outbreak of this infection, 29 infants with microcephaly underwent detailed eye examinations at a tertiary center in Brazil [15]. Twenty-three of the 29 mothers had symptoms consistent with Zika exposure during pregnancy. Ten of the 29 infants had ocular abnormalities such as chorioretinal atrophy, pigmentary mottling of the retina, or optic nerve disease. These findings are consistent with Zika exposure in utero resulting in scarring of the uveal tract. Both anterior and posterior uveitis have also been reported as a component of active infection with Zika in case reports [16,17]. (See "Zika virus infection: An overview".)

- **COVID-19 infection or vaccination –** A variety of retinal and/or choroidal inflammations including microvascular disease have been rarely reported in the setting of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (coronavirus disease 2019 [COVID-19]) [18,19]. Similarly, vaccination against COVID-19 has been reported to be a rare cause of uveitis or a trigger to exacerbate uveitis [20].

- **Fuchs heterochromic iridocyclitis** – Fuchs heterochromic iridocyclitis, a form of chronic unilateral, primarily anterior uveitis, is now considered to be most often secondary to a remote infection with rubella [21].

Systemic immune-mediated causes — Uveitis can occur as a manifestation of many systemic inflammatory conditions, including the spondyloarthritis (SpA) family of disorders, sarcoidosis, other systemic rheumatic diseases, and other systemic disorders (table 1C). Uveitis is only rarely due to a reaction to a medication.

Systemic inflammatory diseases

- **Spondyloarthritis** – Spondyloarthritides, such as ankylosing spondylitis and reactive arthritis, are the most common systemic immune disorders associated with uveitis in

North America and Europe [22]. Twenty to 40 percent of patients with either of these HLA-B27-related disorders develop the sudden onset of anterior uveitis. When it occurs, uveitis is often the manifestation to suggest the diagnosis of the systemic illness. As an example, one study found that 40 percent of patients presenting to an ophthalmology emergency department for acute anterior uveitis without a prior diagnosis had a form of SpA as the underlying cause [23]. Uveitis in association with SpA is approximately twice as common in males as in females.

Uveitis in association with SpA is typically unilateral and tends to resolve within three months of its onset. Recurrences are common and can occur in the contralateral eye. The prognosis for this form of uveitis is generally excellent. (See "Clinical manifestations and diagnosis of peripheral spondyloarthritis in adults" and "Clinical manifestations of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults" and "Reactive arthritis".)

Patients with recurrent anterior uveitis without back or joint symptoms or the diagnosis of SpA, particularly those who are HLA-B27-positive, may have an incomplete form of SpA. A strong association was seen between patients with recurrent acute anterior uveitis and the presence of inflammation at the tendon or ligament insertion (enthesitis) demonstrated by ultrasound, despite the absence of clinical symptoms of spondyloarthropathy [24].

- **Sarcoidosis** – Sarcoidosis accounts for a significant percentage of patients with uveitis in most series from referral centers [25-27]. Approximately 20 percent of patients develop eye disease as their initial presentation of sarcoid. The eye disease can take on many forms, including uveitis, dry eyes, optic neuritis, lid inflammation, or orbital disease [28]. Uveitis in patients with sarcoid is frequently associated with retinal vasculitis, which may be either perivascular or involve retinal vascular changes (picture 6) [29]. The eye disease may persist despite the resolution of adenopathy [30]. (See "Clinical manifestations and diagnosis of sarcoidosis".)

- **Juvenile idiopathic arthritis** – Juvenile idiopathic arthritis (JIA) may be associated with uveitis, particularly in the subset of patients with oligoarticular disease and a positive antinuclear antibody. The onset of uveitis is usually between the ages of two and eight and is asymptomatic in the majority of patients.

  The uveitis associated with JIA is usually bilateral, insidious in onset, chronic in duration, and anterior. The eye disease is commonly associated with complications such as band keratopathy, posterior synechiae (picture 7), cataract formation, and glaucoma. The uveitis sometimes lasts for decades, long after the joint disease has disappeared. Uveitis in

children with oligoarticular disease and recommendations for screening are discussed in detail elsewhere. (See "Oligoarticular juvenile idiopathic arthritis", section on 'Uveitis'.)

- **Psoriatic arthritis and inflammatory bowel disease** – Seven percent of patients with psoriatic arthritis and 2 to 9 percent of patients with inflammatory bowel disease (IBD, Crohn's disease, or ulcerative colitis) may develop uveitis [31,32]. The uveitis is associated with HLA-B27 in approximately 45 percent of cases with IBD. (See "Clinical manifestations and diagnosis of psoriatic arthritis" and "Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults" and "Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults".)

  Both psoriatic arthritis and the arthritis associated with IBD are considered forms of SpA; however, in contrast to the uveitis associated with ankylosing spondylitis and reactive arthritis, uveitis associated with IBD or psoriatic arthritis is frequently bilateral, posterior to the lens, insidious in onset, chronic in duration, and more common in females than males [32,33]. Approximately 75 percent of patients with uveitis and IBD have an associated arthritis that may be axial and/or peripheral. In 10 of 17 patients in one series, the uveitis preceded signs of IBD [32].

- **Tubulointerstitial nephritis and uveitis syndrome** – Tubulointerstitial nephritis and uveitis (TINU) syndrome is an uncommon disorder that occurs most often in adolescents and young women, who may also exhibit additional systemic symptoms and findings including fever, myalgias, mild anemia, and abnormal liver function tests. Patients may experience bilateral, recurrent, or chronic uveitis. Because interstitial nephritis and uveitis can also occur together in sarcoidosis and in Sjögren's disease, patients with TINU syndrome should be evaluated for these disorders as well. The TINU syndrome is discussed in more detail elsewhere. (See "Tubulointerstitial nephritis and uveitis (TINU syndrome)".)

- **Multiple sclerosis** – Multiple sclerosis (MS) is most commonly associated with optic neuritis, but may also cause a granulomatous anterior uveitis or pars planitis. Females with pars planitis in association with a periretinal vascular infiltrate, known as periphlebitis (picture 8), have about a 30 percent risk of developing MS [34,35]. (See "Manifestations of multiple sclerosis in adults".)

- **Vogt-Koyanagi-Harada syndrome** – Vogt-Koyanagi-Harada syndrome (VKH) is the second leading cause of uveitis in Japan after Behçet syndrome [36]. VKH is presumably an autoimmune disease that is manifested by bilateral posterior uveitis with characteristic fluid accumulation beneath the retina, leading to retinal elevation and detachment [37,38].

It often presents as a panuveitis. The diagnosis of VKH is based upon the clinical presentation; there are no serologic tests or specific histological changes. Patients with VKH may also develop vitiligo, poliosis (loss of color from a patch of hair), sterile meningitis, alopecia, and eighth cranial nerve disease. The disease is common among Hispanic populations in addition to southeast Asian populations. VKH has a strong HLA class II association (specifically with the HLA-D locus and DR4 allele) [39]. Similar retinal elevation may occur in central serous chorioretinopathy, a rare disorder that has been associated with glucocorticoid use (see "Major adverse effects of systemic glucocorticoids", section on 'Ophthalmologic effects'). Scleritis affecting the posterior sclera is also a potential cause of multiple serous elevations of the retina.

- **Behçet syndrome** – As many as 80 percent of patients with Behçet syndrome develop uveitis [40]. Uveitis is often the dominant manifestation of this disease and is typically bilateral. Similar to HLA-B27-associated iritis, it is frequently episodic; but, unlike HLA-B27-associated disease, the uveitis generally does not resolve completely between episodes. Behçet uveitis often presents as a panuveitis, and retinal vasculitis is a frequent manifestation of Behçet syndrome (picture 9). The uveitis typically leads to blindness if the eye inflammation is not treated [41]. (See "Clinical manifestations and diagnosis of Behçet syndrome", section on 'Ocular disease'.)

- **Kawasaki disease** – Kawasaki disease may be associated with a mild anterior uveitis, which may be accompanied by conjunctivitis. (See "Kawasaki disease: Clinical features and diagnosis", section on 'Ocular manifestations'.)

- **Relapsing polychondritis** – A high percentage of patients with relapsing polychondritis also have ocular involvement. The eye disease occurs in many forms, including episcleritis, scleritis, and uveitis. Ocular involvement in relapsing polychondritis is discussed in more detail elsewhere. (See "Clinical manifestations of relapsing polychondritis", section on 'Eye involvement'.)

- **Sjögren's disease** – In Sjögren's disease, a very small percentage of patients develop chronic anterior and posterior uveitis, and it is possible that uveitis causes secondary ocular dryness [42]. (See "Clinical manifestations of Sjögren's disease: Exocrine gland disease".)

- **Systemic lupus erythematosus** – Systemic lupus erythematosus (SLE) can involve the eye in a variety of forms [43]. Dryness is the most common ocular manifestation; cotton wool spots (picture 10) occur in about 7 percent of patients and indicate local retinal ischemia

[44]. Anterior uveitis is a rare manifestation. (See "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults", section on 'Clinical manifestations'.)

- **Systemic vasculitis** – Except for Behçet syndrome, uveitis is infrequently associated with other systemic vasculitides, including polyarteritis and granulomatosis with polyangiitis [45]. More typical vision-threatening manifestations of granulomatosis with polyangiitis are scleritis and orbital disease. The term retinal vasculitis often causes confusion. In part, this results from diagnosing retinal vasculitis on the basis of vascular leakage as seen by a fluorescein angiogram or on the basis of perivascular infiltrate as seen on examination. Similar criteria are not used to diagnose systemic vasculitis. Retinal vasculitis can be secondary to a disease such as sarcoidosis or birdshot chorioretinopathy, which are not generally categorized as vasculitides. (See "Clinical manifestations and diagnosis of polyarteritis nodosa in adults" and "Granulomatosis with polyangiitis and microscopic polyangiitis: Clinical manifestations and diagnosis".)

- **Primary angiitis of the central nervous system** – Granulomatous angiitis of the central nervous system may also be accompanied by inflammation of the uvea [46]. (See "Primary angiitis of the central nervous system in adults".)

- **Blau syndrome** – One of the rarest forms of uveitis is Blau syndrome. This disease, transmitted in an autosomal dominant pattern, is characterized by the development of noncaseating granulomatous inflammation of the uvea, skin, and joints. (See "The autoinflammatory diseases: An overview".)

The Standardization of Uveitis Nomenclature (SUN) working group has relied on machine learning to develop classification criteria for multiple forms of uveitis [47].

Drugs and hypersensitivity reactions — Drug or hypersensitivity reactions are a rare cause of uveitis. The following drugs are among those that have been implicated:

- Rifabutin – Rifabutin (used in the treatment of atypical mycobacterial infection) appears to be frequently associated with a florid anterior uveitis [48]. The inflammation resolves despite continuing the medication, suggesting that the inflammation may result from a hypersensitivity reaction triggered in part by the death of mycobacterial organisms induced by the antibiotic.

- Cidofovir – Cidofovir, an antiviral drug that can be injected intravitreally, is also frequently associated with uveitis [49,50]. Other drugs administered by intravitreal injection and associated with eye inflammation include vancomycin [51] and brolucizumab [52], a light chain monoclonal antibody that inhibits vascular endothelial growth factor.

- Fluoroquinolone antibiotics – Several fluoroquinolone antibiotics have been associated with an increased risk of uveitis, including moxifloxacin and ciprofloxacin, but not levofloxacin [53]. Moxifloxacin is implicated in a rare form of uveitis characterized by some loss of pigment in the iris [54].

- Bisphosphonates – Bisphosphonates, especially when administered intravenously, are an infrequent cause of uveitis [55]. (See "Risks of bisphosphonate therapy in patients with osteoporosis", section on 'Ocular side effects'.)

- BRAF kinase inhibitors – Vemurafenib and dabrafenib, which are inhibitors of BRAF kinase that are used for the treatment of metastatic melanoma, may infrequently cause uveitis. (See "Systemic treatment of metastatic melanoma with BRAF and other molecular alterations", section on 'Toxicities of BRAF and MEK inhibitors'.)

- Cancer immunotherapy – Immune checkpoint inhibitor immunotherapy, including the use of ipilimumab, pembrolizumab, atezolizumab, durvalumab, and nivolumab, has been associated with uveitis and other ocular inflammatory manifestations and is discussed in more detail separately [56]. (See "Toxicities associated with immune checkpoint inhibitors", section on 'Eye'.)

Uveitis syndromes usually restricted to the eye — Although many forms of uveitis are associated with systemic inflammatory or infectious disease, a variety of uveitis syndromes generally occur without extraocular or infectious involvement (table 1B):

- **Pars planitis** – Pars planitis is a relatively common form of uveitis characterized by the presence of inflammatory debris over the pars plana, the portion of the eye between the retina and the ciliary body [57]. Thus, pars planitis is an anatomic description of the location of inflammation. Pars planitis is sometimes called peripheral uveitis and is a subset of intermediate uveitis.

  Pars planitis is usually not associated with a systemic disease, but it can be a manifestation of systemic conditions including MS [58] or sarcoidosis [59]. Because of its association with MS, an evaluation to identify evidence for MS may be appropriate in some patients. (See "Manifestations of multiple sclerosis in adults" and 'Diagnostic testing' below.)

- **Birdshot chorioretinitis** – Birdshot chorioretinitis is a chronic, bilateral, posterior uveitis associated with multiple focal inflammatory aggregates that resemble tiny birdshot pellets (picture 11) [60,61]. Ninety-five percent of patients with this disorder possess the HLA-A29 antigen [62].

- **Sympathetic ophthalmia** – Sympathetic ophthalmia is an inflammation of the contralateral eye of a small percentage of patients who have experienced penetrating trauma to one eye [63]. Multiple surgeries to either eye are another recognized, rare trigger for sympathetic ophthalmia. It usually begins as an anterior uveitis several weeks to a year following the trauma and is thought to result from an autoimmune response to a retinal antigen [64].

- **Post-traumatic inflammation** – Most experts do not include trauma as a category of uveitis, although cataract surgery and other intraocular surgeries routinely do cause some postoperative inflammation that is generally self-limited. Since cataract surgery is performed in the United States more than 1 million times annually, some would argue that cataract surgery is the most common cause of uveitis. This form of post-traumatic inflammation should not be confused with sympathetic ophthalmia, which is immune-mediated, persistent, and often severe, but much less common than routine postsurgical inflammation.

- **Immune recovery uveitis** – Immune recovery uveitis is a phenomenon most often recognized in association with the use of antiretroviral therapy (ART) for HIV infection. This phenomenon is referred to as the immune reconstitution inflammatory syndrome (IRIS). As this treatment allows recovery of CD4 T cell counts, some patients with prior CMV retinitis develop intraocular inflammation, presumably due to an enhanced immune response. (See "Pathogenesis, clinical manifestations, and diagnosis of AIDS-related cytomegalovirus retinitis" and "Overview of immune reconstitution inflammatory syndromes", section on 'Viral infections'.)

- **Idiopathic** – Approximately 30 percent of patients with uveitis have disease that does not fit into any apparent etiologic category [25,65]. Many patients with this disorder, sometimes called idiopathic or undifferentiated uveitis, may have a form of sarcoid that is limited to the eye [66]. Viral infections may account for some cases of this form of uveitis [67] (see 'Systemic inflammatory diseases' above and 'Infectious causes' above). Transcriptomic analysis of gene expression in peripheral blood is being explored as a means to subclassify idiopathic uveitis [68].

CLINICAL MANIFESTATIONS

Symptoms and findings — The symptoms of uveitis, which are all nonspecific, depend upon the portion of the uveal tract that is involved (see 'Differential diagnosis' below). Findings also differ depending upon the location of the involvement, and visual loss may occur with anterior,

intermediate, or posterior involvement. Anterior uveitis is about four times more common than posterior uveitis [69].

- **Anterior uveitis** – Anterior uveitis may produce pain and redness, although these symptoms are minimal if inflammation begins insidiously (eg, in juvenile idiopathic arthritis [JIA]). In anterior uveitis (iritis), the redness, if present, is primarily noted at the limbus (the junction between the cornea and the sclera); such patients often have a constricted pupil and pain. The degree of visual loss associated with anterior uveitis is variable.

  The presence of leukocytes in the anterior chamber of the eye on slit lamp examination is characteristic of anterior uveitis, but is nonspecific (see 'Differential diagnosis' below). Leukocytes are not normally found in the aqueous humor that fills the space between the cornea and the lens. A haze, described by ophthalmologists as "flare," may also be appreciated by slit-lamp examination and reflects protein accumulation in the aqueous humor secondary to disruption of the blood aqueous barrier.

- **Posterior and intermediate uveitis** – In contrast to anterior uveitis, posterior or intermediate uveitis is more likely to be painless, but may result in nonspecific visual changes such as floaters and/or reduced visual acuity. Redness of the eye is not a prominent feature of posterior inflammation unless there is an accompanying anterior uveitis.

  In posterior or intermediate uveitis, direct visualization of active chorioretinal inflammation and/or leukocytes in the vitreous humor can be detected on ophthalmic examination. Complete examination of the eye posterior to the lens usually includes a technique called scleral depression. This maneuver allows the examiner to look for an inflammatory exudate over the pars plana, the portion of the eye just between the retina and the ciliary body. Exudates or "snowbanks" are characteristic of a relatively common form of intermediate uveitis known as pars planitis.

- **Panuveitis** – In patients with panuveitis, inflammation is detected simultaneously in the anterior chamber, vitreous, and retina or choroid either by use of a slit lamp in conjunction with special lenses to focus the beam posterior to the lens or with an indirect ophthalmoscope and a handheld lens.

Complications — Uveitis can be associated with a variety of complications. Evaluation by an ophthalmologist is important in the recognition and management of potential complications of uveitis. Such complications may include:

- Band keratopathy (deposition of calcium in the epithelium of the cornea).
- Posterior synechiae (adhesion of the iris to the lens which lies posterior to it).
- Cataract (resulting from inflammation in some patients or glucocorticoid treatment in others). (See "Cataract in adults".)
- Intraocular hypertension (OHT) and glaucoma. (See "Open-angle glaucoma: Epidemiology, clinical presentation, and diagnosis" and "Angle-closure glaucoma".)
- Cystoid macular edema (fluid accumulation in the area of central vision). Optical coherence tomography is frequently used to detect cystoid macular edema.

The risk of specific complications can differ, depending on the underlying illness and the treatment. As examples, the uveitis associated with JIA is frequently associated with band keratopathy (see 'Systemic inflammatory diseases' above); and in one study OHT occurred in half of patients with varicella zoster virus-associated iridocyclitis, but in only about a quarter of patients with Behçet syndrome, acute anterior uveitis, or sarcoidosis [70]. The OHT in patients with nongranulomatous uveitis was mainly glucocorticoid-induced open-angle OHT, with some cases of angle-closure OHT caused by pupillary block; in granulomatous uveitis it was typically inflammation-induced OHT with no pupillary block-related angle-closure OHT.

DIAGNOSIS AND REFERRAL

When to refer to an ophthalmologist — Referral to an expert in ophthalmology for slit-lamp examination and a dilated fundus examination is required for the diagnosis of uveitis in patients suspected of uveal tract inflammation based upon their symptoms and findings or the presence of other illnesses strongly associated with uveitis. (See "Slit lamp examination" and 'Symptoms and findings' above and 'Etiology' above.)

The mnemonic RSVP can be useful in guiding when to refer a patient to an ophthalmologist. R stands for redness, which for this purpose should be persistent, since redness is common and is often a manifestation of problems that usually do not threaten vision such as ocular allergy, dry eye, or mild chemical irritation (see 'Differential diagnosis' below). S stands for sensitivity to light. Although this is not specific for acute anterior uveitis (it frequently occurs, for example, with migraine headache), it might indicate intraocular inflammation. V stands for visual change. Anyone complaining of visual loss or obscuration needs an ophthalmic exam or sometimes a neurologic exam. The P is for pain, which is prominent in acute anterior uveitis but generally absent in more common diseases such as dry eye or allergy. In general, symptoms that begin acutely require prompt ophthalmic evaluation, while there is less urgency to assess a chronic complaint.

Diagnostic evaluation and findings — In patients with uveitis, leukocytes are seen in the anterior chamber of the eye on slit lamp examination. In comparison with anterior uveitis, posterior or intermediate uveitis is diagnosed by direct visualization of active chorioretinal inflammation and/or by detection of leukocytes in the vitreous humor on ophthalmic examination.

The diagnosis of panuveitis is made when inflammation is detected simultaneously in the anterior chamber, vitreous, and retina or choroid. These findings are identified either by use of a slit lamp in conjunction with special lenses to focus the beam posterior to the lens or with an indirect ophthalmoscope and a handheld lens. Complete examination of the eye posterior to the lens usually includes a technique called scleral depression. This maneuver allows the examiner to look for an inflammatory exudate over the pars plana, the portion of the eye just between the retina and the ciliary body, to determine if findings of pars planitis are present.

A thorough ophthalmic examination can generally exclude alternative diagnoses that can result in similar symptoms and general examination findings.

DIFFERENTIAL DIAGNOSIS

Some of the symptoms or findings seen in uveitis may also occur in other conditions, and a number of noninfectious processes, sometimes termed masquerade syndromes, can be mistaken for an inflammatory process involving the uveal tract; most of these latter conditions are malignancies, and the most common is a B-cell lymphoma (table 2). The differential diagnosis includes:

- **Differential diagnosis by symptom or finding:**
  - **Red eye** – Although many patients with anterior uveitis have a red eye, uveitis can generally be distinguished from other causes of a red eye, such as corneal inflammation (keratitis), conjunctival inflammation (conjunctivitis), blood vessel inflammation in the episclera or sclera (episcleritis and scleritis, respectively), and acute closed-angle glaucoma, on ophthalmic examination. In iritis (anterior uveitis), the redness is primarily noted at the limbus (the junction between the cornea and the sclera), in association with a constricted pupil and pain. The evaluation and differential diagnosis of the red eye is discussed in detail separately. (See "The red eye: Evaluation and management".)
  - **Cells in the anterior chamber** – Leukocytes in the anterior chamber of the eye are characteristic of anterior uveitis (iritis), although other conditions may cause white cells

in the anterior chamber; these include a bacterial corneal ulcer and scleritis, which can often be differentiated from uveitis on a careful ophthalmic examination, aided by slit-lamp examination. However, in some patients, uveitis may occur in association with scleritis. White cells in the anterior chamber may also occur due to a "spillover" phenomenon arising from inflammation in the posterior compartment of the eye. Cellular infiltration without inflammation may occur due to hematologic and lymphoproliferative disorders as well. Occasionally, pigmented cells in the anterior chamber as in pigment dispersion syndrome could be mistaken for leukocytes. (See "Clinical manifestations and diagnosis of scleritis" and "The red eye: Evaluation and management", section on 'Bacterial keratitis' and "Corneal abrasions and corneal foreign bodies: Clinical manifestations and diagnosis", section on 'Differential diagnosis'.)

- **Floaters** – Patients with posterior or intermediate uveitis may have floaters, but floaters or debris in the visual field may also result from noninflammatory processes such as normal aging, in which other findings suggesting uveitis will be absent. Floaters can also occur in patients with a retinal detachment or tear, which can be distinguished from uveitis on the dilated retinal examination with indirect ophthalmoscopy and slit lamp examination. (See 'Symptoms and findings' above and "Retinal detachment".)

- **Masquerade syndromes:**

  - **Intraocular lymphoma** – The most common malignancy that presents like uveitis in adults is lymphoma, typically a B-cell type that is confined to the eye and the central nervous system (picture 12). The eye disease is usually bilateral and generally presents as the insidious onset of visual obscuration, such as floaters. Ocular lymphoma may be difficult to diagnose, but should be suspected when inflammation is refractory to glucocorticoids, when neurological symptoms are present, or when bilateral posterior eye inflammation has begun after age 45. If lymphoma is suspected, the ophthalmology specialist may obtain a sample for vitreous humor cytology to exclude ocular lymphoma or perform a retinal biopsy. (See "Primary central nervous system lymphoma: Clinical features, diagnosis, and extent of disease evaluation", section on 'Eyes'.)

  - **Others** – Several other conditions, both malignant and nonmalignant, may also infrequently mimic uveitis (table 2). These conditions are generally differentiated from uveitis on ophthalmic examination.

POSTDIAGNOSTIC APPROACH

A detailed history and general physical examination, with particular attention to potential causes of uveitis (see 'Etiology' above), will provide complementary information to that gained from the slit-lamp and dilated funduscopic examination that is needed to document and characterize uveitis. Establishing an etiology can help to determine the most appropriate treatment (see 'History and examination' below and "Uveitis: Treatment"). In patients in whom the etiology remains uncertain based upon the history and examination alone, selected laboratory testing may help to elucidate the cause. (See 'Diagnostic testing' below.)

History and examination — A detailed history is the most important step in the initial evaluation of a patient presenting with symptoms suggesting uveitis. In general, when uveitis is related to a systemic disorder, the associated diagnosis will be apparent at the time of the initial history and physical examination. As examples:

- Patients with anterior uveitis should be queried regarding features of spondyloarthritis (SpA), such as low back pain, typically before age 45 and especially if lasting more than three months; joint pain or swelling, especially for which care was sought with a clinician; or a family history of SpA. Answering yes to either of the first two questions (ie, back pain or joint pain), followed by testing that is positive for human leukocyte antigen (HLA)-B27, had high specificity and sensitivity for the diagnosis of SpA in patients with acute, unilateral anterior uveitis of previously unknown etiology [23]. SpA was identified by this strategy in about 40 percent of these patients. (See "Clinical manifestations of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults".)

  Further support for this approach comes from a large collaborative study in Spain by rheumatologists and ophthalmologists in which about 90 percent of patients with acute anterior uveitis of unknown etiology who were HLA-B27-positive had sufficient additional features on history and examination to establish a diagnosis of axial or peripheral SpA [71]. A diagnosis of SpA could also be made in about 30 percent of patients who were HLA-B27-negative.

- The history should also include questions regarding risk factors for HIV infection. Patients with HIV infection are at increased risk for several infectious causes of uveitis, including cytomegalovirus (CMV) retinitis. (See 'Infectious causes' above and "The natural history and clinical features of HIV infection in adults and adolescents" and "Pathogenesis, clinical manifestations, and diagnosis of AIDS-related cytomegalovirus retinitis".)

- In patients with pars planitis, particular attention should be given in the history and physical examination to features suggestive of multiple sclerosis, which is present in increased frequency in such patients. (See 'Drugs and hypersensitivity reactions' above and "Manifestations of multiple sclerosis in adults".)

- In patients with panuveitis, the differential diagnosis includes Behçet syndrome, Vogt-Koyanagi-Harada (VKH) syndrome, sarcoidosis, sympathetic ophthalmia, and infection. (See 'Systemic inflammatory diseases' above and 'Infectious causes' above.)

Diagnostic testing — Only limited diagnostic testing is useful when an associated condition is not apparent despite a thorough medical history and physical examination (see 'Testing when no potential cause is apparent' below). In patients in whom the history and examination does suggest a possible cause, diagnostic testing, which is focused upon confirming or excluding the suspected etiology, is warranted for confirmation of the specific diagnosis (see 'Etiology' above and 'History and examination' above and 'Testing when clinical features suggest an etiology' below). In either situation, the use of multiple screening tests (a "shotgun approach") should be avoided.

The location, acuity, and response to therapy can help guide diagnostic considerations and testing. For example, acute unilateral anterior uveitis suggests the possibility of a spondyloarthropathy, about which patients should be specifically questioned to identify whether symptoms warranting further evaluation may be present (see 'History and examination' above), while bilateral chronic anterior and posterior uveitis may suggest sarcoidosis.

Testing when no potential cause is apparent — In patients with uveitis in whom the etiology remains unknown despite a detailed history and thorough examination, only limited testing is generally indicated. The location and response to therapy may help guide diagnostic considerations and testing. We perform two tests in this population:

- Plain radiography of the chest to seek evidence of pulmonary sarcoidosis or infection associated with uveitis, such as tuberculosis
- Serologic test for syphilis, which may be clinically silent

We perform selected testing in uveitis of unknown etiology because the underlying conditions may otherwise be clinically silent and treatment may be required, even though the likelihood of these diagnoses may be low [72,73]. A careful history and examination in patients with acute noninfectious anterior uveitis frequently reveals evidence of SpA that had not previously been recognized. (See 'History and examination' above.)

Sarcoidosis and syphilis are among the most common of the disorders causing uveitis in which the systemic (non-ocular) manifestations of the underlying disease may be clinically inapparent. Patients with ocular sarcoidosis should be questioned about cardiac symptoms such as presyncope or palpitations and may benefit from cardiology evaluation [74]. (See "Clinical manifestations and diagnosis of sarcoidosis" and "Overview of extrapulmonary manifestations of sarcoidosis".)

The frequency with which sarcoidosis is a cause of what would otherwise be labeled idiopathic uveitis is illustrated by a study that found that 57 percent of women with uveitis between the ages of 61 and 83 had hilar adenopathy on chest computed tomography (CT) scanning, although routine radiographs were unremarkable [66]. Although extrapolation of these findings to other patient populations is uncertain, a CT scan of the chest may be of benefit in some patients with a normal chest radiograph and uveitis in whom the diagnosis is unclear. The diagnostic value of the CT scan must be weighed against the risks from the radiation exposure from the study. As an example, a patient older than 60 with ophthalmic examination findings that suggest granulomatous inflammation, who has a normal chest radiograph and no other known etiology for the uveitis, is a good candidate for a chest CT scan. By contrast, a patient who is 30 years old with ocular findings described by an ophthalmologist as nongranulomatous might also have sarcoidosis, but the risk of the radiation and the low probability that the eye disease is sarcoid would dissuade the author from ordering a chest CT scan in this setting. Cardiac sarcoidosis is being increasingly recognized thanks to imaging modalities such as cardiac magnetic resonance imaging (MRI) or positron emission tomography (PET) scanning. Cardiac sarcoidosis can cause arrhythmia and may cause sudden death. Uveitis is frequently the first recognized symptom of sarcoidosis.

Testing when clinical features suggest an etiology — Diagnostic testing should be directed to the suspected cause when there is clinical information that suggests one of the myriad conditions that may be associated with uveitis. As examples:

- In patients with acute anterior uveitis and a history of symptoms or findings that might suggest SpA (eg, inflammatory back pain, enthesitis [eg, Achilles tendonitis or plantar fasciitis], dactylitis [ie, a "sausage digit"], or a family history of SpA) HLA-B27 testing and further evaluation of a SpA is useful to assess the possible diagnosis of SpA [23]. (See "Diagnosis and differential diagnosis of axial spondyloarthritis (ankylosing spondylitis and nonradiographic axial spondyloarthritis) in adults" and "Clinical manifestations and diagnosis of peripheral spondyloarthritis in adults".)

  By using an algorithm to evaluate patients with acute anterior uveitis in a Dublin emergency department, one group found that 40 percent of these patients who did not

previously have a known diagnosis of ankylosing spondylitis had evidence of a SpA [23].

- Testing for tuberculosis may be of value in patients at increased risk for tuberculous uveitis, such as patients from tuberculosis-endemic regions [75-77]. (See "Tuberculosis infection (latent tuberculosis) in adults: Approach to diagnosis (screening)".)

- HIV testing is **not** routinely obtained in evaluating patients with uveitis, but should be obtained in patients with a known opportunistic infection or a presumed infectious or immunologic cause of uveitis that is not responding to therapy in the expected manner. HIV testing may also be indicated in uveitis patients with risk factors for HIV infection. Opportunistic infections, such as CMV retinitis, should be considered in immunocompromised patients. (See "The natural history and clinical features of HIV infection in adults and adolescents" and "Screening and diagnostic testing for HIV infection in adults" and "Pathogenesis, clinical manifestations, and diagnosis of AIDS-related cytomegalovirus retinitis".)

- Serologic testing for systemic lupus erythematosus and for Lyme disease should be performed in patients with signs or symptoms of these conditions but are generally **not** suggested in the absence of other clinical signs or symptoms of these disorders [75,78]. (See "Clinical manifestations and diagnosis of systemic lupus erythematosus in adults" and "Diagnosis of Lyme disease".)

- In patients with pars planitis, because of its association with multiple sclerosis (MS), a thorough neurologic history and examination are indicated, and MRI of the brain may also be appropriate in these patients [79]. The author's preference is to obtain an MRI only in those patients with neurological symptoms.

- In patients who have had intraocular lens implantation temporally related to the onset of uveitis, vitreous humor aspiration and culture might be indicated to determine if infection is present.

- In patients with intraocular inflammation and suspected infectious retinitis, early polymerase chain reaction testing of ocular fluid for specific infections such as herpes zoster or herpes simplex can be useful in making a timely diagnosis [6,80]. (See "Epidemiology, clinical manifestations, and diagnosis of herpes simplex virus type 1 infection", section on 'Ocular manifestations' and "Epidemiology, clinical manifestations, and diagnosis of herpes zoster".)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Uveitis".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Uveitis (The Basics)" and "Patient education: Chorioretinitis (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Definitions** – The presence of leukocytes in the anterior chamber of the eye is characteristic of anterior uveitis but may also occur due to an infection of the cornea or a "spillover" phenomenon arising from inflammation in the posterior compartment of the eye. The presence of leukocytes in the vitreous humor and evidence of active chorioretinal inflammation are diagnostic of intermediate uveitis and posterior uveitis, respectively. Panuveitis is defined as simultaneous inflammation in the anterior chamber, vitreous humor, and retina or choroid (figure 1). (See 'Definitions' above.)

- **Etiology** – Uveitis frequently occurs in association with other systemic medical conditions, especially infections and inflammatory diseases, but may occur as an isolated process. Approximately 30 percent of patients with uveitis do not have an identifiable infectious etiology, a distinct pattern such as pars planitis, or any apparent associated systemic disease. (See 'Etiology' above.)

- **Infectious causes** – The infectious causes of uveitis include bacterial and spirochetal diseases, viral diseases, fungal infections, and parasitic infections (table 1A). Cytomegalovirus (CMV) infection is an important etiology in patients with HIV/AIDS. Ocular toxoplasmosis can affect both normal and immunocompromised hosts but is far more common in immune competent patients, in contrast to central nervous system toxoplasmosis that is seen almost exclusively in the immune-compromised. (See 'Infectious causes' above.)

- **Noninfectious (systemic inflammatory diseases, drugs, and hypersensitivity) causes** – Various systemic inflammatory diseases are associated with uveitis, including spondyloarthritis (SpA, eg, ankylosing spondylitis, psoriatic arthritis, and reactive arthritis), inflammatory bowel disease (IBD), sarcoidosis, Behçet syndrome, and juvenile idiopathic arthritis (JIA). Multiple sclerosis (MS), more commonly associated with optic neuritis, may also cause uveitis. Several medications may cause uveitis. (See 'Systemic inflammatory diseases' above and 'Drugs and hypersensitivity reactions' above.)

- **Symptoms** – Uveitis symptoms depend on the portion of the uveal tract affected. Anterior uveitis may produce pain and redness; posterior or intermediate uveitis is more likely to be painless, but is often associated with floaters and/or some degree of visual loss. Visual loss may occur with anterior, intermediate, or posterior involvement. (See 'Symptoms and findings' above.)

- **Diagnosis and diagnostic techniques** – Slit lamp and funduscopic examination are necessary to establish the presence of uveitis. Examination should include scleral depression to assess for inflammation just posterior to the lens (the pars plana of the uveal tract). (See 'Diagnosis and referral' above.)

- **Differential diagnosis** – Cellular infiltration that is not due to inflammation may occur in hematologic and lymphoproliferative disorders. Central nervous system lymphoma may "masquerade" as uveitis. (See 'Differential diagnosis' above.)

- **Postdiagnostic evaluation** – A detailed medical history is the most important step to diagnose an associated systemic disease. A chest radiograph and serologic test for syphilis should be performed in patients for whom there is no apparent cause. Further diagnostic testing may include chest CT scan and evaluation to exclude other infections, systemic inflammatory disease, or MS (table 1C). Because of a strong association between uveitis affecting the pars plana (pars planitis) and MS, particular attention should be given to the neurologic history in patients with pars planitis. (See 'Postdiagnostic approach' above.)

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