Diagnostic Testing in Uveitis

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Introduction

The recognition of active uveitis is established upon slit lamp examination, dilated funduscopy, or ancillary imaging studies. Identifying the specific etiology, however, is not simple. Perhaps the most important step in this process is differentiating infectious from noninfectious processes. Differentiating an infectious disease from a noninfectious disease allows for a more precise diagnosis and can help direct therapy or inform prognosis. A thorough history and clinical exam can uncover helpful clues, which are important when combined with the clinical features of inflammation. These constellations of findings and history can then serve as the basis for making a directed approach of investigative studies. There is no "usual" uveitis workup. Rather, tests are ordered that will help include or exclude certain uveitic processes that the clinician is considering. It is of utmost importance, then, that the clinician understands the purpose and utility of each test ordered. This chapter recommends a basic diagnostic approach and discusses common laboratory tests used in the evaluation of various uveitic entities.

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Diagnostic Strategy

Numerous causes, complex mechanisms, and overlapping clinical features do not allow for a perfect diagnostic algorithm in uveitis. For this reason, recommendations are generally driven by expert opinion. These entail the utilization of medical history and clinical exam clues to formulate a more directed (or oriented) approach [1–7]. This approach is most likely to aid in diagnosis while avoiding impractical evaluation for rare conditions with low pretest probability, and limits the utilization of tests with low positive predictive value (PPV) [8]. It should be noted that differences in prevalence of uveitic entities in certain US or foreign populations will alter pretest probability and likely change the diagnostic strategy. Universally, however, a comprehensive medical, family, social, and travel history is necessary to uncover certain risk factors, as is a thorough review of systems to evaluate for signs of infection or systemic involvement [3]. Distinguishing clinical features is integral in developing an efficient diagnostic approach. This involves classifying the type of uveitis, including laterality (bilateral vs. unilateral), type of inflammation (granulomatous vs. nongranulomatous), and structural location (anterior vs. intermediate vs. posterior vs. panuveitis vs. scleritis) [1, 3, 4, 7]. Additionally, factors such as age, sex, and race of the patient can give important direction when considering etiology.

Note: Chest radiography, testing for tuberculosis, and syphilis serology should be included in all uveitis workups. This is due to the ability of sarcoidosis, tuberculosis, and syphilis to masquerade as almost any type of uveitis [1, 9].

Non-ocular Imaging (Table 5.1)

Pulmonary Imaging

Chest radiography is typically ordered during the initial workup of all uveitis patients; it is an important step when evaluating for pulmonary signs of tuberculosis and sarcoidosis, both of which can present with almost any combination of uveitic features. *Chest X-ray (CXR)* is safe and inexpensive, and can be performed expeditiously. It is widely used as the first-line screening tool when evaluating for features of pulmonary involvement in sarcoidosis or tuberculosis [1, 10]. *Chest computed tomography (CT)* is more expensive and exposes the patient to higher levels of radiation than CXR, but is more sensitive and specific than CXR when evaluating for concomitant pulmonary disease with uveitis [6, 10–12], particularly in females older than 50 years of age [10, 12]. High-resolution chest CT should be considered as a follow-up to a negative CXR when there is a persistently high index of suspicion for tuberculosis or sarcoid uveitis. It is important to note that sarcoid and TB uveitis presents frequently without signs of pulmonary involvement and absence of pulmonary signs does not necessarily exclude these diagnoses [10, 13].

Table 5.1 Overview of non-ocular imaging

Non-ocular imaging				
	Overview	When to order	Important entities	Utility
Pulmonary				
Chest X-ray (CXR)	Inexpensive, safe, lacks sensitivity	New uveitis patients	Sarcoidosis Tuberculosis	[a] [a]
Chest computed tomography (CT)	Expensive, more radiation. More sensitive and specific than CXR for TB and sarcoidosis	After negative CXR with high index of suspicion for sarcoidosis	Sarcoidosis Tuberculosis	[b] [b]
Cerebral				
Brain magnetic resonance imaging (MRI)	Safe but expensive and not recommended for routine use due to low specificity. Specific patterns of enhancement may suggest central nervous system involvement	To rule out MS before initiating anti-TNF therapy in intermediate uveitis, and in suspected primary vitreoretinal lymphoma (PVRL)	Multiple sclerosis PVRL	[b] [b]

Anti-TNF Antitumor necrosis factor-alpha
[a]Almost always useful
[b]Useful under given circumstances

Brain Imaging

Brain magnetic resonance imaging (MRI) has the potential to show manifestations of neurologic disease that may not be present on clinical exam. This is most useful when evaluating for demyelinating lesions in multiple sclerosis (MS), for as many as 10% of patients with intermediate uveitis eventuate to MS [14, 15]. However, routine imaging for periventricular white matter lesions consistent with MS should not be performed as a screening tool in patients with intermediate uveitis. Rather, MRI should be considered in cases of intermediate or anterior uveitis with neurological findings or symptoms consistent with MS, and to rule out demyelinating features before institution of anti-TNF-alpha therapy, as this may be associated with the development or progression of MS in those predisposed to developing it [15]. Behçet's disease (T1 iso-hypointense and T2 hyperintense lesions of the white matter, brain stem, basal ganglia, and thalamus) and Vogt-Koyanagi-Harada (hyperintense white matter lesions) with neurologic involvement may also show characteristic patterns of enhancement [16–18]. In cases of suspected primary vitreoretinal lymphoma (PVRL), MRI with gadolinium should be performed to evaluate for brain involvement, as this finding will affect the treatment regimen [19, 20]. In the setting of neurological symptoms or mental status changes elicited on review of systems, and typical clinical ophthalmic examination findings, obtaining an MRI can help expedite the diagnosis of MS or CNS lymphoma, given that occasionally these conditions manifest first in the eye. Despite these associations, brain MRI is typically

low yield in the inital uveitis workup and should be reserved for patients with signs of neurologic involvement that necessitate further characterization.

Infectious Testing (Table 5.2)

Ocular Fluid

Polymerase chain reaction (PCR) uses targeted primers to amplify a segment of DNA from a suspected infectious pathogen. As a directed test, one must specify the infectious agent(s) being sought, which will inform the appropriate primer to be used for genetic amplification. The number of tests is therefore limited by the sample volume and some pathogens are not routinely identified by standard laboratory testing protocols. PCR of ocular fluid can be helpful when establishing the causative

Table 5.2 Overview of infectious testing

Infectious testing				
	Overview	When to order	Important entities	Utility
Ocular fluid				
Polymerase chain reaction (PCR)	Targeted primers to amplify DNA. Number of pathogens tested is limited by volume	Unilateral, hypertensive uveitis consistent with infectious (such as viral) etiology	Herpes family viruses (EBV, CMV, HSV, VZV) *Toxoplasma gondii*	[a] [a]
Culture	Allows for culturing of pathogens and antimicrobial susceptibility testing	Suspected endophthalmitis, particularly following ocular trauma or intraocular surgery (exogenous), or systemic infection (endogenous)	Bacteria or fungus	[b]
Goldmann-Witmer coefficient (GWC)	Intraocular to serum antibody ratio. Indirect way of implicating local infection. May improve pathogen detection when paired with PCR	Consider in cases where clinical suspicion of infectious pathogen is high but directed PCR is negative	Difficult diagnoses	[b]
Metagenomic deep sequencing (MDS)	Novel molecular assay, indiscriminate amplification, and bioinformatics processing	Limited availability and expensive. Useful in research and elusive diagnoses	Elusive diagnoses of rare infectious pathogens	[b]
Tuberculosis (TB)				
Interferon-gamma release assay (IGRA)	Detects release of interferon-gamma from sensitized T cells after TB protein exposure. Minimal BCG interference	Consider as the first-line TB test in most cases of uveitis	Tuberculosis	[a]

Table 5.2 (continued)

Infectious testing				
	Overview	When to order	Important entities	Utility
Tuberculin skin test (TST)	Measures delayed T-cell response to TB purified protein. High false positives following BCG vaccine	May be used when IGRA not available or in patients from highly endemic regions	Tuberculosis	[b]
Syphilis				
Treponema specific	TP-EIA, FTA-ABS, and TP-PA. Detect Treponemal-specific antibodies. Sensitive and specific. Reverse sequence screening starts with TP-EIA	All unknown uveitis (TP-EIA is first test in reverse sequence screening algorithm)	Syphilis	[a]
Nonspecific treponemal	RPR or VDRL. Detect nontreponemal antibodies to cardiolipin and lecithin lipids that are released by damaged cells. Titer correlates with disease activity. Ordered following positive TP-EIA	RPR is second test in reverse sequence screening algorithm following positive TP-EIA	Syphilis	[a]
Cerebrospinal fluid (CSF) analysis	Nontreponemal testing of CSF in suspected ocular syphilis due to potential for CNS involvement	Provides a baseline marker to monitor response to neurosyphilis treatment	Syphilis	[b]
HIV	HIV status has important systemic and therapeutic implications in ocular syphilis	Should be determined in all cases of ocular syphilis (common coinfection)	Syphilis	[b]
Other				
Serology/PCR	Various serological/PCR testing can detect IgG (previous or chronic infection), IgM (acute infection), or pathogen DNA	May be useful in difficult diagnoses. Serum values must be correlated with ocular findings as positive results do not confirm infection in the eye	*Bartonella henselae* [b] Toxoplasma gondii [b] Herpes viridae [b]	

CMV Cytomegalovirus, *HSV* Herpes simplex virus, *VZV* Varicella zoster virus, *BCG* Bacillus Calmette-Guérin vaccine, *TP-EIA* Treponema pallidum enzyme immunoassay, *FTA-ABS* Fluorescent Treponemal antibody absorption test, *TP-PA* Treponema pallidum particle agglutination assay, *RPR* Rapid plasma reagin, *VDRL* Venereal disease research laboratory test, *CNS* Central nervous system, *HIV* Human immunodeficiency virus, *Ig* = Immunoglobulin

[a]Almost always useful

[b]Useful under given circumstances

pathogen in suspected infection and either anterior or posterior involvement [21–26]. Commonly tested pathogens include cytomegalovirus (CMV), herpes simplex virus (HSV), varicella-zoster virus (VZV), and *Toxoplasma gondii*. Ebstein-Barr virus (EBV) can also be tested.

Culture of aqueous or vitreous for bacteria and fungus may be important to perform particularly in suspected cases of endophthalmitis. A patient with a history of ocular trauma, intraocular surgery, or those who are immunosuppressed and at risk for endogenous endophthalmitis might prompt investigation for bacterial or fungal etiology. It is important to note that vitreous culture is much more sensitive for bacterial or fungal endophthalmitis, and if suspected, vitreous tap should be performed over an anterior chamber paracentesis, unless the vitreous is unable to be obtained safely [27]. Culture may determine the causative pathogen and antimicrobial susceptibility.

Goldmann-Witmer coefficient (GWC) is a ratio of intraocular antibody to serum antibody as measured by enzyme-linked immunosorbent assay (ELISA). The GWC is defined by X/Y; where X = specific antibody in aqueous or vitreous divided by total IgG in aqueous or vitreous; and Y = specific antibody in serum divided by total IgG in serum. A GWC > 4 is highly suggestive of local production of antibody against the suspected pathogen. Like PCR, the pathogen in question must be specified for the test. This test can complement PCR testing particularly when there is a high suspicion for a specific etiology, but directed PCR is negative. In such cases, it is possible that at the time of ocular fluid sampling, a sufficiently high enough pathogen load was not present for the PCR assay's sensitivity to detect. GWC could detect local antibodies for said pathogen, which would be an indirect way of implicating that particular pathogen [28, 29]. GWC, however, is not routinely done in many locations, including the United States.

Metagenomic-deep sequencing (MDS) is a novel molecular assay that indiscriminately amplifies all DNA or RNA (depending on the assay used) in a sample, and is followed by bioinformatics processing (removal of human, contaminant, and non-pathogenic DNA reads) and comparison to a known database of pathogens [30, 31]. It is capable of providing unbiased pathogen detection from the minute volumes frequently obtained from ocular fluid sampling, and may be particularly useful for detecting an elusive or rare causative pathogen [31]. MDS is currently exploratory, expensive, and not routinely available.

Tuberculosis

Interferon-gamma release assay (IGRA) is the preferred serologic testing for tuberculosis and most commonly in the form of QuantiFERON-TB Gold (utilizes ELISA) or T-SPOT.TB (Enzyme-Linked ImmunoSpot) (Fig. 5.1). IGRAs detect the release of interferon gamma from previously sensitized T cells upon re-exposure to specific *Mycobacterium tuberculosis* (TB) proteins. There is minimal interference from Bacille Calmette-Guérin (BCG) vaccine and other mycobacteria.

Fig. 5.1 An example of an interferon gamma release assay test, the QuantiFERON-Gold TB. The assay tubes are processed in the following order: Nil, Mitogen, and TB antigen

Mantoux tuberculin skin test (TST) measures the delayed T-cell-mediated (Type IV) hypersensitivity response to an intradermal injection of tuberculin purified protein derivative (PPD). Criteria for positive induration vary between populations with certain risk factors and immune dysfunction. Limitations include a high false-positive rate following BCG vaccine or nontuberculous mycobacteria exposure.

Although IGRA testing has been shown to be more sensitive and specific than TST in cases of non-ocular TB (sensitivity and specificity for IGRA of 92.3% and 84.6%, respectively vs. sensitivity and specificity for TST of 56.4% and 61.5%, respectively) [32], these results have not been demonstrated in cases of isolated ocular involvement. Ang et al. have demonstrated in multiple studies that IGRA may be less sensitive than TST in detecting ocular TB (36–91% vs. 72–96%), although it is more specific (75–82% vs. 51–73%) [33–35]. Discordance rates up to 26.5% between IGRA and TST testing leave us without a gold standard for detecting ocular TB, though a Bayesian analysis from Ang et al. suggests that the chances of ocular TB are highest with both positive IGRA and TST results [35, 36]. IGRA should be the initial test in populations with low rates of tuberculosis [35].

Note: TST can be useful in the diagnostic workup of sarcoidosis. See sarcoidosis biomarkers.

Syphilis

Treponema-specific testing includes the treponemal enzyme immunoassay (TP-EIA), fluorescent treponemal antibody absorption (FTA-ABS), and *Treponema pallidum* particle agglutination (TP-PA). These tests detect antibodies to Treponema antigens and are sensitive for detecting very early syphilis, prior treated syphilis, late and latent syphilis. Treponema-specific tests are more sensitive and specific than nontreponemal tests, though they frequently remain positive for life, and are therefore not useful in determining whether current active ocular inflammation is due to syphilis in the setting of previously treated infection.

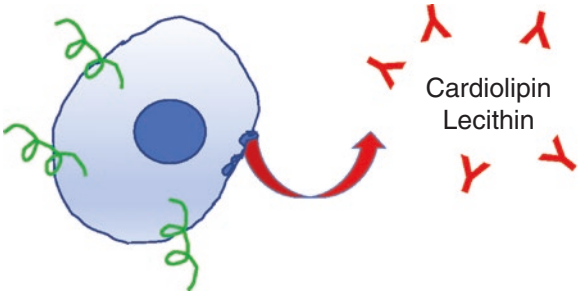

Fig. 5.2 Syphilitc cell damage. When Treponema pallidum (green spirochetes here) invades cells, damage to the cell wall releases cardiolipin and lecithin, which stimulates the production of antibodies (red) against these lipid products

Nontreponemal (nonspecific) testing includes the rapid plasma reagin (RPR) and venereal disease research laboratory test (VDRL). These tests detect antibodies to cardiolipin and lecithin lipids that are released from cells damaged by *Treponema pallidum* (Fig. 5.2). Titers correlate with disease activity and are reliably elevated during primary and secondary infection, although they may fall during latency, tertiary infection (during which you may have active uveitis), or following appropriate treatment. False-negative results may rarely occur during active syphilis due to the prozone effect, a phenomenon in which high antibody titers interfere with precipitation of antibody-antigen complex necessary for visualization of a positive test [37]. In such cases, the laboratory should be instructed to perform serial dilutions of the original sample, which may yield a true-positive result [37, 38].

Historically, nontreponemal tests were used for syphilis screening and followed with a treponema-specific test to confirm a positive result [38]. This method of testing is less sensitive, particularly during early and late syphilis when RPR titers are low. In 2008, the CDC recommended a more sensitive reverse-sequence methodology, which is more sensitive, but has a higher false-positive rate. This method begins with a treponema-specific test (TP-EIA) followed by reflexive quantitative RPR following a positive result. A positive RPR indicates a past or current infection, while a negative RPR would trigger TP-PA testing. A positive TP-PA indicates past or current infection, while a negative result suggests that syphilis is unlikely [38]. Figure 5.3 shows the reverse-sequence algorithm.

Ocular syphilis is considered a form of neurosyphilis, with accompanying cerebrospinal fluid (CSF) abnormalities in as high as 72% of patients [38–40], and the CDC currently recommends treatment with neurosyphilis therapy (10–14 days of IV penicillin) in all cases [41]. VDRL should be performed on CSF before treatment initiation to provide a baseline marker necessary to monitor adequate treatment response [38].

Note: High-risk activities that pose a risk for contraction of syphilis also include a risk for human immunodeficiency virus (HIV) *exposure. For this reason, HIV testing should be ordered in all cases of suspected ocular syphilis as coinfection can have important systemic and therapeutic implications* [38].

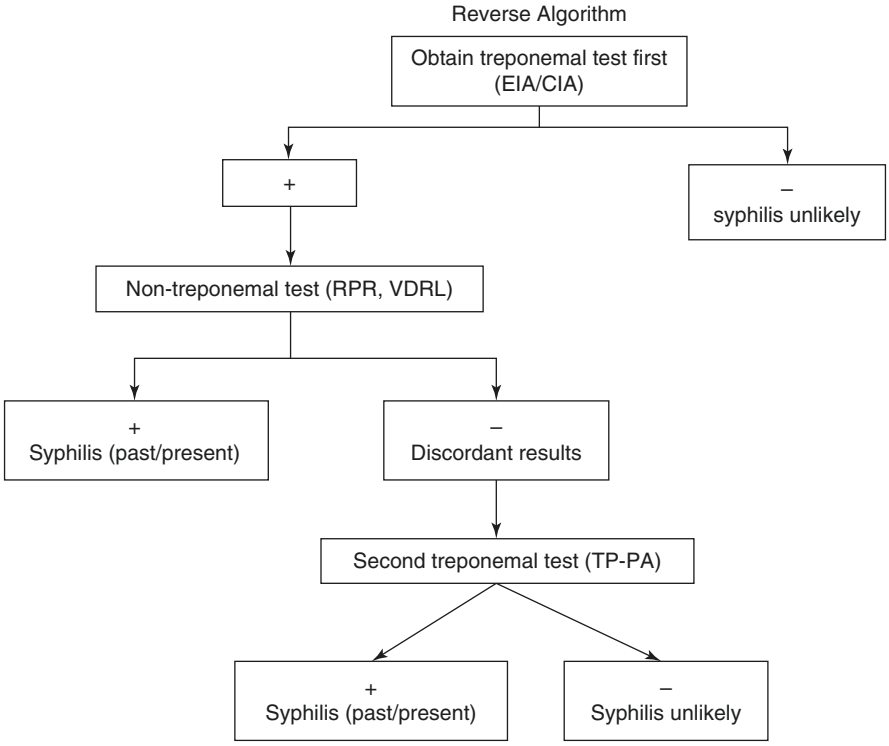

Fig. 5.3 Syphilis reverse screening algorithm. Adapted from Tong et al. [93]

Other Infectious Testing

There are various serological tests that measure the amount of a specific antibody in the serum. This can be in the form of *IgG (previous or chronic infection) or IgM (acute infection)*. PCR can also be used to detect pathogen DNA in the blood. Quantitative Ig titers and PCR can be useful in distinguishing active from latent or past infection, but serum values cannot confirm disease activity in the eye and should therefore be correlated with clinical findings. Some potentially useful infectious serology tests (aside from syphilis and TB tests discussed previously) include IgG and IgM for *CMV, HSV, VZV, Toxoplasma gondii, Toxocara, and Bartonella henselae* [42]. Ocular infection with *Toxoplasma gondii can frequently be diagnosed by clinical exam alone; however, PCR of ocular fluid or serologic testing for exposure with IgG and IgM may be warranted when the presentation is atypical* [43]. *Borrelia burgdorferi* (Lyme disease) serology has a low positive predictive value alone and should be avoided in the absence of systemic findings of Lyme disease and travel to endemic areas [44, 45].

Noninfectious Testing (Table 5.3)

Autoantibody Testing

Circulating serum autoantibodies are frequently associated with a variety of rheumatologic disease. While certain autoantibodies may confer some risk for the development of specific conditions, the relatively high prevalence of those antibodies in

Table 5.3 Overview of noninfectious testing

Noninfectious testing			
	Overview	When to order	Utility
Autoantibody			
Antinuclear antibody (ANA)	Autoantibodies directed against cell nucleus antigens. Detected via microscopic visualization of fluorescent patterns. ANA titers correlate with disease activity	Suspected JIA-associated uveitis or in cases where clinical or systemic findings of SLE exist	[b]
Rheumatoid factor (RF)	Autoantibodies against fc region of IgG detected by ELISA. Nonspecific marker of many rheumatologic conditions	Scleritis and JIA-associated uveitis	[b]
Anticyclic citrullinated peptide (anti-CCP)	Autoantibodies against cyclic citrullinated peptide (CCP). Gold standard diagnosis of RA due to high specificity, although less sensitive than RF	Scleritis associated with rheumatoid arthritis (RA)	[b]
Antineutrophil cytoplasmic antibodies (ANCA)	Autoantibodies against proteinase 3 (PR3) and myeloperoxidase (MPO). Cytoplasmic (C-ANCA) staining pattern is specific for granulomatosis with polyangiitis (GPA) and PR3 antibodies	Scleritis associated with granulomatosis with polyangiitis (GPA)	[b]
Human leukocyte antigens (HLA)			
HLA-A29	Associated with birdshot chorioretinitis (BSCR). Low specificity due to 8% prevalence in general Caucasian US population. Cannot confirm BSCR but negative result could rule it out	When evaluating white dot syndrome consistent with BSCR	[b]
HLA-B27	One of the strongest known HLA disease associations with seronegative spondyloarthropathies (JIA, ankylosing spondylitis, reactive arthritis)	Very important when evaluating young patient with uveitis (especially anterior) and joint pain	[b]
HLA-B51	Associated with Behçet's disease	Not included in current Behçet's diagnostic criteria	[c]
HLA-DRB1∗0102	Strongly correlated with tubulointerstitial nephritis and uveitis syndrome (TINU)	Not widely available and not recommended due to other accurate testing for TINU	[c]
TINU biomarkers			
Urine beta-2 microglobulin and serum creatinine	Elevated levels suggest loss of proteins/decreased glomerular filtration rate due to tubulointerstitial nephritis	Young patients with uveitis. Elevation of both levels has a 100% positive predictive value for TINU	[b]

Table 5.3 (continued)

Noninfectious testing			
	Overview	When to order	Utility
Sarcoidosis biomarkers			
ACE and lysozyme	Noncaseating granulomas in sarcoidosis actively secrete serum angiotensin converting enzyme (ACE) and lysozyme. However, a variety of pulmonary conditions can result in elevated levels ACE levels will be negatively affected in patients on ACE inhibitors	Suspected ocular sarcoidosis	[b]
Ocular fluid and tissue biopsy			
Histopathology/ cytopathology	Evaluation of molecular morphology. Biopsy of affected tissue in sarcoidosis shows noncaseating granulomas. Biopsy in PVRL may show large, atypical lymphocytes with prominent nucleoli and scanty basophilic cytoplasm	Gold standard for diagnosing pulmonary sarcoidosis or PVRL. Low yield of cells in the biopsy of suspected PVRL may limit sensitivity	[b]
Immunochemistry/ IgH gene rearrangement	Molecular techniques to detect monoclonality of leukocytes. Commonly done in the form of PCR to detect rearrangement of immunoglobulin heavy chain (IgH) of malignant cells	Suspected primary vitreoretinal lymphoma (PVRL)	[b]
IL-10/IL-6 ratio	B-cell lymphomas produce high levels of interleukin-10. Therefore, a high IL-10/ IL-6 ratio can support a PVRL diagnosis	Suspected PVRL	[b]
MYD-88 (L265P) mutation	The leucine to proline change at position 265 in the *MYD-88* gene is associated with PVRL	Suspected PVRL	[b]
CSF analysis			
Cytopathology/ Flow Cytometry	Cytopathology and flow cytometry of the CSF may be helpful to evaluate for central nervous system involvement in PVRL Pleocytosis (increased white blood cell count) in the CSF reflects inflammatory changes in the CNS	Suspected PVRL MS, VKH, Behçet's disease	[b] [b]
Oligoclonal bands	Large amounts of few Ig cell lines detected as characteristic immunoblotting patterns. Seen in MS, SLE, neuro-sarcoidosis, and neuro-Behçet's	Lumbar puncture is not routinely performed for uveitis diagnoses, but could be considered in cases of MS-associated uveitis, particularly if there are neurologic features present	[b]

JIA Juvenile idiopathic arthritis, *ELISA* Enzyme-linked immunosorbent assay, *CSF* Cerebrospinal fluid, *MS* Multiple sclerosis, *VKH* Vogt-Koyanagi Harada disease, *SLE* Systemic lupus erythematosus

[a]Always useful

[b]Useful under given circumstances

[c]Rarely useful

the healthy population limits the specificity of these tests. The only autoantibody test with proven utility is the antinuclear antibody (ANA) in uveitis associated with juvenile idiopathic arthritis (JIA) [46]. All others have limited positive predictive value and should not be ordered routinely.

Antinuclear antibodies (ANA) are autoantibodies directed against cell nucleus antigens and detected via microscopic visualization of fluorescent markers in characteristic patterns. ANA titers may correlate with rheumatologic disease activity. Despite being an important prognostic marker for many conditions, particularly connective tissue diseases such as systemic lupus erythematosus (SLE), the low positive predictive value (PPV) limits its use in uveitis [8, 47]. It is useful in the evaluation of juvenile inflammatory arthritis (JIA)-associated uveitis [46] or cases where there are systemic findings consistent with systemic lupus erythematosus (SLE) [47]. In most cases of uveitis (besides JIA), ANA is not ordered since SLE is usually associated with scleritis as opposed to uveitis. An exception occurs in the rare presentation of SLE-associated occlusive retinal vasculitis and/or ischemic choroiditis, which might prompt ANA testing, especially when patients also report other systemic symptoms or findings that are part of SLE clinical criteria.

Rheumatoid factors (RF) are autoantibodies directed against the Fc region of immunoglobulin G. These are detected via enzyme-linked immunosorbent assay (ELISA), and are a nonspecific biomarker found in multiple rheumatologic conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), SLE, and Sjögren's Syndrome. RF is also frequently positive in Hepatitis C cryoglobulinemia. There is low utility for RF testing in uveitis, although RF titers may predict progression from isolated ocular RA (which does not usually cause uveitis, but rather, scleritis) to systemic involvement [48].

Anticyclic citrullinated peptide (Anti-CCP) autoantibodies are less sensitive than RF but have emerged as the more specific gold standard for diagnosis of RA [49, 50]. Anti-CCP may be helpful in confirming the diagnosis in cases with ocular involvement such as RA-associated scleritis.

Antineutrophil cytoplasmic antibodies (ANCA) are autoantibodies against proteinase 3 (PR3) and myeloperoxidase (MPO) and detected by ELISA or indirect immunofluorescence of ethanol-fixed neutrophils. The perinuclear pattern (P-ANCA) is nonspecific, correlates with MPO antibodies, and can be associated with microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis. Cytoplasmic pattern (C-ANCA) is highly specific for granulomatosis with polyangiitis (GPA) and usually correlates with PR3 antibodies [51]. ANCA testing may be considered in cases of scleritis consistent with GPA, and may predict progression from isolated GPA to systemic involvement [48].

Note: While ANA, ANCA, RF, and anti-CCP are not typically useful tests in uveitis aside from rare scenarios, these tests are useful in scleritis.

Serum antiretinal antibodies (ARA) may be found in autoimmune retinopathy, in association with nonparaneoplastic or paraneoplastic processes, including cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR) [52]. Retina-specific antibodies are crucial in confirming the diagnosis of autoimmune retinopathy, and can be demonstrated using Western blot, immunohistochemistry, or

ELISA testing. However, ARA have also been found in association with various uveitic entities [53] including retinitis pigmentosa, Vogt-Koyanagi-Harada, Birdshot chorioretinopathy, and Behçet's, and as high as 62% of normal control sera [54]. Due to the rarity of autoimmune retinopathy and low specificity of ARA, the utility of ARA testing in uveitis is limited.

Human Leukocyte Antigens (HLA)

The HLA are a collection of genes encoding the major histocompatibility complex (MHC), antigen-presenting proteins integral to appropriate immune function (Fig. 5.4) [55]. HLA A, B, and C correspond to MHC class I, proteins found on most nucleated cells that present intracellular antigens to CD8+ T-cells. HLA DQ and DR (plus others) correspond to MHC class II; this class of proteins are found on antigen-presenting cells (APCs) such as dendritic cells, mononuclear phagocytes, and B cells, and present extracellular antigens to CD4+ T cells. Abnormal structure and function of either class of MHC proteins predispose carriers to immune dysfunction and autoimmune pathology. Despite disease association with certain HLA alleles, the positive predictive value of HLA testing in uveitis is very low (<0.50) and should not be included in routine screening [56]. Nevertheless, the use of HLA testing may prove useful in supporting or excluding a difficult diagnosis, and remains a powerful tool for researching pathogenetic mechanisms [56–59].

The *HLA-A29 allele* may be useful when evaluating a white dot syndrome consistent with birdshot chorioretinopathy (BSCR) [60–64]. Due to the 8% prevalence of the HLA-A29 allele in the US Caucasian population, its presence does not

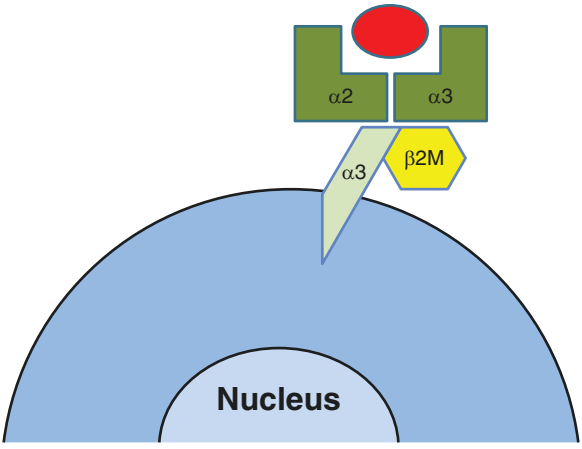

Fig. 5.4 Human leukocyte antigen (HLA) structure. HLAs are part of the major histocompatibility complex or proteins expressed on the surface of nucleated cells. The polymorphic alpha chains are encoded by the *HLA* gene. The beta-2 microglobulin (B2M) subunit is encoded by the beta-2-microglobulin gene. HLA (of the MHC class I genes) presents endogenous or exogenous peptides (red circle) to cytotoxic CD8+ T-cells

confirm BSCR, although its absence may exclude the disease since the presence of HLA-A29 in BSCR approaches 100% [65].

The *HLA-B27 allele* is strongly associated with the seronegative spondyloarthropathies, such as ankylosing spondylitis, reactive arthritis, and JIA, and remains one of the strongest HLA-disease associations [66]. Uveitis, particularly acute anterior uveitis, is a common finding in these seronegative spondyloarthropathies, and therefore, HLA-B27 may be helpful when evaluating a young patient with unilateral acute anterior uveitis and joint pain [67, 68]. It is important to note that the US non-Hispanic white population carries HLA-B27 at a prevalence of 7.5% [69]. The majority never develop signs of systemic inflammatory disease, and those with HLA-B27 develop acute anterior uveitis (AAU) at a cumulative incidence rate of 1% [70]. Conversely, greater than 50% of patients with AAU are HLA-B27 positive, and 30–40% of patients with ankylosing spondylitis develop at least one episode of AAU [70].

The *HLA-B51 allele* has been associated with Behçet's disease and related uveitis [71, 72]. However, current diagnostic criteria for Behçet's disease do not include the HLA-B51 allele and its absence in a patient suspected of having Behçet's disease should not preclude such a diagnosis if clinical features are compatible.

The *HLA-DRB1∗0102 allelic variant* is strongly correlated with tubulointerstitial nephritis and uveitis syndrome (TINU) [73, 74]. Testing is not widely available and not currently recommended, given that the positive predictive value of combining elevated urine beta-2 microglobulin and serum creatinine is high in cases of TINU (see below).

Urine Beta-2 Microglobulin and Serum Creatinine

Elevated levels of *serum creatinine and urinary beta-2 microglobulin* suggest renal tubule dysfunction (loss of proteins and decreased glomerular filtration rate) and may indicate tubulointerstitial nephritis. When evaluating a young uveitis patient for tubulointerstitial nephritis and uveitis syndrome (TINU), which typically presents with a bilateral anterior uveitis, a combined elevated urinary beta-2 microglobulin ($\geq$0.20 mg/L) and elevated serum creatinine (>0.74 mg/dL in those of age $\leq$15 years and >1.17 mg/dL in those older than 15 years) has been shown to provide a positive predictive value (PPV) of 100% and a negative predictive value of 97% [75].

Sarcoidosis Biomarkers

Elevated serum levels of *angiotensin-converting enzyme (ACE)* or *lysozyme* can be found in multiple pulmonary disease processes as a result of injury and increased metabolic activity [76]. The noncaseating granulomas in sarcoidosis actively secrete ACE and lysozyme [77], which may directly mediate inflammation. These markers are not specific to sarcoidosis, although elevation of one or both of these values is a

supportive investigational test according to the International Workshop on Ocular Sarcoidosis (IWOS) criteria [77]. It is important to note that patients on ACE inhibitors may exhibit low levels of ACE and these results should be interpreted with caution. It should also be noted that definitive diagnosis of sarcoidosis requires a biopsy demonstrating a sarcoid granuloma on histopathology.

Note: The tuberculin skin test (TST) is useful in the diagnostic workup of sarcoidosis. A negative TST, in a patient with the BCG vaccine or previously positive TST, indicates a suppressed delayed-type hypersensitivity and cutaneous anergy consistent with sarcoidosis; this is supportive investigation for diagnosis according to the IWOS criteria [77].

Ocular Fluid and Tissue Biopsy

When evaluating an eye with presumed noninfectious uveitis, it is important to keep in mind the possibility of a masquerade process. *Sarcoidosis* is capable of mimicking almost any type of uveitis, and *primary vitreoretinal lymphoma (PVRL)*, a subset of primary central nervous system lymphoma (PCNSL), is a notoriously lethal malignancy that can masquerade as a chronic anterior, posterior, intermediate, or pan-uveitis. In these cases, it may become necessary to obtain ocular tissue in order to rule in or rule out a diagnosis.

Histopathology/cytopathology/immunohistochemistry can be used to evaluate the molecular morphology. Biopsy of affected tissue (conjunctiva, choroid, and retina) showing *noncaseating granulomas* from an eye with a compatible uveitis meets definite ocular sarcoidosis criteria [77]. Vitreous samples or chorioretinal biopsy in PVRL may reveal *atypical lymphocytes* characterized by large irregular nuclei, prominent nucleoli, and scant basophilic cytoplasm [19, 78, 79]. Reactive lymphocytes may also be present. Visualization of atypical cells may be the most specific for confirming PVRL, but there can be a low yield of cells obtained during diagnostic sampling, thereby lowering sensitivity [79]. Immunohistochemistry can be used to identify B-cell or T-cell lineage.

Immunoglobulin heavy chain (*IgH*) or *T-cell receptor* (*TCR) gene rearrangement* is a molecular technique capable of detecting monoclonality of a specific B- or T-cell population in the sampled tissue or fluid [78, 80]. This is performed by way of polymerase chain reaction (PCR) to detect rearrangements of the *IgH* or *TCR* gene of malignant cells in suspected cases of PVRL in B- and T-cell lymphomas, respectively [79].

Interleukins (IL) are a class of inflammatory cytokines secreted by white blood cells. B-cell lymphomas produce large amounts of IL-10, whereas inflammatory cells typically secret IL-6. Therefore, since PVRL is typically of B-cell origin, a *high IL-10/IL-6 ratio* can support a diagnosis of PVRL [19, 78, 80].

Polymerase chain reaction (PCR) and next-generation sequencing techniques (such as MDS) are capable of detecting specific gene mutations that are associated with certain malignancies. There are many mutations of the gene *MYD-88* associated with the development of several types of lymphoma, and the *MYD-88* L265P

mutation in particular is present in an overwhelming majority of patients with PVRL [81–84]. The advantage of newer assays, such as MDS, is that both rare and common mutations associated with lymphoproliferative disorders can be detected with very minute ocular fluid volumes [83, 84].

Cerebrospinal Fluid (CSF) Analysis

CSF pleocytosis, or increased white blood cell count in the CSF, reflects inflammatory changes in the central nervous system (CNS). Certain CNS inflammatory conditions, such as Vogt-Koyanagi-Harada (VKH) disease [85, 86], multiple sclerosis (MS) [87, 88], and Behçet's disease [89], may manifest with both uveitis and CSF pleocytosis on lumbar puncture. Due to the nonspecificity of pleocytosis, routine lumbar punctures are not recommended for diagnosing uveitic entities. Additionally, fluorescein angiography findings alone may support a diagnosis of VKH without the need for lumbar puncture [85].

Oligoclonal bands, or large amounts of just a few immunoglobulin clonal lines, can be detected as a characteristic pattern of immunoglobulin G using immunoblotting techniques. This pattern can be seen in CNS infection or neuroinflammatory diseases such as multiple sclerosis [87, 88], SLE [90], neuro-sarcoidosis [90–92], and neuro-Behçet's [89, 90].

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