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Impact of HLA-B51 on uveitis and retinal vasculitis: data from the AIDA International Network Registries on ocular inflammatory disorders

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Abstract

Background: Non-infectious uveitis (NIU) represents a difficult-to-manage condition characterized by intraocular inflammation that can potentially cause irreversible ocular damage, ultimately leading to a poor visual outcome. Genetic predisposition, including the human leukocyte antigen (HLA), is strongly associated with the development of several diseases. The pathogenetic and clinical relevance of HLA subtypes such as HLA-B51 on Behçet's disease (BD)-related uveitis and NIU unrelated to BD is largely unknown.

Methods: Data were prospectively collected from the International AIDA Network Registry for BD and the International AIDA Network Registry for uveitis. We assessed differences between groups (NIU unrelated to BD and positive for HLA-B51, BD-related uveitis positive for HLA-B51 and BD-related uveitis negative for HLA-B51) in terms of long-term ocular complications, visual acuity measured by best corrected visual acuity (BCVA), and anatomical patterns. The occurrence of retinal vasculitis and macular edema over time was also examined.

Results: Medical charts of 213 patients meeting inclusion criteria (for a total of 341 eyes) were enrolled in the study. No differences in terms of complications were observed between groups (p=0.465). With regard to visual acuity, an overall significant difference was detected in median BCVA (p= 0.046) which did not maintain statistical significance after Bonferroni correction during post-hoc analysis of pair comparisons (p=0.060). Concerning anatomical pattern, anterior uveitis was significantly overrepresented among patients with NIU testing positive for HLA-B51 (p<0.001). Retinal vasculitis demonstrated a significantly higher prevalence in NIU-affected patients who tested positive for HLA-B51, irrespective of the associated systemic diagnosis of BD (p=0.025). On the contrary, no differences emerged between groups in the occurrence rate of cystoid macular edema (p=0.99).

Conclusions: Patients with NIU testing positive for HLA-B51 exhibit an overall unfavorable visual prognosis and an increased likelihood of experiencing episodes of retinal vasculitis throughout the course of the disease, irrespective of a systemic diagnosis of BD. The rate of long-term structural complications as well as visual acuity are comparable between NIU cases unrelated to BD but testing positive for HLA-B51 and uveitis associated with BD. Therefore, it is recommended to screen patients with NIU for HLA-B51, even in the absence of typical Behçet's disease features, emphasizing the necessity for a closer follow-up schedule.

1 TABLE OF CONTENT

1 INTRODUCTION

Despite being classified as an “immune privileged” site characterized by a controlled adaptive immune surveillance in comparison to other organs, the eye is often target of inflammatory clinical manifestations. In such cases, ocular symptoms and signs include the onset of dry eye, conjunctival and perikeratic injection, itching, photophobia, pain, sense of a foreign body, and visual alterations up to blindness. These manifestations can represent the initial symptom of various severe and potentially life-threatening systemic immune-mediated disorders (1). Therefore, in patients with rheumatic diseases and ocular symptoms, a proper ocular evaluation, including analysis of eye movements, pupillary reflexes, visual acuity, visual field, inspection with a slit lamp, evaluation of the *fundus oculi*, and tear assessment with Schirmer test or break up time (BUT) test, as well as tonometry and, when appropriate, second-level instrumental exams such as optical coherence tomography (OCT), angio-OCT, and retinal angiography with sodium fluorescein and/or indocyanine, would always be appropriate.

Uveitis in particular represents one of the most dangerous and potentially damaging conditions to visual acuity. It is, an inflammatory process that primarily affects the uvea, the vascular layer of the eye, between the outer fibrous coat and the inner nervous coat (also known as retina). In fact, uveal inflammation is responsible for 10-15% of cases of legal blindness in industrialized countries with an incidence calculated around 12-15 cases per 100,000 inhabitants per year, with a higher frequency between the ages of 20 and 50 (2,3). In this regard, it has been demonstrated how the quality of life of patients with uveitis significantly decreases including those cases not characterized by significant loss of visual function, especially in relation to the physical component of well-being, perception of one's social and physical role, and assessment of pain and health status (4).

Over time, various classifications of uveitis have been proposed, among which the most relevant is based on the anatomical distinction between anterior, intermediate, posterior, and diffuse (panuveitis) uveitis depending on the uveal sector involved (5). Other classifications include the distinction of uveitis into exogenous and endogenous or granulomatous and non-granulomatous. This has progressively improved the recognition of different clinical entities also from an etiological point of view, although the origin of uveitis remains unknown in over 50% of patients (6).

In the last decade, scientific research on uveitis has undergone rapid evolution, allowing a more comprehensive clinical-instrumental framework, but also a more precise etiopathogenetic evaluation and a more suitable therapeutic approach to protect ocular structures and preserve visual acuity. Furthermore, increasing emphasis has been given to the interdisciplinary approach to patients with uveitis in order to optimize the correct management of a complex and potentially insidious pathology, which therefore may require the intervention of the rheumatologist, infectious disease specialist, gastroenterologist, and internist, as well as the ophthalmologist. Despite recent advances and the promotion of multidisciplinary approach, uveitis can often pose significant differential diagnosis problems, while the increasingly precise and selective therapeutic arsenal requires diagnostic certainties. Therefore, the approach to uveitic patients requires a meticulous clinical examination that allows a correct etiological interpretation and the precise recognition of specific clinical pictures, which can only be done with the necessary precision in specialized contexts with sufficient experience. Only by operating in this way, in fact, will it be possible to establish the most correct therapy, capable of positively changing the ocular prognosis of patients affected by uveitis.

1.1 CLASSIFICATION OF UVEITIS

The first step for a correct interpretation of uveal inflammation is represented by the identifying of the ocular clinical picture into a specific classification that facilitates the etiological recognition and pathogenetic attribution for each individual patient, also allowing standardization of the terminology used in the clinical and scientific fields. In this regard, the certainly most useful classification is the anatomical one, which allows immediate diagnostic and prognostic verification, as well as therapeutic intervention. Other types of classifications, which we define as functional, represent an additional tool to facilitate the etiological attribution of uveal inflammation based on different morphological, pathogenetic, onset, and duration characteristics, all aimed at avoiding the use of inappropriate therapies, but also at establishing the most effective therapeutic approach.

1.1.1 ANATOMICAL CLASSIFICATION

The uvea comprises three distinct segments with highly specialized specific functions: the iris, the ciliary body, and the choroid, whose exact anatomical location is shown in Figure 1A, taken from Sève P et al (7). These structures, abundantly vascularized and rich in immunocompetent elements, have the ability to react to various pathogenic *noxae*, realizing different uveitis pictures: exudative, plastic, granulomatous inflammation. "Pure" uveitis is actually rare, and the inflammatory process often involves contiguous structures such as the corneal endothelium, vitreous, sclera, retina, and

optic nerve. Based on the anatomical location of inflammation, a classification has been proposed that also has practical implications from a diagnostic and prognostic point of view. The anatomical classification should be understood in terms of structures directly involved in the inflammatory process rather than based on secondary structural complications. Starting from these assumptions, uveitis can be distinguished as anterior, intermediate, posterior, or diffuse (panuveitis) (5).

Anterior uveitis refers to inflammatory involvement of the anterior chamber and vitreous, with a more pronounced involvement of the anterior chamber. Anterior uveitis includes iritis, iridocyclitis (concomitant inflammation of the anterior part of the vitreous), and anterior cyclitis. The term intermediate uveitis should be used in that subset of patients in whom the vitreous body represents the site of major inflammation. The concomitant identification of peripheral vascular exudation (sheathing) or macular edema does not modify the classification.

The term pars planitis, on the other hand, should only be used in those cases where intermediate uveitis manifests with snowball or snowbank exudates in the absence of systemic infectious or autoimmune diseases, i.e., in idiopathic forms. Intermediate uveitis/pars planitis includes the terms posterior cyclitis and hyalitis.

The term posterior uveitis should be used in cases with predominant inflammation affecting the retina or choroid. Posterior uveitis includes focal, multifocal, or diffuse choroiditis, chorioretinitis, retinocoroiditis, retinitis, and neuroretinitis.

The term panuveitis should be reserved for situations where there is no predominant site of inflammation, but inflammation can be identified indiscriminately in the anterior chamber, vitreous, and retina and/or choroid (in the latter case, retinitis, choroiditis, or retinal vasculitis). Structural complications such as macular edema and neovascularization phenomena should not be considered in defining panuveitis.

As for the term retinal vasculitis, some clarifications should be added. In particular, retinal vasculopathic occlusion in the absence of signs of inflammation should not be included among retinal vasculitides. On the contrary, according to the current guidelines of the Standardization of Uveitis Nomenclature (SUN) working group, it is necessary to identify the presence of perivascular exudate or evidence of occlusion on fluorescein angiography in order to define retinal vasculitis (5).

Figure 1, taken from Sève P *et al.* (7), illustrates the details of the anatomical classification of uveitis."

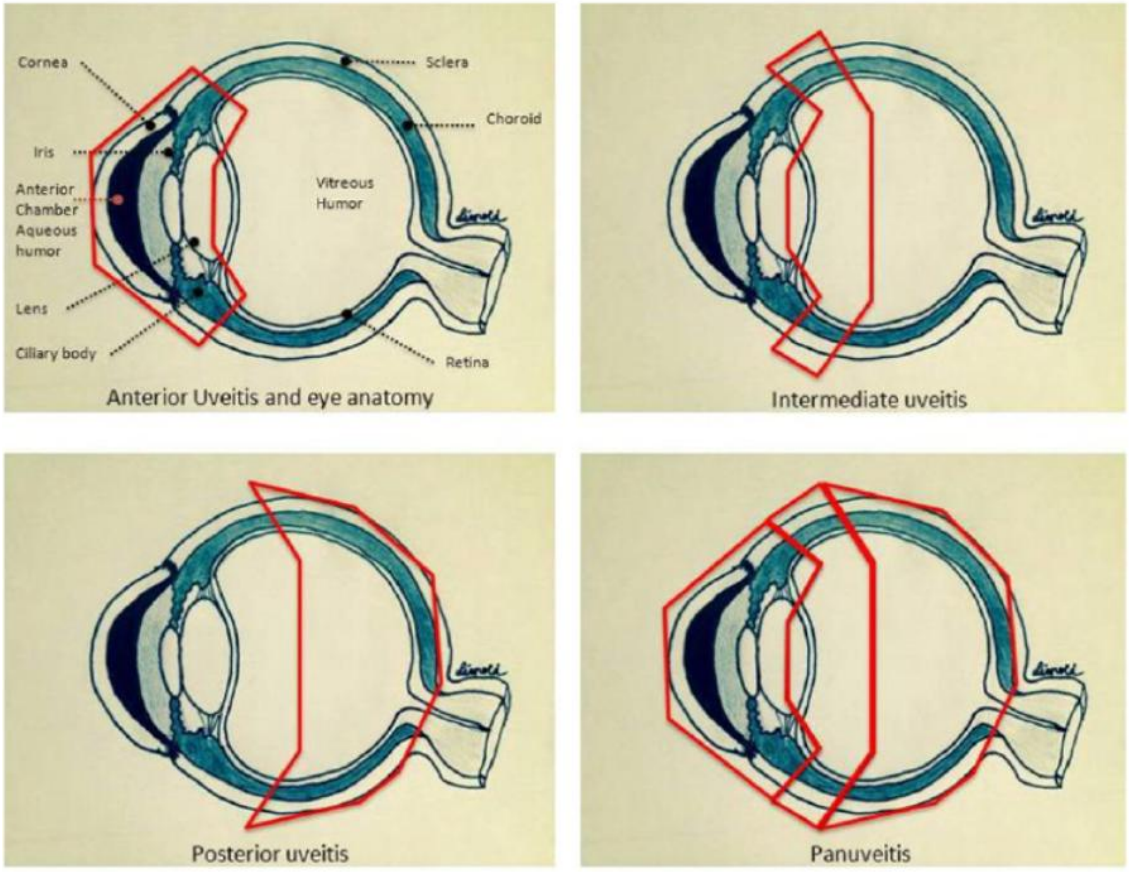

FIGURE 1. Graphical illustration of the inflammatory process involving anterior segment (a), intermmediate (b), posterior segment (c) and panuveitis (d) according to the *standardization of uveitis nomenclature (sun) working group* criteria (reference n° 5).

1.1.2 FUNCTIONAL CLASSIFICATION

Uveitis can also be classified based on the type of onset, the duration of the inflammatory process, and the type of clinical course (5). The onset of uveitis should be described as sudden or insidious. The duration of the attacks should be described as limited if the episode lasts less than 3 months; otherwise, it is referred to as persistent uveitis. Based on the type of clinical course, uveitis can be classified as acute, recurrent, or chronic. Acute uveitis refers to a condition characterized by a sudden onset and limited duration. Uveitis is recurrent if there are multiple episodes intertwined with periods of inactivity lasting at least 3 months without treatment. Uveitis is chronic if the inflammatory process persists with relapses within the first 3 months after discontinuing treatment. Uveitis is also classified as exogenous and endogenous. The former is determined by pathogenic factors external to the body, such as following surgical or accidental eye trauma, while endogenous forms are determined by pathogenic processes related to the body's immune response, such as the presence of pathogens reaching the ocular structures hematogenously or in the case of systemic or

specifically localized immune-mediated diseases affecting the eye. The classification of uveitis into granulomatous and non-granulomatous is currently used less frequently than in past decades. According to this distinction, granulomatous uveitis is clinically characterized by large "mutton-fat" corneal precipitates, an intense cellular reaction in the anterior chamber associated with modest Tyndall due to the low protein and fibrinogen content of the aqueous humor, the formation of nodules on the iris surface and pupillary margin, and a generally chronic course. In contrast, non-granulomatous uveitis is characterized by small and fine corneal precipitates, a modest cellular exudation in the anterior chamber associated with intense Tyndall. In the past, granulomatous uveitis was typically associated with infectious forms such as tuberculosis and syphilis or parasites, while non-granulomatous forms were more often associated with autoimmune processes (8). However, the scientific community is not unanimous on this distinction, as it appears misleading in some cases (5). In fact, in clinical practice, it is often difficult to make this classification because in the initial stages of inflammation, there may be an absence of differential characteristics, while in the final stages, the picture is often overlapping.

1.2 PATHOGENESIS

Until the first half of the 20th century, uveitis was considered an expression of a bacterial infection localized to the uveal tract. Subsequently, with the advances of several techniques identifying pathogenic microorganisms, it was determined that not all uveitis cases were of infectious origin. Some were determined by immune-mediated issues, as also supported by the brilliant response to corticosteroid drugs. The spectrum of diseases connected to the genesis of uveitis has changed over time in the Western world, thanks to improvements in socio-sanitary conditions and the eradication of severe endemic infections. This shift is also attributed to progresses in diagnostic and microbiological techniques.

While in the early 20th century, most uveitis cases were attributed to tuberculosis and syphilis, from the 1960s onward, new etiological entities emerged, such as forms caused by toxoplasmosis, histoplasmosis, Toxocara canis, and more recently, herpetic infections. In addition, in recent decades, the general clinical study of patients with uveitis has revealed significant correlations between systemic diseases and uveitis. Examples include associations between ankylosing spondylitis or Reiter's syndrome and acute anterior uveitis, and between juvenile idiopathic arthritis (JIA) and chronic anterior uveitis (CAU).

Similarly, syndromes such as Vogt-Koyanagi-Harada (VKH) disease and Behçet's disease (BD), in which ocular involvement is of particular importance, have been better re-defined. Recent developments have identified mechanisms specific to innate immunity in the pathogenesis of uveitis. This finding has highlighted an autoinflammatory basis in the uveal inflammatory process, in addition to an autoimmune background. Finally, numerous well-defined ocular-specific clinical entities have been described, such as Fuchs' heterochromic iridocyclitis, multiple evanescent white dot syndrome (MEWDS), serpiginous choroiditis, and "Birdshot" chorioretinopathy.

1.2.1 MOLECULAR MECHANISMS

Regarding the purpose of the study in this thesis, the etiopathogenetic discussion will focus on uveitis of non-infectious origin. The exact pathogenesis is still unclear in many conditions capable of causing uveal inflammation, but it is now established that non-infectious uveitis (NIU) is an immune-mediated manifestation influenced by various endogenous factors. Additionally, genetic factors may play a central role in facilitating endocular inflammation. The eye is the prototype of "privileged" tissues from an immune standpoint, capable of resisting immune-mediated inflammatory processes through at least four different mechanisms: i) the presence of a blood-retinal barrier that isolates the eye from systemic immunity; ii) the absence (or limited presence) of direct lymphatic drainage; iii) the ocular microenvironment composed of various immunoinhibitory molecules; iv) the ability to elicit systemic regulatory mechanisms aimed at limiting damage if the inflammatory process has developed. From a phylogenetic perspective, the ocular microenvironment has evolved to control the immune and inflammatory processes to limit potential structural damage that would otherwise lead to severe impairment of visual capacity (10).

1.2.2 REGULATION OF THE INNATE IMMUNITY IN THE EYE

The activation and function of innate immune cells such as natural killer (NK) cells, monocytes-macrophages, and neutrophils are regulated by factors within the ocular microenvironment (11,12). Among innate immune cells, macrophages play a crucial role in many cases of endocular inflammation. However, their function appears to be inhibited by the neuropeptide α-melanocyte stimulating hormone (α-MSH) and the calcitonin gene-related peptide (CGRP) found in endocular fluids. Interleukin (IL)-10 produced by Tγδ lymphocytes may also play a role in modulating macrophage functions. Although direct evidence is still lacking, the identification of IL-10 as a factor involved in the regulation of ocular macrophage infiltrate and in the polarization of macrophages into the regulatory M2 form suggests a key role for this cytokine in conferring immunological privilege in the eye (13,14). Ocular fluid contains at least two factors that suppress the function of NK cells: macrophage inhibitory factor (MIF) and transforming growth factor

(TGF)-β2 (15). Regarding neutrophil inhibition, a key role has been identified in Fas ligand (FasL), a protein acting as an interface between innate and acquired immunity. Surface FasL is expressed by corneal cells, iris cells, and retinal pigment epithelium. It induces apoptosis in Fas-expressing leukocytes and promotes immunological tolerance to endocular antigens (16). FasL can also be present in endocular fluid in its cleaved form (17). In the context of innate immunity, a separate mention should be given to the role of complement. A baseline level of ocular complement cascade activation is almost constantly present, likely to safeguard the eye from pathogenic germs. However, ocular fluids contain numerous complement regulatory proteins to prevent excessive activation that could otherwise damage ocular tissues. These proteins include complement factor H (CFH), complement receptor 1-related gene/protein y (Crry), and decay-accelerating factor (DAF) (18,19).

1.2.3 REGULATION OF ADAPTIVE IMMUNITY IN THE EYE

The elements of acquired immunity that actively operate at the ocular level include CD4+ and CD8+ T lymphocytes as well as antibodies. Numerous molecules are capable of modulating the acquired immune system at the endocular level, including Fas ligand (FasL), programmed death ligand-1 (PD-L1), and the action of CD4+ T lymphocytes (20). As for CD8+ T lymphocytes, they share many effector characteristics with NK cells and can be controlled at least in part by mechanisms similar to those described for NK cells. However, CD8+ T cells can also act as regulatory cells whose production depends, in part, on NKT cells in the spleen (21). Naïve retina-specific CD4+ T lymphocytes are converted into (Fox)p3+ regulatory T lymphocytes and IL-10-secreting cells with reduced effector function. This is allowed by the ocular recognition of the specific antigen and the presence of retinoic acid and TGF-β, both abundant in the ocular milieu (22). In contrast, CD4+ T lymphocytes that are already activated outside the ocular environment seem to be insensitive to the endocular immunomodulatory microenvironment and continue to express their effector functions (23). Additionally, the inflamed eye is less capable of converting naïve retina-specific CD4+ T lymphocytes into regulatory T cells. This may be partly related to the presence of abundant pro-inflammatory mediators but also to the depletion of anti-inflammatory factors that induce T cell formation (primarily retinoic acid and TGF-β) (24,25).

Altogether, these pathogenetic *milieu* may, at least partially, explain why NIU can affect the eye despite its immunologically "privileged" environment.

1.2.4 THE MOLECULAR PROCESS INVOLVED IN THE UVEITIS DEVELOPMENT

Uveitis presents with inflammation mediated by a mixed infiltrate containing elements of both innate and acquired immunity. The autoimmune nature of the process is supported by the absence of infections, the association with specific major histocompatibility complex (MHC) antigens, and the role played by T cells in pathogenesis, as evidenced by the effectiveness of drugs acting on T cells, including cyclosporine, rapamycin, and IL-2 inhibition with daclizumab (26). However, it has been recently proposed that some forms of uveitis may actually have an autoinflammatory substrate, more closely linked to dysregulation of innate immunity (27). This assertion is based on the observation of certain associations between uveitis and specific allelic variants of innate immune receptors such as the NOD-like receptor family and NLR family pyrin domain-containing 3 (NLRP3). It also considers the central role played by IL-1 in uveitis genesis, a key cytokine in the pathogenesis of autoinflammatory diseases (28). Nevertheless, this should not be understood in a strictly dichotomous sense since typical elements of acquired immunity such as increased Th1 and Th17 responses are also detectable in autoinflammatory disorders (29). Based on data from murine models, it is clear that antigen-specific T cells play a key role in the pathogenesis of uveitis. Particularly during uveitis, various T cell effector lines have been identified, normally involved in fighting infectious agents but also capable of accruing tissue damage. Both Th1 and Th17 cells specific for retinal antigens have been identified, involved in recruiting neutrophils and monocytes, respectively, and capable of inducing tissue damage and causing uveal inflammation (30). In this context, the following pathogenetic sequence in the genesis of uveitis can be described: i) autoreactive T cells against retinal antigens are activated peripherally as a consequence of currently unknown stimuli; ii) these cells transit through retinal vessels and adhere to vascular endothelium; iii) due to their activated state, T cells produce matrix-degrading enzymes and metalloproteinases capable of breaking vascular junctions forming the blood-retinal barrier, allowing endocular transmigration of autoreactive cells; iv) once inside the eye, autoreactive T cells recognize their specific ocular antigen; v) autoreactive T cells produce cytokines and chemokines that activate antigen-presenting cells (APCs) at the endocular level, thus amplifying the inflammatory process and causing uveitis (26,31,32). The amplification of the inflammatory cascade, in turn, acts on local microvasculature, amplifies the recruitment of leukocytes and APCs, causes further disruption of the blood-retinal barrier, and ultimately results in the passage of retinal antigens to the lymphatic system, leading to amplification of the adaptive immune process. In this context, Th1 or Th17 lymphocytes also stimulate innate immune cells that contribute to tissue damage (23,25).

1.2.5 GENETIC PREDISPOSITION

Various genetic factors have been associated with an increased risk of developing uveitis. In particular, the most studied genes are those encoding for MHC, pro-inflammatory cytokines, chemokines, and the complement system.

1.2.5.1 THE MAJOR HISTOCOMPATIBILITY COMPLEX

"The MHC represents a surface complex for all cells of vertebrate species, allowing leukocytes to interact with other leukocytes and with other cells of the organism. Among other functions, the MHC allows APCs to present antigens to CD4+ lymphocytes as part of the adaptive immune response. In humans, the MHC is called the human leukocyte antigen (HLA) and is genetically expressed at position 6p21.3, a region containing about 200 genes, over 40 of which are HLA genes. These genes encode a large number of antigen-presenting molecules on the cell surface and proteins with immunological functions (33). HLA genes are classified into 3 classes. Class I MHC, expressed to varying degrees on all nucleated cells, includes genes encoding for HLA-A, HLA-B, HLA-C, which form complexes with antigenic peptides inside the cell and then export these peptides to the cell surface to present them to CD8+ T lymphocytes. Class II MHC includes genes encoding for HLA-DM, HLA-DO, HLA-DP, HLA-DQ, and HLA-DR, which are expressed in professional APCs (dendritic cells, macrophages, and B lymphocytes) and bind extracellular antigens to present them to CD4+ T cells. Class III HLA contains genes that play a key role in the immune response, including components of the complement system, tumor necrosis factor (TNF)-α, and heat shock proteins. Human uveal cells, except for vascular endothelium, do not express or express at low concentrations class I molecules. The retinal pigment epithelium under normal conditions does not contain cells expressing HLA-II. HLA-B27 is closely linked to the onset of non-granulomatous acute anterior uveitis (AAU), being present in up to 50% of cases affected by this clinical condition. However, the frequency of this antigen in the general population varies, being found in about 8% of the Caucasian population and about 0.5% of the Japanese population. Despite the intense research, the precise molecular mechanism related to the onset of uveitis remains unknown. Interestingly, among patients with HLA-B27-associated AAU, there is also a concomitant spondyloarthritis in about two-thirds of patients (34,35).

HLA-Bw51 represents the strongest genetic marker associated with BD, although it appears to be uncorrelated with increased disease severity (36). HLA-A29, on the other hand, shows a strong association with the development of "Birdshot" chorioretinitis (37), present in about 96% of patients and in 7% of the general population. HLA-A29 is divided into over twenty subtypes, of which the major ones are HLA-A29:01 and HLA-A2902, which differ by only one amino acid. Between the

two alleles, HLA-A*2902 has the strongest association with disease development and is also the subtype most expressed in the Caucasian population (48% of total HLA-A29 carriers) (38). HLA-B12 and its splicing products (HLA-B44 and -B45) have been found in 68% of patients with "Birdshot" chorioretinitis. However, HLA-B12 is in linkage disequilibrium with HLA-A29 (39). Various associations have been identified with VKH. The strongest ones are with HLA-DRB10405 and HLA-DRB10410, as well as with HLA-DRB10407. In general, the HLA-DRB14 haplotype gives CD4+ T lymphocytes a greater predisposition to attack melanocytes. In a study conducted in California, 84% of Hispanics with VKH had HLA-DR1 and HLA-DR4, with the former having the strongest correlation (40). Another study on a Japanese population also showed an association between VKH and HLA-DQ4 and HLA-DQA1*0301 (41). Regarding patients with chronic anterior uveitis associated with JIA, only the protective role of HLA-DR1 has been confirmed to date, while data on other allelic associations are rather controversial (33). HLA-DR2, -DR15, -B8, and -B51 are associated with the onset of pars planitis. In particular, HLA-DR15 is also associated with the onset of multiple sclerosis, a condition associated with intermediate uveitis (42). Sympathetic ophthalmia is correlated with HLA-DQw3 in Americans and HLA-DQw53 in Japanese (33). The tubulointerstitial nephritis and uveitis (TINU) syndrome is finally associated with HLA-DQA101, -B105, and -DRB1*01 (43). Acute multiple placoid pigment epitheliopathy has been associated with a higher frequency of HLA-DR2 and -B7. This latter haplotype has also been found more frequently in patients with serpiginous choroiditis (44,45). The major associations are summarized in Table 1."

Disease	Associated HLA
Acute anterior uveitis associated to HLA-B27 **Ankylosing Spondylitis** **Reiter Syndrome** **Uveitis in Psoriatic arthritis** **Uveite in Enteroarthritis**	HLA-B27
Behçet's disease	HLA-Bw51
"*Birdshot*" chorioretinopathy	HLA-A29 HLA-B12
Vogt-Koyanagi-Harada syndrome	HLA-DRB1*0405 HLA-DRB1*0410 HLA-DR1 HLA-DR4 HLA-DQ4 HLA-DQA1*0301
Pars Planitis	HLA-DR2 HLA-DR15 HLA-B8 HLA-B51
Sympathetic ophthalmia	HLADQw3 HLA-DQw53
Tubulointerstitial nephritis and uveitis (TINU) syndrome	HLA-DQA1*01 HLA-B1*05 HLA-DRB1*01
Coroidite serpiginosa	HLA-B7
Acute multiple placoid pigment epitheliopathy	HLA-B7 HLA-DR2

TABLE 1. Summarizes the most known associations of some HLA haplotypes with specific diseases

1.2.5.2 INTERLEUKINS

Interleukins are powerful mediators of the inflammatory process, also involved in the pathogenesis of uveitis. They enable long-distance communication between inflammation cells, ultimately resulting in the regulation of the inflammatory system in terms of induction or inhibition. In particular, IL-1, IL-2, IL-21, IL-27, IL-6, and tumor necrosis factor (TNF)-α are all cytokines involved in the induction of uveal inflammation. For this reason, various studies have been conducted to identify any associations between the onset of uveitis and specific gene polymorphisms in genes encoding for these cytokines, particularly IL-1 and TNF-α. In detail, certain polymorphisms in the IL-1 gene, such as *IL-1A* and *IL-1B*, have been associated with the onset of BD (46), while polymorphisms in TNF-α or its receptors have been associated with the susceptibility and severity of AAU (47,48). However, there are various discrepancies among different studies, and it is challenging to determine whether these associations result from linkage

disequilibrium with HLA genes or not. Regardless, a meta-analysis has confirmed the association between BD and TNF-α polymorphisms 857T, -238A, and -1031C (49).

1.2.5.3 CHEMOKINES

Chemokines are a family of peptides secreted during the inflammatory cascade by endothelial cells in response to cytokines, mainly TNF-α and IL-1. The main function of chemokines is to recruit leukocytes to the inflammation site, but some of them also act as inducers of neovascularization. The number of cysteine residues and their position along the primary structure of the peptide allow classification of chemokines into four groups: i) CC, where the first two cysteines are adjacent; ii) CXC, where the first two cysteines are separated by one amino acid; iii) CX3C, where the first two cysteines are separated by three amino acids; iv) C chemokines, in whose primary chain there are only two cysteines instead of four, corresponding to the second and third residues found in other chemokines (50). A long series of chemokines has been identified as active participants in the recruitment of inflammatory cells during uveitis, particularly IP-10, a ligand for the CXCR3 receptor present on activated T cells, especially Th1 (51,52). Moreover, the RNA messenger of some chemokines has been found to increase before the onset of experimental uveitis in murine models, suggesting a role in the initial recruitment of inflammatory cells. Among these, monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1 (MIP-1), and interferon-γ-induced protein 10 (53,54) are worth mentioning. Various polymorphisms have been found in genes encoding for chemokines or their receptors, particularly MCP-1, CCL2, CCL5, CX3CR1, CCR2, and CCR5. Additionally, polymorphisms in the promoter regions of CCL2 and CCL5 have been identified, which may play a role in regulating their gene expression (55-58).

As for the gene encoding for the CX3C receptor 1 (CX3CR1), the I249/M280 haplotype has been associated with the onset of non-ischemic retinal vasculitis (59).

1.2.5.4 THE COMPLEMENT SYSTEM

The complement system is a central element of the innate immunity and includes over thirty serum and surface proteins involved in defense against infections and the induction of the inflammatory process. Complement factors are predominantly synthesized in the liver, but local secretion can also occur in endothelial cells, fibroblasts, and monocytes/macrophages. Activation of the complement system occurs through three different pathways: classical, alternative, and lectin-mediated (60). Under normal conditions, the complement system is active at a low degree and is regulated by various control mechanisms, including CFH. Regarding CFH, a 184G polymorphism has been associated with the onset of anterior uveitis, while V62I and E936D polymorphisms have been

associated with the onset of intermediate and posterior uveitis (61,62). Complement factor B (CFB), a component of the alternative pathway, shares the same binding site with CFH for the complement protein C3b. In this regard, a study has highlighted an association between anterior uveitis and the CFB-rs1048709 polymorphism (63).

1.3 EPIDEMIOLOGY

Uveitis accounts for 5%-20% of cases of legal blindness in the United States and Europe and probably up to 25% of cases in developing countries (2.64). In the Western world, uveitis occurs with an incidence ranging from 17 to 52 cases per 100,000 inhabitants per year and a prevalence of 38-714 cases per 100,000 inhabitants (3.65-67). Infectious forms are more common in developing countries and collectively represent 30%-50% of all uveitis cases (68,69). Regarding non-infectious forms, the most common causes of uveitis are idiopathic uveitis, Fuchs' heterochromic iridocyclitis, uveitis associated with HLA-B27, sympathetic ophthalmia, multifocal choroiditis, and those related to sarcoidosis, VKH, BD, and autoimmune inner ear disease (AIED). Also frequent are masquerade syndromes, neoplastic conditions capable of creating an intraocular picture very similar to that found in a patient with uveitis and therefore needing to be excluded in the context of appropriate differential diagnosis. Most uveitis cases associated with sarcoidosis are reported in the United States, Japan, and the Netherlands. BD, on the other hand, is more commonly found in Turkey, Iran, Greece, Japan, China, and Saudi Arabia. VKH is more prevalent in Europe and Asia. "Birdshot" chorioretinopathy is more prevalent in Western countries (70-74).

1.3.1 EPIDEMIOLOGY BASED ON ANATOMICAL CLASSIFICATION

1.3.1.1 ANTERIOR UVEITIS

In Western countries, anterior uveitis is by far the most common form of uveal inflammation, affecting approximately 50% of patients with uveitis. In most cases, these are idiopathic forms, followed by those associated with HLA-B27 positivity and ankylosing spondylitis. Fuchs' heterochromic iridocyclitis and herpetic forms follow suit (64,75,76). The prevalence of anterior uveitis is relatively lower in Asian countries, where the frequency of HLA-B27 is much lower (64,71,75,77).

1.3.1.2 INTERMEDIATE UVEITIS

Intermediate uveitis represents the least common form of uveitis and is idiopathic in the majority of patients, a condition referred to as pars planitis. According to studies conducted in California, the

incidence of intermediate uveitis is 1.5 cases per 100,000 inhabitants per year (3). Pars planitis is more prevalent among Caucasians and typically begins before the age of 40 in all cases (78,79).

The form of intermediate uveitis caused by human T-cell lymphotropic virus type 1 (HTLV-1) is present in specific geographical areas, such as Japan, the Caribbean, and certain regions of Africa and Latin America, despite the virus having a global distribution (76). Many studies have shown that intermediate uveitis has been identified in patients with multiple sclerosis, although there are no temporal associations between the onset of uveal inflammation and neurological manifestations (78,80-82). In particular, the prevalence of intermediate uveitis is 10 times higher among patients with multiple sclerosis compared to the general population (80,83). Other relatively common causes of intermediate uveitis include sarcoidosis and Lyme disease.

1.3.1.3 POSTERIOR UVEITIS

Posterior uveitis is the most commonly encountered form of uveitis after anterior uveitis, accounting for 15%-30% of uveitis cases (75,76). The most common etiology is toxoplasmosis, followed by idiopathic forms. The highest incidence of posterior uveitis due to Toxoplasma is found in Latin America. In India, posterior tubercular uveitis is more common, while in Africa, posterior uveitis related to onchocerciasis is epidemiologically relevant. Histoplasmosis-related uveitis is almost exclusively observed in the United States, particularly in the Mississippi-Ohio Valley. Posterior uveitis forms related to VKH disease and BD are more prevalent in developing countries, with BD being more common along the historical "Silk Road" route (84).

1.3.1.4 PANUVEITIS

Panuveitis is the most prevalent form of uveitis in South America, Africa, and Asia, where it is often associated with infectious factors such as onchocerciasis in Africa. In the Western world, on the other hand, the most common form is idiopathic panuveitis, followed by BD in Asia (6).

1.3.2 EPIDEMIOLOGY ACCORDING TO SPECIFIC AGE GROUPS

Uveitis can affect individuals of all ages, but it is more frequently observed between the ages of 20 and 60 (2,65,85). Anterior uveitis is the most common form of uveitis in both adults and pediatric patients. However, in children, uveitis associated with JIA prevails, while in adults, anterior uveitis associated with HLA-B27 is more common (2,64,70,75).

1.3.2.1 CHILDREN

In children, the incidence of uveitis is approximately five times lower than in adults, and the prevalence is about ten times lower. Anterior uveitis represents 30%-40% of all pediatric uveitis

cases, with the most common cause being JIA. Intermediate uveitis follows in frequency. Pediatric posterior uveitis is more commonly associated with infections like Toxoplasma, Toxocara canis, or idiopathic forms, but their frequency has decreased compared to several decades ago. Conversely, there has been a percentage increase in panuveitis, while the frequency of intermediate uveitis remains stable (6). In children, uveitis can lead to visual deficits in approximately one-third of cases (86-90). It's important to exclude masquerade syndromes in children, as conditions like retinoblastoma and leukemia can be associated with misdiagnosed uveitis.

1.3.2.2 ELDERLY PATIENTS

Uveitis with an onset beyond the age of 60 is not particularly common, and uveal inflammation often acts as a masquerade syndrome covering other issues such as ocular lymphoma and paraneoplastic syndromes (65). Excluding infectious forms and masquerade syndromes, uveitis in the elderly is more often idiopathic (91).

1.4 PREDISPOSING FACTORS

In relation to genetic predisposition, much has been discussed. As for other factors, age, gender, and ethnicity/geographical origin are worth discussing. *Age*: Excluding infectious forms, uveitis is rare after the age of 60 and infrequent in pediatric populations, possibly due to the immaturity of the immune system. *Gender*: There are generally no significant differences in uveitis incidence based on gender. However, certain forms of uveitis are more common in either men or women. Uveitis associated with ankylosing spondylitis (UAA) is more common in men, while CAU related to sarcoidosis or rheumatoid arthritis is more frequent in women. Posterior uveitis due to VKH disease is more common in women.

Ethnicity: Uveitis associated with HLA-B27 and JIA is more characteristic of the Caucasian ethnicity. In contrast, VKH disease is less prevalent among Caucasians and more common in darker-skinned populations but not among sub-Saharan Africans.

Geographical Origin: Geographical origin plays a role in uveitis epidemiology due to different exposures to specific infectious agents.

These factors, in combination with genetic predisposition, contribute to the diversity of uveitis presentation in different populations and age groups.

1.5 CLINICAL AND ANATOMICAL DIAGNOSIS

In order to reach a correct clinical and anatomical diagnosis, a proper physical examination is of paramount importance. The focal light inspection alone can provide useful diagnostic elements by allowing the detection of ciliary reactions, alterations in iris color, the shape of the pupil, involvement of the episclera and sclera, and the transparency of the dioptric media. Slit-lamp biomicroscopy with or without the use of lenses is also a crucial tool, which enables a detailed assessment of all inflammatory, degenerative, and structural alterations at the level of the cornea, anterior chamber, aqueous humor, iris, lens, vitreous body, optic disc, and retina. The ophthalmoscopic examination must be carried out in all types of uveitis, including anterior uveitis, in which the study of the retinal periphery and the papillo-macular region is of particular interest. Indirect ophthalmoscopy with or without scleral buckling and biomicroscopic examination with Goldman's three-mirror lens allow, in addition to a complete study of the deep membranes, the examination of the posterior vitreous and the evaluation of its inflammatory and degenerative alterations. Other instrumental tests should be requested as needed, depending on whether the clinician deems additional diagnostic investigations useful. The following will describe in detail the clinical scenarios that can be highlighted by ophthalmoscopy in the context of various uveitic pictures (9).

1.5.1 Anterior Uveitis

1.5.1.1 Symptoms

From a symptomatic perspective, anterior uveitis is characterized by the presence of pain, photophobia, tearing, and blurred vision. The pain in AAU is deep and comes as a result of the irritation of the ciliary nerves; it intensifies with pressure, exposure to light, and near vision. In CAU, pain may be absent or dull. Photophobia and tearing are particularly pronounced in acute and subacute iridocyclitis, while they are mild or absent in CAU. Photophobia is dependent on ciliary spasm and corneal involvement. In severe cases, there is persistent blepharospasm, while in milder forms, the disturbance occurs only with illumination. Tearing is secondary to the irritation of corneal and ciliary nerves. The reduction of vision can vary in degree, ranging from mild to severe. In AAU, it is mainly related to corneal changes (endothelial precipitates, edema) and the clouding of the aqueous humor and vitreous due to exudation in the anterior and vitreous chambers. In recurrent and chronic forms, visual deficits may be more closely linked to lenticular and vitreal opacities, epipupillary proliferative changes, papillary and macular edema, which are long-lasting complications of anterior inflammation.

1.5.1.2 Signs

The signs that characterize anterior uveitis, on the other hand, include perikeratic reaction, endothelial corneal precipitates, Tyndall effect, cellular exudation in the anterior chamber, miosis, irregularities of the pupil secondary to posterior synechiae, and intraocular hypotonia.

1.5.1.2.1 Congestion

Generally, it is the first sign of anterior uveitis, and in more severe forms, it can also spread to the conjunctiva, which may become chemotic. Its absence is characteristic in Fuchs' heterochromatic iridocyclitis. The differential diagnosis should be made with conjunctivitis, episcleritis, and scleritis; in the latter two conditions, the reaction is generally sectorial and never involves the entire limbal circumference. In conjunctivitis, on the other hand, the dilation of small vessels is more superficial, resulting in a bright red color compared to the more bluish color of uveitis.

1.5.1.2.2 Corneal precipitates

The corneal precipitates are aggregates of inflammatory cells present in the aqueous humor and deposited on the surface of the corneal endothelium. Studying the characteristics of corneal precipitates can provide useful information for the diagnostic and prognostic assessment of uveitis. The "mutton fat" precipitates consist of macrophages and epithelioid cells that aggregate to form whitish masses with a greasy, flattened potato-like shape. Over time, they tend to increase in size and change color, while the edges become jagged and serrated. They could, in some cases, never completely resolve, acquiring a translucent appearance. Generally, they have a triangular arrangement on the cornea with the apex at the top. Mutton fat precipitates are more typical of granulomatous and chronic uveitis; however, they can also be observed in particularly severe non-granulomatous inflammations. Figure 2 shows an example of mutton fat precipitates in a patient with anterior uveitis due to HZV (Herpes Zoster Virus).

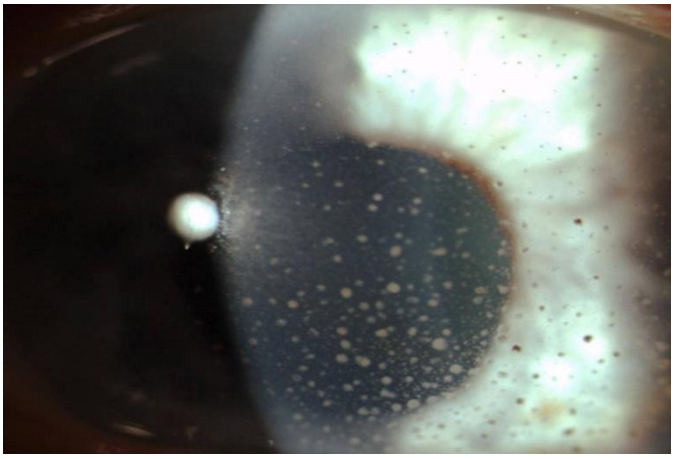

FIGURE 3. Mutton-fat precipitates distributed mainly on the inferior region of the corneal endothelium. Courtesy of Dr. Claudia Fabiani.

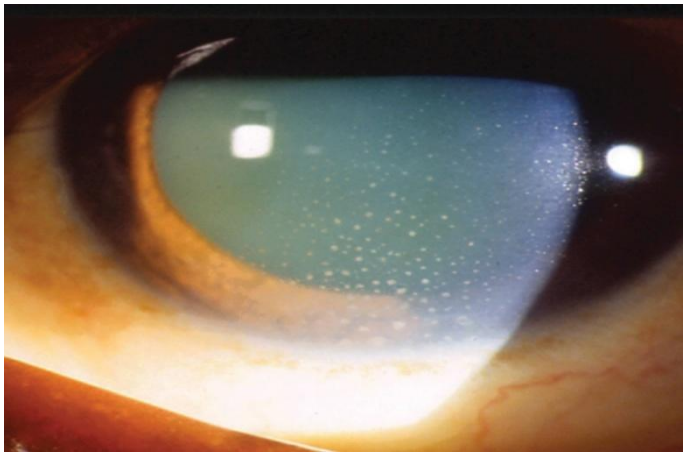

FIGURE 2. White corneal precipitates (reference n° 92).

On the other hand, white precipitates are generally composed of lymphocytes and plasma cells. They are small, white, numerous, do not tend to merge, have clear margins, and disappear with the resolution of inflammation. They are typical of non-granulomatous forms and are found in the heterochromatic Fuchs' iridocyclitis, widely distributed across the entire corneal endothelium. This diffuse arrangement (not triangular) is also characteristic of herpetic keratouveitis. Figure 3 shows a typical example of white precipitates (image is taken from Herbort et al.) (92).

1.5.1.2.3 TYNDALL SIGN AND INFLAMMATORY INFILTRATES IN THE ANTERIOR CHAMBER

The aqueous humor is normally clear and optically empty during biomicroscopic examination. In anterior uveitis, however, vascular exudation of proteins, fibrin, and inflammatory cells compromises its transparency. In particular, the increase in protein content is responsible for the Tyndall phenomenon and is indicative of the presence or persistence of the inflammatory process in the anterior chamber. As illustrated in Figure 4, the Tyndall phenomenon is an assessment of particulate matter present in the anterior chamber, perceptible when a beam of light passes through it. Tyndall, in accordance with the SUN (5) recommendations outlined in Table 2, is quantified on a scale ranging from 0 to 4+ based on the quantity of proteins present in the anterior chamber. In AAU, Tyndall is generally intense and proportional to inflammation but regresses completely with the resolution of inflammation. In chronic uveitis, however, Tyndall without cells is observed, more or less intense even during periods of remission. In this case, it is more indicative of vascular permeability damage associated with chronic inflammation. In such cases, disease relapse will be assessed by the presence of cells.

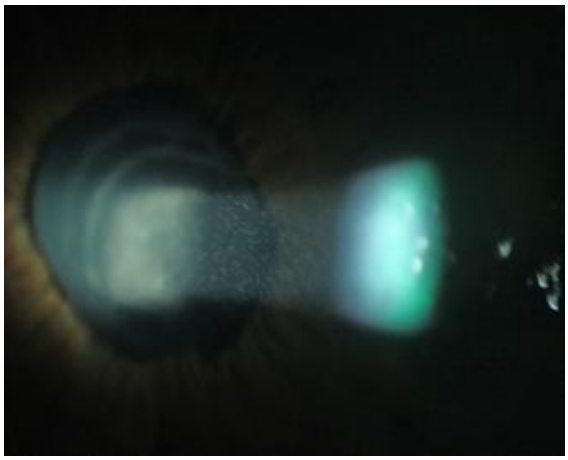

FIGURE 4. Tyndall effect on anterior chamber. it is possible to observe an intense reaction which can be quantified as 3+ according to S*tandardization of Uveitis Nomenclature* (SUN) *working group*.

Tyndall	Caracteristics
0	Absent
1+	Mild
2+	Moderate (iris and lens are clearly visible)
3+	Marked (iris and lens are cloudy)
4+	Rich fibrin levels/deposits

TABLE 2. Grading of inflammatory infiltrate in the anterior chamber evaluated by tyndall phenomenon. classification proposed in the table follows the guidelines of the standardization of uveitis nomenclature (sun) working groups (reference n° 5).

The cells of the aqueous humor are best identified in contrast to the dark background of the pupil and when Tyndall is not very intense. The presence of inflammatory cells is always indicative of inflammation, and their quantity varies with the severity and the state of the disease activity. It is possible to quantify the presence of cells in the anterior chamber (5). In this case as well, quantification ranges from 0 to 4+, according to the scheme shown in Table 3. The presence of cellular precipitates in the angle of the anterior chamber, the lens, and the iris with the same characteristics as those found on the corneal endothelium (sheep fat, white precipitates) represents a more severe pathogenetic significance.

Grading	Number of cells per field (1 mm x 1 mm at lamp biomicroscopy)
0	<1
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

TABLE 3. Grading of anterior chamber cells according to Standardization of Uveitis Nomenclature (sSUN) working group (reference n° 5).

In cases of intense uveal inflammation, the passage of fibrin into the anterior chamber can result in a gelatinous appearance of the aqueous humor with almost immobile cells and strands of fibrin depositing on structures moistened by the aqueous humor. In such cases, it is referred to as plastic iritis.

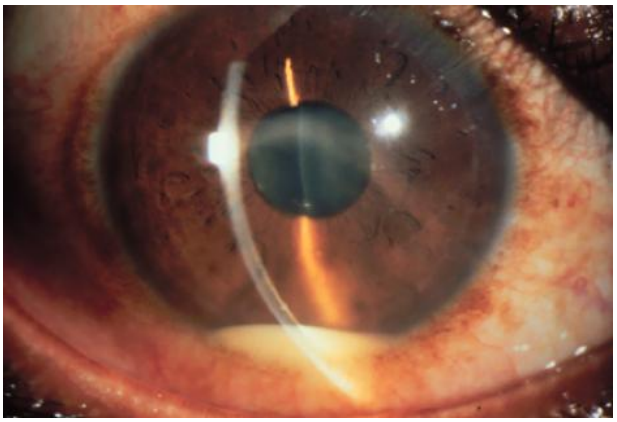

FIGURE 5. Hypopion in a patient suffering from acute anterior uveitis associted to HLA-B27. Courtesy of Dr. Claudia Fabiani.

1.5.1.2.4 HYPOPION

An excessively intense inflammatory reaction can induce such cellular presence in the anterior chamber that, due to gravity, leads to the settling of cells in the lower part, forming a white-yellowish layer. The type of cells that form this layer depends on the specific pathology: in BD, it is primarily composed of polymorphonuclear cells, while in the form caused by Toxocara, there is a predominant concentration of eosinophils.

The hypopyon must be differentiated from pseudo-hypopyon in non-inflammatory syndromes, including intraocular tumors, lymphomas, leukemias, and intraocular foreign bodies. In certain cases, an adequate differential diagnosis can be made solely on assessment of cellularity. Figure 5 illustrates a typical example of a hypopyon.

1.5.1.2.5 IRIDAL CHANGES

At the iris level, it is possible to identify a congestion that renders the iris opaque, with a clouding of the normal texture and a change in color: blue irises tend to become greenish, and brown irises become yellow-reddish. Protein and cellular exudation lead to the formation of iris nodules, anterior and posterior iris synechiae, and eventually pupillary occlusion.

1.5.1.2.5.1 NODULES AND GRANULOMATOUS FEATURES

Nodular manifestations, which are more typical of slowly evolving chronic uveitis, can be found in both granulomatous and non-granulomatous forms. They consist of aggregates of lymphocytes and plasma cells, and less frequently, macrophages. Two types of nodules are known: Busacca nodules and Koeppe nodules.

Busacca nodules are located in the iris stroma, away from the pupil area. They vary in size and appear as protrusions on the anterior surface of the iris. When situated at the iris base, they can promote anterior synechiae.

Koeppe nodules are located on the pupillary margin, are minute in size, and have a whitish or translucent color, but they may pigment over time. They can represent the starting point for posterior iris synechiae.

Busacca nodules are more indicative of a granulomatous form compared to Koeppe nodules. Both Busacca and Koeppe nodules are illustrated in Figure 6, taken from Herbort et al (92).

Granulomas are larger than nodules, often single, with a pinkish color and vascularization. They are specific to tuberculosis, syphilis, and sarcoidosis.

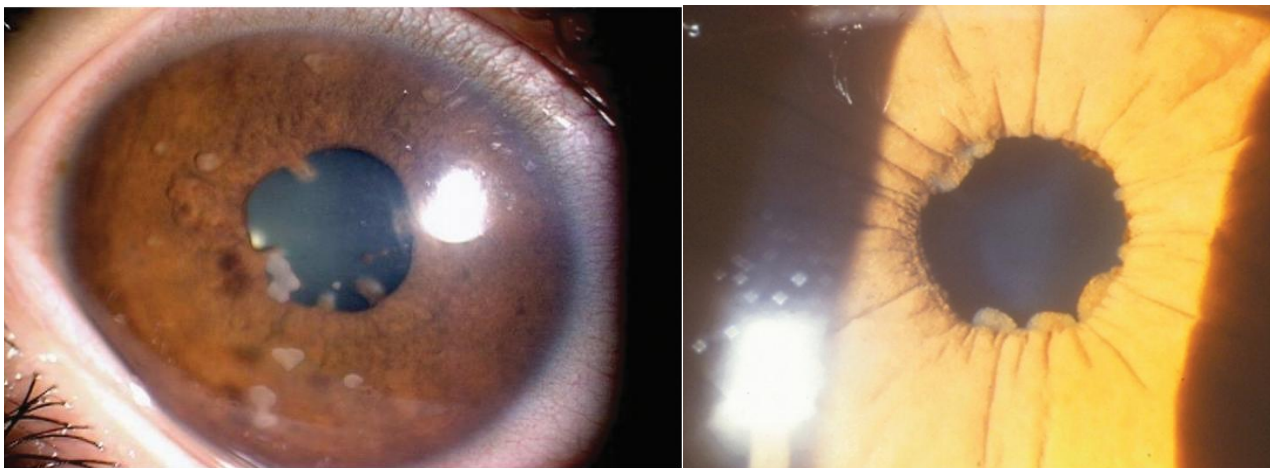

FIGURE 6. Busacca nodules on the left, far away from the pupillary margin; Koeppe nodules on the right, near the pupillary margin (reference n° 92).

1.5.1.2.5.2 IRIDAL SYNACHIAE

Synechiae are adhesions between the iris and adjacent structures, generated by the deposition of fibrin and pigments subsequently organized by inflammatory cells and iris fibroblasts. They are distinguished as posterior and anterior. Posterior synechiae develop between the iris and the anterior capsule of the lens. They tend to form mainly in forms characterized by a high Tyndall effect and in acute and recurrent subacute forms. On the contrary, in Fuchs' heterochromic iridocyclitis, posterior synechiae never form. Posterior synechiae can also visibly deform the pupillary opening, sometimes giving it a flower-like appearance, as observed in Figure 7. When the synechiae are arranged in a circular peripupillary manner, complete pupil occlusion (pupillary block) can occur. Anterior synechiae form between the iris and angular structures. However, the following predisposing events are required to bring the iris closer to the cornea: iris edema, pupillary block that causes the aqueous humor to push the iris forward, and the

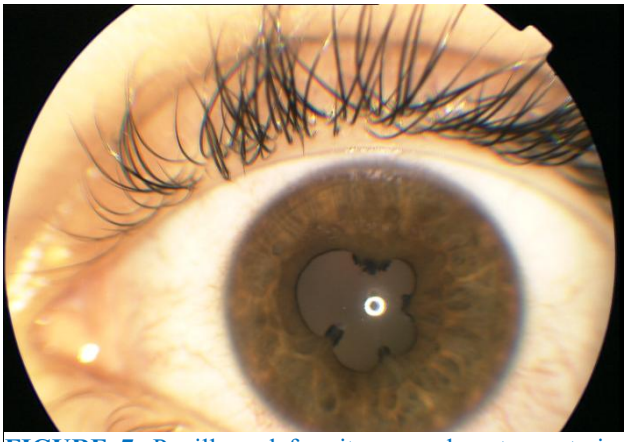

FIGURE 7. Pupillary deformity secondary to posterior synechiae in a patient with idiopathic anterior uveitis. Courtesy of Dr. Claudia Fabiani.

organization of exudates in the iridocorneal angle that create traction between the iris and angular structures. The formation of anterior synechiae is more frequent in CAU.

1.5.1.2.5.3 Pupillary occlusion and iridal atrophy

Pupillary occlusion is often associated with the presence of an epipupillary inflammatory membrane or with the presence of organized posterior sinechiae in the context of uveitis characterized by a high exudative component. A characteristic feature of anterior uveitis is miotic eye (constricted pupil), which is due to spasm of the pupillary constrictor muscle, as well as edema that increases iris volume. Iridal atrophy results from chronic recurrent uveitis, which leads to degenerative changes in both the stromal and posterior pigmented epithelium. Atrophy is characterized by the flattening of the normal iris structure and the presence of depigmented areas. Atrophy can be diffuse, patchy, sectoral, or involve the pupillary margin. The sectoral variant is typical of viral iridocyclitis, especially herpetic iridocyclitis. It's worth noting that essential iris atrophies can mimic post-zoster forms, as well as sectoral ischemic atrophy secondary to acute glaucoma. Figure 8 shows a case of anterior uveitis caused by herpes zoster virus (HZV) with sheep fat-like corneal precipitates and patchy iris atrophy.

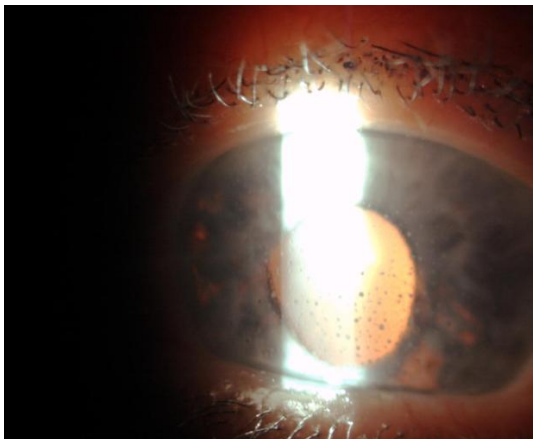

FIGURE 8. Anterior uveitis caused by hzv showing patchy idial atrophy. Courtesy of Dr. Claudia Fabiani.

1.5.1.2.6 Lens changes

The alterations of the lens in the course of anterior uveitis include precipitates, pigmented deposits, and opacities. The precipitates are equivalent to corneal ones and deposit on the anterior capsule in iritis and also on the posterior side in iridocyclitis. Aggregates of pigment, consisting of iridal pigmented epithelium, indicative of detached posterior synechiae, can also be identified. The changes in the transparency of the lens are partly caused by the toxic action of inflammatory molecules on the lens and partly by the degeneration induced by the formation of posterior synechiae, leading to liquefaction of the superficial fibers of the capsule. The severity of opacities is related to the intensity and duration of the inflammatory process. Prolonged iridocyclitis causes degenerative subcapsular alterations, primarily at the central area.

The progression towards cataracts represents a relatively frequent complication of recurrent and chronic anterior uveitis.

1.5.1.2.7 VITREAL CHANGES

Iridocyclitis is distinguished from iritis by the presence of cellularity and opacities in the retro-lental space and in the anterior vitreous, caused by an inflammatory involvement of the ciliary body (cyclitis). Vitreous opacities are associated with the presence of cellular aggregates, exudates, fibrin, and collagen residues, which, based on distribution and morphological and kinetic characteristics, can be classified as anterior, posterior, diffuse, filiform, powdery, fixed, and mobile. The vitreous debris never regress completely; however, the opacities decrease in number by aggregating in the vitreous framework. The classification of vitreous opacity ranges from 0 to 4+ (93), as more clearly illustrated in Table 4.

Grading of vitreous haze	Morphologic characteristics
0	Buon esame di tutti i dettagli del polo posteriore
Traces (±)	
1+	Posterior pole clearly visible (retinal vessels and optic disc)
2+	Posterior pole details slightly hazy (retinal vessels not detectable)
3+	Posterior pole details very hazy (optic disc visible, but blurred margins)
4+	Fundus details not visible

TABLE 4. Vitreous haze grading proposed by Nussenblatt *et al.* (reference n° 93).

In recurrent or chronic forms, the vitreous undergoes degenerative processes with the breakdown of the collagen framework and retraction. Vitreous detachment is nearly constant in long-lasting anterior uveitis. The collapsed vitreous forms areas of condensation and opacity, which, together with cellular infiltrates, result in the characteristic "snowball" exudates more typical of intermediate and posterior uveitis. These are visible as high-sized, mobile exudates, mainly found in the vitreous periphery.

1.5.1.2.8 ENDOCULAR PRESSURE CHANGES

Anterior uveitis, especially iridocyclitis, is characterized by a reduction in intraocular pressure due to decreased production of aqueous humor by the inflamed ciliary body. Typically, the pressure returns to normal values as soon as the inflammatory process subsides. In chronic forms, however, hypotonia can persist, and in such cases, it is linked to degeneration of the ciliary body, which can result in atrophy of the eyeball. In some cases, acute uveitis can be associated with hypertonia due to the obstruction of Schlemm's canal and the iridocorneal angle, secondary to the deposition of proteinaceous and cellular material that characterizes the inflammatory process in the outflow pathways. Hypertensive uveitis is more typical of viral forms, especially Herpes zoster virus (HZV) and Herpes simplex virus (HSV), but it can also be found in Posner-Schlossmann syndrome.

1.5.2 Intermediate uveitis

1.5.2.1 Symptoms

The symptoms of intermediate uveitis are very mild, primarily characterized by floaters and transient blurriness, while pain, congestion, and photophobia are typically absent.

1.5.2.2 Signs

Objective signs are found in the periphery of the ocular fundus. Inflammatory signs may be observed in the anterior chamber, but with a mild Tyndall effect (reaching a maximum of 1+) and some corneal endothelial precipitates essentially related to the "spill-over" phenomenon (migration of cells into the anterior chamber). Conversely, the perikeratic reaction is always absent.

1.5.2.2.1 Vitreal changes

In the anterior vitreous, it is possible to find inflammatory cells, pigment, and protein exudation that aggregate to form "snowball" exudates, resembling "snowballs" or "ant eggs" that may coalesce to form banks adhering to the pars plana of the choroid, creating a whitish preretinal membrane (snow banks). These membranes can give rise to finger-like extensions into the vitreous. These structures may organize into more or less contractile formations or even be subject to neovascularization, leading to intraretinal hemorrhages. Figure 9 illustrates the characteristic "snowball" opacities, while Figure 10, taken from Herbort et al (92), demonstrates how vitreous opacities coalesce to create a structure resembling "ant eggs" or a "string of pearls." A constant feature in intermediate uveitis is the posterior detachment of the vitreous, with or without vitreous collapse.

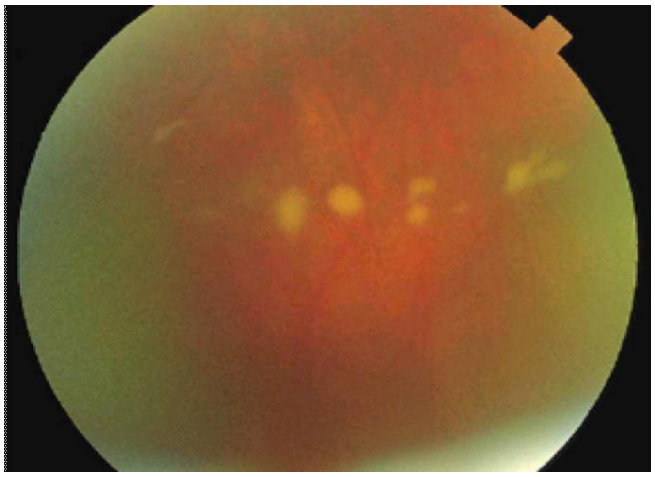

FIGURE 10. Vitreous opacities with a snowball appearance. Courtesy of Dr. Claudia Fabiani.

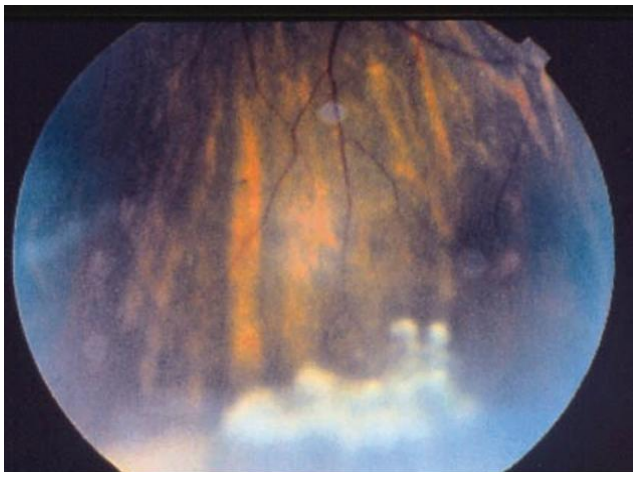

FIGURE 9. Vitreous opacities coalescing in a "string of pearls" appearance (reference n° 92).

1.5.2.2.2 Retinal changes

Frequent in intermediate uveitis is peripheral segmental vasculitis associated with preretinal vitreal exudates. The affected vessels are predominantly venules, showing periphlebitis, and, more rarely, retinal vasculitis. The vasculitis is mostly confined to the retinal periphery, but it can occasionally extend to the posterior pole. Periphlebitis is identified on ophthalmoscopic examination as a segmental sheathing with a granular or bead-like appearance. In such cases, it is advisable to complement the ocular assessment with retinal fluorescein angiography and indocyanine green angiography, while OCT (optical coherence tomography) can identify and quantify macular edema, which is commonly observed in such cases.

1.5.3 Posterior uveitis

1.5.3.1 Introductory notes

The inflammatory processes affecting the retina and choroid rarely remain localized to the initial tissue. If the inflammatory process starts in the choroid and then spreads to the retina, it is called chorioretinitis; conversely, if inflammation primarily affects the retina and then spreads to the choroid, it is called retinochoroiditis. This distinction is easier in the early stages and becomes more complicated in advanced stages. However, identifying the primarily affected area has practical implications for etiological identification and therefore therapy. In fact, among the most common causes of retinochoroiditis and retinitis are toxoplasmosis, viral, and fungal infections; on the other hand, bacterial infections and sarcoidosis more often manifest as choroiditis or chorioretinitis.

From a clinical-morphological perspective, uveoretinitis can be distinguished into focal, disseminated, and diffuse forms.

1.5.3.1.1 Focal variants

Focal forms are characterized by easily distinguishable inflamed tissue from the surrounding healthy tissue. The foci can also be multiple (multifocal), as shown in Figure 11. When active, the focus appears elevated, with blurred margins, whitish-yellow or grayish in color, sometimes surrounded by signs of hemorrhage or periphlebitis. When the focus is inactive, the lesion flattens and results in a whitish scar surrounded by a hyperpigmented border; sometimes the scar may directly reveal the sclera. Generally, more depigmented lesions, correspond to a more intense inflammatory process.

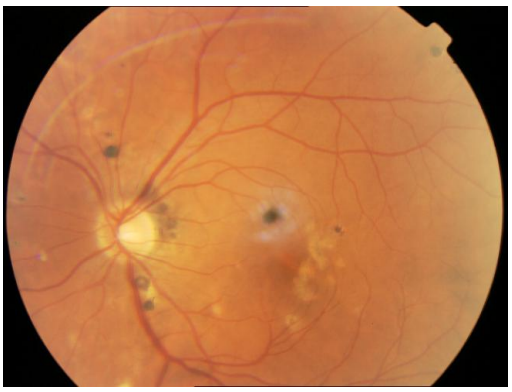

FIGURE 11. Multifocal choroiditis. Courtesy of Dr. Claudia Fabiani.

1.5.3.1.2 Disseminated variants

The form is disseminated when the inflammatory foci are numerous, concentrated in a certain quadrant, or identifiable throughout the posterior pole. The lesions have the same characteristics as those of focal forms and can all be at the same stage of activity or at different stages of inflammation. Figure 12 is an iconographic example taken from Vasconcelos-Santos *et al*. (94).

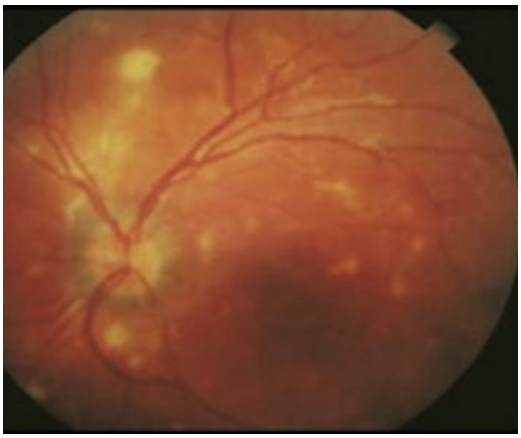

FIGURE 12. Multiple chorioretinal infiltrates associated to a mild macular and retinal edema, in a patients with subacute neuroretininitis (reference n° 94.)

1.5.3.1.3 Diffuse variants

In diffuse forms, it is difficult to identify healthy areas among the numerous inflammatory foci. Overall, the lesions give the posterior pole an edematous, grayish-yellow, opaque appearance. During the healing phases, retinal atrophy allows the identification of exposed choroidal vessels, while disintegrated pigment gives the picture a resemblance to retinitis pigmentosa. Depending on the arrangement of the lesions, one can speak of macular, equatorial, peripheral, or juxtapapillary localization. In the latter case, the optic nerve head is often involved, leading to a characteristic fascicular visual field deficit (Jensen's scotoma).

A satellite focus is mentioned when a new active lesion appears proximal to an old inactive lesion. The satellite focus is generally smaller and is separated from the old scar by a thin layer of healthy tissue.

1.5.3.2 Symptoms

Symptoms are primarily characterized by visual acuity alterations. Pain, redness, and photophobia, if present, are determined by a secondary involvement of the anterior segment related to inflammation of the ciliary body. It's worth noting that redness can be intense in the case of secondary involvement of the sclera (sclerocoroiditis). Floaters are indicative of vitreal exudation and, therefore, the spread of inflammation to the vitreous humor. Photopsias (flashes of light), on the other hand, are linked to the irritating stimulus that inflammation exerts on the photoreceptors at the periphery of the lesions. Metamorphopsias (distorted images) are related to retinal edema; in particular, micropsias are more often typical of macular edema and generally associate with macropsias. Scotomas, positive in the acute phase, become negative in advanced stages. While less relevant in cases of peripheral involvement, scotomas can become significant, leading to central vision loss in the case of macular involvement. Blurred vision is extremely variable, ranging from mild to moderate, intermittent to constant, reversible to irreversible, depending on the degree of secondary vitreal exudation and the precise localization of chorioretinal inflammation.

1.5.3.3 Signs

1.5.3.3.1 Vitreal changes

Characteristic of posterior uveitis is the cellular exudation in the posterior vitreous. The exudation resembles snowball-like opacities, diffuse or localized, small or large. The intensity of vitreous opacity can be classified according to the scheme shown in Table 4, as proposed by Nussenblatt et al (93). In the initial stages, vitreal exudation can give rise to precipitates on the hyaloid (the membrane that surrounds the vitreous body), similar to the corneal precipitates in the anterior chamber.

1.5.3.3.2 Chorio-retinal changes

1.5.3.3.2.1 Retinitis/retinohoroiditis

Characteristics include edema and exudation in the retinal layers. During ophthalmoscopy, the retina appears swollen, whitish, without reflections, with hemorrhages and exudates in the superficial layers. In early stages, the inflammatory process can be so intense as to create the "headlight in the fog" effect, identifying a whitish, cotton-like spot secondary to intense vitreal exudation. In the area affected by retinitis, perivascular lesions can be distinguished, possibly associated with perilesional hemorrhages that take on a bright red color if the more superficial retinal layers are involved. The inflammatory process spreads to the underlying choroid by crossing the pigmented retinal epithelium. In such cases, a differential diagnosis must be made with choroiditis, but often also with primary retinal vasculitis. A primary focus of choroiditis differs from retinitis in the absence of vitreal cellular reaction, while the retina appears swollen not due to intraretinal edema but due to subretinal exudation. Furthermore, there are no hemorrhages or retinal necrotic lesions. Primary retinal vasculitis is characterized by the absence of retinal alterations despite the progressively encasement and narrowing of the affected vessels, while vitreal reaction is absent or minimal. However, the two conditions can coexist, as in the case of patients with BS. Figure 13, provides an example or retinal vasculitis in a patient with BD (95).

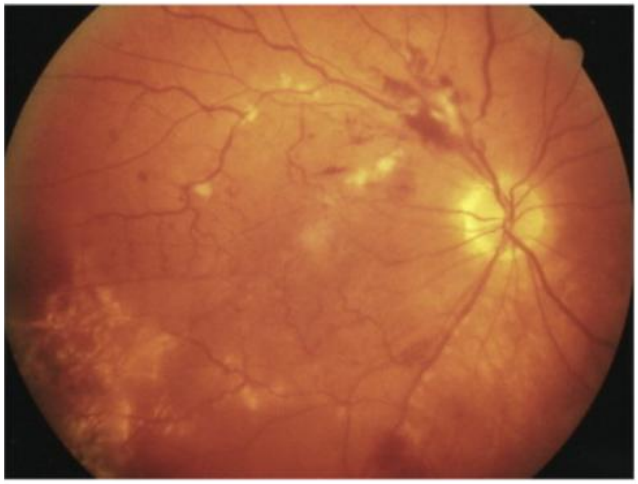

FIGURE 13. Retinitis and retinal vasculitis in a patient affected by Behçet's disease (reference n° 95.)

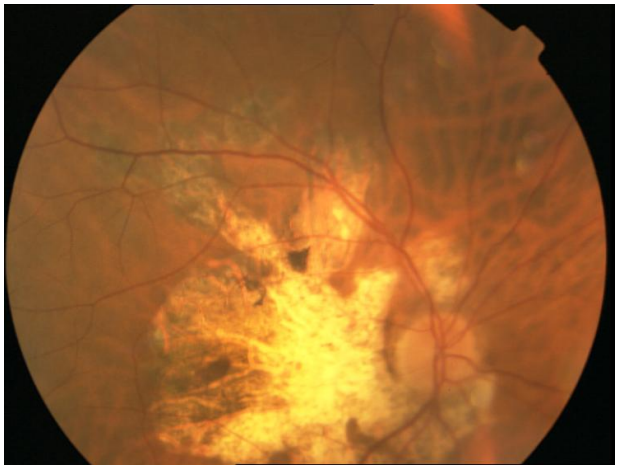

FIGURE 14. Retinography in a patients affected by serpiginous coroiditis. Courtesy of Dr. Claudia Fabiani.

1.5.3.3.2.2 CHOROIDITIS/CHORIORETINITIS

The foci of choroiditis appear as pale, yellowish-white, or grayish patches with poorly defined, blurred borders, over which retinal vessels normally course. These areas vary in depth according to the degree of edema and subretinal exudation. Intravitreal cellular reaction is absent, at least until the inflammatory involvement of the retina. Secondary involvement of the retina is almost inevitable; at this point, the retina appears

thickened, without reflections, but generally without signs of retinal vasculitis or necrosis. In diffuse choroiditis, such as in VKH disease or sympathetic ophthalmia, subretinal exudation can be so intense as to cause exudative retinal detachment. Cicatricial processes result in choroidal atrophy and proliferation of the retinal pigment epithelium. This gives rise to a whitish patchy appearance with clear and pigmented margins and variable accumulations of peri- and endo-lesional pigment. Figure 14 shows a color retinography in a patient with serpiginous choroiditis. Figure 15 consists of an upper part corresponding to retinal fluorangiography in a patient with serpiginous choroiditis; in the lower part, the corresponding indocyanine green angiography is identified.

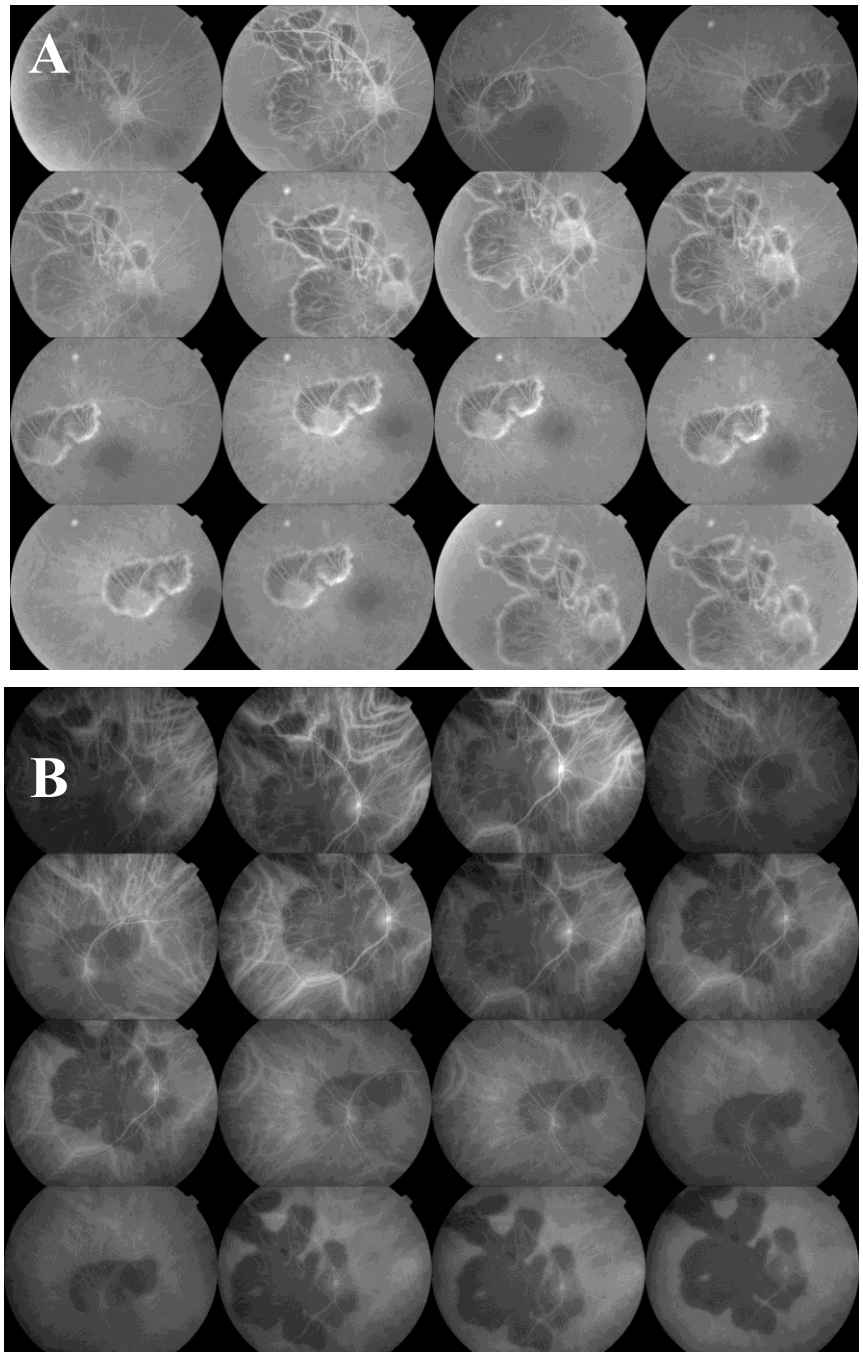

FIGURE 15. (A) Typical lesions of serpiginous choroiditis and (B) their corresponding indocyanice angiography highlighting choroidal vessels. Courtesy of Dr. Claudia Fabiani.

1.5.3.3.3 RETINAL VASCULITIS

Retinal vasculitis is a common manifestation in cases of posterior uveitis and panuveitis, both as a consequence of chororetinal inflammation and, potentially, underlying systemic pathology associated with uveitis, as in the case of BD. Inflammation can affect both arteries and veins, involving phenomena of perivascular and endovascular inflammation. Periphlebitis, or venous involvement, is the most frequently observed. Characteristics of any vasculitis include sheathing and cellular infiltration of the vessel walls. In the case of periphlebitis, the

vein appears bordered by a double whitish streak parallel to its wall, ranging from segmental to diffuse. In segmental forms, the vessel takes on a granular or beaded appearance, while diffuse forms may exhibit some degree of perivascular edema. As the vasculitic process regresses, there can be alterations in vascular caliber with segmental constrictions or partial occlusions. Complications are linked to alterations and occlusions of venous flow, resulting in retinal and vitreal hemorrhages, neovascularization, and consequently, proliferative retinitis. In most cases, periphlebitic alterations begin at the retinal periphery before extending to the posterior pole. Figure 16, taken from Fabiani et al (96), shows a fluorangiographic image of retinal vasculitis in a patient with BD. Periarteritis presents with similar signs to periphlebitis during the clinical examination, but vascular obstruction phenomena with secondary edema and areas of retinal infarction are much more common. These are visible as "cotton wool spots," ischemic areas, and vascular neovascularization. The progression of retinal vasculitis inevitably involves the posterior pole with macular and optic nerve edema, and in advanced stages, optic nerve atrophy.

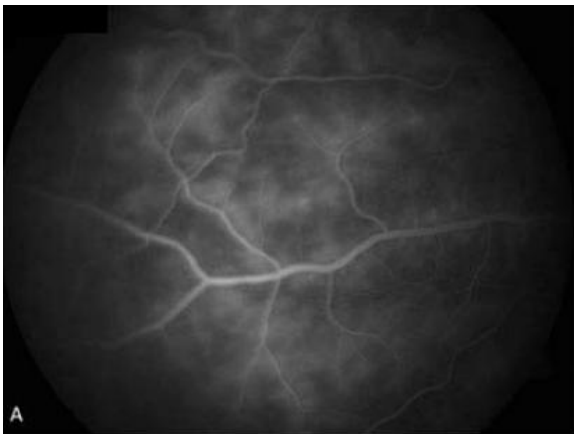

FIGURE 16. Retinal vasculitis detected in fluorescein angiography by perivascular exudates.

1.5.4 PANUVEITIS

The symptomatology of panuveitis is characterized by the overlap of multiple manifestations typical of both anterior and posterior uveitis, with a prevalence of one or the other depending on specific etiologies and syndromes. From a semiological point of view, panuveitis is characterized by the presence of pain, chemosis, eyelid edema, marked conjunctival congestion, and a reduction in visual acuity up to complete loss of light perception. These manifestations are generally very intense in bacterial panuveitis, associated with intense exudation, a high content of fibrin, with hypopyon and coarse vitreal opacities (endophthalmitis). Fungal forms are less acute and later than contamination, with cotton-like vitreal opacities, marked Tyndall effect, and ivory-white hypopyon. Acute focoanaphylactic panuveitis is similar to bacterial panuveitis with corneal precipitates resembling mutton fat and white hypopyon; however, light perception is better preserved. Rheumatologic-based panuveitis is generally less intense but tends toward chronicity. Additionally, there is often an association with retinal vasculitis and papillary involvement. From a semiological standpoint, panuveitis is characterized by the patterns encountered in anterior, intermediate, and

posterior uveitis, with various ocular segments simultaneously present and more or less severe depending on the extent of inflammation and which ocular segment is predominantly involved.

1.6 LABORATORY EXAMINATION

The laboratory plays a central role in the diagnosis of uveitic diseases, especially in excluding forms caused by pathogens and identifying forms related to immune dysregulation. In each patient, the evaluation begins with a complete blood count (CBC), where the leukocyte formula can be helpful in suspecting a bacterial or parasitic form (presence of neutrophilia or eosinophilia, respectively). Inflammatory markers, including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), can confirm or exclude systemic inflammatory involvement without providing, however, a high specificity. A similar consideration applies to the assessment of the protein profile, which may highlight a systemic inflammatory background and/or an increase in the gamma fraction. However, these findings are present in both infectious and systemic inflammatory conditions, including connective tissue diseases. The measurement of IgM and IgG levels can provide more information about the chronicity of an infectious process. In cases of suspected parasitic forms, IgE levels can be supportive. It's important to note that these laboratory findings serve as adjuncts to clinical evaluation and may help guide further diagnostic investigations. The interpretation of results should be done in the context of the patient's overall clinical presentation and medical history.

1.6.1 RULING OUT AN INFECTIVE ETIOLOGY

If Toxoplasma infection is suspected, it is useful to measure serum IgM and IgG levels. IgM anti-Toxoplasma antibodies appear as early as 5 days after infection, while IgG antibodies appear around 15 days after infection, peak at about two months, and then decrease to remain at low levels for life.

For tubercular infection, the Quantiferon test and the Mantoux tuberculin skin test (purified protein derivative) are useful. In cases of strong clinical suspicion, a culture test on sputum (or bronchoalveolar lavage) for the detection of the tubercle bacillus, along with a chest X-ray to identify any radiological signs of tuberculosis, may be necessary.

In cases of syphilis infection, the FTA-ABS (Fluorescent Treponema Antibody Absorption) test and the VDRL (Venereal Disease Research Laboratory) test are valuable. FTA-ABS is the most sensitive and specific test for identifying individuals who have come into contact with Treponema. VDRL measures specific antibodies to Treponema and, provides information about the activity of the disease and the response to therapy, despite being less accurate.

In infections caused by Toxocara canis, eosinophilia and the presence of specific IgG and IgE antibodies are often detectable. However, in cases of ocular involvement, eosinophilia and serum antibody titers may not be significant, making the examination of the aqueous humor essential.

1.6.2 AQUEOUS HUMOR PARACENTESIS

The cytological examination of the aqueous humor can be decisive when suspecting a masquerade syndrome, such as in cases of neoplastic diseases and focoanaphylactic syndromes, with the latter presenting dispersed lenticular material in the aqueous humor. Determining specific antibodies in the aqueous humor can be much more significant than their respective serum levels, especially when considering the antibody concentrations in both biological fluids. Specifically, according to the Goldman-Witmer quotient, the ratio of specific antibodies in the aqueous humor to the corresponding serum antibodies should be divided by the ratio of total immunoglobulins in the aqueous humor to serum immunoglobulins. Quotient values greater than or equal to 1 indicate intraocular antibody synthesis, thus suggesting a local infection. The use of this quotient can be helpful in confirming the diagnosis of infectious uveitis due to Toxoplasma, tuberculosis, Toxocara, syphilis, or herpes viruses. Finally, culturing and performing a polymerase chain reaction on the aqueous humor can be valuable in cases of suspected subtle viral or bacterial forms.

1.6.3 AUTOIMMUNITY WORK-UP

Search for certain autoantibodies may come in help when an underlying autoimmune disease is hypothesized.

Rheumatoid factor, which can be found in patients with rheumatoid arthritis, systemic lupus erythematosus (SLE), Sjögren's syndrome, mixed connective tissue disease, and chronic systemic infections, is absent in Reiter's syndrome, ankylosing spondylitis, psoriatic arthritis, and enteropathic forms.

The positivity of anti-nuclear antibodies (ANA) is typical of connective tissue inflammatory diseases, but their assessment becomes particularly important in the context of an autoimmune gastritis (AIG). In this case, the positivity of ANA can have predictive and prognostic value for the development of autoimmune gastritis (102,103).

Anti-phospholipid antibodies can, on the one hand, cause retinal vascular thrombosis in the context of an anti-phospholipid antibody syndrome but can also be associated with autoimmune optic neuritis.

Anti-neutrophil cytoplasmic antibodies (ANCA) is more classically associated with vasculitis. Their detection is useful when ocular involvement is the initial expression of systemic disease (97,98).

HLA typing is also useful as it can reveal predispositions to the onset of diseases, as extensively described in the dedicated paragraph (3.5.1).

1.6.4 DIAGNOSTIC TEST FOR SARCOIDOSIS

There are no specific laboratory tests for the diagnosis of sarcoidosis, and the biopsy finding of a non-caseating granuloma remains the gold standard from a diagnostic point of view. However, the measurement of angiotensin-converting enzyme (ACE) and lysozyme levels can be useful when sarcoidosis is suspected. In particular, an increase in ACE levels is correlated with the presence of active granulomatous lesions. It is important to note that ACE can also be positive in syphilis, tuberculosis, Hodgkin's lymphoma, Gaucher's disease, and carcinomatosis. Lysozyme levels are also an indicator of sarcoidotic granuloma activity, but this test is less sensitive and specific. Around a quarter of patients with sarcoidosis present with hypercalcemia and hypercalciuria. For an accurate diagnosis of sarcoidosis, laboratory tests should be complemented by imaging studies such as chest X-rays, high-resolution computed tomography of the chest, and total-body scintigraphy with Gallium-67 (104,105).

1.7 IMAGING TECHNIQUES

Among the additional instrumental examinations, retinal fluorescein angiography covers a central role, allowing for the identification of retinal vasculitis, macular edema, choroiditis, retinitis, papillitis, as well as the activity, extent, and progression of inflammatory lesions towards the formation of scar outcomes. Indocyanine green angiography, by specifically visualizing choroidal circulation, allows for the identification of choroidal inflammatory processes with greater sensitivity than retinal fluorescein angiography. This examination is particularly useful in identifying subretinal neovascularization and multifocal choroiditis. In particular, indocyanine green retinography allows distinguishing between choriocapillaritis and stromal choroiditis, with the former being more typical of multiple plaque acute pigment epitheliopathy and idiopathic multifocal choroiditis, and the latter being more typical of VKH, serpiginous choroiditis, and "Birdshot" retinochoroiditis (106,107).

OCT can provide information about the presence, extent, and characterization of posterior vitreous, retinal, or choroidal lesions when dioptric media are opaque and do not allow for adequate assessment of the fundus. The routine use of OCT is gaining an increasingly central role in clinical

practice due to the reliability and non-invasiveness of the examination (108). The combination of OCT with angiography (angio-OCT) is very useful as a complementary examination in macular studies but does not provide information about the involvement of the retinal periphery (109).

Electroretinography is useful in detecting retinal pathologies in the context of adequate differential diagnosis with degenerative pathologies, also providing prognostic information (110,111).

Dynamic perimetry can provide important elements in the differential diagnosis between posterior uveitis and hereditary degenerative retinal diseases. Nevertheless, visual field assessment should be carried out mainly to identify campimetric damage secondary to glaucoma. Furthermore, perimetry is useful when it is necessary to differentiate uveopapillitis from optic neuritis of neurological interest.

1.8 COMPLICATIONS

This chapter will focus on the main complications encountered in everyday clinical practice. Some of them are secondary to inflammation specific to a particular ocular region, as in the case of band-shaped calcific keratopathy affecting patients with persistent chronic anterior uveitis. However, most complications can be found in all forms of uveitis, regardless of the anatomical segment involved in uveal inflammation (112).

1.8.1 BAND KETAOPATHY

Characteristic of all chronic and persistent anterior uveitis, the changes begin at the ends of the horizontal corneal meridian with uneven white-grayish opacities that slowly progress toward the center, merging to form an uneven band crossing the cornea with a whitish and uneven appearance (113). Figure 17 illustrates an advanced case of band-shaped calcific keratopathy.

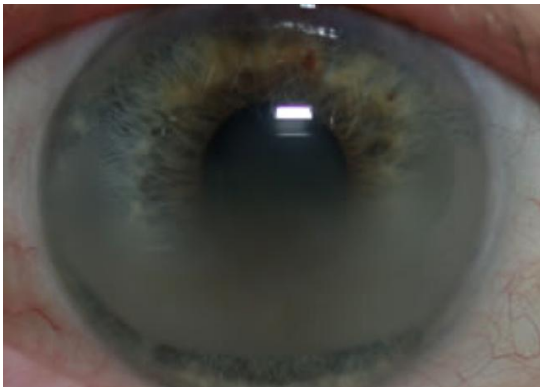

FIGURE 17. Band keratopahty at an advance stage. Courtesy of Dr. Claudia Fabiani.

1.8.2 COMPLICATED CATARACT

Cataract is a common complication of all forms of uveitis and is a consequence of both chronic inflammation and local or systemic steroid therapy. Lens opacities primarily affect the central and posterior parts (posterior subcapsular cataract), which are more susceptible to inflammation, but later, the anterior cortical part is also affected (total cataract). Early involvement of the central lens results in visual deficits from the outset, especially for near vision and in case of exposure to intense light sources (114).

1.8.3 SECONDARY GLAUCOMA

Secondary glaucoma is found in about 6% of endogenous uveitis cases, especially in CAU and in patients with panuveitis and significant anterior involvement, regardless of the etiology, and more prominent in cases of severe inflammatory involvement. In fact, secondary glaucoma due to uveitis can have various causes, but they can all be related to the intense exudation during acute inflammation: papillary occlusion due to the formation of pupillary membranes or posterior synechiae; angle blockage due to the deposition of cellular and protein deposits at the iridocorneal angle, where they are destined to organize; and trabecular blockage due to scarring degeneration of the outflow pathways. The last event is typical of Fuchs' heterochromic iridocyclitis, of which glaucoma is an integral part. In addition to forms secondary to the inflammatory process, iatrogenic glaucoma due to corticosteroids is not uncommon (115).

1.8.4 MACULAR EDEMA

Macular edema can be found in all types of long-lasting uveitis, especially when associated with intense vitreal inflammatory reactions. It is present in up to a quarter of patients with other types of uveitis, including the anterior form. Prolonged intraretinal edema can result in cystic degeneration and macular pseudohole or macular hole with permanent loss of central vision. Macular edema represents the most common cause of visual impairment in patients with uveitis and contributes to the worsening of the prognosis (2,116). The diagnosis is made through OCT, which has become the gold standard for evaluating macular thickness. Fluorescein angiography and indocyanine green angiography are additional useful methods for studying the macula, especially to exclude concomitant retinal vasculitis or choroidal neovascularization (116). The latest clinical approach, however, has also focused on OCT angiography, which provides additional information in macular studies, although it does not have a role in studying the peripheral region of the retina and therefore should complement rather than replace retinal fluorescein angiography and indocyanine green angiography (117).

Figure 18 shows a case of macular edema in a left eye studied both with color retinography of the posterior pole and with fluorescein angiography. Figure 19, on the other hand, depicts a characteristic fluorescein angiographic image of cystoid macular edema.

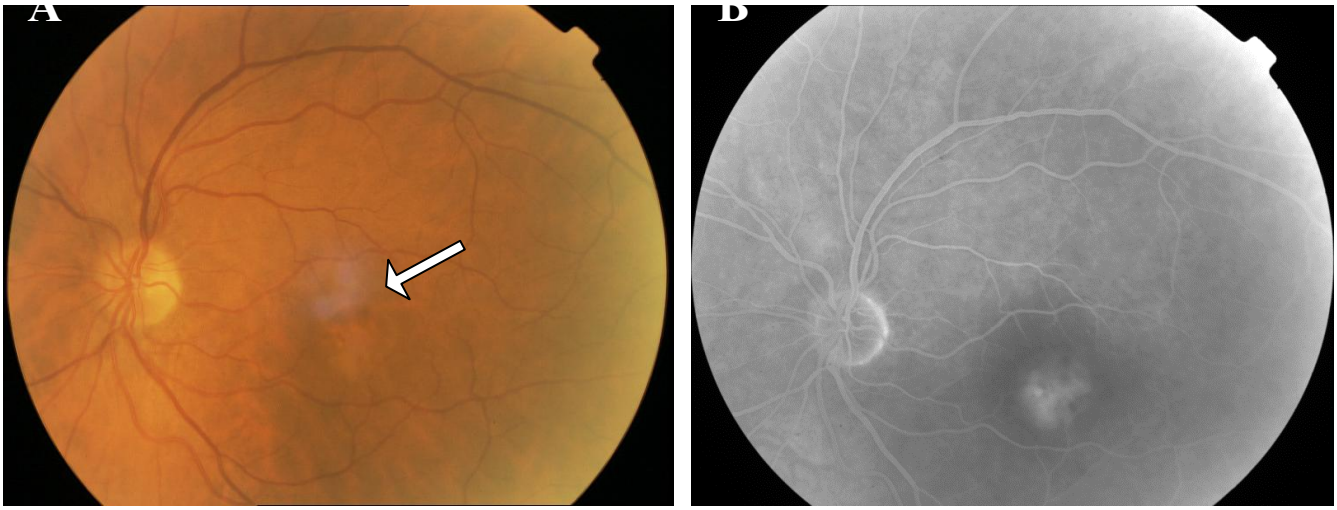

FIGURE 18. (A) retinography showing macular edema with (B) corresponding fluorescein angiography. Courtesy of Dr. Claudia Fabiani.

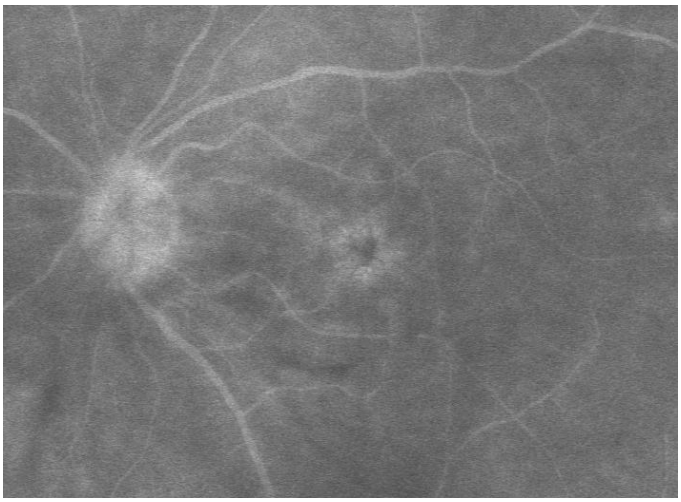

FIGURE 19. Cystoid macular edema on fluorescein angiography. Courtesy of Dr. Claudia Fabiani.

1.8.5 RETINAL DETACHMENT

Retinal detachment is a late complication of uveal inflammation. It can be secondary to vitreous contraction, retraction of cyclitic membranes, or intense retinal exudation. More common in intermediate and panuveitis, it can also be found in patients with anterior uveitis. Figure 20 [Hafidi et al (118)], illustrates a case of retinography in a patient with panuveitis associated with BD, retinal vasculitis, and retinal detachment.

It should be emphasized that retinal detachment can itself cause mild to moderate inflammation in the anterior chamber, thus requiring a careful an accurate differential diagnosis. Rarely, choroidal detachment can also be observed, determined by effusion secondary to posterior uveitis and may be associated or not with retinal detachment. On ophthalmological examination, choroidal detachment appears as a fixed semicircular gray-brownish swelling, to be considered in the differential diagnosis with neoplasms (112).

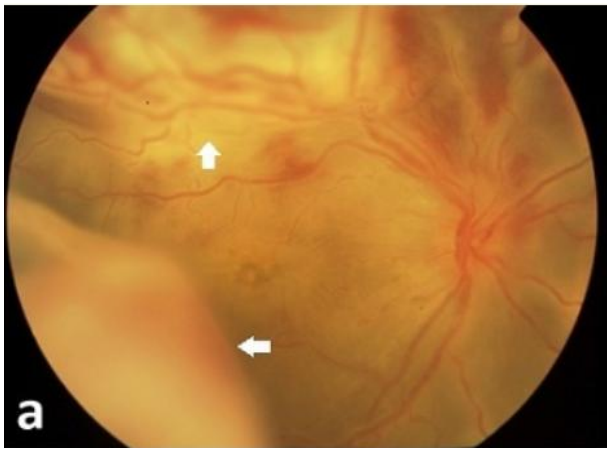

FIGURE 20. Panuveitis in Behçet's syndrome complicated with retinal detachment (arrow in the temporal inferior quadrant) (reference n° 118).

1.8.6 Intraviretal hemorrhages

The formation of vitreal bands in correspondence to organized preretinal exudates can facilitate vitreoretinal hemorrhages and retinoschisis. Inferior lamellar retinal holes are also relatively common.

1.8.7 Phthisis bulbi

In severe chronic uveitis, the persistent inflammation of the ciliary body leads to a degeneration that alters its function both qualitatively and quantitatively. The result is hypotony of the eyeball and a progressive shrinkage due to reduced formation of aqueous humor. Over time, phenomena of fatty degeneration and ossification can also occur. Irreversible hypotony is typically marked, generally below 6 mmHg.

1.9 Prognosis of uveitis

1.9.1 Anterior uveitis

Only 30% of acute uveitis cases are recurrent, but iridocyclitis has a higher tendency to recur compared to iritis. Visual prognosis is relatively good in cases of recurrent acute forms, as visual impairment below 2/10 is found in only 12% of cases, primarily due to lens alterations and cystoid maculopathy. The prognosis for chronic forms, on the other hand, is considerably worse due to a higher incidence of complications such as cystoid macular edema, secondary glaucoma, and complicated cataracts. The prognosis is influenced by the severity of the inflammatory process, the duration of the condition, and whether surgical intervention for complications is feasible or not (9,112).

1.9.2 INTERMEDIATE UVEITIS

Intermediate uveitis, often bilateral, follows a chronic course with an insidious onset, but the majority of patients maintain a visual acuity of at least 5/10 ten years after the onset of inflammation (9).

1.9.3 POSTERIOR UVEITIS

The prognosis of posterior uveitis is extremely variable and depends on factors such as localization, extent, etiology, and the reoccurrence rate. Chronic forms may progress to significant complications such as irreversible hypotony and retinal detachment. However, visual function can be well preserved if the macular area is not involved in the inflammatory process.

1.9.4 PANUVEITIS

The course and prognosis are severe in septic forms of uveitis. In particular, the formation of an intraocular abscess, a possible manifestation of endophthalmitis, leads to a destructive process that ultimately causes bulbar atrophy and complicated cataract.

The prognosis is better in focal allergic and toxic forms. However, the chronic evolution of inflammation is still responsible for the high incidence of complications and generally poor prognosis in panuveitis (9,112).

1.10 DISEASE ACTIVITY AND CLINIMETRIC INDEXES

Uveitis activity cannot be assessed through laboratory parameters. Instead, the intensity of uveal inflammation can be quantified through the assessment of Tyndall effect, anterior chamber cellularity, and vitreal opacity, as described in tables 2, 3, and 4 (5,93).

The Standardization of Uveitis Nomenclature (SUN) has provided definitions to establish variations in the activity of uveitic disease, inactivity, or remission based on changes in anterior chamber cellularity and vitreal opacities (5). Table 5 illustrates these definitions.

SUN criteria defining uveitis activity	
Inactive disease	Cells in anterior chamber equal to "0" (applied for inflammation in anterior chambre only)
Worsening activity	Two step increase in level of inflammation (e.g. anterior chamber cells, vitreous haze) or increase from grade 3+ to 4 +
Improvement activity	Two step decrease in level of inflammation (e.g. anterior chamber cells, vitreous haze) or decrease to grade 0
Remission	Inactive disease for ≥3 months after discontinuing all treatments for eye disease

Table 5. Definition of Standardization of Uveitis Nomenclature (SUN) Working Group on uveitis disease activity.

Recently, following similar experiences widely adopted in rheumatological clinical practice, Pato et al. (119) have proposed a disease activity index for uveitis. This index aims to unify anterior chamber cellularity and vitreal opacities into a single score, while also considering additional elements indicative of ocular inflammatory activity not currently classified by the Standardization of Uveitis Nomenclature (SUN) (5). These additional elements include the presence or absence of papillitis, macular edema, retinal vascular exudation, and the number of retinal lesions. Additionally, the score takes into account the patient's opinion on the activity of their ocular disease, assessed through a visual analog scale (VAS) ranging from 0 to 10 cm, where 0 represents the best disease state and 10 the worst.

These variables, identified through meticulous statistical analysis, have been reorganized into a model capable of providing a score aimed at quantifying uveitis activity. This model is named UVEDAI (Uveitis Disease Activity Index). The primary advantage of UVEDAI resides in its standardized clinical metric based on clinical variables commonly assessed during everyday clinical practice. Furthermore, UVEDAI does not rely on a specific etiological diagnosis, making it applicable in various clinical contexts. Therefore, this composite index is a candidate for use in outpatient settings, but especially in clinical trials to enable the best possible standardization of study endpoints.

1.11 SPECIFIC ENTITIES OF UVEITIS

The etiology of uveal inflammation is highly heterogeneous, either idiopathic or associated with systemic diseases ranging from infectious to autoimmune and autoinflammatory origin.

Peculiarities of uveitic forms associated with non infectious immune-mediated systemic disease will be addressed below. The order in which individual entities will be discussed follows a decreasing frequency, as described among patients with uveitis in Italy (120).

1.11.1 BD-RELATED UVEITIS

BD is a systemic inflammatory disease characterized by the appearance of oral, genital ulcerations, and uveitis, although the condition can also manifest with inflammatory processes affecting the gastrointestinal tract, vascular system, skin, and central and peripheral nervous systems (121). Ocular involvement typically occurs in the second to fourth year from the onset of the disease. However, ocular involvement in BD can represent the initial manifestation of the disease, found in approximately 10-20% of cases. The average age of onset of ocular symptoms, according to a study conducted on 1465 cases in 25 centers, is 27.4 ± 10 years (122). The frequency of ocular Behçet's is higher among patients carrying the HLA-B51 haplotype, but no association has been found with severity (123). Despite including numerous relatively rare entities, such as keratoconjunctivitis, conjunctival ulcers, keratitis, episcleritis, scleritis, ocular inflammation involving the lacrimal glands, corneal neovascularization, and paralysis of extraocular muscles, the most common event is undoubtedly represented by uveitis (122). Figure 21 illustrates a retinography and the corresponding retinal fluorescein angiography in a patient with BD and associated posterior uveitis with retinal vasculitis and retinal hemorrhages. Uveitis in BD tends to relapse frequently and have a worse prognosis than other types of endogenous uveitis, including those related to VKH disease and HLA-B27-associated AAU. In the majority of cases, uveal inflammatory processes are bilateral, recurrent, and manifest as panuveitis and posterior uveitis, preceded by predominantly unilateral inflammatory events involving the anterior segment of the eye. However, unilateral uveitis is not uncommon. Generally,

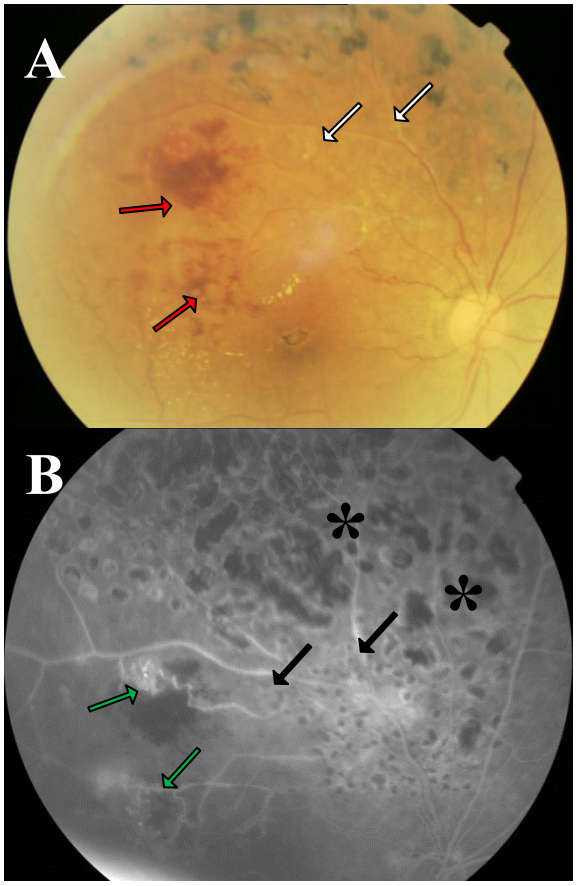

FIGURE 21. (A): Posterior uveitis with retinal vasculitis of the right eye in a patients suffering from Behçet's syndrome. Retinal hemorrhages (red arrows) alongside ghost vessels (white arrows). (B): corresponding fluorescein angiography showing vascular leakage (black arrows) and areas of retinal ischemia (green arrows). scar tissue as a result of previous laser treatment over ischemic regions.

ocular inflammatory attacks in BD are self-limiting. It should be noted that BD-related uveitis does not display granulomatous features. A very common finding in patients with BD is retinal perivasculitis, mostly in the form of periphlebitis and frequently associated with retinal hemorrhages. In severe cases, periphlebitis can be accompanied by retinal vein occlusion, resulting in retinal ischemia, macular degeneration, alterations in the pigmented epithelium, and optic atrophy. Capillaritis, visible exclusively in fluorescein angiography, is also quite common (122). Secondary glaucoma has been reported in approximately 11% of Behçet's patients, half of which were steroid-induced open-angle glaucoma (124). Cataracts are also a frequent complication, especially in cases characterized by anterior chamber involvement. In fact, cataracts are the most common cause of ocular surgery in patients with BD (125). In the case of involvement of the posterior segment, the most common complication is optic nerve atrophy. In certain cases, retinal and/or optic disc neovascularization may develop, often followed by intravitreal hemorrhages and traction retinal detachment (122). The frequency and severity of uveitic attacks show marked interindividual variability. Risk factors associated with an unfavorable prognosis include male sex, involvement of the posterior segment versus the anterior segment, more than 3 uveitis attacks per year, the presence of marked vitreous opacity during attacks, identification of fluorescein angiographic findings compatible with neovascularization of the optic disc, and the presence of macular ischemia. However, the use of highly effective immunosuppressive therapy, including the use of biotechnological drugs, has allowed a significant improvement in visual outcomes in recent years. Nevertheless, the management of patients with uveitis associated with BD is still very challenging due to numerous cases of multidrug resistances to various therapies currently available (126,127). The diagnosis of BD is currently clinical, as no laboratory parameters or pathognomonic signs have been identified. In particular, the diagnosis is possible when at least one of the two sets of major diagnostic criteria most widely used worldwide is satisfied, namely the International Study Group Criteria (ISGC) and the International Criteria for Behçet’s Disease (ICBD) (128,129) (Table 6).

ISGC	ICBD
Recurrent oral aphthous (at least 3 episodes per year) (mandatory item)	Oral aphthous (2 points)
Recurrent genital ulcers	Genitl aphthous (2 points)
Uveitis or retinal vasculitis	Ocular features compatible with BD (2 points)
Skin lesions (pseudofollicolitis, erythema nodosum)	Skin lesions (1 point)
Positive pathergy test	Neurological involvment (1 point)
	Vascular involvement (1 point)
	Positive pathergy test (1 point)

TABLE 6. Diagnostic criteria for the diagnosis of Behçet's disease. The International Study Group Criteria (ISGC) (128) require the mandatory presence of recurrent oral aphhtous in addition to at least 2 of the 4 items listed in the table. International Criteria for Behçet's Disease (ICBD) (129) are a score-based set: each manifestation receives 1 or 2 points. diagnosis can be formulated if the total score is ≥4. when icbd set is applied, the pathergy test if optional.

1.11.2 Juvenile idiopathic arthritis-related anterior uveitis

Although the incidence has been decreasing in recent decades, anterior uveitis can affect 10%-30% of patients with JIA (130,131). The major risk factors associated with the onset of CAU in the context of JIA are early onset, female gender, oligoarticular JIA (involving 2-4 joints), and positivity for antinuclear antibodies (ANA). Male patients and those positive for HLA-B27, on the other hand, have a higher predisposition to AAU. The presence of anti-histone antibodies has also been associated with the onset of uveitis, but only among female patients (102). Regarding ethnicity, currently available data are inconclusive, but several studies have suggested a higher predisposition in the Caucasian population (103). Uveitis can precede the onset of joint disease in some instances or appear later during disease course. In particular, over 80% of patients experience the onset of uveal inflammation within 4 years of the onset of juvenile idiopathic arthritis (130). Anterior uveitis associated with juvenile idiopathic arthritis exhibits all the semiotic characteristics described in relation to this type of uveitic localization. Since anterior uveitis is often completely asymptomatic, patients with juvenile idiopathic arthritis should regularly undergo ophthalmic check-ups to identify any uveal inflammation early on, which, can have a severe prognosis on long-

term visual capacity. This is especially true for younger patients who may not be able to report any ocular symptoms (132). In particular, ophthalmic visits should be performed every two months for the six months following the diagnosis. Subsequently, ophthalmic check-ups should be conducted every 3-4 months for a number of years depending on the age of onset of joint disease, the type of juvenile idiopathic arthritis (monoarticular, oligoarticular, polyarticular, systemic), and the positivity or negativity of ANA. Additionally, since immunosuppressive therapy initiated following the onset of joint manifestations might inhibit the potential onset of uveal inflammation in patients who had not shown previous signs of uveitic activity, close ophthalmic monitoring (1 check every 2 months for 6 months) is recommended in case of systemic therapy suspension (133). Ophthalmic assessment should include slit-lamp examination, measurement of intraocular pressure, and best-corrected visual acuity using age-appropriate tests. Complications of uveitis in juvenile idiopathic arthritis are common and include glaucoma, ocular hypotonia, cataracts, calcareous band keratopathy, formation of posterior synechiae, macular edema, papillitis, and the formation of epiretinal membranes (132).

1.11.3 VOGT-KOYANAGI-HARADA SYNDROME

Vogt-Koyanagi-Harada (VKH) is an autoimmune systemic inflammatory disease capable of affecting melatonin-containing organs, including the eyes, inner ear, skin, and central nervous system. It frequently affects ethnicities with darker skin tones, but it is less common among both whites and blacks from sub-Saharan regions. The condition tends to affect women more, with the exception of the Japanese population (134).The clinical history of the disease can be divided into a prodromal phase, a convalescent phase, and a chronic recurrent phase. The prodromal phase, usually lasting 3-5 days, presents with neurological and auditory signs, particularly headache, neck stiffness, and hearing loss (135). Analysis of cerebrospinal fluid shows lymphocytic pleocytosis that can persist for several weeks. This is followed by a uveitic phase with diffuse choroiditis, retinal detachments, and papillitis. Inflammation can spread to the vitreous and the anterior chamber. Skin and adnexal manifestations, particularly poliosis, vitiligo, and alopecia, also appear during the convalescent phase. The characteristic ocular feature during this phase is depigmentation of the choroid, resulting in an ophthalmoscopic appearance termed "sunset glow fundus," as illustrated in Figure 22, adapted from Burkholder et al (136). In some patients, especially Japanese individuals, there may also be limbal depigmentation. Additional semiotic signs include the presence of diffuse pigment residues and retinal scars (136). The chronic recurrent phase is characterized by repeated episodes of anterior uveitis. The most frequent ocular complications in VKH patients are glaucoma, choroidal neovascularization, and subretinal fibrosis. The latter complication, associated with

recurrent inflammation of the posterior pole, requires more resolute immunomodulatory therapy (136). The diagnosis of VKH is clinical and is based on the application of specific diagnostic criteria. Among the most widely applied criteria worldwide are the Revised Diagnostic Criteria (RDC) of 2001, which have demonstrated better performance than other sets of criteria (137,138). The RDC identify three clinical entities: the complete form, the incomplete form, and the probable form. In all three cases, bilateral ocular involvement is necessary, and a history of trauma must be absent to exclude sympathetic ophthalmia, which can present with signs indistinguishable from VKH. Additionally, the absence of clinical or laboratory manifestations indicative of other uveitis-associated pathologies should be confirmed. The complete form requires involvement of the eyes, central nervous system, or otologic system and the skin. The incomplete form requires ocular involvement and at least one of the central nervous system and skin. The probable VKH requires the recognition of uveitic manifestations with characteristic signs when extraocular involvement is absent (137).

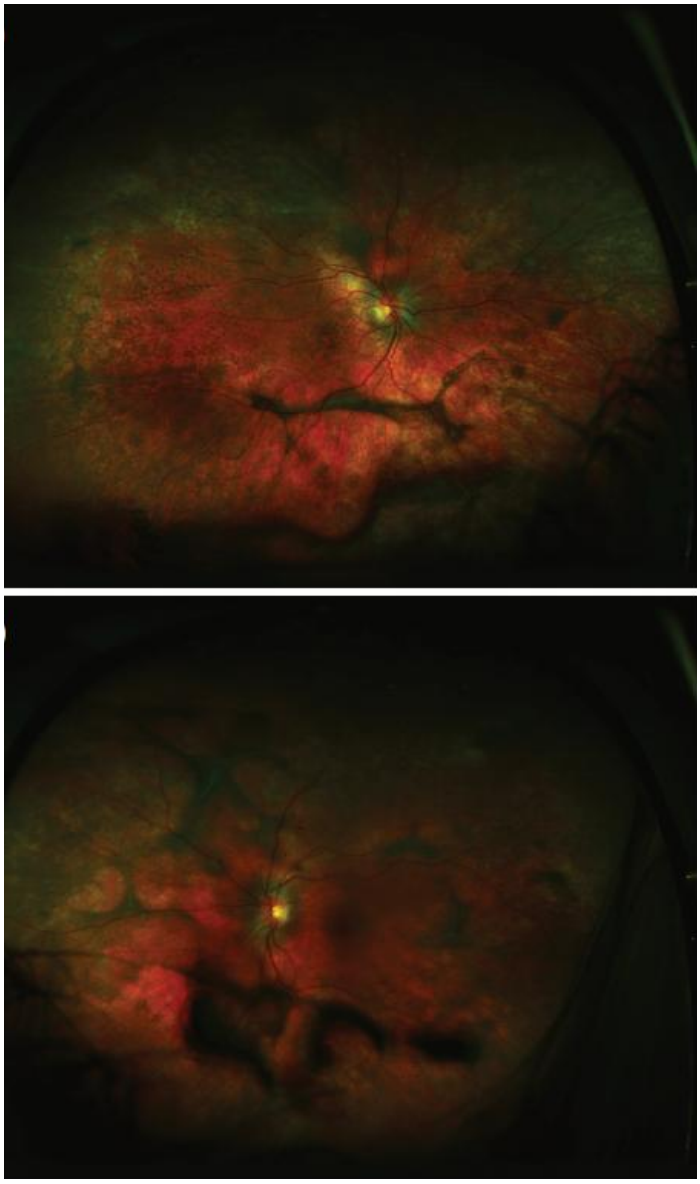

Figure 22. Typical "*sunset glow fundus*" assessed at ophthalmoscopy examination in Vogt-Koyanagi-Harada patient: it is evident the architectural disruption and retinal pigment mifration (reference n° 136).

Recently, Yang et al (138) proposed and validated another set of diagnostic criteria aimed at simplifying the diagnostic nomenclature and overcoming some issues shown by the RDC, especially the significant importance assigned to the evaluation of the fundus oculi, a significant limitation when vitreal opacities make a correct assessment of the posterior pole impossible. Furthermore, the old criteria do not consider cases where therapy has prevented ocular outcomes. Like the RDC, the new criteria also require the absence of ocular trauma in the history, bilateral ocular involvement (uveitis should involve both eyes within a maximum of 2 weeks), and the

absence of signs suggestive of other forms of uveitis such as infectious conditions, immune-mediated rheumatologic conditions, and pathologies limited to the eye. The new criteria distinguish between early-stage VKH and late-stage VKH. In both cases, the diagnosis is possible by combining the various items included in the criteria set in three different ways (138). However, this set of criteria has been constructed on a population of Chinese ethnicity and should be validated in other ethnicities before its application. Favorable prognostic factors include the presence of good visual acuity during the first month of the disease, early treatment with high-dose steroids, and the young age of patients (134,139). In general, current evidence does not show differences in ocular outcomes between patients taking systemic or intravenous steroids; however, patients should take oral steroids for at least 6 months. Corticosteroid monotherapy was shown to be insufficient in controlling the disease, even when given early and in high doses (140). The use of immunomodulatory therapy with conventional or biologic immunosuppressants has also been associated with a reduced risk of visual acuity loss (141).

1.11.4 The HLA-B72 "spectrum"

Uveitis associated with HLA-B27 is a well-defined and recognized clinical entity, regardless of systemic or joint involvement (34,35). However, several systemic pathological conditions facilitated by HLA-B27 positivity have been identified, where extraocular inflammatory involvement (sacroiliitis, arthritis, inflammation of intestinal walls) represents an additional risk factor for the onset of uveitis (142-146).

1.11.4.1 Ankylosing Spondylitis

Ankylosing spondylitis, is the rheumatological disease most commonly associated with anterior uveitis. Uveitis involves approximately one-third of patients with ankylosing spondylitis and is the most frequent extra-articular manifestation (147). Uveitis can also precede joint manifestations, representing the initial symptom of the disease in such cases (148). It is quite common for undiagnosed ankylosing spondylitis to be present in patients with anterior uveitis (149,150). A predisposing factor for the onset of ankylosing spondylitis is the positivity of the HLA-B27 haplotype, which itself represents a genetic risk factor for the onset of acute anterior uveitis (34,35). In this context, it has been observed that patients with anterior uveitis associated with HLA-B27 present enthesitic manifestations on joint ultrasound similar to those found in patients with spondyloarthritis, even in the absence of radiographic evidence of sacroiliac involvement. Therefore, it has been suggested that patients with anterior uveitis associated with HLA-B27 positivity may fall into a category compatible with an abortive or incomplete form of spondyloarthritis (151). However, the relatively recent introduction into clinical practice of the

Assessment of SpondyloArthritis international Society (ASAS) criteria for the diagnosis of spondyloarthritis has allowed for the early identification of patients with spondyloarthritis not yet characterized by a clear radiological sacroiliac lesions. In fact, according to ASAS criteria, it is possible to diagnose spondyloarthritis in patients with uveitis associated with HLA-B27 who also present inflammatory low back pain, worsened by rest and during nighttime, associated with morning stiffness lasting more than 30 minutes, responsive to nonsteroidal anti-inflammatory drugs (NSAIDs), and occurring preferably before the age of 40 (152). Table 7 illustrates the ASAS criteria for the diagnosis of spondyloarthritis, including the classification of radiological sacroiliac damage according to modified New York criteria (153).

Sacroiliitis confirmed on MRI or plain X ray + at least one clinical criteria for SpA	or	HLA-B27 + two or more clinical criteria for SpA

Clinical criteria for SpA	**Sacroiliitis on imaging**
• Inflammatory low back pain • Arthritis • Enthesitis • Uveitis • Dactilytis • Psoriasis • Crohn's disease / ulcerative colitis • Response to NSAIDs • Positive famility history for SpA • HLA-B27 • Increased C-reactive protein levels	Active inflammation on MRI highly suggestive of sacroiliitis on SpA Sacroiliitis defined on X ray according to the modified New York criteria: bilateral sacroiliitis bilaterale of grade 2-4 or grade 3-4 if monolateral. • **Grado 1**: Suspicious. • **Grado 2**: Minimal (loss of definition at the edge of the joints, sclerosis, small erosions) • **Grado 3**: Definite (sclerosis, blurring and indistinct marings, loss of joint space) • **Grado 4**: ankylosis (complete fusion of the joint).

TABLE 7. ASAS (Assessment of Spondyloarthritis International Society) diagnostic criteria (152) and modified New York criteria (153). list of abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; HLA, human leukocyte antigen; MRI, magnetic resonance imaging; SpA, spondyloarthritis.

However, while collaboration between ophthalmologists and rheumatologists is essential for the correct management of this patient group, it is necessary to adequately select which patients truly requiring rheumatological evaluation. An attempt to answer this question has been made by creating an algorithm to be applied to patients with anterior uveitis, the Dublin Uveitis Evaluation Tool (DUET), which is described in Figure 23. It has been shown to be capable of identifying patients with spondyloarthritis with a sensitivity of 96% and a specificity of 97% (154). In patients with spondyloarthritis, uveitis has a sudden onset, is generally acute, recurrent, and involves significant inflammation. It should be noted, however, that ocular pain may precede the presence of cells in the anterior chamber by up to two days. In the acute phase, the presence of hypopyon is often describable, and it is the hyperacute nature of the inflammation that easily leads to the formation of posterior synechiae, occlusion, and pupillary seclusion. Involvement is more often unilateral, and when it is bilateral, it generally affects one eye at a time ("flip-flop" pattern) (148).

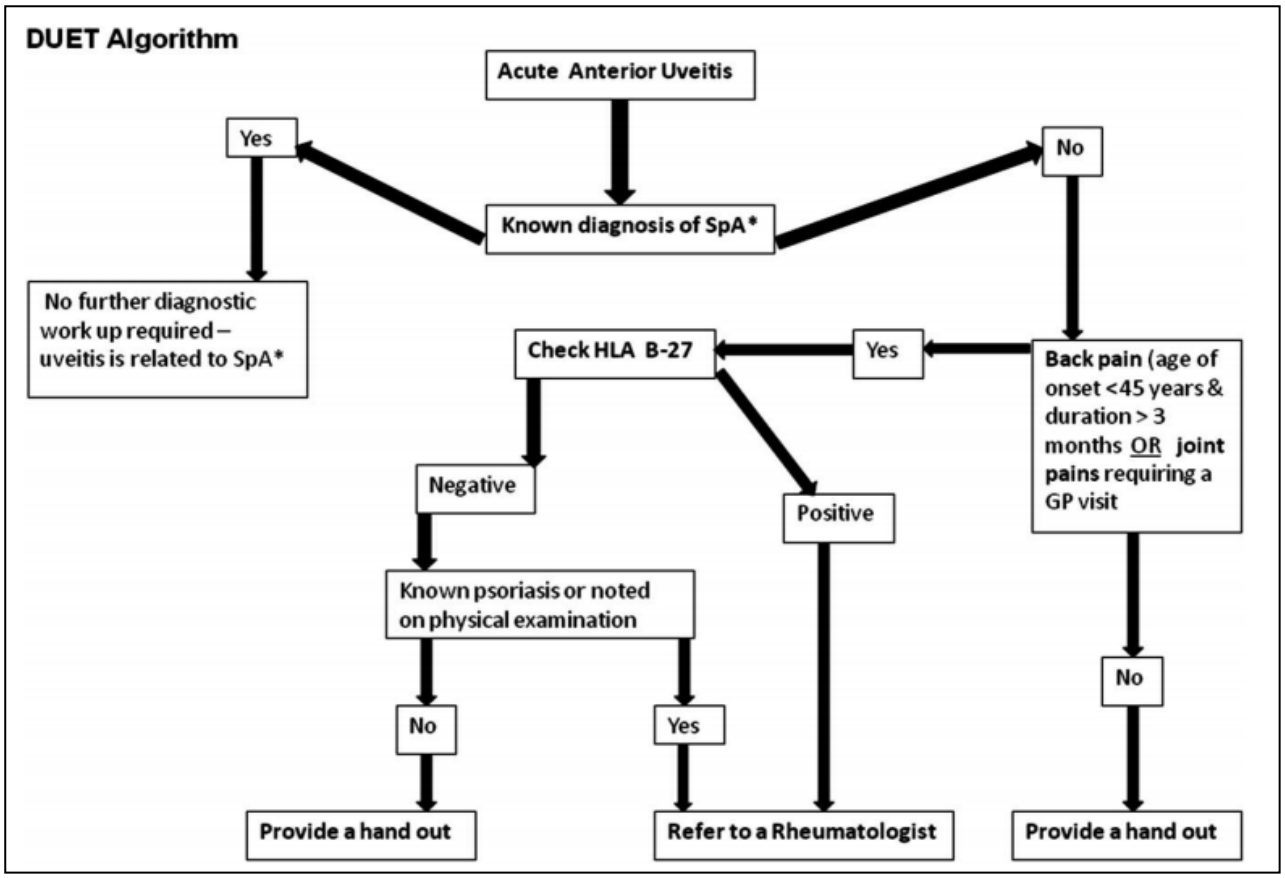

Figure 233. DUET algorythm for proper rheumatological referral of patients affected by anterior uveitis and positive to HLA-B27. The proposed algorithm have demonstrated a high sensitivity 96% and specificity 97% in detecting HLA-B27 patients affected by ankylosing spondylitis.

CAU in spondyloarthritis is rarer than in undifferentiated axial arthritis and tends to be more frequently bilateral. Generally, these forms are more typical in women and in uveitis associated with HLA-B27 negativity. The impact of uveitis on the course of ankylosing spondylitis has been studied in two different studies, demonstrating that patients with spondyloarthritis exhibit greater disease severity and radiographic progression when AAU is present (155,156). Another study highlighted an association between uveitis presence, cervical spine involvement, and a significant reduction in physical role in quality of life assessment through the short form 36 (SF-36). However, the analysis also identified factors such as the presence of inflammatory bowel disease and a history of infection prior to the onset of inflammatory lower back pain (142). The prognosis is generally good since the response to specific therapies for ankylosing spondylitis is optimal, both on ocular and extraocular manifestations (157-159). Nevertheless, there is evidence of a significant reduction in the quality of life among patients with AAU.

1.11.4.2 Spondyloarthritis Post-Infectious (Reiter's Syndrome)

Reiter's syndrome is characterized by urethritis, oligo-polyarthritis, and conjunctivitis, often accompanied by mucocutaneous lesions (circinate balanitis, keratoderma blennorrhagic, and oral ulcers). The disease is often preceded by bacterial infection of the gastrointestinal or urinary tract. Articular involvement typically affects the large joints of the lower limbs and the sacroiliac joints. Ocular involvement, besides conjunctivitis, may manifest with recurrent anterior uveitis, always bilateral, similar to that observed in patients with ankylosing spondylitis. Reiter's syndrome, like ankylosing spondylitis, is more common in males and is associated with HLA-B27 positivity. Inflammatory involvement of the sacroiliac joints is a risk factor for the development of anterior uveitis. The onset of ocular disease may precede joint involvement, but it can also be synchronous or appear later (160).

1.11.4.3 Uveitis in Psoriatic Arthritis

Anterior uveitis affects 7% of patients with psoriatic arthritis. Various studies demonstrate that joint involvement increases the risk of anterior uveitis in patients with psoriasis (143,144), especially in those with inflammatory involvement of the sacroiliac joints and HLA-B27 positivity (145,146). Uveitis associated with psoriatic arthritis is quite different from that typical of ankylosing spondylitis and Reiter's syndrome, being generally insidious, continuous, bilateral, and with a higher chance of posterior segment involvement (161).

1.11.4.4 Uveitis in Patients with Inflammatory Bowel Diseases

Both ulcerative colitis and Crohn's disease can complicate with arthritis and uveitis, in addition to cutaneous (pyoderma gangrenosum, erythema nodosum), hepatic, and renal lesions. Inflammatory bowel diseases may involve peripheral migrating arthritis, more frequently affecting large joints, or sacroiliitis, especially in individuals with HLA-B27 positivity. Ocular involvement, in the form of non-nodular episcleritis and/or uveitis, is detectable in a considerable percentage of patients (162,163). Factors associated with ocular involvement include female gender and, only in ulcerative colitis, smoking (164,165). Early introduction of mesalazine therapy appears to be a protective factor against ocular involvement (166,167. The extent of uveitis does not depend on the severity of inflammatory bowel disease, and colectomy does not impact the recurrence of ocular inflammation. However, some authors have identified an association between the severity of intestinal and ocular disease in patients with ulcerative colitis but not in those with Crohn's disease (168-170). Ocular involvement appears to be more frequent in patients with ulcerative colitis with pancolitis and in patients with Crohn's disease and colonic or ileocolic involvement (171-173). Uveitis is often recurrent with an insidious onset; it can be both unilateral and bilateral, but in the latter case, it is unlikely that both eyes are simultaneously affected (162). Subacute or chronic iridocyclitis with significant vitreal involvement, as well as posterior uveitis with retinitis, obliterating vasculitis, or papillitis, can also be found, although less commonly.

1.11.5 Sarcoidosis

During disease course, the eye can be the first site affected by the pathology, potentially involving all intra- and peri-orbital structures. Ocular manifestations of the disease may include dry eyes, conjunctival nodules, scleritis, and granulomatous uveitis, as well as lesions localized to the optic nerve. In other cases, sarcoidotic lesions may involve periorbital fat or the extrinsic eye muscles (174).

Regarding uveal inflammation, the uveitis associated with sarcoidosis is characterized by the presence of corneal deposits resembling mutton fat, as well as iridial and choroidal granulomas. While the latter two are common in sarcoidosis, they are not pathognomonic as they can also be found in patients with tuberculosis or syphilis. Moreover, they may not always be present in patients with uveitis from sarcoidosis, being more frequent when uveal inflammation is moderate or intense (175). In sarcoidosis patients, uveitis more commonly involves the anterior chamber (in over 90% of cases), but exclusive involvement of the anterior chamber occurs in less than 40% of patients (176). Inflammation can vary in severity from mild to intense, but the formation of hypopyon is unlikely (177). However, increased intraocular pressure due to trabecular obstruction

by inflammatory cells and sarcoid granulomas, or as a result of posterior synechiae, is frequent. The latter can also be a cause of complicated cataracts. Sarcoidosis may sometimes present with intermediate uveitis characterized by floaters and reduced visual acuity related to macular edema and/or vitreal opacities. Snow banks and snowballs in the anterior vitreous can be identified during the examination, along with signs of peripheral retinal involvement such as intravitreal hemorrhages and neovascularization (178). In cases of posterior uveitis, there is predominantly choroidal involvement. Uveitis is generally bilateral, though asymmetric, and sarcoidotic choroidal granulomas can be unifocal or multifocal, mimicking a "Birdshot" retinochoroiditis, with small or even large granulomas, sometimes resembling a neoplasm (179-181). Granulomas affecting the macular region can lead to severe visual impairment. Choroidal granulomas can be responsible for exudative retinal detachment. Retinal vasculitis manifests as periphlebitis, especially in the mid-peripheral posterior pole, and is associated with perivascular exudates described as "candle-wax drippings" (180). A characteristic example is shown in Figure 24, taken from Herbort *et al* (92). In advanced stages, choroidal scars similar to those described in idiopathic multifocal choroiditis can be identified. Regarding the diagnosis of ocular sarcoidosis, in 2009, the first International Workshop on Ocular Sarcoidosis (IWOS) published international criteria for the diagnosis of sarcoidosis-associated uveitis, as illustrated in Table 8 (92).

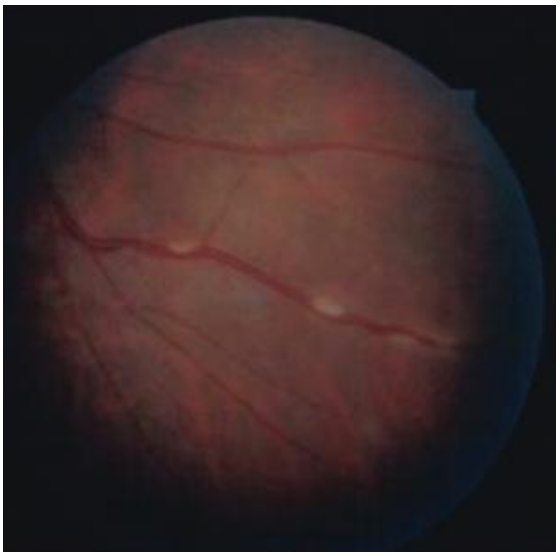

FIGURE 24. Segmental and nodular periphlebitis and with “candle-wax drippings” (reference n° 92).

International criteria for the diagnosis of ocular sarcoidosis	
Ocular features suggestive of ocular sarcoidosis 1. Mutton-fat keratic precipitates and/or iris nodules 2. Trabecular meshwork nodules and/or tent shaped peripheral anterior synechiae 3. *Snow balls* or strings of pearls in the vitreous 4. Active or inactive multiple chorioretinal lesions 5. Nodular and/or segmental periphlebitis and/or macroaneurysms in an inflamed eye 6. Optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule **7.** Bilateral involvement	
Laboratory investigations 1. Negative tuberculin test in a BCG with previous positive Mantoux skin test 2. Elevated serum levels of ACE and/or lysozyme 3. Chest X ray showing bilateral hilar lymphoadenopathy 4. Abnormal liver enzyme tests - any 2 of the following: alkaline phosphatase, AST, ALT, LDH, γGT 5. Chest computed tomography in a patients with a negative chest X ray	
Definite	Biopsy proven with compatible uveitis
Presumed	Biopsy not performed, hilar lymphoadenopathy, compatible uveitis
Probable	Biopsy not performed, 3 suggestive ocular signs and 2 laboratory tests
Possible	Biopsy negative, 4 suggestive ocular signs and 2 laboratory tests

Table 8. Diagnostic criteria for ocular sarcoidosis

List of abbreviations: ACE, enzima convertitore dell'angiotensina; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; TC, tomografia computerizzata; γGT, gamma-glutamyl transferase.

1.11.6 Tubulointerstitial nephritis and uveitis (TINU) syndrome

TINU syndrome is a rare multisystem autoimmune condition characterized by the simultaneous presence of acute interstitial nephritis and uveitis. The uveitis is typically bilateral and most often anterior, although cases of intermediate and posterior uveitis have been described. Occasionally, it can be accompanied by neuroretinitis, papillitis, and macular edema. Uveitis in TINU syndrome is generally responsive to treatment with glucocorticoids, thus making its timely identification as the main predictor to an overall good ocular prognosis (182).

1.12 TREATMENT OF UVEITIS

Uveitis is the third leading cause of legal blindness in Western countries, and patients are at high risk of developing complications that can reduce visual acuity, such as cystoid macular edema, glaucoma, and cataracts, in addition to retinal and vascular issues (2,3,64). Therefore, a valid therapeutic approach is necessary, tailored according to the severity and type of the disease, systemic or limited involvement to the eye, and the anatomical location of uveal inflammation.

Despite known side effects, topical and systemic corticosteroid therapy still represents the cornerstone of NIU treatment. Excellent results are also determined by the local administration (intravitreal or periocular) of extended-release corticosteroids, which exert an anti-inflammatory effect on the eye while minimizing systemic exposure. However, oculo-specific side effects, particularly corticosteroid-induced cataracts and glaucoma, are still a major issue.

As a consequence, the use of corticosteroid-sparing immunosuppressive agents is a necessary step to improve visual prognosis, avoid ocular structural damage, and complications of inflammation and long-term steroid therapy, particularly in uveitis associated to systemic immune-mediated disorders specially in forms related to systemic pathology and in the case of chronic or recurrent uveitic disease (183-191). Conventional disease-modifying anti-rheumatic drugs (cDMARDs) such as Azathioprine, cyclosporine, methotrexate, and mycophenolate mofetil are some of the most commonly used immunosuppressants (192-195). In recent years, however, patients refractory to conventional immunosuppressants have benefited from the advent of biotechnological drugs, especially monoclonal antibodies directed against TNF-α. In addition, scientific research has highlighted the possible therapeutic role of additional biotechnological drugs, including IL-1 inhibitors (Anakinra, Canakinumab), IL-6 inhibitors (Tocilizumab, Sarilumab), and CD20 inhibitors (Rituximab) (127,196-200).

Regarding TNF-α inhibitors, the molecules for which the scientific literature provides the most data are Adalimumab (ADA), a fully human monoclonal antibody, and Infliximab (IFX), a chimeric monoclonal antibody. Based on two randomized and controlled clinical trials, ADA is currently the only approved for patients with non-infectious non-anterior uveitis, granted by both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) (201-204). Nevertheless, although randomized and controlled clinical trials attesting to the efficacy of IFX in uveitis patients have not yet been conducted, a significant number of clinical studies have identified this

biotechnological agent as a valid therapeutic alternative in patients with NIU refractory to other immunosuppressive treatments.

1.12.1 Anterior Uveitis

Patients with acute anterior uveitis display an optimal response to topical glucocorticosteroids (1% prednisolone acetate eye drops, 0.05% difluprednate, and 0.1%-0.2% dexamethasone eye drops), cycloplegics, and mydriatics. Cycloplegics in eye drops have a dual action: they alleviate pain by resolving ciliary muscle spasm and break or prevent the formation of posterior synechiae. Among the most commonly used molecules are cyclopentolate, atropine, cyclopentolate, and tropicamide. Among mydriatics, useful for breaking pupillary synechiae, phenylephrine is remembered.

Systemic steroid therapy should be reserved for patients not responsive to the topical approach and is generally required for a period of less than two weeks. It is more frequently necessary in cases of acute anterior uveitis associated with inflammatory bowel diseases and psoriatic arthritis.

A small percentage of patients with anterior uveitis are unresponsive even to systemic corticosteroid therapy. In these cases, as well as in those requiring long-term steroid therapy, an approach with conventional disease-modifying anti-rheumatic drugs (cDMARDs) or even anti-TNF-α biological agents is mandatory. Sulfasalazine (205,206) and methotrexate (207) have been shown to reduce the frequency of uveitic attacks. The use of biological drugs inhibiting TNF-α mechanisms of action is generally reserved for patients with spondyloarthritis, psoriatic arthritis, or enteritis arthritis for whom the biological drug aims to have a systemic effect on the musculoskeletal, gastrointestinal, cutaneous, and therefore ocular condition. Studies available to date have shown a significant effect on reducing the frequency of uveitic attacks (157-159). In particular, monoclonal anti-TNF-α antibodies (ADA and IFX) have been shown to be more effective than etanercept (ETN), a fusion protein of the human p75 TNF-α receptor with the crystallizable antibody fragment (Fc) (208).

Regarding ETN, various experts seem to converge at the conclusion that this agent may lead to paradoxical uveitis both in patients with conditions known to be associated with uveitis and in subjects taking ETN for other indications (209,210).

Currently, there is limited data on the use of IL-17 and -23 inhibitors, while promising results, although based on retrospective studies and case series, have been obtained with Rituximab and Abatacept in acute anterior uveitis in patients with autoimmune gastritis (200,211,212).

1.12.2 Intermediate uveitis and pars planitis

The therapy for intermediate uveitis and pars planitis remains a controversial topic, especially in cases characterized by minimal inflammation of the anterior vitreous and relatively preserved visual acuity. In the past, only those forms with vision lower than 20/40 were treated. However, recent studies have highlighted a better visual outcome for patients undergoing early and aggressive therapy (213). Therefore, with the current therapeutic approach patients with intermediate uveitis receive treatment whenever macular edema, vitreal opacities with reduced visual acuity, retinal vasculitis, and evidence of cataracts or retinoschisis in at least one eye are present (214).

The initial therapy for intermediate uveitis involves the use of corticosteroids systemically or locally. Corticosteroids in eye drops are only used in the case of concomitant inflammatory signs in the anterior chamber, otherwise being ineffective.

Locally administered corticosteroids through peri/endo-ocular routes should be considered, especially in patients with unilateral or asymmetric involvement or with the goal of resolving macular edema. Triamcinolone acetonide at a dosage of 40 mg is the most frequently used corticosteroid periocularly. To determine its real effectiveness, it is recommended to administer 2-3 doses over 6-8 weeks (215,216). More recently, intravitreal implants of dexamethasone have also been approved for the treatment of intermediate uveitis, manifesting a prolonged effectiveness for about six months alongside a good safety profile. However, repeated administration of these intravitreal or periocular formulations facilitates various ocular side effects, particularly cataracts, glaucoma, vitreous hemorrhages, retinal detachment, and infectious endophthalmitis (217). Overall, the frequency of side effects seems to be higher for triamcinolone acetonide than for dexamethasone (218).

Patients with bilateral involvement, intense inflammation, or unresponsive to therapy with corticosteroids administered intravitreally or periocularly should be treated with systemic corticosteroids. Intravenously methylprednisolone in doses of 1 g/day is preferred, followed by 1-1.5 mg/day of prednisone (or equivalent) with a tapering schedule.

Systemic immunosuppressive therapy is indicated in patients who need long-term steroid therapy or who are unresponsive to chronic low-dose steroid therapy. In such cases, the most commonly used cDMARDs are methotrexate (especially in pediatric patients), azathioprine, cyclosporine, mycophenolate mofetil, either as monotherapy or in combination (219,220). Before tapering the corticosteroid, it is advisable to wait 4-8 weeks from the start of cDMARDs to allow them to reach full effectiveness.

Among anti-TNF-α agents, both ADA and IFX have been shown to be useful in unresponsive cases, including pediatric patients. ADA, in particular, has been approved by the FDA in the United States for the treatment of intermediate uveitis in adult patients, while in Europe, ADA has been approved by the EMA for patients with intermediate uveitis unresponsive to steroids or requiring a rapid decrease in daily corticosteroid dosage, or for those for whom steroid treatment is inappropriate (203,204). Therefore, based on these considerations, ADA can be administered as a first-line therapy in appropriate contexts. However, since the use of anti-TNF-α has been associated with a higher incidence of demyelinating diseases, it is crucial to rule out multiple sclerosis as the cause of intermediate uveitis before starting therapy with these biological agents (213). Alternatively, interferon-α or -β can be used instead of anti-TNF-α agents, which have been shown to control ocular inflammation and reduce macular edema in patients with intermediate uveitis (216,221). In cases resistant to therapies, a surgical approach such as pars plana vitrectomy and peripheral cryotherapy may also be considered (222,223).

1.12.3 Posterior uveitis and Panuveitis

Posterior uveitis and panuveitis are clinical entities capable of causing severe and irreversible reduction in visual acuity. Therefore, they must be treated early and aggressively to preserve visual acuity and avoid ocular complications, including cystoid macular edema, retinal detachment, intraretinal and intravitreal hemorrhages, and retinal vasculitis with consequent areas of ischemic damage, retinal necrosis, and neovascularization.

Systemic corticosteroids represent the first-line therapy in this case as well, with the same dosages already described for intermediate uveitis to abort the ongoing inflammatory process, especially in cases of bilateral involvement and early identification of ocular complications. Intravitreal and periocular corticosteroid implants are also useful for posterior uveitis and panuveitis, especially in cases of unilateral involvement and for the treatment of macular edema (183-191,224).

The involvement of the posterior pole, especially if associated with macular edema, is a criterion itself to initiate early systemic therapy with immunosuppressants (194,195). In this case, the most commonly used cDMARDs are azathioprine, cyclosporine, methotrexate, and mycophenolate mofetil, which can be used as monotherapy or in various combinations.

Similar to intermediate uveitis, ADA has been approved by the FDA for the treatment of non-infectious posterior uveitis and panuveitis in adult patients, while the EMA has approved ADA for

patients with non-responsive posterior or panuveitis to steroids, or for those who need a rapid decrease in daily corticosteroid dosage, or for whom steroid treatment is inappropriate (203,204).

Overall, TNF-α inhibitors are the biologic drugs with the most robust scientific body of evidence both on prospective and real-life cohorts (225). More in detail, both ADA and IFX have been successfully tested in patients with uveitis associated with BD, sarcoidosis, inflammatory bowel diseases, VKH disease, and idiopathic cases, showing the ability to control the inflammatory process, reduce recurrences, resolve macular edema, and prevent retinal vasculitis (195,201,202,225-233). Among other anti-TNF-α agents, Golimumab, a human monoclonal antibody, has also been successfully experimented with in retrospective studies conducted on BD patients (96). On the contrary, as described for anterior uveitis, the role of ETN is controversial and not recommended (194,195,209,210).

Over the last few years, the role of biologic agents other than TNF-α inhibitors for the treatment of posterior uveitis and panuveitis has been emphasized, particularly anti-IL-1 and anti-IL-6 agents (127,197-200). Nevertheless, the scientific literature on the subject is not yet extensive enough, and such biologic agents should only be used in those refractory cases that have proven unresponsive to cDMARDs and anti-TNF-α agents.

1.12.4 Which type of NIU should be promptly treated with non-steroidal immunosuppressants

The Table 9, derived from Dick et al. (194), lists the factors that necessitate the initiation of therapy with non-steroidal immunosuppressants. Specifically, the presence of contraindications or intolerance (including poor compliance) to the use of corticosteroids or the need for rapid tapering of steroids represents the main indication for starting non-steroidal immunosuppressant therapy. The presence of factors indicating severe ocular inflammation should similarly prompt the initiation of immunosuppressive therapy. These factors include reduced visual acuity, bilateral involvement, the presence of vitreous opacities, macular and optic disc involvement, evidence of retinal vasculitis, exudative retinal detachments, and structural complications. Chronic or recurrent uveitis in itself is also a clinical entity to be addressed with immunosuppressants (194).

Systemic infectious diseases (tuberculosis, viral hepatitis, acquired immunodeficiency syndrome) should be ruled out before starting therapy with non-steroidal immunosuppressants; the risk of

neoplastic diseases should also be assessed (age, prolonged exposure to immunosuppressants, history of neoplastic diseases, and positive family history of neoplasms) (234,235).

INDICATIONS TO INITIATE SYSTEMIC TREATMENT

Ocular and anatomic
• **Onset and course as defined by SUN Working Group criteria**
  ○ **Acute disease that is sight threatening**
  ○ **Chronic persistent inflammation**
• **Exudative retinal detachment**
• **Posterior and macular involvement**
• **Binocular sight-threatening disease**

Therapeutic
• **Regional failure to respond to:**
  ○ **Periocular steroid injections**
  ○ **Topical corticosteroids in JIA-associated uveitis**
• **Systemic failure**
  ○ **Active uveitis while taking doses of 30 mg or 0.5 mg/kg prednisone per day or more**
  ○ **Relapse of uveitis after reduction of the oral corticosteroid dose to less than 7 to 10 mg/day prednisone**
• **Steroid intolerance**
• **Need for steroid-sparing effect**

Severity (in adults) • **Visual acuity worse than 20/100 (18)** • **Increase in vitreous haze of grade** • **Relapse of cystoid macular edema** • **Disease that impacts quality of life**
Severity (in JIA) includes prognostic factors for visual loss, such as: • **Poorer presenting visual acuity** • **Posterior uveitis** • **Uveitic complications of glaucoma** • **Advanced cataract** • **Macular edema** • **Synechiae Severe** • **band keratopathy** • **Ocular hypotony** • **Rubeosis iridis**

TABLE 9. Criteria supporting the initiation of non-corticosteroid systemic immunomodulatory therapy

1.12.5 CONVENTIONAL DISEASE MODIFYING ANTI-RHEUMATIC DRUGS

The current cDMARDs supported by a more solid evidence are mycophenolate mofetil, calcineurin inhibitors tacrolimus and cyclosporine, azathioprine, and methotrexate. Mycophenolate mofetil has proven useful in controlling uveal inflammation and improving visual acuity (236-238). It has also shown effectiveness in treating "Birdshot" retinochoroiditis (alone or in combination with cyclosporine) (239,240) and in the management of VKH (241).

Tacrolimus and cyclosporine have demonstrated efficacy in both inflammation control and improvement of visual acuity in patients with uveitis (242,243).

Azathioprine has proven its therapeutic role in controlling uveal inflammation and enabling a corticosteroid-sparing effect; however, there is no evidence regarding a positive impact on visual acuity (244). Specifically, scientific literature shows its efficacy in patients with BD (245) and VKH disease (246). Methotrexate is useful in controlling uveal inflammation as a corticosteroid-sparing agent and has shown the ability to preserve or improve visual acuity (247,248). Comparative studies between mycophenolate mofetil, methotrexate, and azathioprine moderately support greater efficacy and a lower incidence of adverse events among patients taking the first two drugs compared to those taking azathioprine (249-251).

1.12.6 Interferon therapy

The use of interferon α-2a is supported by scientific literature in the treatment of non-anterior uveitis, especially in patients with BD. Specifically, interferon α-2a has allowed a significant reduction in the frequency of relapses, an improvement (or maintenance) of visual acuity, and a reduction in the average doses of systemic corticosteroids (252-254). Lesser evidence, on the other hand, has emerged from studies on pegylated interferon α.

The 2018 European League Against Rheumatism (EULAR) recommendations on the therapy of patients with BD include interferon-α among the possible systemic immunosuppressants to be always associated with corticosteroids in the case of uveitis involving the posterior pole. Additionally, the same EULAR recommendations indicate interferon-α as an alternative therapeutic approach to high-dose corticosteroids or IFX in patients with BD and acute episodic or recurrent uveitis capable of compromising visual acuity (195).

Interferon-β, on the other hand, has proven useful in the treatment of pars planitis with a significant improvement in visual acuity and quality of life already three months from the start of therapy (216).

1.12.7 The right time to administer biotechnologic agents

The lack of response of uveitis to a cDMARD should prompt the physician to exclude issues related to non-adherence to therapy by the patient, but also to reconsider a possible subclinical infectious origin or a masquerade syndrome. This should be a priority whenever the introduction of an immunosuppressive agent leads to a worsening or does not allow an improvement in disease activity, following the definitions of the SUN (5), as proposed in Table 5 on page 55.

Once therapeutic failure is observed and infectious forms and masquerade syndromes are definitively excluded, a host of possibilities should then be considered: (i) titrating the dosage of the immunosuppressant used, (ii) adding topical steroid therapy (eye drops or intra- and peri-bulbar formulations), (iii) switching cDMARDs, or (iv) initiating therapy with biotechnological agents. On the contrary, adding a second cDMARD to one already in use is not supported by a broad international scientific literature (194).

Regarding biologics, current scientific literature supports the use of ADA and IFX, while the use of ETN and secukinumab is not recommended (194). In particular, ADA is indicated in the United States for the treatment of adult patients with intermediate, posterior, or panuveitis of non-infectious origin; in Europe, ADA is indicated in adult patients with intermediate, posterior, or panuveitis of non-infectious origin when corticosteroids have produced an inadequate response or require rapid tapering or when steroids are inappropriate (203,204). These indications are based on two randomized controlled clinical trials that have demonstrated the efficacy of ADA in controlling uveal inflammation, reducing relapses, and preventing the loss of visual acuity (201,202); evaluated in patients in the active phase at baseline and in patients in cortisone-induced remission. ADA is also an excellent therapeutic option in pediatric patients with uveitis associated with autoimmune inflammatory diseases unresponsive to methotrexate. According to recent recommendations on the treatment of uveitis in patients with JIA, ADA should be used as the first-line biologic, as it has been shown to be superior to IFX (193,255,256).

IFX has proven useful in the treatment of NIU in adult patients based on evidence from retrospective and prospective open-label clinical trials, especially in patients with BD (226,227,229). In this context, IFX has allowed complete clinical remission in a significant number of patients and a significant reduction in the frequency of uveitic attacks. Furthermore, IFX has enabled the control of macular edema and improvement in visual acuity, as well as indices of quality of life. In addition, the control of inflammation has been shown to be faster in patients treated with IFX compared to those treated only with steroids (257-259). According to a recent retrospective study (229) conducted on patients with uveitis associated with BD, IFX was equally effective whether used as monotherapy or in combination with cDMARDs. Regarding the biologic-line of treatment, IFX was significantly more effective when used as the first-line biologic. Finally, the long-term efficacy and safety of IFX have been highlighted by excellent retention rates (up to 10 years of therapy) (229,230). In the pediatric setting, although IFX is among the TNF-α inhibitors indicated in patients with JIA and uveitis who have not responded to methotrexate, recent

recommendations on the treatment of uveitis in these patients suggest the use of IFX only after ADA failure (193).

Contrarily to monoclonal antibodies against TNF-α, ETN, has been associated with the risk of paradoxical uveitis in patients treated for spondyloarthritis or other non-uveitis-related conditions (209,210), as well as with the inability of controlling uveal inflammation and the number of relapses in randomized controlled trials (260,261).

Golimumab has been suggested in the pediatric setting for the treatment of uveitis associated with autoimmune inflammatory diseases following the failure of ADA and IFX (193). However, in recent years, the first studies demonstrating the efficacy of Golimumab in other clinical contexts associated with uveitis have been published (96,262-264).

In recent years, scientific literature has highlighted a possible role of IL-1 inhibitors in controlling uveitic recurrences, resolving retinal vasculitis, and in terms of corticosteroid sparing, especially among patients with BD (197,265). The IL-6 inhibitor tocilizumab is also proving to be a promising therapeutic choice, allowing improvement in visual acuity, resolution of vitreous opacities, and macular edema within the first six months of therapy in patients with various clinical conditions associated with NIU (198,266,267). As for rituximab, it has been proposed as an effective therapy for uveitis in the context of JIA, BD, and VKH disease (199,264,268-270). However, although promising, the currently available data are not yet sufficiently extensive to include these biotechnological agents in treatment guidelines. Therefore, their use should be reserved to those conditions refractory to therapies suggested by the recommendations.

The IL-17 antagonist secukinumab has proven ineffective in controlling uveal inflammation, reducing the frequency of relapses, resolving vitreous opacities, or improving visual acuity in patients with active or quiescent uveitis (196).

1.12.8 THE CENTRAL ROLE OF BIOTECHNOLOGIC AGENTS ON SPECIFIC DISEASES

According to the Expert Panel Recommendations of 2014 (225), ADA and IFX can be considered as first or second-line treatment in patients with BD and ocular involvement as corticosteroid-sparing agents. IFX can be considered as first or second-line therapy in case of ocular exacerbation. ETN should only be used in patients intolerant to ADA or IFX. EULAR recommendations on the treatment of patients with BD suggest high-dose corticosteroids, IFX, or interferon-α as therapeutic options in patients with BD and acute episodic or recurrent uveitis affecting visual acuity. Furthermore, EULAR recommendations suggest that treatment of posterior uveitis associated with

BD with glucocorticosteroid alone should be avoided ADA and IFX are interchangeable if the patient experiences inefficacy or loss of efficacy with either, or if the patient has to discontinue therapy due to adverse events (195). Whether combination therapy with a cDMARD is superior to monotherapy is still a matter of debate. On this topic, the literature is conflicting, but most studies have not identified statistically significant response differences between monotherapy and combination therapy (229,232,271,272).

In the case of uveitis associated with AIED, ADA or IFX can be used after the therapeutic failure of Methotrexate. On the contrary, ETN should not be used as a first-line biological drug (225). This guidance is consistent with recently published recommendations on the treatment of uveitis in patients with JIA, which, however, recommend ADA as the first choice and IFX as the second choice, adding Golimumab as a third possible anti-TNF-α agent (193). These recommendations are based on the finding of ADA's superiority over IFX in terms of efficacy, achieving and maintaining remission in patients with uveitis and JIA (255,256), and on the identification of IFX's superiority over ETN in pediatric patients with refractory chronic uveitis associated with JIA (273). In this case as well, using a second anti-TNF-α agent in case of loss of efficacy of a first biological agent represents a useful therapeutic option (193).

In patients with uveitis associated with spondyloarthritis, ADA and IFX can be used as corticosteroid-sparing agents. In the acute phase, ADA and IFX can be added to steroid therapy (225). EULAR recommendations for managing patients with spondyloarthritis cite IFX, ADA, Certolizumab, and Golimumab among agents capable of preventing uveitic recurrences and emphasize that data on the role of ETN in this context are conflicting (274).

In patients with sarcoidosis, IFX and ADA can be considered as a second line of immunosuppressive treatment in those patients who have proven unresponsive to cDMARDs; ETN, however, should not be used in patients with uveitis associated with sarcoidosis (225).

Among patients with Vogt-Koyanagi-Harada (VKH) disease, there are several studies suggesting the effectiveness of TNF-α inhibitors and Rituximab in cases refractory to conventional therapy. However, to date, the available data mainly consist of case reports, case series, and a small retrospective study (269,270,275-277).

In patients with Birdshot retinochoroiditis, multifocal choroiditis with panuveitis, serpiginous choroiditis, and idiopathic panuveitis, ADA or IFX can be considered as corticosteroid-sparing agents in patients intolerant or unresponsive to cDMARDs (225).

1.12.9 DISCONTINUING TREATMENT WITH BIOTECHNOLOGIC AGENTS

In the current everyday clinical practice, the main reason for discontinuation of therapy is associated with the observation of a partial response of ocular inflammation by the current drug, followed by primary inefficacy. The number of treatment withdrawals related to the desire for pregnancy is also noteworthy. In contrast, data on therapy discontinuation due to long-term resolution of inflammation are scarce and primarily linked to the use of biologic drugs, especially concerning uveitis associated with AIED (278-280). A recent study has also highlighted that in patients with BD and uveitis, anti-TNF-α treatment combined with azathioprine has allowed long-term remission in a significant proportion of patients (281).

The decision to discontinue therapy should be customized to the patient's needs, taking into account the preferences of the physician, the patient's will, drug tolerance, risks associated with immunosuppressive therapy, disease activity, and the specific cause of uveitis (194).

2 PATIENTS AND METHODS

2.1 STUDY DESIGN AND PARTICIPANTS

Medical records of patients affected by BD enrolled in the AIDA registry were reviewed. The following demographic, clinical, and therapeutic data were collected: age, gender, age at disease onset, disease duration, ocular complications, best corrected visual acuity (BCVA) expressed in decimals, retinal vasculitis, cystoid macular edema, treatment courses. BD was diagnosed according to the ISG criteria and/or ICBD criteria (128,129). All patients were systematically followed-up every 3-to-6 months or in case of necessity (disease flare and/or safety issues). Incomplete records with more than 20% of missing values were excluded from the study. Patients carrying HLA-B27 were also excluded. Patients affected by idiopathic uveitis testing positive to HLA-B51, did not exhibit any signs of BD. Before starting any treatment with biologic or conventional immunosuppressant, patients were screened to rule out active or latent infections by undergoing a complete medical examination, chest X-ray film, QuantiFERON test, hepatitis B and hepatitis C virus markers and urine culture.

2.2 AIMS AND ENDPOINTS

The primary aim of the study was to assess the impact of HLA-B*51 on long-term ocular outcomes of BD-related uveitis and NIU unrelated to BD uveitis with a particular focus on potential

differences between the three subgroups: BD-related uveitis positive to HLA-B51, BD-related uveitis negative for HLA-B51 and NIU unrelated to BD, positive to HLA-B51. Secondary aims were to: (i) assess any differences in the anatomical pattern between groups; (ii) explore its influence on retinal vasculitis and assess differences between BD patients with related retinal vasculitis and patients affected by idiopathic retinal vasculitis positive to HLA-B51; (iii) estimate the effect of HLA-B51 on cystoid macular edema by differentiating between the abovementioned three groups.

The primary endpoint was evaluated by potential statistical significant differences between BD-related uveitis positive to HLA-B51, BD-related uveitis negative for HLA-B51 and NIU unrelated to BD, positive to HLA-B51 in terms of long-term complications and BCVA assessed at last follow-up. Secondary aims were examined by differences in the occurrence rate over time of retinal vasculitis and cystoid macular edema between the three groups.

2.3 PROTOCOL APPROVAL AND ETHICAL STATEMENT

The study conformed to the tenets of the Declaration of Helsinki and received approval by the local Ethics Committee of the University of Siena (Reference No. 14951). Informed consent was obtained from all patients or their legal guardians.

2.4 STATISTICAL ANALYSIS

Statistical analysis was performed using IBMSPSS Statistics for Windows, version 28 (IBM Corp., Armonk, NY, United States). Descriptive statistics was employed to display mean and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Shapiro-Wilk test was used to assess the normality of our data. Cross-tables were analyzed by Pearson's Chi square test and post hoc test with adjusted residuals in case of contingency tables with dimensions greater than 2x2. Potential differences in mean on multiple comparisons were assessed by Kruskall-Wallis H followed by Mann-Whitney U test for post-hoc analysis. Bonferroni correct was subsequently applied. The threshold for statistical significance was set to $p<0.05$, and all p-values were two-sided.

3 RESULTS

Overall, 213 patients were enrolled in the study with a male-to-female ratio of 1.57/1, for a total of 341 eyes. Figure 25 shows the selection process of the cohort taken into examination.

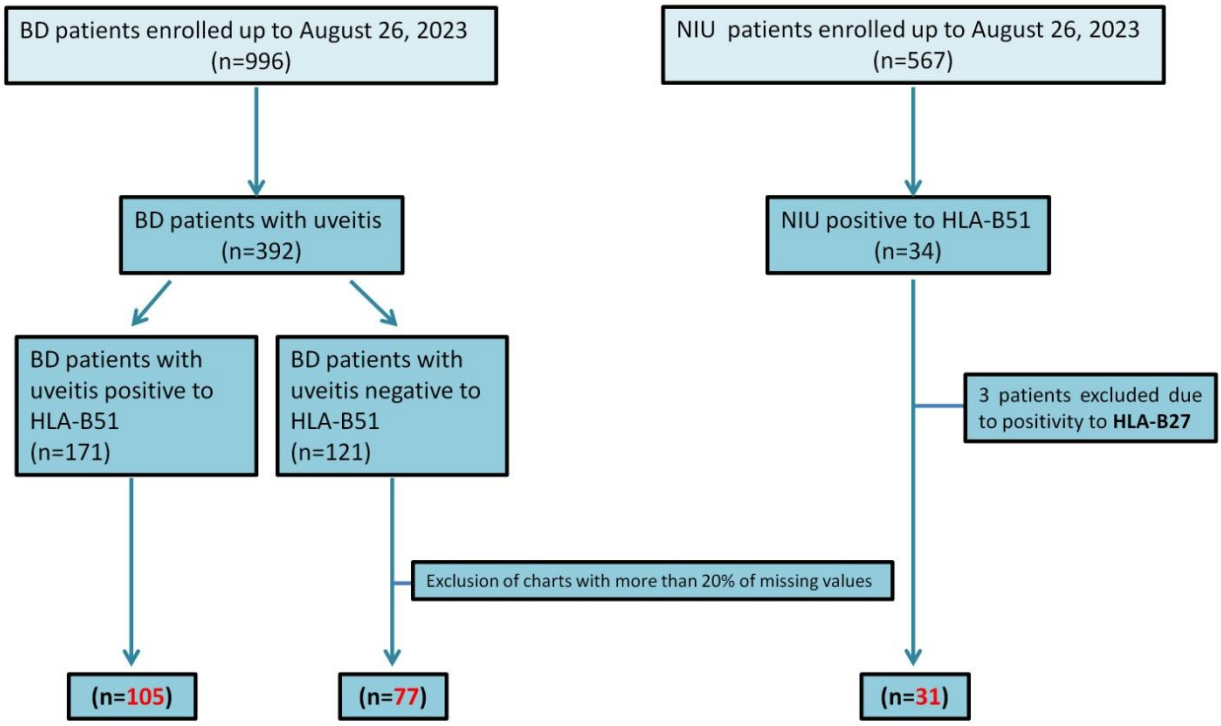

FIGURE 25. Chart showing the selection process for the cohort examined.

List of abbreviations: BD Behçet's disease, HLA human leukocyte antigen, NIU non-infectious uveitis

Ocular involvement was bilateral in 66, 43 and 19 patients with BD-related uveitis positive to HLA-B51, BD-related uveitis negative for HLA-B51 and NIU unrelated to BD, positive to HLA-B51, respectively. Mean age of the entire cohort was 32.18 ± 15.52. Figure 26 illustrates distribution for the 3 subgroups (BD-related uveitis positive to HLA-B51, BD-related uveitis negative for HLA-B51 and NIU positive to HLA-B51). Demographic, clinical and therapeutic data for each of the 3 groups are summarized in Table 10.

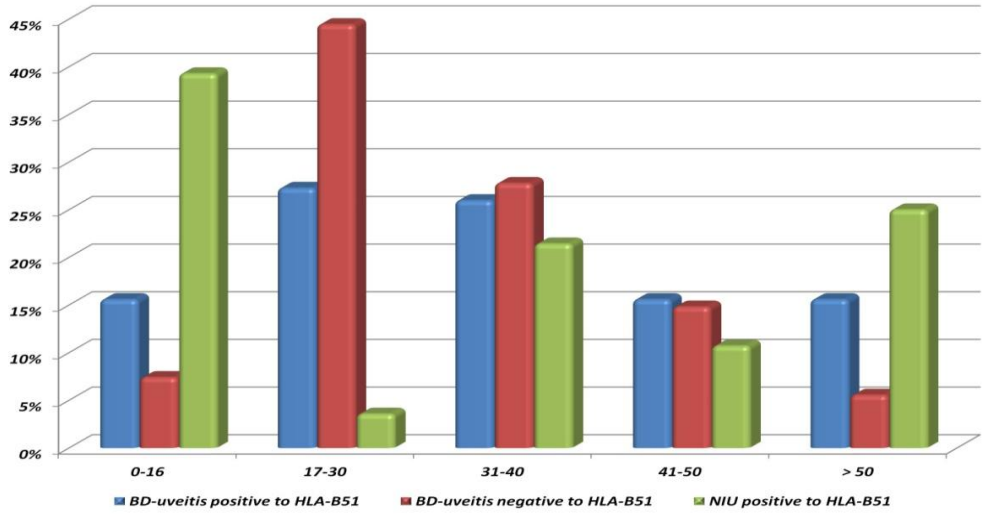

FIGURE 26. Distribution of age at onset for each group in accordance with different age groups, expressed in years.

List of abbreviations: *BD* Behçet's disease, *HLA* human leukocyte antigen

All 3 groups exhibited roughly similar demographic and therapeutic characteristics. Specifically, no differences were observed in terms of age at onset (p=0.945) and laterality (p=0.627). With regard to systemic treatment with advanced therapies, patients with NIU unrelated to BD positive to HLA-B51 received biotechnologic agents in 38.7% of cases while BD patients affected by uveitis positive to HLA-B51 and negative for HLA-B51 were treated with biotechnologic agents in 56,2% and 50,6%, respectively (p=0.67). On the other hand, we observed an overall significant treatment delay (p=0.044) with a tendency of higher mean delay among BD patients with uveitis negative for HLA-B51 which did not preserve the significance after Bonferroni correction (p=0.06 and p=0.069).

No differences in terms of complications were observed between groups (p=0.465). More in detail, 101 complications in 56 out of 171 eyes (32.7%) were recorded for BD-related uveitis positive for HLA-B51, 60 complications in 31 out of 120 eyes (25.8%) were recorded for BD-related uveitis negative for HLA-B51 and 22 complications in 12 out of 50 eyes (24.0%) were observed in patients with NIU who tested positive for HLA-B51. The most frequent complications detected in the entire cohort (341 eyes) were represented by cataract (n=42, 12.31%), followed by macular edema (n=38, 11.1%), epiretinal membranes (n=12, 3.5%), posterior synechiae (n=11, 3.2%), optic nerve atrophy (n=9, 2.6%), retinal detachment (n=9, 2.6%), ocular hypertension or glaucoma (n=7, 2.1%) and peripheral anterior synechiae (n=7, 2.1%). Figure 27 illustrates all complications for each group of patients taken into examination.

	NIU positive for HLA-B51	BD-uveitis positive for HLA-B51	BD-uveitis negative for HLA-B51
N° of patients	31	105	77
Mean age at onset (years)	32.36 ± 23.10	32.67 ± 14.93	31.36 ± 11.21
Male/Female	16/15	60/45	44/33
Laterality	Monolateral (n=12) Bilateral (n=19)	Monolateral (n=39) Bilateral (n=66)	Monolateral (n=34) Bilateral (n=43)
Anatomical Pattern*	AU (n=25) IU (n=2) PU (n=4) PaU (n=18)	AU (n=41) IU (n=6) PU (n=38) PaU (n=86)	AU (n=24) IU (n=4) PU (n=20) PaU (n=72)
Associated systemic disease	SpA (n=4) JIA (n=3) PsA (n=1) MS (n=1)		
Treatment with biologic agents	ADA (n=12)	ADA (n=36) IFX (n=12) GOL (n=4) CZP (n=2) TCZ (n=2) CAN (n=1) ANA (n=1) RTX (n=1)	ADA (n=16) IFX (n=16) GOL (n=3) TCZ (n=1) CAN (n=1) ANA (n=1) SCK (n=1)
Treatment with cDMARDs	AZA (n=1) MTX (n=1) CsA (n=2) SZS (n=1)	AZA (n=17) MTX (n=5) CsA (n=3) SZS (n=3) CYC (n=1) MFM (n=1) HCQ (n=2)	AZA (n=13) CsA (n=4) SZS (n=1) CYC (n=2) MFM (n=1) HCQ (n=1)

TABLE 10. Demographic, clinical and therapeutic characteristics for each subgroup taken into examination.

List of abbrevistions: ADA adalimumb, ANA anakinra, AU anterior uveitis, AZA azathioprine, CAN canakinumab, cDMARDs conventional disease modifying anti-rheumatic drugs, CsA cyclosporine A, CYC cyclophophamide, CZP certolizumab pegol, GOL golimumab, HCQ hydroxychloroquine, IFX infliximab, IU intermediate uveitis, JIA juvenile idiopathic arthritis, MFM mycophenolate mofetil, MS multiple sclerosis, MTX methotrexate, N° number, PaU panuveitis, PsA psoriatic arthritis, PU posterior uveitis, RTX rituximab, SpA spondyloarthritis, SZS sulfasalazine, TCZ tocilizumab

* Classification of anatomical pattern according to the SUN criteria

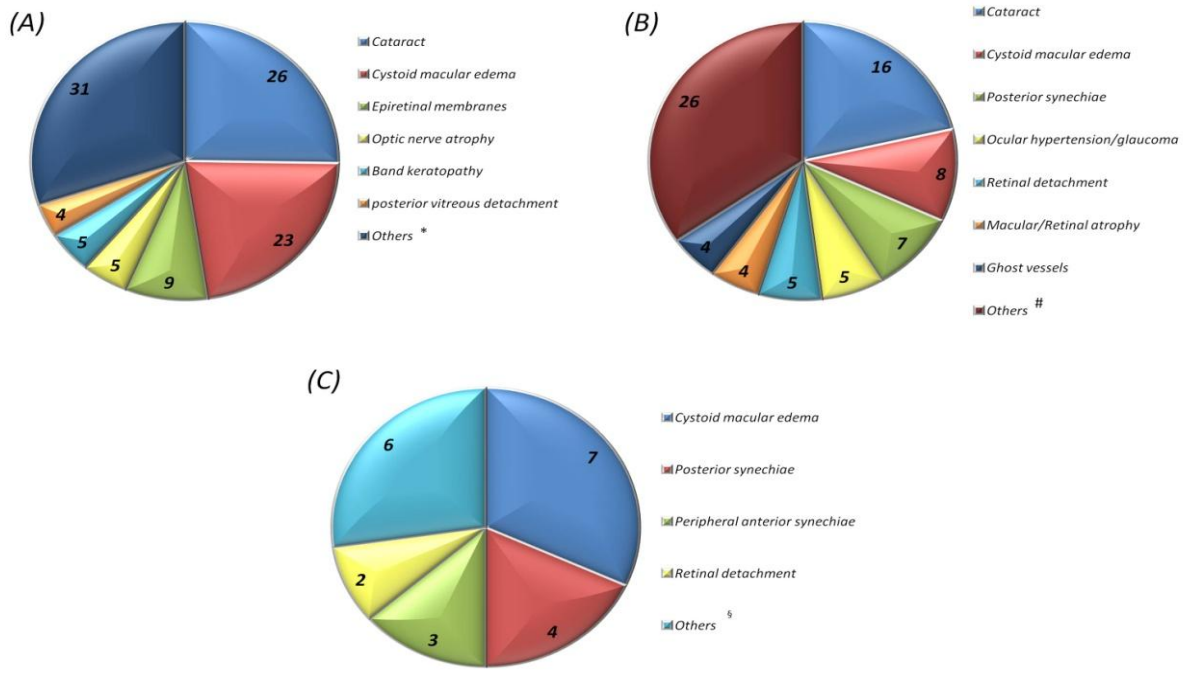

Figure 27. Complications for Behçet's disease (BD)-related uveitis positive to human leukocyte antigen (HLA)-B51, BD-related uveitis negative for HLA-B51 and non-infectious uveitis positive for HLA-B51

* Pigmentation of the anterior capsular bag (*n*=3), peripheral anterior synechiae (*n*=2), ocular hypertension (*n*=2), retinal ischemia (*n*=2), retinal pigment epithelial alteration (*n*=2), retinal scars (*n*=2), retinal detachment (*n*=2), phthisis bulbi (*n*=2), exodeviated bulb (*n*=1), retinoschisis (*n*=1), vitreomacular traction (*n*=1), pupillary seclusion (*n*=1), ghost vessels (*n*=1).

epiretinal membranes (*n*=3), peripheral anterior synechiae (*n*=2), retinal ischemia (*n*=2), optic nerve atrophy (*n*=1), macular ischemia (*n*=1), pupillary seclusion (*n*=1), iris bombè (*n*=1).

§ Vitreomacular traction (*n*=1), papillitis (*n*=1), phthisis bulbi (*n*=1), retinal scars (*n*=1)

With regard to visual acuity, an overall significant difference was detected in median BCVA (p=0.046 which did not maintain statistical significance after Bonferroni correction during post-hoc analysis of pair comparisons (p=0.060). Median (IQR) BCVA for NIU, BD-related uveitis positive to HLA-B51 and BD-related uveitis negative for HLA-B51 was 1.00 (0.10), 1.00 (0.20) and 1.00 (0.30), respectively.

Regarding anatomical pattern, anterior uveitis was significantly overrepresented among patients with NIU unrelated to BD who tested positive to HLA-B51 (p<0.001).

Retinal vasculitis was significantly less prevalent among patients affected by BD-related uveitis who tested negative for HLA-B51 (p=0.025). Retinal vasculitis was present in 10 out of 50 eyes

among patients with NIU unrelated to BD positive to HLA-B51, in 37 out of 164 eyes in BD patients positive to HLA-B51 and in 12 out of 117 eyes in BD patients negative for HLA-B51.

On the contrary, no differences emerged between groups in the occurrence rate of cystoid macular edema (p=0.99).

4 DISCUSSION

Uveitis is a high-morbidity condition and carries a significant impact on patients' quality of life, as visual function may be severely affected by intraocular inflammation and long-term complications. Retinal vasculitis may also represent a serious inflammatory manifestation of patients with uveitis (1-4). Genetic background plays a major role in its development and specific HLA subtypes are known to be relevant also from a prognostic points of view (35).

In the present study, the impact of HLA-B51 on NIU was examined and subsequently compared with BD-related uveitis, either positive or negative for HLA-B51.

Long-term structural complications did not differ between 3 groups, suggesting that the presence of HLA-B51 might have a considerable impact on long-term visual outcome regardless of the systemic/extra-ocular diagnosis. Macular edema was one of the most frequent complications across the board. It represents the most common cause of visual impairment in patients with uveitis and contributes to a worse prognosis. Prolonged intraretinal edema can result in cystic degeneration and photoreceptor damage with permanent loss of central vision. (2,116).

Regarding visual acuity, mean BCVA did not differ significantly among groups. The tendency of BD-related uveitis negative for HLA-B51 to display a slightly lower BCVA over time could be explained by a longer treatment delay. Indeed, the absence of HLA-B51 may delay referral to specialized centers.

As expected, non-BD patients affected by NIU who tested positive to HLA-B51 exhibited a significantly higher rate of anterior uveitis while the predominant anatomical pattern in BD patients was represented by panuveitis. This may, at least partially, be explained by the association with a systemic disease in 26% of NIU cases. In fact, 8 out of 31 patients were diagnosed with SpA, JIA or PsA that are classically coupled with anterior uveitis (132,147).

Interestingly, BD-uveitis patients negative for HLA-B51 were significantly less prone to develop retinal vasculitis during disease course. Its occurrence, indeed, was twice as lower when compared to the other groups. The presence of HLA-B51 may in fact have a direct influence on the development of retinal vasculitis. However, qualitative differences between groups were not assessed. BD-related retinal vasculitis is known to present as an occlusive necrotizing retinal vasculitis with fern-like peripheral leakage (122), while retinal vasculitis in non-BD patients positive to HLA-51 might exhibit distinct features with a different prognostic value.

Altogether, these data advocate for a more severe ocular disease course in patients testing positive to HLA-B51, irrespective of the associated systemic disease. More extensively, the similar rate of long-term structural complications such as cataract, macular edema, epiretinal membranes, posterior synechiae, optic nerve atrophy, retinal detachment etc. alongside a higher chance of experiencing episodes of retinal vasculitis supports the notion of an overall worse evolution of ocular inflammatory disease among patients positive to HLA-B51. In point of fact, HLA-B51 has been identified as an independent predictor of developing complications in BD-related uveitis in a multicenter Italian cohort (282).

Altogether, our findings suggest a tight follow-up schedule in uveitis patients, especially when carrying the HLA-B51 allele, with the aim to prevent the development of irreversible ocular damage and the occurrence of frequent inflammatory attacks. In our cohort, approximately 55% of patients with NIU and 84% of BD patients have been treated with biotechnologic agents (mainly anti-TNF-α agents) or cDMARDs. To this end, real-life multicenter experiences including our tertiary referral center have disclosed excellent results in the management of uveitis either idiopathic or in the context of a systemic immune-mediated disorder with biotechnological agents, mainly TNF-α blockers but also IL-1 inhibitors (96,197,229,230,272,283,284).

Class I, HLA-B5, and its subclass B51 allele have the strongest association with BD (285), but its role in idiopathic uveitis is unclear. The pathogenetic bases of HLA-B51 on NIU is currently unknown. Nonetheless, from an epidemiological standpoint, HLA-B5 was found to be significantly higher in patients with idiopathic uveitis and BD compared to the control group, suggesting a possible causative role of this haplotype in non-infectious intraocular inflammation (286). Anectodal evidence has suggested a pivotal role in aseptic subconjunctival abscess as well as idiopathic retinal vasculitis, aneurysms, and neuroretinitis (IRVAN) syndrome (287,288). Small cases series have also hypothesized a possible association between HLA-B51 positivity and spondyloarthritis or psoriatic arthritis (289,290)

Concerning HLA-B51 influence on BD and its clinical spectrum, a growing body of evidence has determined that HLA-B51 positivity may shape clinical picture and associates with a more frequent major organ involvement, particularly ocular disease (291-293).Whether a similar trend happens for non-BD-related uveitis, is yet to be confirmed. In this regard, future and more specifically designed studies should investigate the influence of HLA-B51 in disease phenotypes by identifying the tendency of certain ocular features of NIU to cluster together.

Finally, future therapeutic novelties could potentially revolutionize treatment of NIU for specific subgroup of patients. Based on molecular studies detecting an impaired HLA-B51:01 recognition by YTS NK cells overexpressing KIR3DL1, individuals carrying HLA-B*51:01-like antigens may be candidates for immunotherapy rooted in pharmacological inhibition of ERAP1 (294).

Despite its international registry-based nature providing solid real-life data, several limitations should be acknowledged: First, the retrospective design may be responsible for some missing data as well as collection bias. Secondly, detailed therapeutic data including treatment duration and/or endpoints related to response to treatment were not retrieved as it was not the main goal of the study. Therefore, the true impact of several and often sequential treatments was not assessed. Thirdly, it is not possible to exclude with absolute certainty that some NIU cases testing positive to HLA-B51 will not be reclassified as BD patients in the future. However, patients with any sign that could be attributable to BD were excluded from the NIU subgroup.

5 CONCLUSIONS

In summary, patients affected by uveitis, testing positive for HLA-B51 may display a more severe disease course that might potentially lead to a worse prognosis. The rate of long-term structural complications as well as visual acuity are similar between NIU unrelated to BD positive for HLA-B51 and BD-related uveitis. Patients testing positive for HLA-B51 are more likely to experience episodes of retinal vasculitis during the disease course. Therefore, patients with NIU should be tested for HLA-B51, even in the absence of typical BD features and placed on a close follow-up schedule with the objective of preventing the accrual of irreversible ocular damage. Nevertheless, the prognostic role of HLA-B51 on such disease needs to be further explored with a more in-depth basic and clinical studies.

6 REFERENCES

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