Rare Anterior Uveitis Entities

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## Table of contents

1. Table of contents
2. List of abbreviations
3. Introduction

### 3.1 Etiology

#### 3.1.1. Differentiation of uveitis by the localization of inflammation
- Posterior vs. anterior uveitis

#### 3.1.2. Differentiation of uveitis by the type of inflammation
- Granulomatous vs. non-granulomatous

##### 3.1.2.1. Granulomatous anterior uveitis
- Sarcoidosis

##### 3.1.2.2. Non-granulomatous anterior uveitis
- HLA-B27 associated anterior uveitis

#### 3.1.3. Differentiation of uveitis by the cause of inflammation
- Infectious vs. autoimmune disease

##### 3.1.3.1. Infectious uveitis
- Bacteria
  - Tuberculosis
- Viruses
  - Herpes viruses
  - Fuchs: Rubella
- Parasites
  - Toxoplasma gondii

##### 3.1.3.2. Autoimmune uveitis
- Sympathetic ophthalmia

##### 3.1.3.3. „Idiopathic“ uveitis

4. Results: Publications

5. Discussion

6. Summary

7. Zusammenfassung

8. References

9. Acknowledgement
2. List of Abbreviations:

α-MSH: α-melanocyte-stimulating hormone
AAU: Acute anterior uveitis
AC: Anterior chamber
ACAI: Anterior-chamber-associated immune deviation
ACE: Angiotensin converting enzyme
APC: Antigen presenting cells
APMPPE: Acute posterior multifocal placoid pigment epitheliopathy
AS: Ankylosing spondylitis
AU: Anterior uveitis
BADI: Acute depigmentation of the iris
BAIT: Bilateral acute iris transillumination
BCG: Bacille-Calmette-Guérin
BHL: Bilateral hilar lymphadenopathy
BRB: Blood-retina-barrier
CMV: Cytomegalovirus
EAU: Experimental Autoimmune Uveitis
EBV: Epstein-Barr virus
FUS: Fuchs uveitis syndrome
HLA: Human leucocyte antigen
HSV: Herpes simplex virus
IFN-γ: Interferon-gamma
IL: Interleukin
KP: Keratic precipitates
PAS: Peripheral anterior synechiae
PDS: Pigment dispersion syndrome
PPD: Purified protein derivative
RPE: Retina pigment epithelium
Rpf: Resuscitation promoting factors
sIL-2R: Soluble interleukin-2 receptor
SO: Sympathetic ophthalmia
SpA: Spondyloarthritis
Tb: Tuberculosis
TJ: Tight junctions
TLR: Toll-like receptors
TM: Trabecular meshwork
TNF-α: Tumor necrosis factor-α
VZV: Varicella zoster virus
3. Introduction

Uveitis is defined as the inflammation of any part of intraocular tissue. This includes the uveal tissue iris, ciliary body, choroid and neural tissue retina, papilla and retinal pigment epithelium as well as the anterior chamber and the vitreous. Depending on the site of the primary inflammation uveitis is classified into 4 major groups: anterior, intermediate, posterior and panuveitis (inflammation of the all structures).

3.1. Etiology

3.1.1. Differentiation of uveitis by the localization of inflammation

Posterior vs. anterior uveitis

Anterior uveitis is the most common and less destructive form of uveitis and accounts for 49\(^2\) to 92\(^3\)% of all uveitis cases in Europe and 76% in Australia.\(^4\) It is more common in young adults between the ages of 20 to 50, but may also affect children and the elderly people. Anterior uveitis is an inflammation of the iris and or the anterior ciliary body of the eye. It is characterized by a breakdown in the blood-aqueous barrier and acute inflammation of the iris and ciliary body due to an infectious or autoimmune cause. This results in leakage of serum proteins and cells into the anterior chamber. On slit lamp examination this can be seen as flare or fibrin in the anterior chamber (AC) and cells either floating in the AC, sedimenting as hypopyon or clustering as keratic precipitates (KP) on the corneal endothelium forming granuloma-like structures. Small nodules (granuloma) can also be seen on the iris named Berlin nodules located on the iris base in the AC angle, Busacca nodules on the iris or Koeppe nodules on the pupillary margin. Other findings are ciliary congestion of the conjunctiva (perilimbal injection) and anterior or posterior synechia.

Intermediate uveitis is defined as an inflammation predominantly involving the pars plana, the peripheral retina and the vitreous.

Posterior uveitis involves the inflammation of the retina (retinitis), choroidea (choroiditis), and/or arteries and veins (vasculitis). Retinitis may be focal, multifocal, geographic or diffuse. Active lesions are characterized by whitish retinal opacities with indistinct borders due to the surrounding oedema. Choroiditis may also be focal, multifocal, geographic or diffuse. A round, yellow nodule in the choroidea is a typical finding of choroiditis. Vasculitis may occur as a primary condition or as a secondary finding.
adjacent to a focus of retinitis. Active vasculitis is characterized by yellowish or grey-white, patchy, perivascular cuffing, which may be associated with haemorrhage.

Panuveitis is the inflammation, which involves the entire uveal tract without a predominant site.

3.1.2. Differentiation of uveitis by the type of inflammation

Granulomatous vs. non-granulomatous

Depending on the clinical findings the type of inflammation seen in AU can be classified into 2 groups: granulomatous and non-granulomatous AU. Frequently other clinical features like type of onset, formation of synechia or secondary iris atrophy are associated with these groups and will be helpful in differentiating these disorders (Tab. 1).

Tab. 1: Clinical features of uveitis associated with granulomatous and non-granulomatous uveitis

<table>
<thead>
<tr>
<th></th>
<th>Non-granulomatous</th>
<th>Granulomatous</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>Acute, recurrent</td>
<td>Slower onset, chronic</td>
</tr>
<tr>
<td><strong>Keratic precipitates (KP)</strong></td>
<td>Dusty</td>
<td>Mutton-fat KP’s</td>
</tr>
<tr>
<td><strong>Anterior chamber (AC)</strong></td>
<td>Flare, isolated cells, fibrin, ± hypopyon</td>
<td>Less flare, cells</td>
</tr>
<tr>
<td><strong>Posterior synechia</strong></td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Iris nodules</strong></td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Iris atrophy</strong></td>
<td>-</td>
<td>+</td>
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</table>
Anterior Granulomatous Uveitis

1. Infectious: (uni-/ bilateral)
   - Viral AU (often unilateral)
     ✓ Herpes simplex virus (HSV)
     ✓ Varizella zoster virus (VZV)
     ✓ Cytomegalovirus (CMV)
     ✓ Epstein-Barr Virus (EBV)
     ✓ Fuchs' Uveitis (mostly chronic rubella virus)
     ✓ Posner-Schlossman syndrome (CMV?)

   - Bacterial AU
     ✓ Tuberculosis
     ✓ Syphilis
     ✓ Leprosy

2. Autoimmune (often bilateral)
   ✓ Sarcoidosis
   ✓ Vogt-Koyanagi-Harada’s Disease (VKH)
   ✓ Sympathetic ophthalmia
   ✓ Lens-induced uveitis

Non-granulomatous Uveitis:

1. HLA-B27 associated anterior Uveitis (AU)
   a. Ocular involvement only (no association with systemic disease)
   b. Associated with systemic disease
      - Axial spondyloarthropathy (SpA)
      - Reactive arthritis
      - Psoriatic arthropathy
      - Inflammatory bowel disease
      - Undifferentiated spondyloarthropathies
      - Juvenile idiopathic arthritis (JIA)
2. Idiopathic acute anterior uveitis
3. Behçet’s disease
4. Tubulointerstitial nephritis and uveitis syndrome (TINU)
5. Kawasaki disease
6. Medication-induced uveitis
7. Traumatic uveitis
8. Infectious causes
   Leptospirosis
   Rickettsioses
   Poststreptococcal syndrome uveitis
   Bacterial endophthalmitis

Taken and modified from Gupta et al. 2009: 31
3.1.2.1. Granulomatous anterior uveitis

Granulomatous anterior uveitis is characterized by mutton-fat keratic precipitates (Fig. 1), which are composed of macrophages or giant cells and additional T- and B-cells. Another typical finding is nodules consisting of inflammatory cells, which can be identified on the pupillary margin (Koeppe nodules: Fig. 2), on the iris (Busacca nodules: Fig. 2) and the iris base in the AC angle (Berlin nodules). Also like in non-granulomatous AU, cells floating in AC and flare can be seen.

Sarcoidosis

Sarcoidosis is a chronic granulomatous multisystem disease of unknown aetiology. Clinical presentation of the disease varies widely from asymptomatic to severe cases. The disease affects predominantly lungs and the thoracic lymph nodes. Other frequently affected organs are eyes and skin. The most common skin lesions are erythema nodosum and sarcoid granulomas. Ocular involvement is seen in 25%–60% of patients with systemic sarcoidosis. The most common ocular manifestations are with 30% to 70% uveitis and with 40% conjunctival nodules.

Clinical manifestations of ocular sarcoidosis:

Uveitis:

Systemic involvement is frequently missing in patients with ocular sarcoidosis. Recently an international workshop has defined criteria for the diagnosis of ocular sarcoidosis.
Results of the First International Workshop on Ocular Sarcoidosis (IWOS)  

I. Clinical signs suggestive for sarcoidosis

1. Mutton-fat KPs (large and small) and/or iris nodules at pupillary margin (Koeppe) or in stroma (Bussacca)
2. Trabecular meshwork (TM) nodules and/or tent-shaped peripheral anterior synechiae (PAS)
3. Snowballs/ string of pearls vitreous opacities
4. Multiple chorioretinal peripheral lesions (active & atrophic)
5. Nodular and/or segmental peri-phlebitis (candlewax drippings) and/or macroaneurism in an inflamed eye
6. Optic disc nodule(s)/ granuloma(s) and/or solitary choroidal nodule
7. Bilaterality (assessed by clinical examination or investigational tests showing subclinical inflammation)

II. Laboratory investigations or investigational procedures

1. Negative tuberculin test in a BCG vaccinated patient or having had a positive PPD (or Mantoux) skin test previously
2. Elevated serum angiotensin converting enzyme (ACE) and/or elevated serum lysozyme
3. Chest x-ray; look for bilateral hilar lymphadenopathy (BHL)
4. Abnormal liver enzyme tests
5. Chest CT-scan in patients with negative chest x-ray

In 1989 Rothova et al. have reviewed retrospectively 121 patients with biopsy proven sarcoidosis and 41% had an associated ocular disease. The most frequently seen ocular involvement was uveitis (28% anterior uveitis, 30% posterior and panuveitis). It is important to consider sarcoidosis in cases with granulomatous AU because in this study uveitis was in 86% an early feature before the diagnosis of sarcoidosis and lung involvement is relatively rare in patients with ocular sarcoidosis.

In spite of having these diagnostic criteria, the diagnosis of sarcoidosis remains challenging. Angiotensin-converting enzyme (ACE), which is a supportive criterion in the diagnosis, is produced in pulmonary macrophages of the sarcoid granuloma and vascular endothelium. The serum ACE shows the total body granuloma burden in sarcoidosis and serum ACE is elevated in 60-90% of patients.
with active sarcoidosis\textsuperscript{11}. However there are other conditions like disseminated tuberculosis, fungal infections, hyperthyroidism, and Gaucher disease, which can also be associated with elevated ACE levels. In children ACE is frequently elevated for unspecific reasons. Therefore this test remains only fairly specific for the diagnosis of sarcoidosis\textsuperscript{12}.

Another surrogate marker for sarcoidosis is the soluble interleukin-2 receptor (sIL-2R). In 1990 Keicho et al. have shown that the elevated serum sIL-2R was significantly higher in untreated sarcoidosis patients in comparison to the healthy population\textsuperscript{13}. This study also showed a positive correlation between the serum concentration of sIL-2R and serum ACE activity suggesting the use of IL-2R level in serum as a surrogate marker for the activity of the disease\textsuperscript{13}.
3.1.2.2. Non-granulomatous anterior uveitis

Non-granulomatous anterior uveitis is characterized by the lack of adhering cells forming granuloma-like structures. Typical clinical findings of non-granulomatous AU are cells, flare, and fibrin in the anterior chamber as well as dusty precipitates composed primarily of neutrophils and few other leucocytes on the posterior corneal surface.

HLA-B27 associated anterior uveitis

Human leucocyte antigen (HLA) B27 is highly associated with several autoimmune diseases like axial spondyloarthritis (former SpA or ankylosing spondylitis) and anterior uveitis. HLA-B27 associated AU is the most common single entity of AU comprising 18 to 32% of AU cases. It also has distinct clinical features that differentiate it from HLA-B27-negative acute anterior uveitis (AAU). Typical presentation of HLA-B27 AAU is sudden onset and limited duration with alternating, unilateral recurrence and symptoms of redness, pain, epiphora, photophobia, and blurred vision.

The clinical findings of HLA-B27-associated AU are perilimbal hyperemia, dusty keratic precipitates (fig. 3), cells, which can accumulate as hypopyon (fig. 4) and flare in AC. In cases of severe inflammation, fibrinous exudation in the AC can be seen. This fibrinous exudation may cause posterior synechiae (fig. 5). The duration of the acute episode is quite variable, but usually lasts for 4-6 weeks. There are many studies about the statistical correlation of HLA-B27 and AU. In one study, 43% of patients with acute anterior uveitis had a positive HLA-B27.

In 2004 Monnet et al. have shown that a HLA-B27-associated extraocular disorder was seen in 77.7% of the cases, who had an HLA-B27-associated AU. Of these patients, 46.3% had an ankylosing spondylitis (AS), 9.7% presumed AS, 12% undifferentiated spondyloarthropathy (SpA), 1.1% psoriatic arthritis, 3.4% reactive arthritis, 2.9% Behcet's disease and 2.3% had inflammatory bowel disease. In 22.3% no systemic disease was found.
The other causes of non-granulomatous AU are Behcet’s disease, tubulointerstitial nephritis and uveitis –TINU- Syndrome, Kawasaki’s disease, traumatic uveitis, bacterial endophthalmitis, borreliosis, rickettsioses, and leptospirosis. These are rare uveitis entities and should be ruled out in therapy refractive cases.
3.1.3. Differentiation of uveitis by the cause of inflammation

Infectious vs. autoimmune disease

Immune characteristics of the eye

For years the eye has been considered as an immune privileged organ. There are many unique characteristics of the eye, like the blood-retinal barriers (BRB), absence of lymphatic drainage and special immunosuppressive factors, which contribute to this immune privilege.

The BRB consisting of inner and outer components plays an important role in the immune privilege. The inner BRB, which is also called the true barrier is formed by tight junctions (TJ) of non-fenestrated endothelial cells and surrounded by, astrocytes, Müller cells and pericytes. The outer BRB, which is also called an immunoregulatory gate, located on the Bruch membrane and outside the subretinal space and the outer neural retina, is formed by the tight junctions between cells of the retina pigment epithelium (RPE) and fenestrated choriocapillaris. The third component of the ocular barrier system is the blood-aquous barrier, which is located at the ciliary body. Ciliary body produces the aqueous humor and this barrier is formed by the tight junctions of non-pigmented ciliary body epithelium on the proximal side of the aqueous humor and by the fenestrated endothelial cells on the other side.

Another known factor is the anterior-chamber-associated immune deviation (ACAID) and immunosuppressive mediators like TGF-β or α-melanocyte-stimulating hormone (α-MSH), which prevent the invasion of the non-activated leucocytes. In this phenomenon the antigens in the anterior chamber are captured by antigen presenting cells (APC), which migrate to the spleen, where they change natural killer cells, CD4+ and CD8+ T cells into a regulatory phenotype. This mechanism is considered as a generation of peripheral tolerance to eye antigens using the systemic immune system.

Another special feature of the eye is the absence of the lymphatic drainage. Like brain, placenta, and testes the eye has no direct lymphatic drainage, which also prevents the immune response.
Since the initiation of immune responses to ocular antigens in the eye is prevented by those mechanisms, an autoimmune response leading to an intraocular inflammation has to be induced outside of the eye with antigens imitating ocular autoantigens (“antigenic mimicry”).

According to the expression of CD8 or CD4, there are two types of T-cells. CD8+ T-cells recognize an 8-10 amino acids long antigen peptide presented by HLA-class-I antigens. These peptides originate most commonly from intracellular metabolism, particularly if this metabolism is aimed to replicate virions after viral infection. CD8+ T-cells have a crucial role as cytotoxic cells in the elimination of virus-infected cells or tumor cells but they can also act as regulatory cells.

CD4+ T-cells recognize antigen peptides presented by HLA-class II molecules. These peptides are more variable in their length compared to peptides presented by HLA-class I molecules. HLA-class II molecules however, often present peptides emanating from lysosomal metabolism. These peptides result from phagocytation and following intracellular degradation. To a lower extent it is also possible that an exchange of peptides from the extracellular environment is presented on the surface of HLA-class II antigens.

Experimental autoimmunuveitis (EAU) in Lewis rats is a well-known model for human uveitis. In rat model it was shown that, S-Ag when injected at a site far from the eye, causes an immune mediated, bilateral inflammatory response in the eye. Retinal S-Ag is one of the most potent uveitogenic antigens. This antigen is localized in the photoreceptor region of the retina and in pineal gland in some species. In 2005 Wildner et al. have described peptides from rotavirus (Rota) and from bovine milk casein (Cas), which could cross-react with retinal S-Antigen, due to the amino acid sequence homologies, causing an inflammatory reaction in the eye.

In 2008 Wildner et al. used a cross-reactive ocular antigen, mimicking ocular proteins in rat model to activate the T-cells. The activated T cells can enter the eye by passing the blood-retina barrier and then they are reactivated by cross-reactive retinal antigen, which is called antigen mimicry. This concludes that activated T-cell of any kind can pass the blood-retina barrier and invade the eye without causing any tissue damage. But if a specific activated T-cell finds its specific or its cross-reactive antigen, then it gets reactivated. Those reactivated T-cells can stimulate the inflammatory cells, which
cause the tissue destruction in the eye. As a conclusion, antigenic mimicry can explain extraocular activation of a cross-reactive immune response finally targeting ocular antigens.

3.1.3.1 Infectious Uveitis

3.1.3.1.1 Bacteria

Tuberculosis

Tuberculosis (Tb) is another multisystem disease, which predominantly affects the lungs, but can involve every organ. With worldwide 8 million new cases approximately and 3 millions deaths per year, tuberculosis remains as the world’s leading infectious cause of death.

Tuberculosis is usually classified as pulmonary Tb and extrapulmonary Tb. Extrapulmonary tuberculosis can involve lymph nodes (30.9 %), pleura (23%), genitourinary system (11.9 %), bone and joint (9.8 %), miliary (7.3 %), meninges (4.6 %), peritoneum (3.3%), and all other forms combined (9.8%).

Tuberculosis is an airborne infection caused by Mycobacterium tuberculosis, primarily affecting the lungs. In a resistant host, the mycobacteria are usually destroyed by the alveolar macrophages. If the alveolar macrophages fail to destroy the mycobacterium, then the bacilli will multiply until the macrophage bursts. The bacilli is released from the macrophage and phagocytosed by non-activated monocytes/ macrophages or other alveolar macrophages and a relationship begins between the host and the bacilli. In this time period bacilli multiplies.

The interaction between the components of mycobacterium and Toll-like receptors (TLR) causes the macrophages to produce inflammatory cytokines and chemokines, which serve as a signal of infection. This signal causes the migration of macrophages and resident dendritic cells to the lungs. The bacteria containing dendritic cells mature and migrate to the regional lymph node. In the regional lymph node CD4 and CD8 T cells are primed against mycobacterial antigens. Those T cells migrate back to the site of infection in the lungs. A delayed type of hypersensitivity reaction produced by T cells, especially cytotoxic T cells, is responsible for the destruction of those bacilli filled macrophages, which causes a formation of granuloma, with a central area of necrosis. But despite of all the efforts of the immune system the bacilli are not completely destroyed. The accumulation of T cells and
macrophages result in the formation of this granuloma. The granuloma of the lungs is a typical finding in Tb and consists of macrophages, CD4 and CD8 T cells, dendritic cells, endothelial cells, fibroblasts, and B cells. However some of those bacilli filled macrophages escape and enter the lymphatic or blood system and reach the extrapulmonary organs. In about 10% of the affected cases a primary infection causes an active disease. However the remaining 90% of the infected cases are non-infectious and symptom-free (latent Tb). The estimated risk of lifetime reactivation is between 2% and 23%.

Reactivation of the disease occurs when the latent bacilli from the old granulomatous lesions become active. The mechanism of reactivation is not known yet. The control of Tb is thought to be mediated by interferon-gamma (IFN-γ) producing T-cells. Also both CD4 and CD8 T lymphocytes play an important role in controlling the growth of M. tuberculosis. The reactivation takes place when the immune response of the host weakens or in cases with suppression of the immune system like in HIV positive individuals with low CD4 T-cell counts. Flynn and Chan have shown in mice that in the immune response associated with the latent phase, CD8+ T-cells play a more significant role in comparison to the primary infection of Tb where CD4+ cells are more important.

Recently there have been many publications speculating the importance of group of proteins, called resuscitation promoting factors (rpf) in the reactivation of the disease. M. Tuberculosis has 5 rpf proteins, which are coded by rpf genes. It is believed that in case of an environmental stress, the bacteria causes a thickening and decreased permeability of the cell wall by heavy cross-linking between peptidoglycan strands. When the stress is removed, rpf genes are activated resulting the production of rpf proteins, which snip the tight peptidoglycan strands and the growth phase of the bacteria restarts. However the real pathophysiology of the reactivations remains still mysterious.

Ocular involvement in tuberculosis is thought to be rare, however some publications show the opposite. Bouza et al. have shown in 1997 that 18 of 100 patients with proven systemic tuberculosis had an ocular involvement. Clinical manifestations of ocular tuberculosis are anterior, intermediate and posterior uveitis. All types of ocular tuberculosis are characterized by granulomatous inflammation.

The anterior uveitis seen in tuberculosis has usually a chronic course with typical signs of
granulomatous uveitis. Moderate to severe vitritis in ocular Tb can be isolated or in association with chorioretinitis.

Posterior uveitis is the most common form of ocular tuberculosis. According to Bouza et al. 17 out of 18 patients with ocular involvement of tuberculosis had chorioditis. A choroidal granuloma localized deep in the choroid is a hallmark of the disease. Those granulomas have a yellow to white appearance, are usually few in number and located at the posterior pole. In this study the other associated lesions were papillitis, retinitis, and vasculitis.

Because of the difficulties in the diagnosis of the ocular Tb, this ocular disease can be overlooked or misdiagnosed. Recently there have been publications about the promising results in the diagnosis of tuberculosis with PCR from the aqueous samples. The first publication was in 1994 by Kotake et al., who detected M. tuberculosis by PCR in aqueous samples in 2 patients with active retinal vasculitis. Then in 1999 Arora et al. have shown in 53 aqueous samples of patients with granulomateous uveitis (including one or more of the following: 1. active vasculitis, 2. anterior vitreous cells, 3. snowball opacities, 4. snowbanks in the pars plana, 5. retinochoroiditis), 20 patients had a positive PCR for M. tuberculosis. In the same study the patients having a positive PCR were treated with anti-tuberculosis treatment and 4 months after the treatment PCR from the aqueous samples were repeated and was negative. Those patients also have shown a clinical improvement of the disease after the Tb-treatment.

The proven DNA of M. tuberculosis indicates an invasion of the bacteria in the eye. The question is: Can the ocular tuberculosis be ruled out after not finding any DNA in the aqueous samples, but having typical clinical features of ocular tuberculosis? More recently developed molecular techniques like PCR, which detects the M. tuberculosis using DNA probes are promising. However the negative samples can be negative due to a low number of organisms in small samples of ocular fluids. The other theory in the ocular involvement is the antigen mimicry, which can explain the negative PCR for M. tuberculosis in spite of having the typical clinical features. According to this theory in addition to our classical knowledge of infectious organisms in the eye, uveitis can also be caused as a result of immune stimulation due to possible antigen mimicry.
3.1.3.1.2. Viruses

Herpes viruses

Human herpes virus infections are one of the major causes of morbidity worldwide. Six members of the herpes virus family are responsible for herpetic eye disease: HSV 1, HSV 2, VZV, EBV, CMV, and human herpes virus 8 47.

Herpetic eye disease can involve almost all parts of the eye. Clinical presentation includes blepharitis, conjunctivitis, scleritis, keratitis, anterior uveitis, acute retina necrosis, choroiditis, and optic neuritis. The diagnosis of herpetic AU is based on clinical features. Clues leading to the diagnosis of herpetic AU, are mutton-fat keratic precipitates (especially in the inferior 1/3 of the corneal endothelium), reduced corneal sensitivity in comparison to the other eye, localized corneal scar or oedema, cells and flare in the AC, focal areas of iris atrophy (transillumination of the iris), and a distorted pupil.

The patients often complain about blurred vision, pain, and photophobia. Herpetic AU is usually unilateral and frequently seen with keratitis. However it can also occur without corneal involvement 47. The treatment of herpetic AU is based on antiviral agents (aciclovir, valaciclovir, and famciclovir). Most of the herpetic AU patients also require topical corticosteroids and/ or mydriasis for the treatment of the AU.

Fuchs: Rubella

Fuchs’ uveitis syndrome is another syndrome, which causes the depigmentation of the iris. Typical clinical findings are unilaterality, generalized, fine, stellate keratic precipitates, iris atrophy, low-grade anterior uveitis and vitritis 48. Other features are iris nodules (more then 30% of the cases) and the smoothening of the stroma at the early stage of the disease. 5-10% of the cases are bilateral. It is mostly asymptomatic and the most common complications are subcapsular cataract and glaucoma. A chronic rubella infection or CMV infection is assumed to be the cause of Fuchs’ uveitis syndrome 49, 50.

In 1997 Muhaya et al. have shown the predominantly elevated levels of CD8+ T-cells in the anterior chamber taps of the patients with Fuchs’ uveitis 51. It can be speculated that the cause of the typical iris transillumination is the direct cytopathic effect of the virus on the infected tissue.
3.1.3.1.3. Parasites

Toxoplasma gondii

Toxoplasma gondii infection is an important cause of chorioretinitis worldwide. The characteristic lesion is a focal necrotizing retinitis that initially appears as a yellowish-white, elevated cotton patch with indistinct margins, usually located in the posterior pole adjacent to pigmented scars. The diagnosis of toxoplastic retinitis is based on clinical features. In atypical presentations, or when the fundus is hidden by vitreal inflammation, aqueous humor analysis could be used as a diagnostic tool.

Figueroa et al. 52 have shown that the detection of T. gondii genoma in aqueous humor by PCR is an effective diagnostic tool. However a negative result does not rule out a possible ocular toxoplasmosis52. The proven DNA of T. gondii indicates an invasion of the parasite in the eye. This could explain that, like in herpes uveitis, the persistence of the agent in the eye can cause the activation of the inflammation.

There are probably many more proteins, e.g. from infectious agents, that might be cross-reactive with ocular autoantigens. In the following, we discuss a rare side effect of the therapeutic use of Bacille Calmette Guérin (BCG) for bladder carcinomas. We described a case of potential antigenic mimicry of proteins from BCG and Mycobacterium tuberculosis with several retinal autoantigens, providing a further link between (extraocular) infections and intraocular autoimmunity 46.

On the other hand, Fuchs uveitis, which has been regarded as „autoimmune“ for a long time, was finally identified to be a chronic infection with rubella or herpes viruses/CMV 49, 53. In these cases, a chronic trigger of the virus-specific T cell response leads to chronic intraocular inflammation and granuloma formation.

While most herpes viruses cause granulomatous anterior uveitis, varizella zoster virus (VZV) induces iris transillumination, which is a cytopathic effect of the virus itself and not caused by a destructive immune reaction. In addition to VZV there might be more viruses able to induce lysis of the iris pigment epithelium that results in iris transillumination, which, however, have not yet been identified 54.
3.1.3.2. Autoimmune Uveitis
Sympathetic Ophthalmia
Sympathetic ophthalmia (SO) is an uncommon bilateral granulomatous panuveitis following uveal trauma to one eye. This trauma causes a break down in blood-retina-barrier (BRB) resulting a local activation of the immune system on one or both eyes.

3.1.3.3. „Idiopathic“ Uveitis
Autoimmune reaction without preceding infection or trauma should not be possible due to:

a) blood-retina barrier (BRB) is sequestering the ocular autoantigens from the immune system. Most of them only expressed in the eye and not in peripheral tissues. Moreover, BRB can only be passed by already activate leukocytes, which cannot be activated to retinal antigens, because they are not available outside of the eye.

b) immune privilege of the eye: induces regulatory T cells/immune tolerance to intraocular antigens (example: ACAID).

c) immunosuppressive factors in the aqueous/vitreous prevent activation of potentially autoaggressive effector cells and help inducing regulatory T cells, respectively.

4. Results: Publications

Both manuscripts are about rare uveitis entities. In the first publication the antigenic mimicry was considered as the cause of the uveitis in a patient with bilateral uveitis after the intravesical application of Bacille-Calmette-Guérin (BCG) for her bladder carcinoma. The second manuscript involves a case series of 26 patients with new described uveitis entity. In this case series the patients present with similar ocular findings of bilateral acute iris transillumination, pigment dispersion, and sphincter paralysis. There are two possible explanations for the destruction of the iris pigment epithelium resulting in transillumination. The first theory involves the direct cytopathic effect of a virus on the infected iris tissue. The second theory is the potential antigenic mimicry of (unknown) viral proteins/peptides of an extraocular (systemic) virus infection and proteins of the iris pigment epithelium, recognized by cross-reactive CD8+ cytotoxic T-cells, which destroy the pigmented cells of the iris.

I have contributed to the first manuscript as a first author and the second manuscript as a co-author. In the first manuscript I was actively involved in processes concerning literature review, performing observations, collecting data, and writing. In the second manuscript I was involved in all processes concerning literature review, establishing material and methods, performing observations, collecting data, statistical analysis using SPSS, and writing.
Uveitis in a Patient Treated with Bacille-Calmette-Guérin

Possible Antigenic Mimicry of Mycobacterial and Retinal Antigens

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Purpose: To investigate the cellular immune response in uveitis developing after intravesical Bacille-Calmette-Guérin (BCG) applications.

Design: Experimental study.

Participants: A 72-year-old HLA-B27–negative patient with bilateral granulomatous anterior uveitis that developed during the third cycle of intravesical BCG applications she was receiving for treatment of bladder carcinoma.

Methods: The patient’s peripheral T cell reactivity to ocular autoantigens was compared with the response to purified protein derivative (PPD) from Mycobacterium tuberculosis. T-cell proliferation and cytokine and chemokine secretion were measured in vitro.

Main Outcome Measures: Anterior uveitis was treated successfully with topical corticosteroids and cycloplegics.

Results: The following were demonstrated: proliferation to PPD, interphotoreceptor retinoid-binding protein (IRBP), and IRBP-peptide R16, as well as secretion of proinflammatory cytokines in response to PPD, retinal soluble antigen (S-Ag), IRBP, cellular retinal-binding protein (CRALBP), and some S-Ag and IRBP peptides.

Conclusions: These data indicate the generation of a polyclonal autoimmune reaction elicited by BCG. Amino acid sequence alignments revealed homologies between proteins from M. tuberculosis, BCG, and retinal antigens, suggesting antigenic mimicry as a potential cause of uveitis in this patient.

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lar inflammatory immune response may be the result of antigenic mimicry, when T cells mistake retinal proteins for antigens from BCG.

Case Report

A 72-year-old woman was referred by an ophthalmologist to the authors’ outpatient department with a bilateral granulomatous anterior uveitis, which had been ongoing for 3 to 4 days. The patient reported painless blurred vision, initially in her left eye. Otherwise, there was no history of previous uveitis. Findings were recorded according to the Standardization of Uveitis Nomenclature criteria. Initially, best-corrected visual acuity was 0.8 in the right eye and 0.6 in the left eye. Both eyes showed endothelial granulomatous precipitates in Arlt’s triangle and 2+ cells in the anterior chamber (Fig 1). There was 1+ flare in the right eye and some fibrin on the temporal part of the iris. Remnants of preexisting posterior synechiae were seen on both lenses. The right eye showed Koeppen nodules. The vitreous in both eyes had some cells and 0.5+ haze. There were no signs of posterior uveitis.

Her medical history revealed ongoing treatment for arterial hypertension and hypercholesterolemia. Three years earlier, she was diagnosed with a high-grade noninvasive papillary urothelial carcinoma (pTaG3). Treatment included transurethral resection, photodynamic therapy with the photosensitizer 5-aminolaevulinic acid, and intravesicular instillations of BCG. One year later, the tumor reoccurred and she was treated again with transurethral resection and intravesical BCG instillations, without tuberculosis prophylaxis. The patient had received neither further chemotherapy nor corticosteroids. At the time of the first ocular symptoms, she was tumor free and had received 3 complete courses of 6 BCG instillations each, the last one 7 days before onset of blurred vision.

The results of the medical examination were negative with the exception of the known disorders. She had no rheumatologic diseases and no history of tuberculosis. A chest radiograph showed a granuloma of 5 mm in diameter (Fig 2) that had first been observed in 2002 (3 years before diagnosis of the bladder carcinoma) and had remained unchanged since then. The radiologist regarded the location of the granuloma in the lower left field as atypical for tuberculosis or sarcoidosis and concluded that it was likely a remnant of pneumonia. The Tine test (intracutaneous prick test) that was performed after diagnosis of uveitis demonstrated negative results, despite prior BCG treatment, and she was not tested before onset of BCG therapy. A tuberculosis quantiferon gold test was not carried out.

Blood chemistry results were unremarkable. She was negative for HLA-B27 and positive for HLA-B8 and HLA-B38, and the ACE level was within normal limits. Serologic analysis for toxoplasmosis, Lyme borreliosis, and syphilis demonstrated negative results. She had low immunoglobulin G and negative immunoglobulin M titers for herpes simplex virus, varicella zoster virus, and cytomegalovirus. Polymerase chain reaction analysis of an anterior chamber tap showed negative results for herpes simplex virus, varicella zoster virus, and toxoplasmosis. Anterior uveitis was treated successfully with topical steroids and mydriatics and the intraocular inflammation had subsided completely 4 weeks later, when the in vitro cultures with peripheral blood lymphocytes were initiated.

Materials and Methods

Peptides and Protein Antigens
Retinal soluble antigen (S-Ag) and interphotoreceptor retinoid-binding protein (IRBP) were prepared from bovine eyes as de-
scribed, and the purity was controlled by gel electrophoresis. Recombinant cellular retinal-binding protein (CRALBP) was obtained and purified as described. Chicken ovalbumin (OVA) was obtained from SIGMA (Deisenhofen, Germany), and tuberculin (PPD) and tetanus toxoid (TT) were gifts from Aventis (Marburg, Germany). Custom peptides were purchased from Biotrend (Cologne, Germany) and had the following sequences: S-antigen–derived peptides: SAg 281, LPLLANNRERRGIALD; SAg 286, NNRERRGIALDG; PepM, DTNLASSTIIKEG; PDSAg, FLGELTSSEVATEV. Interphotoreceptor retinoid-binding protein–derived peptides: PI536, GVYLLTSHRTATAA; PI671, DLYILMSHTSGSAA; PI1137, KSMVILTSTVTAGTAE; R4T, NLYLTIPTARSVGA; R4/R14, PTARSVGAADG; R14, PTARSVGAADGSSWEGVGVVPDV; PDIRBP, VGAADGSSWEGVGV; R16, ADGSSWEGVGVVPDV. Sequence homologies of retinal autoantigens with proteins from M. tuberculosis BCG strain were determined by BLAST sequence similarity search of the NCBI Gene bank.

Antigen-Specific Stimulation of Peripheral Blood Mononuclear Cells

Six weeks after onset of clinical uveitis, peripheral blood was collected with the patient’s informed consent and prior approval of the ethics committee of the clinic of the Ludwig-Maximilians University of Munich. Lymphocytes were separated from heparinized peripheral blood by Ficoll density gradient centrifugation (PAA, Coelbe, Germany) and then were cultivated for 4 days in flat-bottom microtiter plates (Renner, Danzig, Germany) at a density of 2.5×10^5/ml in RPMI 1640 medium (PAA) supplemented with 2 mM L-glutamine, 100 IU penicillin G (PAA), 10 mg/ml streptomycin sulfate (PAA), and 1× MEM essential and nonessential amino acids (PAA). Each culture contained 5% of heat inactivated pooled human serum. Retinal soluble antigen (S-Ag), IRBP, CRALBP, chicken ovalbumin, and tetanus toxoid were used at concentrations of 10 µg/ml, PPD was used as indicated, and the peptides were used at concentrations of 20 µg/ml. Chicken ovalbumin as a common nutritional protein and tetanus toxoid as a general vaccine were used as controls. After 3 days, cells were pulsed with 2 µCi ^3H-thymidine/well and were cultured for another 18 hours. Results are given as stimulation index (mean counts per minute [cpm] of culture with antigen/mean cpm of culture with medium)± standard error.

Cytokine and Chemokine Measurement

Tissue culture supernatants were collected every 24 hours from days 1 to 3 after stimulation (see proliferation assay). Cytokines of pooled samples were measured with the Bio-Plex protein array system (Bio-Rad Laboratories, Inc., Hercules, CA) in combination with Bio-Plex Manager software, which is designed for the multiplexed quantitative analysis of multiple cytokines and chemokines in a single well. Premixed multiplex beads for interleukin (IL)-2, interferon (IFN)-γ, tumor necrosis factor-α, IL-4, IL-10, IL-17, IL-6, IL-8, MIP-1a, and granulocyte-monocyte colony-stimulating factor with a detection limit of 5 pg/ml in 50 µl total test volume were used and the assay was performed following the manufacturer’s instructions. Only amounts of more than 10 pg/ml were regarded as a specific response.
Results

In Vitro Lymphocyte Responses

The patient’s lymphocytes were collected when clinical disease had subsided completely. Proliferation exceeding the medium control by 2-fold was observed only for PPD, TT, IRBP, and R16 (Fig 3). Elevated cytokine responses were detected more frequently, revealing T-helper 1 (Th1)-type reactivity with secretion of IFN-$\gamma$ to all tested retinal antigens and peptides from S-Ag and IRBP as well as to chicken ovalbumin and PPD (Fig 3). Despite the negative tuberculin skin response of the patient, high IL-2 secretion was observed in response to PPD, but not to the other tested antigens (Fig 3), whereas no IL-10 secretion was measured even in cultures stimulated with PPD (data not shown). Tumor necrosis factor-$\alpha$ secretion was induced by R16 and CRALBP as well as by PPD, whereas no IL-4, the typical cytokine of the T helper 2 type, was found in either culture. Variable high levels of at least 200 pg/ml IL-6 were found in all cultures except the medium control, whereas IL-8 levels exceeding the medium control by at least two fold were obtained only after stimulation with PPD, PepM, P731, and R4/R14. In contrast, MIP1-$\alpha$ was secreted in all cultures, with very low levels in response to PepM, P1536, P11137, R14, and PDIRBP. Granulocyte-monocyte colony-stimulating factor was detected in all supernatants except medium control in levels between 36 and 290 pg/ml, whereas IL-17 was not found in any culture supernatant (data not shown). Except for PPD responses, there was no correlation between lymphocyte proliferation and cytokine or chemokine secretion.

Comparison of the amino acid sequences of retinal proteins and peptides that induced the highest Th1 responses with the sequences of BCG proteins resulted in several highly similar or even identical regions of 5 to 11 amino acids (Fig 4, available at http://aaojournal.org). These epitopes might have been responsible for a crossreactivity of the patient’s BCG-specific T cells with retinal autoantigen, resulting in uveitis. For the in vitro stimulation, we used bovine proteins with few amino acid differences from the human protein, the potential antigen for the patient’s autoimmune response. Four alignments with S-Ag protein were found, which are not covered by any of the peptides and 4 homologies with peptide SAg281, which induced the highest cytokine and chemokine responses of all S-Ag peptides. In addition to alignments with peptide R16 and R4T, 5 homologies with the sequence of IRBP protein were detected that are not represented by any of the peptides, and in addition, 2 similarities with CRALBP protein were found. The homologous sequences were from different proteins of BCG, indicating that a variety of different antigens could induce crossreactivity.

Discussion

Bacille Calmette-Guérin instillation is regarded as the most effective treatment and prophylaxis for noninvasive bladder
cancer. Live mycobacteria attach to and invade the bladder tumor cells using fibronectin and integrins and induce inflammation with infiltration of macrophages, T and B lymphocytes, and natural killer cells as well as upregulation of proinflammatory cytokines including IL-1, IL-2, IL-5, IL-6, IL-8, IL-10, IL-12, IL-18, IFN-γ, tumor necrosis factor-α, and granulocyte-monocyte colony-stimulating factor. Overall, a T-helper type 1 immune response is generated that mediates a local antitumor activity, and in addition, tumor cell mobility is inhibited. This local response also induces systemic reactions, including increased specific T-cell proliferation and antibody production.

This therapy also has some immune-mediated side effects, mainly arthritis and uveitis. Compared with the number of patients treated for carcinoma with BCG or vaccinated against tuberculosis, the incidence of autoimmune diseases arising as adverse effects is very low. The reason why autoimmune diseases develop after BCG treatment in some patients could be based on genetic predispositions such as the presence of certain HLA antigens. The patient was negative for HLA-B27 but positive for HLA-B8 and HLA-B38. HLA-B8 is associated with uveitis in black Americans and is more frequent in sarcoidosis than in tuberculosis patients, suggesting a role of HLA-B8 in autoimmunity.

M. tuberculosis infection of ocular tissues results in uveitis; however, intraocular infection is not necessary. Systemic infection with M. tuberculosis may cause inflammation of the eye by a cross-reactive immune response, as observed here after BCG therapy, when T cells recognize mycobacterial antigens as well as ocular proteins. This phenomenon, called antigenic mimicry, was a presumed cause of previously reported uveitis. Thus, the patient’s peripheral T-cell response to PPD and a set of retinal autoantigen proteins and peptides were investigated. Although the patient, according to her own statement, had no positive skin reaction to tuberculin (PPD), a strong in vitro response to PPD with respect to proliferation and Th1-type cytokine production (IL-2, IFN-γ, tumor necrosis factor-α) was observed. The Tine test is an intracutaneous prick test that can give false-negative results because of insufficient antigen application. Furthermore, proliferative or cytokine responses, or both, were detected to 3 retinal autoantigens (S-Ag, IRBP, and CRALBP) and to some of their peptides, which are involved in the autoimmune response of human uveitis. Several homologies on the level of amino acid sequence were found—even identities of up to 7 continuous amino acids—between BCG proteins and these retinal autoantigens that could explain the T-cell reactivities, as we could already previously demonstrate for peptides from rotavirus, bovine milk casein, and retinal S-Ag peptide PDSAg were demonstrated.

The literature describes some M. tuberculosis peptides that are recognized by human T cells—most of them by CD8+ cytotoxic T cells. In these cases, tuberculosis had developed in patients after mycobacterial infection or after they had had contact with tuberculosis patients. None of the peptides recognized by infected individuals is identical with any of the mimicry peptides that potentially imitate retinal autoantigens, indicating that recognition of these mimotopes is not a common event.

The recognition of certain epitopes with the subsequent development of an autoimmune disease has a genetic basis. The potential of peptide recognition depends on the individual T-cell receptor repertoire and the ability of the respective HLA class II molecules to bind and present the peptides. If a strong Th1 response is elicited in an individual with a certain genetic predisposition, there will be an enhanced risk for the development of autoimmune disease. This study has shown potential antigenic mimicry between mycobacterial proteins and retinal autoantigens that likely induces an aggressive immune response that targets the eye. This also may be the initiating cause for uveitis in patients with latent disease or active tuberculosis without intraocular infection.

References

16. Redmond TM, Wiggert B, Robey FA, et al. Isolation and characterization of monkey interphotoreceptor retinoid-binding pro-


### Figure 4

Amino acid sequences of bovine (bov) and human (hu) S-Ag, IRBP and CRALBP (only human sequence) and respective homologous sequences from BCG are given in the one-letter-code for amino acids. The amino acid positions of the respective sequence within the human or the BCG protein are shown for the first (left, N-terminal) and last (right, C-terminal) amino acid. Differences between human and bovine sequence are underlined, differences between human retinal antigens and \textit{M. tuberculosis} sequences are shaded in grey. BCG = Bacille-Calmette-Guérin; CoA = coenzyme A; CRALBP = cellular retinal-binding protein; IRBP = interphotoreceptor retinoid-binding protein; PPE = Pro-Pro-Glu repeat protein; S-Ag = retinal soluble antigen.

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SAG281

| bovSAg | 116 LLANNR | 287 LLANNR | 292 | hypothetical protein BCG_2404c |
| huSAg  | 116 LLANNR | 292 RERRG  | 296 |                                      |
| BCG    | 307 RERRG  | 311 RERRG  | 311 | putative transmembrane protein BCG_2189 |

IRBP

| bovIRBP | TTEIWTLP | 83 SLEFLTLP | 91 | Dctp deaminase: Doutpase |
| huIRBP  | 205 TTEIWTLP | 304 VTGPAEQA | 231 | VGTPAEVA | 238 | MabA protein |
| BCG     | 231 VGTPAEVA | 244 M. tuberculosis chorismate synthase |

| bovIRBP | SGDHLRL  | 693 SGDHLRL | 698 | M. tuberculosis chorismate synthase |
| huIRBP  | 239 SGDHLRL | 244 GGVVPDA | 244 | GGVVPDA | 614 | hypothetical protein BCG_2543c |
| BCG     | 2435 GGVVPDA | 586 GSLALTVPVL | 1778 | GSLALTLPVLT | 596 | PPE family protein |

2462.e1
R16

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cutinase cutl2

Figure 4. (Continued.)
Bilateral Acute Iris Transillumination

Ilknur Tugal-Tutkun, MD; Sumru Onal, MD, FEBOphth; Aylin Garip, MD; Muhittin Taskapili, MD; Haluk Kazokoglu, MD; Sibel Kadayifcil, MD; Philippe Kestelyn, MD

Objective: To describe a series of patients with bilateral acute iris transillumination, pigment dispersion, and sphincter paralysis.

Methods: We reviewed the medical records and clinical photographs of 26 patients seen at 5 centers in Turkey and Belgium between March 16, 2006, and July 6, 2010. Observation procedures included clinical examination, anterior segment color photography, gonioscopy, laser flare photometry, and pupillometry.

Results: All 26 patients (20 women and 6 men; mean [SD] age, 43.2 [10.5] years) had bilateral involvement. Twenty-three patients (88%) had acute-onset disease with severe photophobia and red eyes. Nineteen patients (73%) had a preceding flu-like illness and used systemic antibiotics, including moxifloxacin. Diagnostic laboratory workup was unremarkable. There was pigment discharge into the anterior chamber, and flare was elevated in the absence of inflammatory cells. Most patients had severe diffuse transillumination of the iris and mydriatic distorted pupils. Pupillometry revealed a compromised reaction to light. The most serious complication was an intractable early rise in intraocular pressure. Gonioscopy revealed heavy pigment deposition in the trabecular meshwork. Although symptoms were relieved promptly by application of topical corticosteroid, the median duration of pigment dispersion was 5.25 months.

Conclusions: Bilateral acute iris transillumination with pigment dispersion and persistent mydriasis is a new clinical entity that is not an ocular adverse effect of oral moxifloxacin treatment, as previously suggested. The etiopathogenesis of this entity remains to be elucidated.

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Known causes of acquired iris atrophy with or without transillumination of the iris include herpetic iridocyclitis, pigment dispersion syndrome (PDS), pseudoexfoliation syndrome, Fuchs uveitis syndrome, Vogt-Koyanagi-Harada disease, trauma, and acute angle-closure glaucoma. 

Pigment dispersion is also one of the diagnostic features of the recently described entity bilateral acute depigmentation of the iris (BADI). However, BADI is characterized by a nontransilluminating depigmentation of the iris stroma. More recently, an acquired bilateral diffuse iris transillumination with variable sphincter paralysis has been described as an ocular adverse effect of oral moxifloxacin treatment. We have seen patients with similar ocular findings with or without a history of moxifloxacin intake.

We herein describe the clinical features and course in 26 patients who developed bilateral acute iris transillumination (BAIT) associated with pigment showering and persistent mydriasis.

METHODS

Twenty-seven consecutive patients with BAIT were seen at 4 ophthalmology clinics in Turkey and 1 in Belgium between March 16, 2006, and July 6, 2010. One patient with concomitant Behçet disease was excluded from the study. We reviewed the medical and photographic records of the remaining 26 patients and used a standard data acquisition form at each center to gather retrospective data for this study. Informed consent of the patients was obtained for all procedures and treatments used. The study was approved by the ethics committee of Istanbul Faculty of Medicine, Istanbul University, Istanbul, Turkey, and was conducted according to the tenets of the Declaration of Helsinki.

At the initial visit, a detailed ocular and medical history was obtained from each patient, including onset of ocular complaints, previous systemic findings, and previous treatment(s). A complete ocular examination was conducted at each visit, including best-corrected visual acuity using a Snellen scale from 0.1 to 1.0, slitlamp biomicroscopy, tonometry, and indirect ophthalmoscopy. Gonioscopy was performed in all the patients. Corneal sensation was checked using a cotton yarn. Color photographs of the anterior segment were taken in each patient. We used the Vision Monitor WIN8000E (Metrovision, Perenchies, France) to perform pu-
pilometry and a laser flare photometer (KOWA FC-2000; Kowa Co Ltd, Tokyo, Japan) to measure anterior chamber flare only in patients seen at the Uveitis Service of the Department of Ophthalmology, Istanbul Faculty of Medicine, Istanbul University. The pupil diameters were measured under photopic and scotopic conditions. Pupilometry was performed in age- and sex-matched control subjects for comparison with the retrospective data obtained from the study patients.

Diagnostic laboratory workup included erythrocyte sedimentation rate, complete blood cell count, and biochemical. Serum IgG and IgM antibodies against herpes simplex virus types 1 and 2, varicella zoster virus, cytomegalovirus, and/or Epstein-Barr virus were measured in 10 patients. Patients were treated with topical corticosteroids when they had acute symptoms or ongoing high-grade pigment dispersion in the anterior chamber. Empirical oral acyclovir or valacyclovir therapy was given to the first 8 patients with pigment dispersion. In patients with an intraocular pressure (IOP) higher than 21 mm Hg, topical antiglaucomatous medications were used. If IOP exceeded 40 mm Hg, intravenous mannitol, 20%, infusions were given.

The main outcome measures were demographic features, initial ocular and systemic symptoms, ocular clinical findings, and pupillometry and flare photometry measurements. In patients who had resolution of pigment dispersion during follow-up, time to resolution was also determined.

We used a commercially available statistical analysis program (SPSS, version 16.0 for Windows; SPSS Inc, Chicago, Illinois) for analysis of the data. The Mann-Whitney, Wilcoxon, and Kruskal-Wallis tests were used to test for differences between groups. The Dunn test was used as a multiple comparison post hoc test. Categorical data were analyzed by the χ² test. P<.05 was considered significant.

RESULTS

Twenty patients were women and 6 were men. The mean (SD) patient age when first seen was 43.2 (10.5) years (median, 42 years; age range, 25-69 years). Seven patients were seen only once or had follow-up of less than 1 month. The remaining 19 patients had mean (SD) follow-up of 13.2 (12.2) months (median, 9.7 months; range, 1.5-43.0 months). All the patients had bilateral involvement. The demographic and clinical characteristics of the patients at the first visit are given in Table 1 and in eTable 1 and eTable 2 (http://www.archophthalmol.com).

INITIAL OCULAR SYMPTOMS AND OCULAR HISTORY

All the patients had an acute onset of ocular symptoms. Twenty-three patients (88%) had or reported an acute onset of severe photophobia and red eyes. Three patients reported only red eyes. Both eyes were involved simultaneously; however, symptom severity could be asymmetrical. Seven patients were seen within 1 week of onset of ocular symptoms. The remaining 19 patients were referred with a diagnosis of iridocyclitis with unusual features. The median disease duration in the latter group was 2 months (range, 2 weeks to 14 months). All these patients had been treated with topical corticosteroids. Five patients reported systemic corticosteroid use, and 7 patients had been given oral antiviral medications. Twelve patients (63%) had a history of IOP rise, bilaterally in 10. All these patients had been treated with topical antiglaucomatous medication(s) and 6 with concomitant oral acetazolamide. One patient had undergone trabeculectomy in 1 eye 7 months after onset of the disease. Another patient had required intravenous infusion of mannitol, 20%, to control the IOP rise. Ocular history was otherwise unremarkable.

SYSTEMIC SYMPTOMS AND MEDICAL HISTORY

Nineteen patients (73%) reported a flulike illness or upper respiratory tract infection preceding the onset of ocular symptoms. The mean (SD) interval between the on-
pharmacologic dilation of the pupil. Is mydriatic and unresponsive to light. The photograph was taken without transillumination is evident in the right (C) and left (D) eyes on retroillumination. Note the smeared iris pigment on the surface of the lens (A-D). The photographs were taken without pharmacologic dilation of the pupils.

Figure 1. A 44-year-old woman (eCase1). The mydriatic pupils are poorly responsive to light in the right (A) and left (B) eyes. Severe diffuse iris transillumination is evident in the right (C) and left (D) eyes on retroillumination. Note the smeared iris pigment on the surface of the lens (A-D). The photographs were taken without pharmacologic dilation of the pupils.

Figure 2. A 34-year-old man showing posterior synchiae with a broad base and a thick layer of iris pigment smeared on the surface of the lens. The pupil is mydriatic and unresponsive to light. The photograph was taken without pharmacologic dilation of the pupil.

set of systemic symptoms and the onset of ocular disease was 2.52 (1.46) weeks (median, 2 weeks; range, 1-6 weeks). All these patients had been treated with systemic antibiotics, including moxifloxacin in 9 (35%), ampicillin-sulbactam in 2 (8%), amoxicillin-clavulanate in 2 (8%), and trimethoprim-sulphamethoxazole, cefixime, and penicillin V in 1 (4%) each. Three patients could not recall the name of the antibiotic they had used. In 7 patients (27%), the medical history was unremarkable.

RESULTS OF THE LABORATORY WORKUP

Routine laboratory results were within the reference ranges. Viral serologic analysis in 10 patients showed that the IgM antibodies were negative and the IgG antibodies were not elevated. In patients tested for IgG antibodies against herpes simplex virus type 1 and Epstein-Barr virus, seropositivity was 83% and 75%, respectively. All patients tested for anti–varicella zoster virus and cytomegalovirus were found to have positive IgG antibodies. No patient was found to have IgG positivity against herpes simplex virus type 2.

INITIAL OCULAR FINDINGS

Median visual acuity was 1.0 OU (range, 0.3-1.0 OD and 0.4-1.0 OS). Reduced visual acuity was due to amblyopia in 2 eyes. Another eye with visual acuity of 0.3 had a preretinal hemorrhage at the posterior pole that had occurred after trabeculectomy.

Conjunctival hyperemia was documented in the 7 patients (12 eyes) who were first seen within 1 week of the onset of ocular symptoms. Fine pigment precipitates on the corneal endothelium were recorded in 12 patients (21 eyes): in the form of Krukenberg spindle in 2 (4 eyes), diffusely scattered in 3 (6 eyes), and distributed in the lower half of the cornea in 7 (11 eyes). Inflammatory keratic precipitates were not seen.

None of the patients had inflammatory cells in the anterior chamber at the first visit or during follow-up. There was variable pigment dispersion in the anterior chamber in both eyes of 22 patients. Three patients who were first seen 4 months to 1 year after the onset of ocular symptoms had no circulating pigment in the anterior chamber but had diffuse transillumination of the iris and persistent mydriasis due to sphincter paralysis in both eyes. Another patient who was first seen on day 5 of the onset of ocular disease had pigment in the left eye only. However, pigment dispersion occurred in the other eye during follow-up but did not exceed 0.5+. The iris of this patient exhibited diffuse transillumination in the left eye and only moth-eaten transillumination in the right eye.

Twenty-one patients (42 eyes) had severe diffuse transillumination of the iris and mydriatic pupils poorly responsive or unresponsive to light (Figure 1 and Appendix [eCase 1]). In 4 patients, there was asymmetrical involvement, with diffuse transillumination in 1 eye with a mydriatic pupil and less severe, moth-eaten transillumination without apparent mydriasis in the other eye. One patient had symmetrical bilateral moth-eaten transillumination with normal pupils. An irregular distorted pupil was also noted in 20 patients (32 eyes). Spiraling of the pupil was not apparent. Posterior synchiae were documented in 3 patients (4 eyes). The morphologic features of posterior synchiae were different from those of uveitic synchiae in that a thick layer of iris pigment seemed to be smeared on the surface of the lens and remained adherent with a broad base (Figure 2). In 10 patients (19 eyes), smeared iris pigment (Figure 1) or pigment dusting (Figure 3 and Appendix [eCase 2]) was seen on the surface of the lens. Scattered pigment particles were seen on the surface of the iris as well. One patient had unilateral mild posterior subcapsular lens opacity. The corneal sensation was intact, and the vitreous was clear in all the patients. The fundus was normal in all except 1 patient with preretinal hemorrhage at the posterior pole after trabeculectomy in 1 eye.

Mean IOP values are given in Table 1. An IOP higher than 21 mm Hg was measured in 8 patients (11 eyes). Nine patients were still taking topical antiglaucomatous medi-
Laser flare photometry was performed at the initial visit in 18 patients (36 eyes). Eyes with 3+ to 4+ pigment had significantly elevated mean laser flare photometry readings compared with those with none to 0.5+ pigment ($P<.01$) and those with 1+ to 2+ pigment ($P<.05$).

**PUPILLOMETRY FINDINGS**

Pupillometry was performed in 15 patients and 20 controls (Table 2). Sex and mean age did not differ between the 2 groups. Under scotopic conditions, no significant difference was noted in pupil diameter between patients and controls ($P=.62$ for right eyes and $P=.85$ for left eyes); however, under photopic conditions, patients’ mean pupil diameter was significantly larger ($P<.001$ for right and left eyes). Patients had significantly reduced amounts of miosis. Pupillary reaction to near stimuli was also compromised. Accommodation was not measured in any patient; however, none of the patients required additional plus lenses for near vision.

**TREATMENT AND FOLLOW-UP**

Treatment and follow-up are summarized in Table 2. Seven patients who were first seen within 1 week of the onset of ocular symptoms were treated with hourly topical corticosteroid application, which resulted in prompt relief of their symptoms. Seven patients who were referred 1 to 14 months after disease onset and had less than 2+ pigment and low flare (<15 photon counts per millisecond [ph/ms]) were not given topical corticosteroids. Topical corticosteroid therapy prescribed elsewhere was maintained in 12 patients who were referred with a disease duration of 2 to 16 weeks and ongoing pigment dispersion. Four of them did not return for follow-up. Two of them with flare measurements exceeding 150 ph/ms were also given oral prednisolone (0.5 mg/kg/d), which was tapered and discontinued within 6 weeks. The mean (SD) duration of topical corticosteroid treatment was 3.51 (2.00) months (median, 3 months; range, 1-8 months). In 11 patients, topical corticosteroid therapy was discontinued with slow tapering, and no relapse was seen. Only 1 patient had 2 relapses during tapering, which were controlled with an increased dose and successful discontinuation of treatment at 5 months. Mean (SD) follow-up after withdrawal of treatment in these 12 patients was 13.6 (12.4) months (median, 9.12 months; range, 1-39 months).

Mean (SD) time from onset of ocular symptoms to complete resolution of pigment dispersion in the anterior chamber was 7.30 (5.68) months (median, 5.25 months; range, 1-18 months) in 14 patients (28 eyes). Resolution of pigment dispersion in the anterior chamber occurred simultaneously in both eyes in all except 2 patients. The mean (SD) flare was significantly reduced at the last visit (from 39.23 [132.66] to 4.52 [1.13] in left eyes, $P=.002$; and from 81.92 [132.66] to 4.52 [1.13] in left eyes, $P=.002$).

Two of the 7 patients who were first seen by us developed high IOP during follow-up. The IOP was raised within 1 week in both eyes of 1 patient and at 2 months in 1 eye of the other patient. None of the referred patients who did not have a history of IOP rise developed this complication during follow-up. Thus, 14 patients (54%) had IOP rise during the disease course, and 10 received antiglaucomatous medication(s) during follow-up. The mean (SD) duration of topical antiglaucoma therapy was 9.25 (8.16) months (median, 8.5 months; range, 1 month to 3 years). Seven patients required concomitant oral acetazolamide therapy, and 5 patients required intravenous infusion(s) of mannitol, 20%. Two patients with high IOP despite maximum-tolerated medical therapy required bilateral trabeculectomy combined with mitomycin application 3 to 9 weeks after disease onset. Both of these patients had 4+ pigment in the anterior chamber before surgery, and a dense pigment accumulation occurred inside the bleb (Figure 4). The mean (SD) final IOP was 14.15 (2.87) mm Hg (range, 10-20 mm Hg) in right eyes and 14.20 (3.07) mm Hg (range, 8-21 mm Hg) in left eyes. Six patients were still taking topical antiglaucomatous medication(s) at the final visit. None of the patients developed glaucomatous optic disc changes or visual field defects.

Bilateral cataract developed in 7 patients. After resolution of pigment dispersion, 4 eyes underwent uneventful phacoemulsification and intraocular lens implantation. Visual acuity was well preserved. Median final visual acuity was 1.0 OU (range, 0.4-1.0 OU). Visual acuity decreased to 0.4 in 1 eye due to cataract formation.

We described 26 patients with an unusual bilateral acute iris transillumination associated with symptomatic pigment showering after a flulike illness or an upper respiratory tract infection in most cases. Middle-aged women are more commonly affected. Despite the absence of inflammatory keratic precipitates or cells in the anterior chamber, pigment storm is associated with a flare rise,
and patients may be misdiagnosed as having acute bilateral iridocyclitis. Clinical findings that challenge conventional diagnosis include bilateral severe transillumination of the iris, pigment dispersion in the anterior chamber, and a mydriatic pupil that is unresponsive or poorly responsive to light due to variable sphincter paralysis. Symptoms are rapidly responsive to topical corticosteroid therapy; however, pigment dispersion may last months and even up to more than 1 year. An early rise in IOP is a common complication and can be refractory to treatment. The etiology remains unknown.

There are recent reports on the occurrence of acute pigment dispersion and iris transillumination after oral moxifloxacin treatment. Bilateral abundant pigment dispersion has been reported as a complication of moxifloxacin used for the treatment of pneumonia. More recently, Wefers Bettink-Remeijer et al described 5 patients who had an acute onset of photophobia and pain followed by bilateral diffuse iris transillumination with variable sphincter paralysis and concluded that this was an ocular adverse effect of oral moxifloxacin use. Most patients in the present cohort had a preceding flulike illness or respiratory tract infection before the onset of ocular symptoms; although only approximately 35% reported moxifloxacin intake, 40% were exposed to other antibiotics. Therefore, we believe that the clinical picture described herein may represent a distinct condition probably triggered by a viral infection. Theoretically, such an ocular adverse effect would also be expected to occur with the topical application of moxifloxacin, which has been shown to have efficient ocular penetration. To our knowledge, there is no such reported ocular adverse effect of topical moxifloxacin treatment.

The differential diagnosis of BAIT is summarized in Table 3. Pigment dispersion syndrome is the most difficult to differentiate from the entity described herein.
vere photophobia and markedly red eyes, as seen in the present series, are not characteristic of PDS. Patients described herein developed severe diffuse iris transillumination at a single episode and did not have a midperipheral radial spokelike pattern, which typically develops over a chronic progressive course in PDS. Ocular hypertension or pigmentary glaucoma develops over years in PDS, whereas the IOP rise occurred within weeks to months in the present series. Pupillary reactions to light and near stimuli are not affected in PDS. Compromised pupil-IOP rise was thought to be related to variable amounts of sphincter paralysis in the present patients. Posterior bowing of the iris is a characteristic feature of PDS. Willermaïn et al described a patient with bilateral asymptomatic acute iris transillumination, pigment dispersion, and severe IOP rise after moxifloxacin use. Gonioscopy revealed heavy pigment deposition in the iridocorneal angle, and anterior segment optical coherence tomography showed iris concavity in their patient. Because iris concavity is a typical finding in PDS, their patient probably had PDS and an acute elevation in IOP due to the use of subconjunctival corticosteroids. Although we did not perform anterior segment optical coherence tomography or ultrasound biomicroscopy, we do not have any clinical observation of iris concavity or posterior bowing in any patient. This finding has not been reported by other researchers.

Table 3. Differential Diagnosis of BAIT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Herpetic Iridocyclitis</th>
<th>FUS</th>
<th>PXF</th>
<th>BADI</th>
<th>PDS</th>
<th>BAIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>No predilection</td>
<td>No</td>
<td>Commonly female</td>
<td>Female predominance (2.7:1)</td>
<td>Mostly male</td>
<td>Female predominance (3.3:1)</td>
</tr>
<tr>
<td>Symptoms at onset</td>
<td>Symptomatic, with red eyes, ocular pain, and photophobia</td>
<td>Asymptomatic</td>
<td>Severe photophobia and red eyes</td>
<td>Usually asymptomatic; occasionally headache, blurred vision, and halos around light during pigment showering</td>
<td>Bilateral</td>
<td>Severe photophobia and red eyes</td>
</tr>
<tr>
<td>Laterality</td>
<td>Typically unilateral</td>
<td>Typicaly unilateral</td>
<td>Bilateral asymmetrical pigment</td>
<td>Bilateral symmetrical pigment</td>
<td>Bilateral, mostly symmetrical pigment</td>
<td></td>
</tr>
<tr>
<td>Keratic precipitates</td>
<td>Inflammatory</td>
<td>Inflammatory, diffuse stellate, and medium sized</td>
<td>Pigment</td>
<td>Pigment</td>
<td>Pigment</td>
<td></td>
</tr>
<tr>
<td>Krukenberg spindle</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Sometimes present</td>
<td>Present</td>
<td>Sometimes present</td>
</tr>
<tr>
<td>Pigment particles in the AC</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>Sometimes present</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Inflammatory cells in the AC</td>
<td>Present during exacerbations</td>
<td>Chronic, low grade</td>
<td>Present</td>
<td>Present</td>
<td>Present</td>
<td></td>
</tr>
<tr>
<td>Iris transillumination</td>
<td>Patchy or sectoral</td>
<td>Rarely peripupillary</td>
<td>Peripupillary</td>
<td>Midperipheral spokelike</td>
<td>Diffuse</td>
<td></td>
</tr>
<tr>
<td>Change in the iris configuration</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Iris stromal changes</td>
<td>Patchy or sectoral stromal atrophy</td>
<td>Diffuse stromal atrophy with blunting of iris crypts with or without heterochromia</td>
<td>None</td>
<td>Bilateral symmetrical geographic or diffuse depigmentation and granularity with distinct margins</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Pupillary changes</td>
<td>Usually present, irregular distorted pupil with spiraling</td>
<td>Rarely anisocoria, with larger pupil on the affected side</td>
<td>None</td>
<td>None</td>
<td>Anisocoria in asymmetrical cases, with preserved light and near response</td>
<td>Present; usually symmetrical, dilated atonic pupil with compromised reaction to light and near stimuli</td>
</tr>
<tr>
<td>IOP rise</td>
<td>Acute and transient during exacerbations, related to trabeculitis</td>
<td>Frequent complication developing over years</td>
<td>Frequent complication developing over years</td>
<td>Uncommon, transient</td>
<td>Frequent complication developing over years</td>
<td>Early complication, resistant</td>
</tr>
<tr>
<td>Gonioscopy</td>
<td>Open angle</td>
<td>Open angle, new vessels, occasionally goniocystealne</td>
<td>Pseudoexfoliation material</td>
<td>Pigment deposition</td>
<td>Pigment deposition</td>
<td>Pigment deposition</td>
</tr>
</tbody>
</table>

Abbreviations: AC, anterior chamber; BADI, bilateral acute depigmentation of the iris; BAIT, bilateral acute iris transillumination; FUS, Fuchs uveitis syndrome; IOP, intraocular pressure; PDS, pigment dispersion syndrome; PXF, pseudoexfoliation syndrome.
scribed herein include an acute onset of severe photophobia and red eyes after a flulike syndrome, pigment discharge into the anterior chamber, and exclusive involvement of the iris. Oral antibiotic drug use was reported in 38.5% of patients with BADI, including moxifloxacin use in 30.7% and amoxicillin-clavulanate use in 7.7%. Even if BAIT may be a more severe form of BADI and both conditions have a common etiology, the pigment discharge seems to be only from the iris pigment epithelium in the former and from the iris stroma in the latter. The most important differentiating feature between the 2 entities is that the pupil is not affected in BADI and a symmetrical geographic or diffuse depigmentation of the iris stroma causes a change in iris stromal texture and color without any transillumination defect, whereas patients described herein typically had atomic dilated pupils and diffuse iris transillumination without any visible change to the iris stroma. Furthermore, BADI has a more benign course with a shorter duration of pigment discharge, a lower incidence of IOP rise that is only transient, and reversibility of iris changes reported at least in some patients. Heavy pigment deposition in the trabecular meshwork was a consistent finding in the present series and explained the early severe IOP rise that could occur as early as 1 week and the need for trabeculectomy as early as 3 weeks after onset. On the other hand, a corticosteroid-induced IOP rise cannot be excluded in patients who developed this complication later on.

The present patients clearly differed from those with pseudoexfoliation syndrome, Fuchs uveitis syndrome, and herpet ic anterior uveitis. Sectoral iris atrophy with chronic refractory glaucoma may rarely be seen in immunocompetent patients with cytomegalovirus anterior uveitis. Aqueous humor analysis for local antibody production or demonstration of viral DNA is needed for a definite diagnosis of viral etiology. Diffuse iris atrophy has been reported in 50% and elevated IOP in 100% of eyes diagnosed as having cytomegalovirus anterior uveitis. However, in those eyes, diffuse iris transillumination and sphincter paralysis have not been described. Anterior chamber tap was reported to be negative for herpes viruses in 5 of the 6 cases previously reported in the literature with findings similar to the present series, and the herpes virus genome was found in only 1 patient, who had a history of uveitis. The causative agent of the preceding systemic illness is not known in any of the present patients. With the emergence of new respiratory viruses, new disease entities may develop, and conjunctiva may not be the only ocular tissue affected by these infections. Although we presume that the entity described herein might be related to a systemic viral infection, the pathogenesis of iris involvement remains elusive. Because we could not perform iris angiography, we could not exclude iris ischemia as a possible cause of irreversible damage to the iris pigment layer and the pupillary sphincter. Ischemic iris changes have been reported to occur in 52.5% of cases after an episode of angle-closure glaucoma. Although an iris ischemia may be caused by an episode of angle-closure glaucoma precipitated, for example, by the use of vasoconstrictors during a flulike illness, gonioscopy did not reveal occludable angles in any eye in this series. Moreover, an elevated IOP was not reported at the onset of the disease in any of the referral cases, and the IOP was low to normal in patients who were seen first by us.

This study is limited by its retrospective nature, lack of intraocular fluid analysis, unavailability of iris angiography, and variable treatment and follow-up. We regret that iris specimens obtained by iridectomy in patients who underwent trabeculectomy were not sent to the laboratory for histologic analysis, culture, and other studies that could have shed light on the etiopathogenesis of this condition.

In conclusion, we described an unusual condition with symptoms masquerading as acute iridocyclitis and ocular findings bearing similarities to PDS. An acute onset of severe photophobia and red eyes after a flulike illness or upper respiratory tract infection is the typical presentation. Bilateral severe iris transillumination, an abundant pigment discharge into the anterior chamber, and atomic and distorted pupils are the constellation of findings distinct for this condition. This may be a new entity or may represent an expanded spectrum of BADI. Even if the latter is true, prompt recognition of this condition is essential because of the high risk of early severe IOP rise.

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REFERENCES


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**From the Archives of the ARCHIVES**

Maher (348, On the treatment and prognosis of primary glaucoma). The author aims at a cystoid scar. He draws out a large loop of iris and allows the wound to heal before he excises the iris. . . .

In many cases an iris enucleis, even if it does not lead to septic infection, provides a bridge along which endothelial cells proliferate till they reach the iridic angle which they block and cause a glaucoma which is beyond treatment. Lagrange’s and Herbert’s methods are far preferable in every way. Most surgeons carefully avoid if possible any iris enucleis, which is recognized to be a potent cause of failure. The author only recommends his operation for chronic cases.

5. Discussion

5.1. Uveitis in a patient treated with Bacille-Calmette-Guérin: Possible Antigenic Mimicry of Mycobacterial and retinal Antigens

A good example to this immune stimulation called antigen mimicry is the case of bilateral uveitis after the intravesical Bacille-Calmette-Guérin (BCG) therapy due to bladder carcinoma. BCG is a non-pathogenic strain of Mycobacterium bovis, which was also used for vaccine preparations 55.

The Bacille-Calmette-Guérin (BCG) has been used for routine vaccination against tuberculosis since 1921 56. In a prospective study Turnbull et al. have shown in 918 subjects (age range 1 day- 54 years) only in 45 vaccines an adverse reaction was reported 56. Those adverse reactions included abscess formation (2.5%), lymphadenitis (1%), severe local reaction (1.5%), and other reactions (pronounced scars, marked redness and fever) (0.7%) 56. Of the 23 abscesses, only 7 needed a treatment (2 with surgical excision, 3 with antibiotics, 2 with symptomatic treatment) 56. All others resolved spontaneously. Of 10 vaccines with lymphadenitis, only 1 was treated with antituberculosis treatment, all others resolved spontaneously. 3 cases with severe local reactions including pain, redness, or swelling received antibiotic treatment 56.

Another rare adverse effect of BCG vaccination is ocular inflammation. In 1991 Yen and Liu 57 reported the first case of bilateral optic neuritis following BCG vaccination. Following this case report, Hegde et al 58 reported in 2004 another case report of a 14 year-old girl having a bilateral panuveitis and optic neuritis 5 weeks after the BCG vaccination. The last report to date was in 2008 from Spratt et al. 59 about a 13 year old girl, who developed bilateral chronic anterior uveitis following BCG vaccination. The authors speculated that the BCG-induced ocular inflammation was caused by the mechanism of molecular mimicry 59.

BCG is also one of the most effective treatment and prophylaxis for non-invasive bladder carcinoma. In 2002 the worldwide estimated new cases of bladder carcinoma were 357,000 and 145,000 resulted with death due to the bladder carcinoma. This makes this disease the 9th most common malignancy and the 13th worldwide most common cause of cancer death 60.

For the management of the superficial bladder carcinoma, there are several immunological agents and
chemotherapeutics used intravesically. Immunotherapy with BCG was first reported in 1976 and since then it was used worldwide. Shelley et al. have reported in 2001 a meta-analysis of the published data on the randomized controlled trial with BCG. He showed that in total 585 patients included in 6 randomized controlled trials with BCG, tumor recurrence was significantly reduced (at 12 months 67%) in patients receiving TUR (transurethral resection) plus BCG in comparison to the patients, who received TUR only. In the intravesical treatment with BCG, live mycobacteria attach to and invade the tumor cells using fibronectin and integrins and induce a T-helper-type 1 immune response. This local response also induces systemic reactions including increased specific T-cell proliferation and antibody production.

Intravesical BCG is well tolerated in more than 95% of the cases. Most of the symptoms including increased urinary frequency and burning, mild malaise, and low-grade fever are due to the immune stimulation, which is needed to effectively eradicate the cancer cells. Lamm had published a review of 23 controlled chemotherapy studies involving 4013 patients in 2000. The most common side effect seen in those patients was fever in 2.9% of the cases. The other adverse effects were granulomatous prostatitis (0.9%), pneumonitis and/or hepatitis (0.7%), arthralgia (0.5%), hematuria (1.0%), rash (0.3%), urethral obstruction (0.3%), epididymitis (0.4%), contracted bladder (0.2%), renal abscess (0.1%), sepsis (0.4%), and cytopenia (0.1%). The patients with the evidence of BCG infection (epididymitis, hepatitis, or prostatitis) are treated with isonazid and rifampin 600 mg daily. The most dangerous adverse effect is the systemic septic reaction or a hypersensitivity reaction due to BCG.

In 2000, Wittes had published a hypothesis for the immunological mechanism of BCG. According to his hypothesis first, BCG attaches to the bladder mucosa with fibronectin receptors in lamina propria. Then the macrophages phagocytose the bacteria and BCG is presented to regional lymph nodes. Then the activation of regional T lymphocytes occur and the secretion of various cytokines take place. It is followed by up-regulated expression of HLA-DR (i.e., MHC class II) antigen on the tumor cells and on the adjacent urethelium. According this hypothesis cytotoxic T cells, which recognize the co-expression of HLA and BCG antigens, kill the tumor cells and the adjacent urethelium. Therefore Wittes speculates that this mechanism of BCG is probably a specific anti-BCG cell-mediated immunity. This can also explain the side effects like fever, sepsis, hepatitis, pneumonitis, arthritis, prostatitis, and uveitis after intravesical BCG therapy. To date, only 11 cases of ocular inflammations after intravesical BCG
therapy have been published 69-76.

The first case report was in 1988, about a patient who had an endophthalmitis 5 months following the last intravesical BCG application 75. The next publication was in 1994 from Price et al. about a patient with acute iritis and arthritis 3 weeks after BCG therapy for the bladder carcinoma 69. The cases with ocular inflammation published to date due to intravesical BCG application include 2 cases of endophthalmitis 75, 76, 1 case of chorioretinitis 73, 7 cases of uveitis (3 cases of anterior uveitis 69, 72, 46, 1 case of anterior and posterior uveitis 71, 2 panuveitis 74, 77, 1 bilateral uveitis 70), 1 case of autoimmune retinopathy 73.

In our study 46 on the in vitro lymphocyte responses in a patient with a bilateral granulomatous iritis after intravesical BCG treatment for her bladder carcinoma, we showed elevated cytokine responses to all tested retinal antigens and peptides from S-Ag and IRBP as well as to chicken ovalbumin and PPD that more frequently showing T-helper (Th1)-type reactivity with secretion of IFN-Υ, IL-6, IL-8 and tumor necrosis factor-α (TNF-α) 46. We detected no IL-17 response 46. The blood sample of this patient was collected 6 weeks after the onset of her uveitis. There are many researches trying to find the immunological mechanism of the uveitis in an animal model. Kaufmann et al.78 have published lately a paper about the dynamics of intraocular cytokines during relapsing and monophasic autoimmune uveitis in an experimental rat model. According to this study during the monophasic Experimental Autoimmune Uveitis (EAU) T-cells co-expressing IFN-Υ and IL-17 increased, and those populations were decreased during the primary course of relapsing disease. It could be speculated that in our research with the periphery lymphocytes taken from a patient with iritis after the intravesical BCG application, due to the late time point of taking the blood sample (6 weeks after the first visit) the initial response of IL-17 may be missed.

As a conclusion, mycobacterium tuberculosis can cause uveitis by mycobacterium either invading the eye 79 or due to immune response called antigenic mimicry, when T-cells activated by M. tuberculosis mistake retinal proteins for antigens from BCG. Systemic infection with M. tuberculosis may also cause this inflammation of the eye by a cross-reactive immune response, as observed here after BCG therapy, when T cells recognize mycobacterial antigens as well as ocular proteins. This phenomenon, called antigenic mimicry, was a presumed cause of uveitis 59, 80, 46.
5.2. Bilateral Acute Iris Transillumination

Another rare cause of uveitis is a newly described disease called: Bilateral acute iris transillumination (BAIT). Up to date there is only one article of 26 patients reported with the similar clinical findings. All patients developed bilateral acute iris transillumination associated with pigment dispersion and persistent mydriasis. Twenty patients were women and 6 were men. The mean patient age at the first presentation was 43.2 years. All the patients had bilateral involvement and an acute onset of ocular symptoms. Twenty-three patients (88%) reported having acute onset of severe photophobia and all patients reported bilateral red eyes. Ten patients (38%) reported also having ocular pain and a minority of the patients had blurred vision (27%).

Interestingly, prior to onset of the ocular symptoms, nineteen patients (73%) reported having a flulike illness or upper respiratory tract infection. All these patients had been also treated with systemic antibiotics, including moxifloxacin in 9 (35%), ampicillin-sulbactam in 2 (8%), amoxicillin-clavulanate in 2 (8%), and trimethoprim-sulphamethoxazole, cefixime, and penicillin V in one (4%) each. Three patients could not recall the name of the antibiotic they had used.

Recently, pigment dispersion and iris transillumination were also described after oral moxifloxacin treatment. The first article was published in 2004 as a case report of a 77 year-old patient having an acute anterior bilateral uveitis and pigmentary dispersion after treatment of a pneumonia with moxifloxacin. In 2009, five years later, Wefers Bettink-Remeijer et al. described 5 patients having an acute onset of photophobia and pain followed by bilateral diffuse iris transillumination with sphincter paralysis. Both authors speculated this condition as an ocular adverse effect of moxifloxacin. In the case series of BAIT only 35% of the patients reported moxifloxacin intake prior to the ocular symptoms. Interestingly a majority of the patients (73%) in this case series reported having flulike symptoms, and the authors believed that this condition was triggered by a viral infection. In spite of having so many speculations, the cause of BAIT remains still unknown.

There are also other uveitis entities, which are presumed be caused by a systemic viral infection. Acute posterior multifocal placoid pigment epitheliopathy (APMPPPE) is characterized by plaque-like lesions at the retinal pigment epithelium and causes temporary visual loss. In 1968 Gass described the clinical and angiographic findings of APMPP in 3 young women. Recently there have been reports associating...
it with systemic infection. In 2001 O’Halloran et al.\textsuperscript{84} have described 9 cases diagnosed with APMPP and 5 patients had a prodromal illness. Many other authors have reported it occurring after a viral prodrome\textsuperscript{85–87}. In spite of many speculations like a viral cause or APMPP occurring after varicella vaccination\textsuperscript{88}, the real cause of this disease remains unknown.

The initial clinical findings of BAIT were conjunctival hyperemia (12 eyes, 23%), pigment keratic precipitates (21 eyes, 40%), circulating pigment in the anterior chamber (45 eyes, 87%), transillumination of the iris (52 eyes, 100%), mydriatic pupil with sphincter paralysis (46 eyes, 88%), irregular distorted pupil (32 eyes, 62%), and posterior synechia (4 eyes, 8%)(Fig 6). None of those patients had inflammatory cells in the anterior chamber at the first presentation or during the follow-ups. Twenty-one patients (42 eyes) had severe diffuse transillumination of the iris and mydriatic pupil with poor or no response to light due to sphincter paralysis. Also an irregular distorted pupil was seen in 20 patients (32 eyes). Posterior synechiae was noted only in 3 patients (4 eyes). In ten patients (19 eyes) pigment dusting on lens was seen.

![Image](image.png)

**Figure 6.** Case 1: 44-year-old female patient.

The mydriatic pupils are poorly responsive to light in the right and left eyes. Severe diffuse iris transillumination is evident in the right and left eyes on retroillumination. Note the smeared iris pigment on the surface of the lens. The photographs were taken without pharmacologic dilation of the pupils. (taken from Tugal-Tutkun I, Onal S, Garip A et al. Bilateral Acute Iris
Early rise intraocular pressure (IOP) is a common complication and can be challenging during the acute pigment dispersion. Initial IOP higher than 21 mmHg was measured in 8 patients (11 eyes). Fourteen patients (54%) had IOP rise during the disease course and 10 received anti-glaucomatous medications during the follow-up. Twelve patients needed systemic anti-glaucomatous treatment (7 acetazolamide, 5 intravenous infusions of Mannitol 20%). In spite of maximum systemic and topical treatment 2 patients needed bilateral trabeculectomy combined with mitomycin applications due to the high IOP. Both of those patients had 4+ pigment circulating in anterior chamber prior to surgery and after the surgery had dense pigment accumulation inside the bleb.

Acute symptoms were relieved rapidly with topical corticosteroid therapy. Seven patients who were seen within one week of acute onset of the symptoms were treated with hourly topical corticosteroids. The mean duration of topical corticosteroid treatment was 3.5 months (range 1-8 months). In 11 patients, topical corticosteroid was discontinued with slow tapering and no relapse was seen. Mean time from onset of the ocular symptoms to the complete resolution of the pigment dispersion in the anterior chamber was 7.3 months (range 1-18 months) in 14 patients.

As known, there are many causes of iris transillumination like pigment dispersion syndrome (PDS) 89, herpetic iridocyclitis 90, 91, pseudoexfoliation syndrome 92, Fuchs uveitis syndrome (FUS) 93, 94 and recently described entity named bilateral acute depigmentation of the iris (BADI) 95, 96.

Pigment dispersion syndrome (PDS) is the most difficult disease to differentiate from BAIT. PDS is the pigmentation of the intraocular structures which is characterized with mid-peripheral iris transillumination with spoke-like pattern, iris concavity, pigment deposits on the corneal endothelium-Krukenberg spindle-, trabecular meshwork, surface of the lens and zonula 89, 97. PDS is mostly seen in young men with myopia 89. It is assumed that the friction between the zonula fibers and the peripheral iris causes the destruction of the pigment epithelium and this leads to pigment discharge and the transillumination of the iris 89, 98. In the case series of BAIT the iris transillumination was diffuse and all patients had acute symptoms like photophobia and redness. The patients in PDS are mostly asymptomatic however at the time of intraocular pressure rise headaches and blurry vision due to the
corneal oedema are also described. In asymmetric cases of PDS, anisocoria can also be seen. The pathological mechanism and prevalence of pupil irregularity in PDS are still unknown.

Another differential diagnosis of BAIT is the herpetic iridocyclitis. Herpes simplex virus (HSV) and varicella zoster virus (VZV) are both members of the Herpesviridae family. As mentioned before, typical clinical findings are mutton fat keratic precipitates often in a triangular shape, which is localized at the inferior part of the cornea, unilateral iritis or iridocyclitis, sectoral iris atrophy with well-defined margins and distorted pupil.

Fuchs’ uveitis syndrome is another syndrome, which causes the depigmentation of the iris. Typical clinical findings are unilaterality, generalized, fine, stellate keratic precipitates, iris atrophy, low-grade anterior uveitis and vitritis. Other features are iris nodules (more then 30% of the cases) and the smoothening of the stroma at the early stage of the disease. 5-10% of the cases are bilateral. It is mostly asymptomatic and the most common complications are subcapsular cataract and glaucoma. A chronic rubella infection or CMV infection is assumed to be the cause of Fuchs’ uveitis syndrome. The case series of BAIT is clinically distinct from Fuchs’ uveitis syndrome with diffuse transillumination of the iris, pigment in the anterior chamber without inflammatory cells, bilaterality and no vitreous involvement.

Bilateral acute depigmentation of the iris (BADI) is also a recently described new clinical entity and characterized by acute pigment dispersion in the anterior chamber, depigmentation of the iris stroma and pigment deposition in the anterior chamber angle. The patients have bilateral involvement and present with photophobia, red eyes and ocular pain at the acute onset of the disease. In contrast to BAIT, those patients with BADI do not have pigment deposition on the lens or transillumination of the iris as the pigment dispersion is on the anterior stromal layer of the iris. In the case series with BADI none of the patients except for one patient had pupil irregularity. In BAIT, all patients had diffuse transillumination of the iris and pupil irregularity.

In conclusion, in those two papers we describe two rare entities of anterior uveitis. In the first paper called ‘Uveitis in a patient treated with Bacille-Calmette-Guérin: Possible Antigenic Mimicry of
Mycobacterial and retinal Antigens’, we describe a patient with an anterior uveitis after intravesical BCG treatment for her bladder carcinoma and tried to find out the cause of the uveitis. This study has shown that potential antigenic mimicry between mycobacterial proteins and retinal autoantigens may induce an aggressive immune response that targets the eye.

In the second paper called ‘Bilateral Acute Iris Transillumination’, we describe a rare, new clinical entity, which looks like an acute iridocyclitis, but has distinct features not fitting any form of known causes of uveitis. There are two possible explanations for the destruction of the iris pigment epithelium resulting in transillumination. First theory involves the direct cytopathic effect of a virus on the infected iris tissue. The second theory involves a potential antigenic mimicry of (unknown) viral proteins/peptides of an extraocular (systemic) virus infection and proteins of the iris pigment epithelium, recognized by cross-reactive CD8+ cytotoxic T cells, which destroy the pigmented cells of the iris. It is important to differentiate BAIT from the other causes of uveitis because of the high risk of early severe IOP rise, which needs short-term follow-up of the patients in order to avoid visual loss.
6. Summary

English:

Anterior uveitis is an inflammation of the iris or and the anterior ciliary body of the eye. Besides known infectious and non-infectious causes, recently there have been a few publications on the new entities or possible causes of AU. An infectious agent (bacteria or virus) can either invade the eye and cause inflammation, however a systemic infection can also cause an inflammation of the eye by a cross-reactive immune response, as observed after intravesical BCG treatment of bladder carcinoma. This mechanism called antigen mimicry could be explained by T-cells activated by M. Tuberculosis (either by a systemic infection or by an intravesical application of BCG) mistake retinal proteins for antigens from BCG and cause inflammation.

Another recently described entity named bilateral acute iris transillumination (BAIT) is a disease of unknown cause. There is only one article of 26 patients published with similar clinical findings. The majority of the patients (73%) with BAIT had a flu-like illness or upper respiratory tract infection, prior to the onset of the ocular symptoms. Therefore, the authors believe that this clinical condition can be caused by a viral infection. There are also two reports, which were published in 2004 and 2009, with similar clinical findings, but the authors speculated this disease as an adverse effect of moxifloxacin. However the real cause of this disease still remains mysterious.

In spite of the rarity of these entities, as clinicians, we should be aware of these new clinical entities in order to avoid early visual loss.
7. Zusammenfassung


Trotz der Seltenheit dieser klinischen Manifestationen ist die Kenntnis dieser für Kliniker von besonderer Bedeutung, um auch in diesen Fällen eine Sehschärfenminderung zu vermeiden.
8. References


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