An atypical case of HLA-B27-associated uveitis with hypopyon and posterior segment involvement

BY THOMAS XIE, OD & ETTY BITTON, OD, MSc, FAAO

Introduction

Uveitis, the most common form of inflammatory eye disease, is an important public health concern. It accounts for a significant percentage (estimated at 10–15%) of prevalent cases of legal blindness in the United States. The most frequent subtype is anterior uveitis, representing up to 92% of total cases in community-based ophthalmic practices. HLA (human leukocyte antigen)-B27 positivity, a human major histocompatibility complex (MHC), is the most common identifiable cause of anterior uveitis and accounts for about 50% of the cases in different populations. HLA-B27-associated uveitis is characterized by recurrent alternating acute unilateral attacks of intraocular inflammation of the anterior segment of the eye, and typically affects young male adults. In uveitis related to HLA-B27, the presence of a hypopyon – a layer of white blood cells in the anterior chamber – and posterior segment involvement of the eye are uncommon.

A hypopyon suggests severe anterior segment intraocular inflammation and is a rare occurrence in patients with uveitis, occurring in less than 1% of all uveitis patients. Posterior segment involvement, namely intermediate and/or posterior uveitis, is also infrequent and has been reported in up to 25% of HLA-B27-associated uveitis cases. Furthermore, anterior and intermediate uveitis cases have a lower risk of hypopyon compared to patients with only anterior uveitis.

This report highlights an atypical case of HLA-B27-associated uveitis that presented with both a hypopyon and severe intermediate uveitis in an elderly man.

Case report

A 60-year-old Caucasian male was seen in the eye clinic of a hospital reporting a red, painful right eye with decreased vision. The patient was in fact seen three days earlier for pain and inflammation from a right shoulder injury for which he was put on a narcotic analgesic (oxycodeone 5 mg and acetaminophen 325 mg marketed as Percocet, one tablet every four hours as needed). The onset of his ocular symptoms coincided with the introduction of Percocet so he discontinued the drug after one day, however, his vision continued to worsen. Ocular history was unremarkable with no reports of trauma, surgery, inflammation or infection. Medication was limited to the recent use of Percocet for the shoulder and the occasional nonsteroidal anti-inflammatory drug (naproxen) for nonspecific pain in the body with no reported allergies to any medication. Review of all systems revealed episodes described as podagra (i.e. inflammation on the big toe related to episodes of gout).
within the past year (although he was never officially diagnosed with gout) and a history of papular rashes on his forehead and both his shins with mild erythema and some excoriation (abraded areas where the skin is torn or worn off). Upon further questioning, the patient reported no history of ulcers, sores, irritable bowel disease, bloody stool, urination difficulties or shortness of breath. The patient's family history was unremarkable. The patient also denied excessive nicotine or alcohol use, and had not engaged in any sexual activity recently. The patient was oriented to time, place and person, and was lucid at the time of the examination.

Upon ocular examination, visual acuity (VA) was hand motion OD (without improvement with pinhole) and 20/30 OS. Slit lamp examination of the right eye revealed 2+ injection of the bulbar conjunctiva. Fine keratic precipitates (KPs) were widely distributed throughout the cornea, although no corneal thinning was noted. Anterior chamber (AC) examination of the right eye revealed 4+ cells and flare (without convection current), fibrin production with a 1.5 mm hypopyon in the lower quadrant as seen in Figure 1. Dilated funduscopic examination (DFE) revealed severe vitreous haze (grade 4+ vitreous cells), obstructing all view to the retina. B-scan ultrasound revealed extensive vitreous debris. The left eye revealed only an early nuclear sclerotic cataract with no evidence of active or past inflammation. A summary of the ocular findings is shown in Table 1.

Given the B-scan, the patient was diagnosed with acute unilateral nongranulomatous anterior and intermediate hypopyon uveitis, with a tentative HLA-B27 association. The patient received 125 mg of intravenous anti-inflammatory glucocorticoid (methylprednisolone sodium succinate) coupled with a topical anti-inflammatory corticosteroid (1% prednisolone acetate qh, with a loading dose before bedtime and upon awakening), a cycloplegic/mydriatic agent (atropine 1% tid), and an oral anti-inflammatory corticosteroid (prednisone 80 mg daily). The patient was then sent to the laboratory to have his blood drawn for further analysis.

A subsequent review of his laboratory examination revealed an elevation of ESR, CRP and white blood cells. Laboratory results were positive for the following markers: HLA-B27, HSV IgG and HSV IgM. (See Table 2) The remainder of the work-up, including ACE, Toxoplasma, FTA-ABS, RPR and VZV titre, was negative. The etiology of the uveitis was thus confirmed as HLA-B27 positivity. The patient did not have a primary care provider, so a consultation with a rheumatologist was recommended.

The patient responded well to therapy. Ten days after treatment was initiated, VA of the right eye improved to 20/60, IOP was 16 mmHg, anterior segment revealed few fine KPs inferiorly, 1+ cells and flare in the AC and a <0.5 mm hypopyon. A DFE demonstrated 1+ anterior vitreous cells, snowbanks and snowballs resting

<table>
<thead>
<tr>
<th>Table 1: Clinical findings at initial presentation</th>
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</thead>
<tbody>
<tr>
<td><strong>RIGHT EYE (OD)</strong></td>
</tr>
<tr>
<td>Visual acuity</td>
</tr>
<tr>
<td>Pupil reactions</td>
</tr>
<tr>
<td>Extraocular movements</td>
</tr>
<tr>
<td>Tonometry (Tonopen)</td>
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<tr>
<td>Bulbar conjunctiva</td>
</tr>
<tr>
<td>Cornea</td>
</tr>
<tr>
<td>Anterior chamber</td>
</tr>
<tr>
<td>Crystalline lens</td>
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<tr>
<td>Posterior segment</td>
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</tbody>
</table>

*Figure 1 – A hypopyon (height of 1.5mm) seen at the lower quadrant of the anterior chamber*
inferiorly. The macula, optic disc and the rest of the retina were unremarkable. Due to the marked subjective and objective improvement, tapering of oral prednisone was initiated (60 mg for 5 days, 40 mg for 5 days, 30 mg for 5 days, 20 mg for 5 days, 10 mg for 5 days, 5 mg for 5 days, then discontinued).

At week 3, clinical evolution was favourable with VA at 20/30-2. The KP s and hypopyon disappeared (Figure 2), however grade 0.5+ cells and flare remained in the AC, grade 0.5+ cells in the anterior vitreous, and persistent snowbanks and snowballs. The left eye remained stable and quiet throughout the episode. At his last follow up at week nine, the patient had already discontinued both systemic and topical medication a week prior. His VA was maintained at 20/30+1, IOP was 16 mmHg, anterior segment was unremarkable, and a posterior segment examination revealed grade 0.5+ vitreous cells, inferior snowballs from five to eight o’clock. The patient was to return for regular monitoring in one month.

**Discussion**

The differential diagnosis for this patient included infectious and non-infectious etiologies for the uveitis, which includes, HLA-B27 positivity, Herpes simplex virus (HSV), Behçet’s disease, sarcoidosis, toxoplasmosis, Varicella-zoster virus (VZV), syphilis and tuberculosis. Multiple sclerosis, Lyme disease and Bartonella, although less probable culprits, could also have been on the list of differentials. A brief description of each can be found in Table 3.

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### Table 2: Clinical laboratory results

<table>
<thead>
<tr>
<th>Test</th>
<th>Purpose</th>
<th>Normal Values</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte Sedimentation Rate (ESR)</td>
<td>Inflammation</td>
<td>≤ 30 mm/hr</td>
<td>Elevated (110 mm/hr)</td>
</tr>
<tr>
<td>C-Reactive Protein (CRP)</td>
<td>Inflammation</td>
<td>&lt;6 mg/L</td>
<td>Elevated (19.35 mg/L)</td>
</tr>
<tr>
<td>White blood cells</td>
<td>Inflammation</td>
<td>4 x 10^9 to 1.1 x 10^10/L</td>
<td>Mild leukocytosis (13.1 x 10^9/L)</td>
</tr>
<tr>
<td>Human Leukocyte Antigen B27 (HLA-B27)</td>
<td>Specific protein strongly associated with spondyloarthropathies</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Herpes Simplex Virus (HSV) IgG</td>
<td>Herpes simplex virus-specific antibody</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Herpes Simplex Virus (HSV) IgM</td>
<td>Herpes simplex virus-specific antibody</td>
<td>Negative</td>
<td>Positive</td>
</tr>
<tr>
<td>Angiotensin-Converting Enzyme (ACE)</td>
<td>Sarcoïdosis</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Toxoplasma</td>
<td>Toxoplasmosis</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Treponema Pallidum Antibody (FTA-ABS)</td>
<td>Syphilis</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Rapid Plasma Regain (RPR)</td>
<td>Syphilis</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>Vancella-Zoster Virus (VZV) titer</td>
<td>Vancella zoster virus antibodies</td>
<td>Negative</td>
<td>Negative</td>
</tr>
</tbody>
</table>

The patient was initially diagnosed with an acute nongranulomatous uveitis with a tentative HLA-B27 association, however, the hypopyon and intermediate uveitis were atypical. Ramsay and Lightman (2001) classified the causes of hypopyon into non-infectious causes, infectious agents, neoplasms, and corneal disorders. Table 4 shows the most common differential diagnosis for hypopyon, anterior uveitis and intermediate uveitis.

In both intraocular infection and inflammation, hypopyon consists largely of tissue debris, fibrin, inflammatory by-products and leukocytes, and signifies severe anterior segment intraocular inflammation. A study by Zaidi et al. indicates that hypopyon is an uncommon finding in patients with uveitis, occurring in around 8.57 patients per 1000 person-years (0.86%), even in tertiary uveitis practices. This retrospective study indicated that hypopyon was more common among patients with uveitis limited to the anterior chamber than in patients who also had intermediate uveitis as a part of their diagnosis, but was nearly
as frequent among patients with posterior or panuveitis. The most common risk factors for hypopyon are Behçet’s disease and HLA-B27 positivity, conferring respectively an approximate five-fold and two-fold increased risk of hypopyon. In fact, HLA-B27 hypopyon uveitis occurs in 5.7% of all uveitis cases and is more common among Caucasians. Even though hypopyon is an indicator of remarkably severe inflammation, eyes that develop hypopyon do not appear to have adverse visual outcomes more often than eyes without it. A previous study on Behçet’s disease showed that patients who developed hypopyon were more likely to gain three lines of vision at any point during follow-up, probably because the haze associated with a hypopyon was a reversible cause of vision loss.

Intermediate uveitis is diagnosed when intraocular inflammation primarily involves the vitreous, peripheral retina and pars plana ciliaris. It is the type of uveitis with the longest clinical duration. The syndrome is more frequent in the third and fourth decade. Intermediate uveitis has been reported to make up 1.4 – 22% of all uveitis cases. Although the majority of cases are of unknown etiology, a significant association between intermediate uveitis and multiple sclerosis, sarcoidosis and Lyme disease has been reported. Intermediate uveitis is bilateral 80% of the time. Main clinical features are vitreous cells, with or without snowballs and snow banking. The intermediate uveitis found in this case was atypical in that it was monocular and not associated with the aforementioned diseases.

In the case reported here, the patient’s laboratory results were positive for HLA-B27, HSV IgG and HSV IgM, which pointed towards an etiology of either an HLA-B27-associated uveitis or Herpes simplex uveitis. Acute HSV uveitis is typically secondary to herpetic keratitis, although 15% of patients may not experience corneal involvement. Clinical signs of HSV uveitis include corneal scarring, focal or patchy iris atrophy, iris transillumination defects, KP,
posterior synechiae, and elevated IOP. A unilateral anterior uveitis coupled with an elevated IOP point to HSV uveitis. The presence of patchy iris atrophy and transillumination defects corroborates the diagnosis. Since the clinical presentation of this case did not involve the iris or an elevated IOP, HSV uveitis was rejected as a potential diagnosis and HLA-B27 positivity was favoured as the main etiology.

Despite the atypical presentation, the prognosis was positive for this patient, like in most HLA-B27-associated uveitides. With only topical and systemic steroids, the clinical progression was favourable and the patient regained VA to 20/30 within 9 weeks. The patient suffered from inflammation of his right shoulder just before the onset of his uveitis attack. It is unclear at this time whether the shoulder inflammation and the uveitis are two separate inflammatory events, or whether they are part of a single systemic problem. HLA-B27-associated anterior uveitis patients with concomitant posterior segment manifestations have a significantly higher incidence of associated systemic diseases, namely ankylosing spondylitis, inflammatory bowel diseases or reactive arthritis (formerly referred to as Reiter’s syndrome). Thus, a referral to rheumatology was recommended to rule these out. The patient has been educated that recurrences are highly possible, and that this process may be part of a systemic inflammatory condition, which may require steroids and/or chronic immunosuppressive therapy. However, the patient was not seen in a follow-up after the referral.

**HLA-B27-associated uveitis**

As the most common specific uveitis diagnosis, HLA-B27-associated uveitis accounts for approximately 13–17% of all uveitis cases. About 50% of patients suffering from acute anterior uveitis are HLA-B27 positive. HLA-B27-associated uveitis is three times more common in males. The average age of onset of the disease is 35, although cases have been reported in children (10% of cases begin prior to 20 years old) and late adulthood (5% after 55 years of age).

The classic presentation of HLA-B27-associated ocular disease is acute anterior uveitis (AAU). The onset is typically abrupt and symptoms include photophobia, ocular pain, epiphora, ocular redness, and mild-to-severe visual blurring. Cases are generally unilateral but a recurrent attack may affect the contralateral eye. Although the inflammation is usually nongranulomatous, it may be severe enough to cause a hypopyon or a plasmoid aqueous. HLA-B27-associated AAU is in fact the most common cause of hypopyon uveitis in North America.

Uncommon cases (less than 25.1%) cases may involve the posterior segment. Such posterior segment involvement is recognized as vitritis, cystoid macular oedema, papillitis and retinal vasculitis, and is thought to be secondary to anterior segment inflammation. Thus, HLA-B27-associated uveitis may be unusually severe and may cause a panuveitis, which is an under-recognized phenomenon. During an acute attack, IOP is generally lowered due to the shutdown of the ciliary body. Nevertheless, increased IOP and secondary glaucoma is a

**Table 4: Most common differential diagnosis of hypopyon, anterior uveitis and intermediate uveitis**

<table>
<thead>
<tr>
<th>Hypopyon</th>
<th>Anterior Uveitis</th>
<th>Intermediate Uveitis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-infectious</td>
<td>HLA-B27</td>
<td>Idiopathic</td>
</tr>
<tr>
<td></td>
<td>Behçet’s disease</td>
<td>HLA-B27</td>
</tr>
<tr>
<td></td>
<td>Spondyloarthropathy</td>
<td>Reactive arthritis (Reiter’s syndrome)</td>
</tr>
<tr>
<td></td>
<td>Iatrogenic/Neoplasm/Trauma</td>
<td>Ankylosing spondylitis</td>
</tr>
<tr>
<td>Infectious</td>
<td>Endogenous endophthalmitis</td>
<td>Sarkoidosis</td>
</tr>
<tr>
<td></td>
<td>Toxoplasmosis</td>
<td>Syphilis</td>
</tr>
<tr>
<td></td>
<td>Syphilis</td>
<td>HSV</td>
</tr>
<tr>
<td></td>
<td>Hansen’s disease</td>
<td>Trauma</td>
</tr>
<tr>
<td></td>
<td>Brucellosis</td>
<td>Posner-Schlossman Syndrome</td>
</tr>
<tr>
<td></td>
<td>HSV</td>
<td>Neoplasm</td>
</tr>
<tr>
<td></td>
<td>Keratitis</td>
<td>Lymphoma, leukemia, retinoblastoma</td>
</tr>
<tr>
<td>Other</td>
<td>Other</td>
<td>Other</td>
</tr>
</tbody>
</table>

The classic presentation of HLA-B27-associated ocular disease is acute anterior uveitis (AAU). The onset is typically abrupt and symptoms include photophobia, ocular pain, epiphora, ocular redness, and mild-to-severe visual blurring. Cases are generally unilateral but a recurrent attack may affect the contralateral eye. Although the inflammation is usually nongranulomatous, it may be severe enough to cause a hypopyon or a plasmoid aqueous. HLA-B27-associated AAU is in fact the most common cause of hypopyon uveitis in North America. Uncommon cases (less than 25.1%) cases may involve the posterior segment. Such posterior segment involvement is recognized as vitritis, cystoid macular oedema, papillitis and retinal vasculitis, and is thought to be secondary to anterior segment inflammation. Thus, HLA-B27-associated uveitis may be unusually severe and may cause a panuveitis, which is an under-recognized phenomenon. During an acute attack, IOP is generally lowered due to the shutdown of the ciliary body. Nevertheless, increased IOP and secondary glaucoma is a
well-recognized complication due to iris bombé or synechial angle closure. Uveitis attacks are normally short-lived and resolve within three months. Recurrent episodes are common, but the frequency varies between multiple attacks per year to single attacks separated by one or more decades.46

There is a stepladder approach to the management of uveitis.47 The immediate goal is to control the inflammation and ciliary spasm, with a long-term goal of addressing the underlying cause of the uveitis. First-time occurrences and uncomplicated recurrences can be treated with topical corticosteroid, such as prednisolone acetate 1%, which has a moderate potency and is appropriate for many cases. Although the risk of systemic side effects is low, 1% of patients experience increased IOP, in which case a milder formulation such as rimexolone and lotoprednol can be utilized.48 The concomitant use of a cycloplegic/mydriatic drop, such as atropine sulphate 1%, reduces pain from ciliary spasm and may break or prevent posterior synechiae.

More severe cases may require a combination of oral, topical, periocular or intravitreal treatments. Systemic corticosteroid administration is required in 24% of patients. A typical oral starting dose is 1 mg/kg of prednisone daily. Side effects resulting from a short course of systemic steroids are infrequent but include sleep disturbances, weight gain, increased appetite, mood imbalance and more.49 In extreme cases of uveitis involving the posterior segment, periocular or intravitreal corticosteroids may be considered.50

Periocular injections (transseptally, in the sub-tenon’s space or subconjunctivally) are designed as depot injections (e.g. triamcinolone acetate) and therefore, are effective for an extended period of time.51 Intravitreal injections are effective for three to six months, minimize systemic side effects, and have the benefit of treating macular oedema caused by posterior uveitis.52 On the other hand, ocular complications (e.g. cataracts and increased IOP) are more common with intravitreal injections than with systemic steroids.

Extreme sight-threatening cases may require pulse intravenous (IV) steroids to bring the inflammation under control more quickly and to prevent irreparable damage. The recommended regimen for such cases is methylprednisolone 1 g IV per day for 3 days, with subsequent transition to oral therapy, starting at 1 mg/kg per day.47, 53, 54 For recalcitrant cases, steroid-free strategies can be considered, such as oral NSAID therapy or immunosuppressive therapy.55, 56, 47

Patients on topical or systemic steroids for an extended period of time (i.e. over two weeks) should be tapered off over the course of several weeks to avoid rebound inflammation after topical use, or inducing adrenal crisis from abrupt stoppage of oral corticosteroid use. Patients requiring immunosuppressive therapy should remain on their regimen without dose reductions to prevent any recurrences, which may be difficult to control.

HLA-B27 testing in patients with uveitis is useful because it may help to identify a previously undiagnosed systemic disease. Among patients with HLA-B27-associated uveitis, around 70% will have an associated (rheumatoid factor) seronegative spondyloarthropathy of which approximately 50% will not have been diagnosed or will have been misdiagnosed. Seronegative spondyloarthropathy includes ankylosing spondylitis, reactive arthritis (Reiter’s syndrome), psoriatic arthropathy, and arthritis associated with inflammatory bowel disease. Patients with posterior segment manifestations have a significantly higher incidence of such systemic diseases.42, 57 In addition, around 30 – 90% of patients with HLA-B27-associated uveitis suffer from associated joint disease.58

As a result, HLA-B27 testing can be beneficial in improving management of the patient’s overall systemic health.

Summary
In this case report, a final diagnosis of HLA-B27-associated uveitis was made following an extensive clinical and laboratory evaluation despite the atypical presentation. The hypopyon and its associated anterior and intermediate uveitis were successfully treated with topical and systemic steroids. This case is an important reminder that, although uncommon, hypopyon and posterior segment involvement may be present in an HLA-B27-associated uveitis, and can even affect the elderly. Furthermore, it is important to include a comprehensive assessment of both the anterior and posterior segments of any presenting painful, red eye for a full clinical appreciation.
Acknowledgement

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References


