American Academy of Optometry: Case Report #1

HLA B-27 Associated Anterior Uveitis

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Abstract: Human leukocyte antigen B27 (HLA-B27) is the most common identifiable cause of anterior uveitis. HLA-B27 is highly associated with systemic disease, including ankylosing spondylitis, reactive arthritis, psoriatic arthritis, irritable bowel syndrome, and other undifferentiated spondylarthropathies. Ophthalmic manifestations may be one of the first signs that raises suspicion for an underlying systemic disease. Although the visual prognosis is generally favorable, ocular complications such as posterior subcapsular cataracts and macular edema can cause vision loss. Further studies are needed to better understand the role of HLA-B27 in the pathogenesis of uveitis, which will aid in better targeted therapy.

Key Words: *human leukocyte antigen, HLA-B27, anterior uveitis, corticosteroid*

Introduction:
Uveitis is the most common ophthalmic finding in rheumatology and clinical immunology. It is an inflammatory disease process stimulated by T-cells and inflammatory cytokines.[1] The Standardization of Uveitis Nomenclature (SUN) Working Group[2] published a consensus on standardization of methods for reporting clinical findings in uveitis. Classification is based on the primary anatomical site of inflammation. The primary site of inflammation in anterior uveitis is the iris and ciliary body. Intermediate uveitis encompasses primary inflammation of the vitreous. Posterior uveitis involves primary inflammation of the retina and/or choroid. Panuveitis is reserved for presentations where there is no predominant site of inflammation and inflammation is found in the anterior chamber, vitreous, and retina and/or choroid. It is important to note that structural complications, such as macular edema or neovascularization are not contributory in classifying the primary site of inflammation. Onset is classified as either sudden or insidious. Duration of the disease is either limited ($\leq$3 months duration) or persistent (>3 months duration). Lastly, course is either acute (sudden onset and limited duration), recurrent (repeated episodes separated by periods of quiescence without treatment $\geq$3 months duration), or chronic (persistent with relapse <3 months after discontinuing treatment).

Acute anterior uveitis is the most common form of uveitis and makes up about 75-90% of cases of uveitis in Western countries.[1] Within anterior uveitis, human leukocyte antigen B27 (HLA-B27) is the most common identifiable cause.[3,4] HLA-B27 associated uveitis typically affects males more so than females, has an acute onset, is unilateral alternating, non-granulomatous, and often recurs. In contrast, non-HLA-B27 acute anterior uveitis affects both sexes equally and tends to be bilateral, chronic, and granulomatous. HLA-B27 is commonly associated with systemic disease, including ankylosing spondylitis, reactive arthritis, psoriatic arthritis, irritable bowel syndrome, and other undifferentiated spondylarthropathies. Ophthalmic manifestations may be one of the first signs of systemic disease and it has been reported that in more than half of patients with spondylarthropathies and uveitis, a diagnosis was made due to an ophthalmic evaluation.[3] Therefore, eye care providers play an integral in identifying these patients and referring for rheumatologic evaluation and management. The visual prognosis is generally favorable, but studies have reported up to 11% of patients qualifying as legally blind.[5,6]

Case Report:
A 75-year-old Caucasian male presented on January 7th, 2019 to a colleague as a new patient with a chief complaint of left eye discomfort that had started that morning. He described it as a dull 3/10 pain with mild light sensitivity. He reported multiple similar episodes in the past that alternated between eyes, but occurred more frequently in the left.

His ocular history was significant for HLA-B27 associated anterior uveitis OU with his first documented episode OS in February 2007, managed by an outside facility.

Listed below is the patient's previous work-up:

TEST	RESULT
Reactive plasma reagin (RPR)	Negative
Treponema pallidum antibody (TP-AB)	Negative
Fluorescent treponemal antibody absorption (FTA-ABS)	Negative
Angiotensin converting enzyme (ACE)	Normal
Serum lysozyme	Normal
HLA-B27	**Positive**
Human immunodeficiency virus (HIV) antibody	Negative
Purified protein derivative (PPD)	Negative
Chest x-ray	Normal
Head computerized tomography (CT)	Normal

Although the patient lacked rheumatologic symptoms at presentation, he was referred for an evaluation of HLA-B27 associated spondylarthropathies with a rheumatologist. No evidence of underlying systemic disease was reported. He was treated with topical and oral steroids until resolution. He subsequently underwent cataract extraction with intraocular lens implantation OS.

Over the subsequent years, he developed several recurrences of anterior uveitis that alternated between eyes. He underwent cataract extraction with posterior chamber intraocular lens implantation and a vitrectomy OS. During the vitrectomy, a vitreous sample was taken and potassium hydroxide test and gram stain were negative, ruling out fungal and bacterial presence. His most recently recorded flare was one year ago that resolved within one month on topical prednisolone acetate 1% therapy alone. Since his last recurrence, he was not on any maintenance therapy.

His medical history was significant for diabetes mellitus type 2, stage 3 chronic kidney disease, coronary artery disease, prostate and bladder cancers in remission, and chronic schizophrenia. His medications included aspirin 81mg, rosuvastatin Ca 10m, and diltiazem 120mg for coronary artery disease; fluoxetine HCl 40mg and quetiapine fumarate 100mg for schizophrenia; repaglinide 1.5 mg and insulin glargine human 100 unit/mL 37 units for injection for diabetes. His family history was unremarkable. He had no known drug allergies.

Upon ocular examination, his best corrected visual acuities were $20/60^{+1}$ OD and $20/50^{-2}$ OS with a low myopic and astigmatic prescription. His right pupil was unreactive to light and the left was minimally reactive. There was no relative afferent pupillary defect. Ductions and versions were full OU. Cover test was significant for a large angle constant alternating esotropia, which he reported to be longstanding. Confrontation visual fields were full to finger counting OU. Upon slit lamp examination, he had mild plugged Meibomian glands and flakes of both eyelids. There was no conjunctival hyperemia of the right eye and trace hyperemia of the left. The right cornea was clear aside from a nasal pterygium extending 1.6mm past the limbus. The left cornea had peripheral iridocorneal adhesions from 10-11:00 and 5-7:00 with adjacent endothelial pigment, anterior stromal vascularization superiorly, and a nasal pterygium extending 1.4mm past the limbus. The right iris had posterior synechiae 360 degrees, which explained his non-reactive

right pupil. There were no posterior synechiae in the left eye. The right anterior chamber had rare cell and no flare while the left eye had 2+ cell and 2+ flare (grading based on the Standardization of Uveitis Nomenclature Working Group[2] criteria). His intraocular pressures (IOPs) by Goldmann applanation tonometry were 19 mmHg OD and 9 mmHg OS after instillation of one drop of Fluress. This large asymmetry is not surprising given the inflammation of the affected left ciliary body causing decreased aqueous humor production. Four-mirror gonioscopy OD revealed open angles with 2+ trabecular meshwork pigment, convex iris insertion, and no peripheral anterior synechiae. The patient was unable to tolerate gonioscopy OS.

The patient was dilated with 1 drop of 1% tropicamide and 1 drop of 2.5% phenylephrine in each eye. However, the right eye remained undilated after twenty minutes due to the posterior synechiae. The right lens had iris pigment and a fibrotic membrane on the central anterior capsule that explained his reduced vision. In the right eye, a 1-2+ nuclear sclerotic cataract was noted. The left eye was pseudophakic with a clear and well-centered posterior chamber intraocular lens. There was no fibrotic membrane. The anterior vitreous of the right eye was not fully viewable, the left anterior vitreous was clear and had no cells. The optic nerves had distinct margins and a cup-to-disc ratio of 0.6 round OD and 0.5 round OS. The maculae had no exudates, but the left macula had a mild epiretinal membrane. There was no evidence of vasculitis, retinitis or choroiditis OU. The periphery was intact 360 degrees OU. An optical coherence tomography (OCT) of the left macula was obtained in order to document the epiretinal membrane and screen for subclinical macular edema associated with the anterior uveitis. OCT OS confirmed a mild epiretinal membrane, and there was no cystoid macular edema or subretinal fluid. Given the limited posterior view OD, a B-scan was performed and there were no retinal or choroidal detachments, mass lesions, or evidence of vitreous inflammation.

Differential diagnoses:

- HLA-B27 associated anterior uveitis without seronegative arthritis
- HLA-B27 associated anterior uveitis with seronegative arthritis[7,8]
    - Ankylosing spondylitis
    - Reactive arthritis
    - Psoriatic arthritis
    - Enteropathic arthropathy
    - Undifferentiated spondarthritis
    - Inflammatory bowel disease
    - Isolated peripheral enthesitis
- Non-HLA-B27 associated anterior uveitis
    - Infectious
        - Herpetic
        - Syphilis
        - Tuberculosis
        - Fungal or bacterial endophthalmitis
    - Inflammatory

        - Sarcoidosis
        - Behcet's disease
        - Vogt Koyonagi Harada's disease
    - Neoplastic

HLA-B27 associated anterior uveitis without seronegative arthritis: Given the patient's known history of recurrent anterior uveitis in the setting of a positive HLA-B27 test, and supported by an extensive prior work-up that ruled out other etiologies, this was the top differential diagnosis.

HLA-B27 associated anterior uveitis with seronegative arthritis: The patient's previous rheumatologic evaluation was negative for any associated underlying systemic disease and he remained without signs or symptoms of seronegative arthritis. He denied back pain, swelling/stiffness/pain of joints, new skin lesions, gastrointestinal upset, or changes in urination or bowels. He was also above the typical age of onset for these systemic diseases, even at the time of his initial diagnosis at the outside facility.

Herpetic: Although herpes simplex virus (HSV) associated anterior uveitis can occur at any age, it is more common in those under 60 years old. Varicella zoster virus (VZV) associated anterior uveitis on the other hand, tends to occur in those over 60 years old. The patient did not have any dermatologic or corneal lesions consistent with a herpetic etiology. Additionally, at his initial presentation of anterior uveitis, he was placed on a therapeutic dose of oral acyclovir in the setting of elevated intraocular pressure (IOP). He did not exhibit any therapeutic response to acyclovir and the medication was subsequently discontinued.

Syphilis: Syphilis is a great masquerader and must be considered in *all* cases of uveitis. However, the patient did not endorse high risk sexual or drug behaviors. His prior treponemal and non-treponemal tests were negative.

Tuberculosis: The patient did not endorse recent travel to endemic countries and was born in the United States. He denied a persistent cough, chest pain, unexplained weight loss, or night sweats.

Fungal or bacterial endophthalmitis: The patient did not have any recent ocular injections/surgeries or systemic surgeries or penetrating trauma. He had no known active systemic infection.

Sarcoidosis: The patient had no known history of sarcoidosis, a prior normal chest x-ray without granulomas, and previously normal Angiotensin-Converting Enzyme (ACE) and lysozyme laboratory results. He had no ocular granulomas on clinical exam. He denied shortness of breath, persistent cough, chest pain, fatigue, or new skin lesions.

Behcet's disease: The patient was well outside the typical age of onset, which is the second to fourth decades of life. He also lacked the International Study Group for Behcet's disease

criteria[18] of oral ulcers, typical cutaneous lesions, or recurrent genital ulcers. He did however meet the criterion of at least two recurrent typical eye lesions (uveitis), although Behcet's is typically associated with posterior uveitis. Additionally, Behcet's is associated with the HLA-B51 gene.

Vogt-Koyanagi-Harada disease: Ocular manifestations of Vogt-Koyanagi-Harada (VKH) disease are classically a severe bilateral granulomatous posterior uveitis with serous retinal detachments, disc edema, and vitritis, which contrasts the anterior uveitis of this patient.[18] The disease does tend to recur and extraocular manifestations include headache, hearing loss, poliosis, and vitiligo, of which the patient lacked. It is less common in Caucasian patients as it tends to affect those of darker pigmentation. The patient is also older than the typical age of onset for VKH. If the concern for this disease were higher, laboratory tests would include examination of cerebrospinal fluid for evidence of pleocytosis and elevated protein.

Neoplastic: Although the patient had a history of bladder and prostate cancers, both were in remission without other evidence of metastasis. Malignant etiologies of uveitis are rare and of the malignancies, B cell lymphoma is most common, which the patient had no known history of.

The patient was started on 1 drop of prednisolone acetate 1% four times a day and 1 drop of cyclopentolate 1% twice a day OS. The right eye was not treated due to its quiet status. The following work-up was obtained:

TEST	RESULT	NOTES
Complete blood count (CBC)	Normal	
Human immunodeficiency virus (HIV) antibody	Negative	
Reactive plasma reagin (RPR)	Negative	Non-treponemal test for syphilis
Treponema pallidum antibody (TP-AB)	Negative	treponemal test for syphilis
Angiotensin converting enzyme (ACE)	Normal	Non-specific test for sarcoidosis
Serum lysozyme	Normal	Non-specific test for sarcoidosis
HLA-B27	***Positive***	
QuantiFERON-TB Gold	Negative	Blood test for tuberculosis
Chest x-ray	Normal	Pulmonary involvement of sarcoidosis or tuberculosis

The patient was diagnosed with a sudden onset, unilateral alternating, non-granulomatous, HLA-B27 associated anterior uveitis. Since the patient had not been on therapy since his last flare one year prior, his uveitis was classified as recurrent. However, this classification could change to chronic if he relapses within three months after discontinuing treatment.

Follow-up #1 (Day 7):
One week later, the patient presented to a colleague optometrist with improved symptoms and reported good compliance with topical medications. His visual acuity improved one line to

20/50^{-1} OD and remained stable OS at 20/50^{-2}. His IOPs were 19 mmHg OD and 14mmHg OS via Goldman tonometry after instillation of one drop of Fluress OU. This increase in IOP OS compared to the previous visit is explained by the decreased inflammation of the left ciliary body and therefore more normal aqueous humor production. Upon slit lamp examination, he had mild Meibomian gland dysfunction and flakes of both eyelids. There was no conjunctival hyperemia of the right eye and trace hyperemia of the left. The right cornea was clear aside from a nasal pterygium extending 1.6mm past the limbus. The left cornea had peripheral iridocorneal adhesions from 10-11:00 and 5-7:00 with adjacent endothelial pigment, anterior stromal vascularization superiorly, and a nasal pterygium extending 1.4mm past the limbus. The right iris had posterior synechiae 360 degrees, which explained his non-reactive right pupil. There were no posterior synechiae in the left eye. The right anterior chamber was deep and quiet. The anterior chamber reaction OS had improved to 0.5+ cell and 1+ flare.

Since cystoid macular edema can be associated with anterior uveitis, a macula OCT was obtained. The OCT OS revealed a mild epiretinal membrane and no evidence of intraretinal or subretinal fluid(Figure 1).

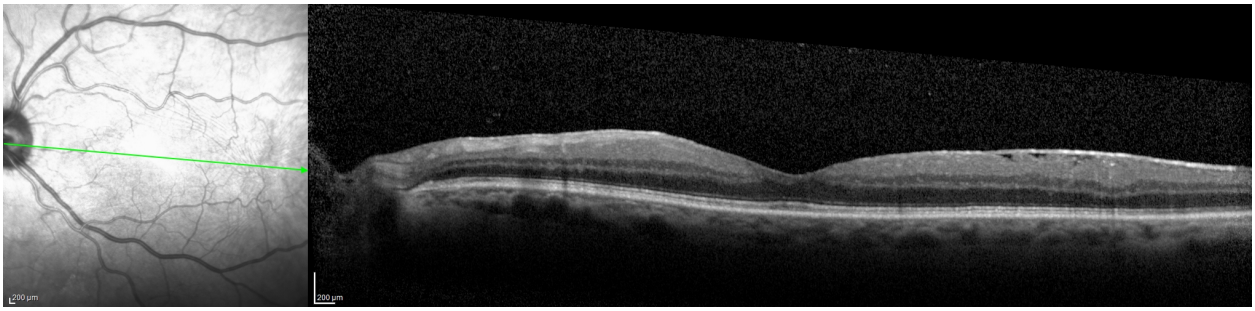


Figure 1. OCT high definition line scan OS with a mild epiretinal membrane and no intraretinal or subretinal fluid.

Given the significant improvement and now minimal anterior chamber reaction, the patient was started on a taper of 1 drop prednisolone acetate 1% three times a day OS for one week, then one drop twice a day for a week, and finally one drop once a day for a week. Cyclopentolate 1% was discontinued. The patient was to follow-up in two weeks.

After his optometric examination, a cornea specialist was consulted, who did not recommend attempting to break the posterior synechiae OD given its white and quiet status.

Follow-up #2 (Day 15):
Two weeks after the initial visit, the patient was referred to the optometry clinic from the emergency department for a red left eye. The patient complained of increased ocular redness and blurred vision OS. Visual acuity OD remained stable at 20/50^{-1} and OS was reduced to 20/100, with no improvement with pinhole testing OU. Upon slit lamp examination, he had mild Meibomian gland dysfunction and flakes of both eyelids. There was no conjunctival hyperemia of the right eye and 3+ diffuse hyperemia of the left. The right cornea was clear aside from a nasal pterygium extending 1.6mm past the limbus. The left cornea had peripheral iridocorneal

adhesions from 10-11:00 and 5-7:00 with adjacent endothelial pigment, anterior stromal vascularization superiorly, and a nasal pterygium extending 1.4mm past the limbus. The right iris had posterior synechiae 360 degrees. There were no posterior synechiae in the left eye. His IOPs were 12 mmHg OD and 11 mmHg OS via Goldman tonometry, after instillation of one drop of Fluress OU. The right anterior chamber was deep and quiet. The patient displayed an increased anterior chamber reaction OS with 3+ cell and 4+ flare. This rebound was not surprising given his short and low dose course of topical corticosteroids with a known history of recurrent anterior uveitis associated with HLA-B27. Therefore, a more aggressive treatment strategy was needed.

The patient was dilated with 1 drop of 1% tropicamide and 1 drop of 2.5% phenylephrine in each eye to confirm no posterior involvement with this rebound in inflammation. The right eye remained undilated due to the posterior synechiae. The right lens had iris pigment and a fibrotic membrane on the central anterior capsule that explained his reduced vision. In the right eye, a 1-2+ nuclear sclerotic cataract was noted. The left eye was pseudophakic with a clear and well-centered posterior chamber intraocular lens. There was no fibrotic membrane. The anterior vitreous of the right eye was not fully viewable, the left anterior vitreous remained clear and had no cells. The optic nerves had distinct margins and a cup-to-disc ratio of 0.6 round OD and 0.5 round OS. The maculae had no exudates, but the left macula had a mild epiretinal membrane. There was no evidence of vasculitis, retinitis or choroiditis OU. The periphery was intact 360 degrees OU.

After his optometric examination, the same cornea specialist was consulted, and a collaborative decision was made to place the patient on a loading dose of prednisolone acetate 1% one drop every 5 minutes for the first 15 minutes in the morning, then one drop every hour while awake OS. One drop of cyclopentolate 1% twice a day OS was re-initiated. The patient was to follow-up in one week.

Follow-Up #3 (Day 21):
Three weeks after initial onset, patient's care was transferred to fellowship candidate, who took over the patient's care on all subsequent visits. The patient reported improved vision in the left eye. He also reported that he was diligent about using his drops until two days ago, when he stopped taking them because he was prioritizing his mental health and also his vision was improving. However, he did endorse taking two drops of prednisolone acetate 1% last night OS. Visual acuity OD remained stable at $20/50^{-1}$ and OS declined to 20/150, with 20/70 on pinhole. Upon slit lamp examination, he had mild Meibomian gland dysfunction and blepharitis of both eyelids. There was no conjunctival hyperemia of the right eye and 2+ diffuse hyperemia of the left. The right cornea was clear aside from a nasal pterygium extending 1.6mm past the limbus. The left cornea had peripheral iridocorneal adhesions from 10-11:00 and 5-7:00 with adjacent endothelial pigment, anterior stromal vascularization superiorly, and a nasal pterygium extending 1.4mm past the limbus. The right iris had posterior synechiae 360 degrees. There were no posterior synechiae in the left eye. IOPs were 21 mmHg OD and 6 mmHg OS (with no other signs of hypotony), via Goldman tonometry after installion of one drop of Fluress OU. Although his IOP OD was elevated compared to the prior week, his IOP was 19mmHg on two

consecutive visits prior (one before the initiation of any topical steroid, and one after one week of topical prednisolone acetate 1%) therefore not suggestive of a contralateral steroid response. The anterior chamber reaction OS had slightly improved to 2+ cell and 3+ flare. Small pupil examination of the left eye revealed an optic nerve C/D ratio of 0.5 round OS. The left macula had a mild epiretinal membrane and no frank edema. OCT of the macula of the left eye was obtained in order to screen for subclinical macular edema after his rebound. OCT revealed a new small shallow area of subfoveal subretinal fluid(Figure 2). This area was to be watched closely for progression and consider periocular steroids if not responding to current therapy.

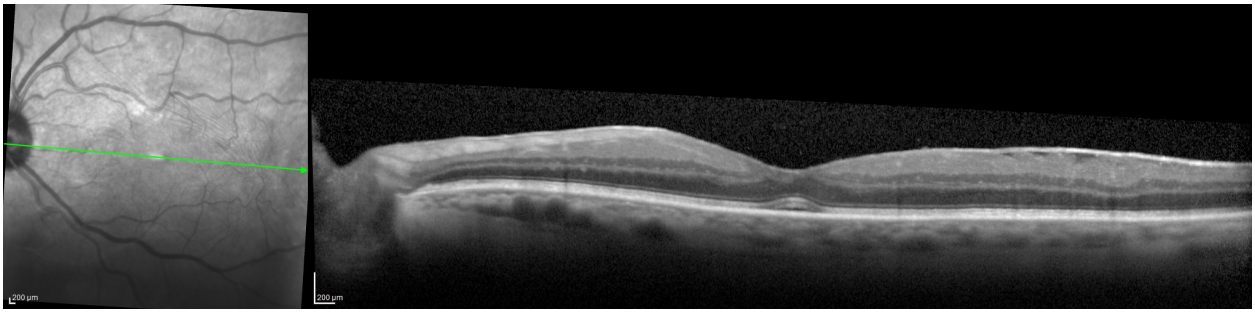


Figure 2. OCT high definition line scan showing a small shallow subfoveal serous detachment.

The patient was directed to continue prednisolone acetate 1% OS one drop every 5 minutes for the first 15 minutes in the morning, then one drop every hour while awake, and 1 drop of cyclopentolate 1% twice a day. He was to follow-up in one week.

Follow-Up #4 (Day 28):

Upon presentation after four weeks of treatment, the patient reported improved vision OS and good compliance with his drops as he was admitted as an inpatient for suicidal ideation. Visual acuity OD remained stable at $20/50^{-1}$ and OS improved to $20/80^{+2}$, with no improvement with pinhole. Upon slit lamp examination, he had mild Meibomian gland dysfunction and blepharitis of both eyelids. There was no conjunctival hyperemia of the right eye and 1+ diffuse hyperemia of the left. The right cornea was clear aside from a nasal pterygium extending 1.6mm past the limbus. The left cornea had peripheral iridocorneal adhesions from 10-11:00 and 5-7:00 with adjacent endothelial pigment, anterior stromal vascularization superiorly, and a nasal pterygium extending 1.4mm past the limbus. The right iris had posterior synechiae 360 degrees. There were no posterior synechiae in the left eye. There was no anterior chamber reaction of the right eye. His anterior chamber reaction OS improved to 1+ cell and 2+ flare. IOPs were 17mmHg OD and 11mmHg OS, via Goldman tonometry after instillation of one drop of Fluress OU. The shallow area of subfoveal subretinal fluid OS displayed trace progression on OCT(Figure 3).

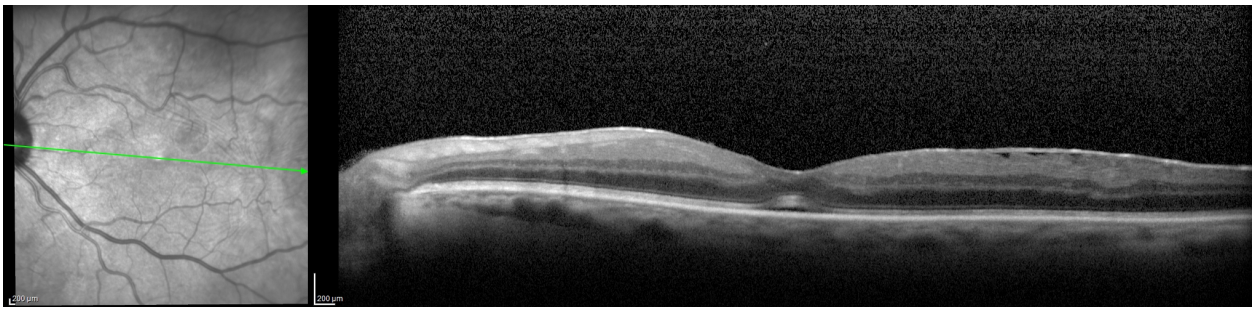


Figure 3. OCT high definition line scan showing slight progression of a small shallow subfoveal serous detachment.

Although there was trace progression of the subretinal fluid, it was not significant enough to warrant escalating therapy at the time, also given his improvement in and now mild anterior chamber reaction. The loading dose of prednisolone acetate 1% was discontinued and the patient was continued on one drop every hour while awake in the left eye only. Additionally, given the improvement in anterior chamber reaction and symptoms, cyclopentolate 1% was discontinued. He was to follow-up in one week.

Follow-Up #5 (Day 36):

One month after initial presentation, the patient was seen for follow-up and denied any changes in symptoms from the prior examination. He reported using the prednisolone acetate 1% about 6-8 times a day, less than the q1h prescribed. Visual acuity OD remained stable at $20/50^{-1}$ and OS decreased from $20/80^{+2}$ to $20/100^{-1}$, with no improvement on pinhole. Upon slit lamp examination, he had mild Meibomian gland dysfunction and blepharitis of both eyelids. There was no conjunctival hyperemia of the right eye and 1+ diffuse hyperemia of the left. The right cornea was clear aside from a nasal pterygium extending 1.6mm past the limbus. The left cornea had peripheral iridocorneal adhesions from 10-11:00 and 5-7:00 with adjacent endothelial pigment, anterior stromal vascularization superiorly, and a nasal pterygium extending 1.4mm past the limbus. The right iris had posterior synechiae 360 degrees. There were no posterior synechiae in the left eye. IOPs were 19 mmHg OD and 16 mmHg OS, via Goldman tonometry after instillation of one drop of Fluress OU. There was no anterior chamber reaction of the right eye and the left eye continued to improve, now with 0.5+ cell and 1+ flare. OCT of the macula was obtained due to the decrease in vision despite improved anterior chamber reaction. OCT revealed stable subretinal fluid, but now a new area of intraretinal fluid just superior to the foveal center(Figures 4-7).

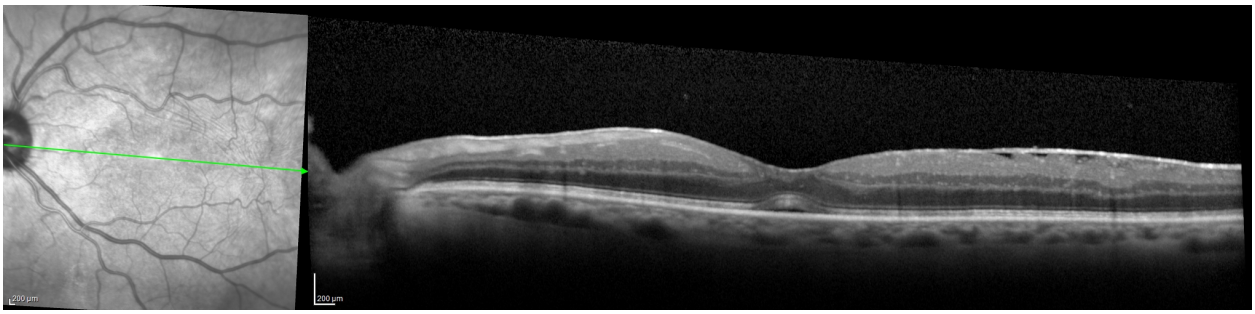
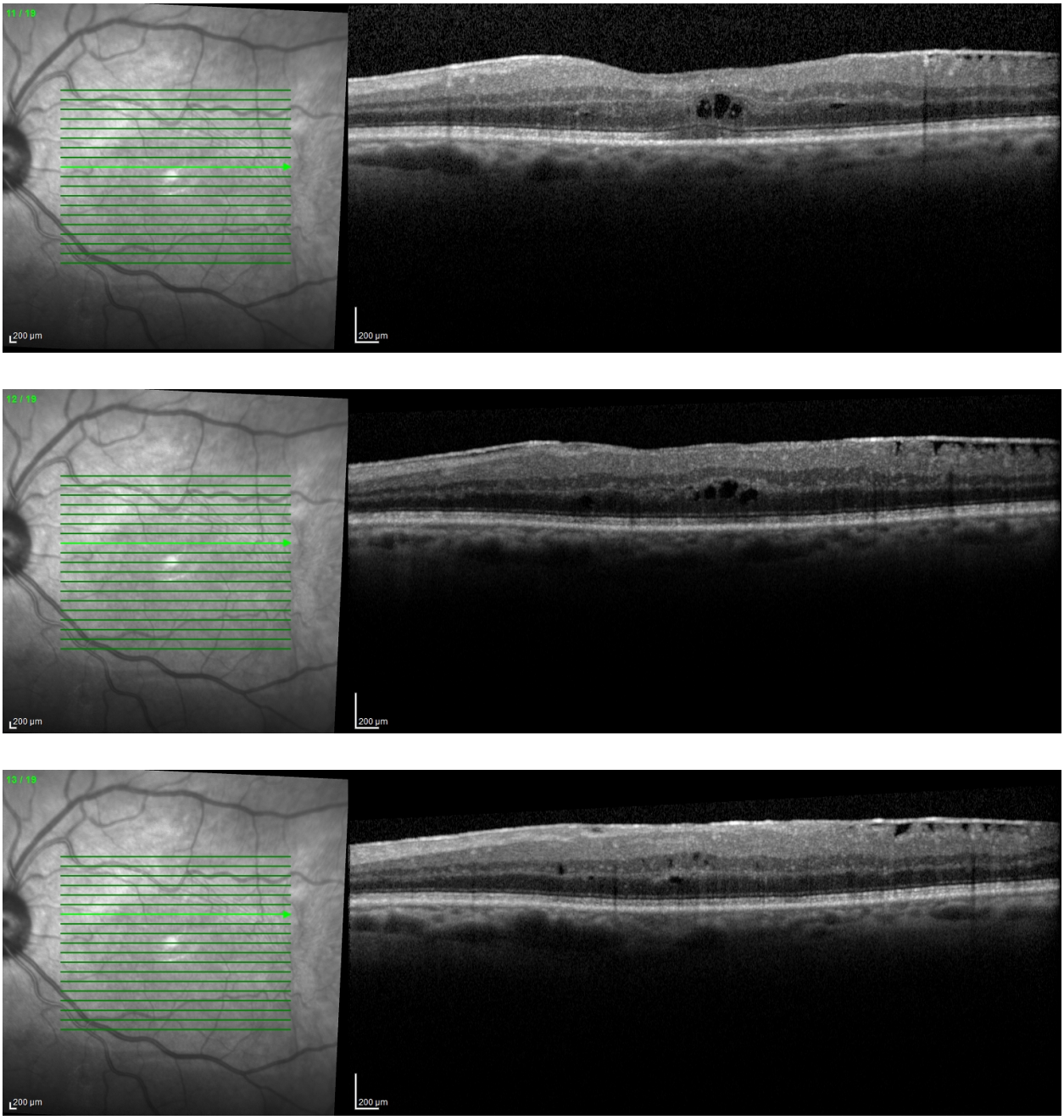


Figure 4. OCT high definition line scan showing a stable small shallow subfoveal serous detachment.



Figures 5-7. Macula OCT of the left eye superior to the foveal center showing new mild cystoid macular edema.

The progression of macular edema along with his reduced compliance with topical therapy now that he was no longer an inpatient, warranted escalated therapy in the form of periocular corticosteroid. Posterior corticosteroid would allow better posterior penetration than his current topical regimen, and would also reduce the patient's burden of topical medication.

After his optometric examination, the same cornea specialist was consulted and agreed with the need for escalated therapy. The cornea specialist performed a superotemporal sub-Tenon's injection of 0.3cc of Kenalog-40. The patient tolerated the procedure well. Prednisolone acetate 1% was decreased to one drop four times a day OS. The patient was to follow-up in three weeks.

Follow-Up #6 (Day 58):
On follow-up two months after initial presentation, the patient reported mild improvement in vision since the last exam and reported good compliance with prednisolone acetate 1% qid. Visual acuity OD remained stable at $20/50^{-1}$ and OS improved back to baseline $20/50^{-2}$. Upon slit lamp examination, he had mild Meibomian gland dysfunction and blepharitis of both eyelids. There was no conjunctival hyperemia of either eye. He had a small episcleral or deep scleral hemorrhage adjacent to the bleb from the sub-Tenon's injection. The right cornea was clear aside from a nasal pterygium extending 1.6mm past the limbus. The left cornea had peripheral iridocorneal adhesions from 10-11:00 and 5-7:00 with adjacent endothelial pigment, anterior stromal vascularization superiorly, and a nasal pterygium extending 1.4mm past the limbus. The right iris had posterior synechiae 360 degrees. There were no posterior synechiae in the left eye. The right anterior chamber remained quiet and the left anterior chamber had rare cell and stable 1+ flare. IOPs were 19 mmHg OD and 17 mmHg OS, via Goldman tonometry after instillation of one drop of Fluress OU. Based on the SUN[2] Working group descriptors of uveitis, this case was classified as a sudden onset, limited duration, recurrent anterior non-granulomatous uveitis.

However, a new fibrovascular membrane had started to form over the intraocular lens. The patient's cystoid macular edema had resolved and the associated subretinal fluid was almost resolved(Figure 8). The prednisolone acetate 1% was reduced to three times a day now that the anterior chamber cell reaction had resolved. The patient was to follow-up in three weeks.

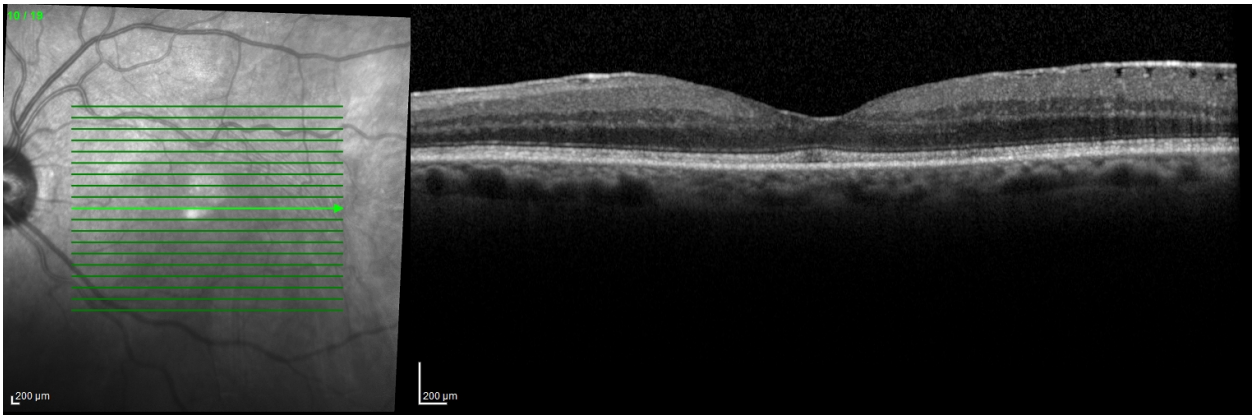


Figure 8. OCT of the left fovea showing near resolution of the subfoveal subretinal fluid.

Follow-Up #7 (Day 78):
Eleven weeks after initial presentation, the patient presented for follow-up and reported continued good compliance with medication and stable vision. Visual acuity remained stable OU at $20/50^{-1}$ OD and $20/50^{-2}$ OS. Upon slit lamp examination, there was mild Meibomian gland

dysfunction and blepharitis of both eyelids. There was no conjunctival hyperemia of either eye. The right cornea was clear aside from a nasal pterygium extending 1.6mm past the limbus. The left cornea had peripheral iridocorneal adhesions from 10-11:00 and 5-7:00 with adjacent endothelial pigment, anterior stromal vascularization superiorly, and a nasal pterygium extending 1.4mm past the limbus. The right iris had posterior synechiae 360 degrees. There were no posterior synechiae in the left eye. There was no anterior chamber reaction of the right eye and the left was stable at rare cell and 1+ flare. Intraocular pressure measured 18 mmHg OD and 15 mmHg OS, via Goldman tonometry after instillation of one drop of Fluress OU. The fibrovascular membrane had become more organized. The subretinal fluid was fully resolved(Figure 9).

Prednisolone acetate 1% was tapered to one drop twice a day OS for a month, then plan for one drop once a day likely indefinitely due to the long history of recurrence. The patient was to follow-up in one month.

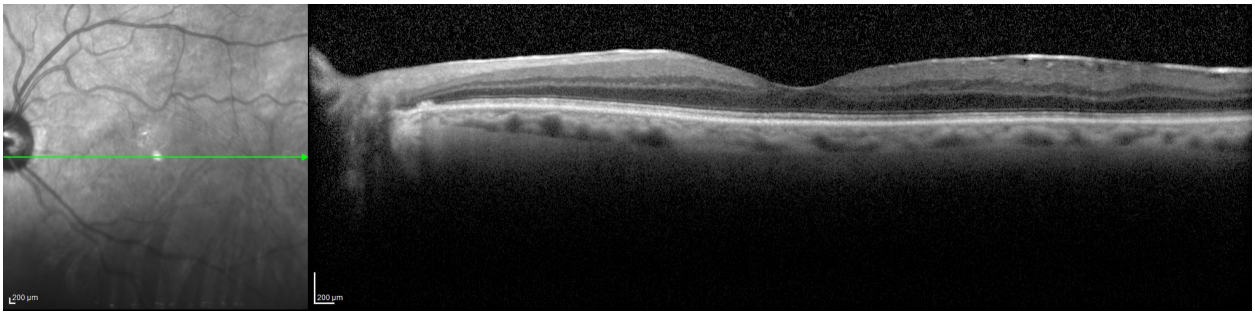


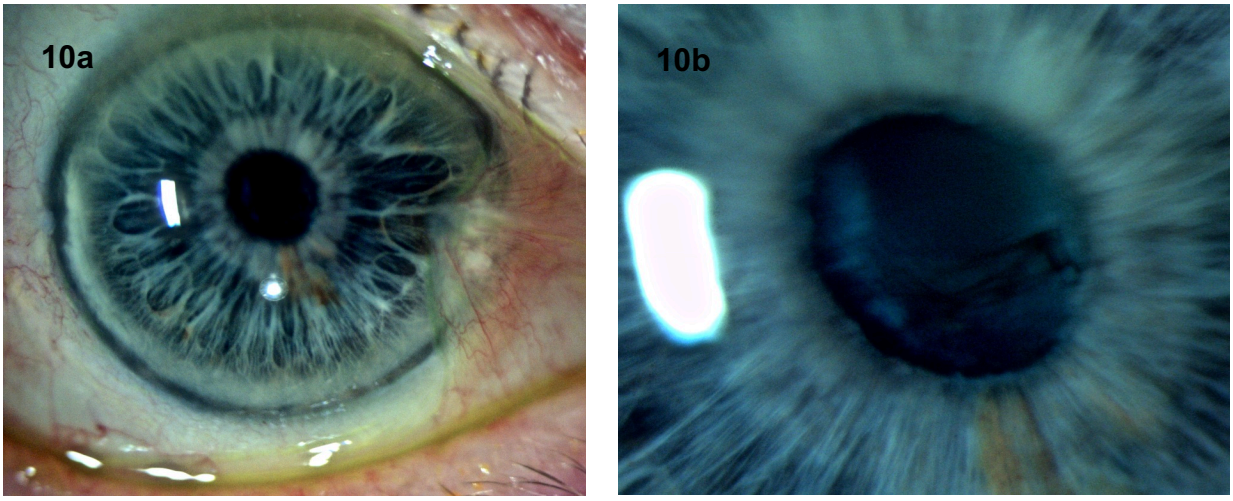
Figure 9. OCT high definition line scan of the left eye with resolution of the subfoveal serous detachment.

After optometric evaluation, the same cornea specialist was consulted due to the presence of the fibrovascular membrane despite near null anterior chamber cell. Given that the membrane was directly overlying the intraocular lens(IOL), the corneal specialist thought that laser photodisruption would be extremely difficult. Surgical removal would only be recommended if the membrane persisted with visual significance after being quiet for three months.

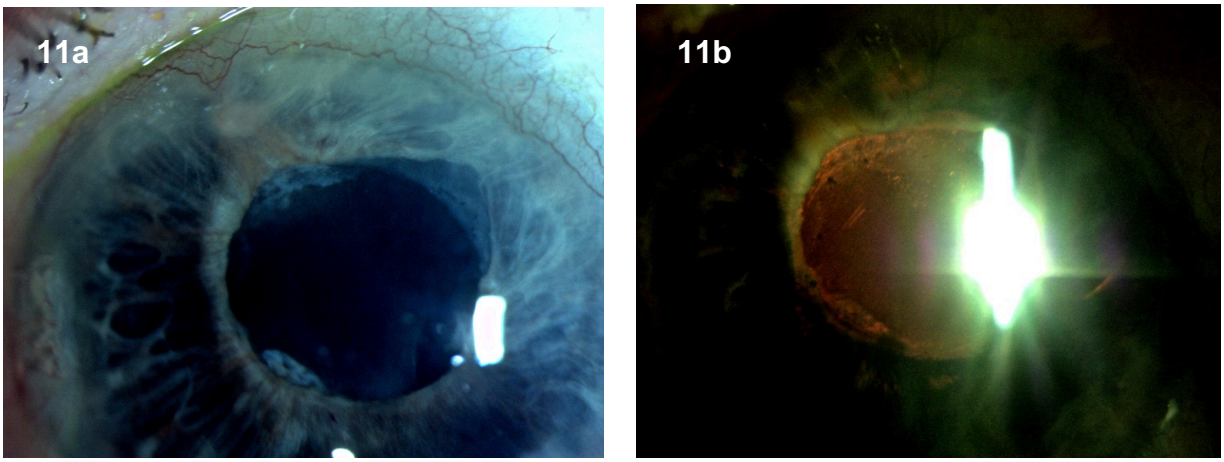
Follow-Up #8 (Day 106):
On follow-up one month later (3.5 months from initial presentation, the patient reported stable vision and symptoms and therefore, had not used prednisolone acetate 1% for the last eight days. He denied any difference in symptoms with and without medication. Visual acuity remained stable OU at $20/50^{-1}$ OD at $20/50^{-2}$ OS. Upon slit lamp examination, there was mild Meibomian gland dysfunction and blepharitis of both eyelids. There was no conjunctival hyperemia of either eye. The right cornea was clear aside from a nasal pterygium extending 1.6mm past the limbus. The left cornea had peripheral iridocorneal adhesions from 10-11:00 and 5-7:00 with adjacent endothelial pigment, anterior stromal vascularization superiorly, and a nasal pterygium extending 1.4mm past the limbus. The right iris had posterior synechiae 360 degrees. There were no posterior synechiae in the left eye. His anterior chambers were quiet with no cells OU, but trace flare remained OS. The fibrotic membrane had continued to organize but remained outside of the visual axis(Figures 10-11). Intraocular pressure measured 18

mmHg OD and 17 mmHg OS, via Goldman tonometry after instillation of one drop of Fluress OU. The patient was placed on a maintenance dose of 1 drop of prednisolone acetate 1% once a day OU.

The patient was educated on the importance of continued use of prednisolone acetate 1% despite lack of symptoms to prevent future recurrences and resulting vision-threatening complications. In the future, this maintenance dose may be increased to twice a day if the uveitis recurs despite good compliance with once a day dosing. The patient was to follow-up in three months with strict return precautions given if symptomatic for another flare.



Figures 10a and 10b. Slit lamp photos of the right eye with a magnified view of the fibrotic membrane and pigment on the anterior lens capsule (b)



Figures 11a and 11b. Slit lamp photos of the left eye a) corneal neovascularization superiorly, iridocorneal adhesion 11:00, fibrotic membrane over the IOL b) retro illumination highlights the fibrovascular membrane on the IOL adjacent to the pupil border

Based on the literature review and recommendations from an expert committee by Seve et al[9] further recommended tests to consider if the patient had another recurrence include radiography or magnetic resonance imaging (MRI) of the spine and sacroiliac joints looking for active

inflammatory lesions and structural changes consistent with spondylarthritis. However, positive predictive value of these tests is low if not symptomatic for insidious back pain, as he has been thus far. Additionally, for chronic uveitis, ACE, interferon gamma release assay (also known as QuantiFERON-TB Gold) and a chest computerized tomography (CT) are recommended, however the patient had already had ACE and QuantiFERON-TB Gold. He had not yet had a chest CT, but has had two normal chest x-rays.

Discussion:

HLA-B27 associated anterior uveitis is the most common identifiable cause of anterior uveitis. Among patients with acute anterior uveitis, the prevalence of the HLA-B27 allele is approximately 50%, but ranges greatly from 19-88% due to variation across different racial groups. HLA-B27 associated uveitis has a predilection for males 1.5 to 2.5 times more than females. The age of onset tends to be from the second to fourth decades of life, a decade earlier than non-HLA B27 associated anterior uveitis.[3,4] The clinical presentation is typically an acute onset, unilateral or unilateral alternating, non-granulomatous anterior uveitis with a high tendency for recurrence.[3,10] However, this recurrence tends to decrease with increased duration of the disease.[5]

HLA-B27 is highly associated with systemic disease, including ankylosing spondylitis, reactive arthritis, psoriatic arthritis, inflammatory bowel disease, and juvenile spondylarthritis. There are over 130 subtypes of HLA-B27, of which most are associated with acute anterior uveitis and/or spondylarthropathies. It has been proposed that differential peptide binding of HLA-B27 subtypes may explain differences in disease associations.[7] There are several theories on the pathogenesis of HLA-B27 associated diseases. One prominent theory is the arthrogenic/uveitogenic peptide hypothesis[11] in which HLA-B27 molecules present self peptides or antigens to HLA-B27 CD8+ T cells. These T cells are autoreactive and cross-reactivity with peptides induces inflammation in at these sites, including the eyes, joints, and other tissues. There is also evidence that C. *trachomatis* T cells and *helicobacter pylori* may be implicated in the pathogenesis of HLA-B27 associated disease. Additionally, misfolding of HLA-B27 heavy chains and innate immunity are also proposed mechanisms.[7] Further studies are needed to better understand the pathogenesis of HLA-B27 associated diseases, which will lead to better targeted therapy.

Although the patient in this case report did not systemic signs or symptoms of underlying systemic disease associated with HLA-B27, these cases of anterior uveitis are often associated with the spondylarthropathies. Monnet et al[5] conducted a large observational case series of one hundred seventy-five patients with HLA-B27 associated uveitis over a five-year period at a single center. All patients had both ophthalmic and rheumatologic evaluation. The median age at first attack of uveitis was 31 years and 66.9% of study participants had at least one prior attack of uveitis recorded prior to the study period. The first extraocular symptoms of HLA-B27 associated disease occurred at a younger age (26.4$\pm$11.1 years of age) than the first attack of

uveitis. Although the majority of patients exhibited extraocular symptoms prior to their first uveitis, in 88 of 136 patients, the rheumatologic diagnosis was made only at the time of diagnosis of uveitis. For those whose first presenting sign was uveitis, there was a greater delay (8.6±6.3years) in diagnosis of extraocular disease. Spinal pain was by far the most frequently reported early symptom (41.9%). Other symptoms included alternating buttock pain, oligoarthritis, prosiasis, dactylitis, urethritis, and acute diarrhea. Lastly, the study commented on treatment. Those with extraocular disease had a greater number of attacks than those with uveitis alone (5.4±8.8 for spondylarthropathy and 3.15±3.3 for uveitis alone). All patients were treated with topical steroids, and periocular steroid injections of corticosteroids were used in 49.7%. About a quarter (24%) received systemic corticosteroids during at least one episode.

The Assessment of Spondylarthritis International Society proposed and tested criteria for classifying spondylarthropathies into axial and peripheral categories.[19] These criteria are useful in guiding exploration of the patient's past medical record and during the case history. It is essential that patients with suspected underlying seronegative spondylarthropathies have a rheumatologic evaluation for proper diagnosis and management of their underlying disease.

Criteria for axial spondylarthritis	Criteria for peripheral spondylarthritis
Sacroiliitis on imaging plus one of the following: *or* HLA-B27 plus two of the following:	Arthritis/enthesitis of dactylitis plus one or more of the following:
Dactylitis	Uveitis or psoriasis
Psoriasis	Crohn's disease or colitis
Inflammatory back pain	Antecedent infection
Good response to non-steroidal anti-inflammatory medications	HLA-B27
Elevated C-reactive protein	Sacroiliitis on imaging *or* more than two of the following:
Inflammatory bowel disease	Arthritis
HLA-B27	Enthesitis
Uveitis	Dactylitis
Family history of spondylarthropathy	Inflammatory back pain
	Family history of spondylarthropathy

There exists a great variability in diagnostic work-up for patients with anterior uveitis, which has important implications for healthcare costs. Lee et al[12] conducted a cross-sectional survey in 2016 presented to the Executive Committee and Trustees of the American Uveitis Society to examine the variability of laboratory testing in practice and its impact on healthcare costs. Thirteen case scenarios were presented and executive committee members and trustees reported the investigations they would order for each scenario. The mean number of tests ordered per scenario per provider was 5.47 +/- 2.71 with a median of 5.0 tests. There was almost no consensus on evaluation between providers and most of the tests were ordered by less than half of the providers. The most commonly ordered tests were treponemal antibody tests (79.72%), chest x-ray (63.63%), CBC (39.86%), non-treponemal tests (33.57%), purified

protein derivative (PPD)/QuantiFERON (27.27%), fluorescein angiogram (27.27%), and ACE (23.78%). The average cost per clinical scenario per provider was $282.80 with a range from $0 to $1,145.50. Therefore, evidence-based guidelines are needed to more efficiently guide diagnostic work-up.

More recently, Seve et al[9] published evidence-based guidelines for the diagnostic work-up of uveitis etiologies. These recommendations were generated by a multidisciplinary panel of expert internists, ophthalmologists, and rheumatologists based on a review of the current literature. The first step of the recommended diagnostic strategy is based on findings from a thorough ophthalmic evaluation. Then, in the absence of clinical findings that orient towards a diagnosis or diagnoses, work-up is guided by the anatomic location of uveitis. For all types of uveitis, the recommended work-up includes CBC, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), tuberculin skin test, syphilis serology, and a chest x-ray. The authors emphasize the importance of syphilis serology regardless of the anatomic location of uveitis. Groen-Hakan et al [18] conducted a retrospective case review of ESR and CRP levels in patients with a first episode of acute uveitis in the Netherlands. Of those with anterior uveitis, the majority (48%) had both CRP and ESR within norms (ESR <20mm/hr, CRP <10mg/L). Twenty-four percent had both elevated ESR ($\geq$20mm/hr) and CRP ($\geq$10mg/L), 21% had elevated ESR but normal CRP, and 6% had elevated CRP but normal ESR. The cause of uveitis was established in 95% of patients with highly elevated ESR ($\geq$60mm/hr) and/or CRP ($\geq$60mg/L). ESR and CRP were not included in the patient's laboratory work-up and were not ordered once the fellowship candidate took over the patient's care because he was responding well to therapy, without signs of underlying systemic disease, and these tests are non-specific for inflammation. As highlighted by Groen-Hakan[18] most cases have normal ESR and CRP levels and the diagnostic value of these tests was greater when both were highly elevated, especially for sarcoidosis. If the patient were to re-flare, ESR and CRP testing should be performed.

For acute anterior non-granulomatous uveitis, HLA-B27 testing is recommended, as well as imaging of the sacroiliac region if the patient has insidious back pain.[13] For chronic uveitis, ACE, chest CT, and QuantiFERON-TB Gold are recommended. The diagnostic value of more invasive and complex studies, such as lumbar puncture, magnetic resonance imaging, and nuclear imaging needs to be further investigated in prospective studies. New genetic sequencing techniques and measurements of inflammatory markers may shift these guidelines in the future.[13]

Delving into the clinical characteristics of HLA-B27 associated uveitis, Loh and Acharya[10] examined the rates of ocular complications and vision loss in a retrospective longitudinal cohort study of ninety-nine patients with HLA-B27 associated anterior uveitis. The course of 75% of the patients was either acute or recurrent, with 20% chronic. The remaining were classified as indeterminate because the patients were on corticosteroid-sparing medications at presentation and thus, it was unable to be determined whether the patients' inflammation could be controlled unmedicated. Among those with at least six months of follow-up, 60% had recurrent and 31% had chronic disease. Over half (52%) had unilateral uveitis, followed by unilateral alternating in 39%. The inflammatory reaction was almost always non-granulomatous (98%) and anterior in

location (96%). Common ocular complications included vision loss (18%), posterior synechiae (17%), and posterior subcapsular cataracts (14%). Seventy-three percent of those that developed vision loss of 20/50 or worse improved to better than 20/50 by the end of the disease course. Of the seven patients that developed visual acuity of 20/200 or worse throughout the disease course, the majority (67%) of patients had improvement in vision by resolution of the disease. Statistically significant risk factors for vision loss included posterior synechiae at presentation, inflammation during follow-up, oral corticosteroids, corticosteroids injections and topical steroids.[7]

One ocular complication with the potential to cause vision loss as described above is macular edema. The prevalence of macular edema varies widely across studies. Studies have reported between 4.6-21%[5, 13, 14] of patients exhibit macular edema, however with improved detection via OCTs, the prevalence may actually be higher. Wexler et al[15] conducted a prospective study of thirty patients with anterior uveitis, all of whom were tested for HLA-B27 with 70% testing positive. All patients were treated with topical dexamethasone 0.1% and dosing was dictated by the severity of their anterior uveitis. Macular thickening was observed in 70% of patients compared to gender and age matched controls. The mean difference of the mean foveal thickness between those with HLA-B27 and those without was statistically significant at 14.1 microns. The prevalence was highest among those with acute episode (79%) ,but still common in those with recurrent or chronic disease (55%).

As with the need for evidence-based guidelines for the diagnostic work-up of uveitis, evidence-based guidelines are needed for the management and treatment of uveitis. The Ocular Immunology and Uveitis Foundation published preferred practice patterns for uveitis management in 2015.[16] These guidelines advocate for a treatment strategy that is aimed to cure, where cure encompasses any method needed to achieve a durable, corticosteroid-free remission, while inducing no harm to the patient's clinical condition or quality of life via side effects or complications of the disease. A step-wise approach to medical therapy is recommended, starting with the lowest but appropriately aggressive therapy and escalating as needed when the treatment fails to control inflammation or the patient becomes intolerant to the treatment.

This first step is often topical corticosteroids, especially in the case for anterior uveitis, as was used in the case report above. However, it is important to note that topical corticosteroids may also be effective in the management of vitritis or macular edema in pseudophakic, aphakic, or status-post vitrectomy patients. It has been reported that over 90% of acute anterior uveitis associated with HLA-B27 have been successfully treated with topical corticosteroids and cycloplegics.[7]

The next step in the escalation of therapy is periocular corticosteroids. This route of administration is effective when the desired site of action is more posterior in the globe, such as those with intermediate or posterior uveitis, or in cases of cystoid macular edema, as in the patient in this case report. One benefit of periocular steroids is that while delivering a therapeutic dose in approximation with the site of inflammation, they have few systemic side effects in adults.

Intravitreal corticosteroid injections are used typically for acute inflammation that is recalcitrant to periocular injections or to bridge the therapeutic gap between current corticosteroids and initiating corticosteroid sparing immunomodulatory therapy. A single pars plana intravitreal injection of 4 mg triamcinolone may produce sustained visual acuity improvement for three to at six plus months.

Corticosteroid implants can be inserted via intravitreal injection or surgical fixation to the sclera via the pars plana, often combined with a vitrectomy. These are indicated for patients with severe or recalcitrant noninfectious uveitis or are intolerant to systemic corticosteroids or immunomodulatory therapy (IMT). Ozurdex is a sustained release biodegradable implant containing dexamethasone 0.7mg in a polymer drug delivery system. Its average therapeutic effect averages three to six months. Retisert is sustained release non-biodegradable implant containing fluocinolone acetonide 0.59mg with a longer therapeutic effect at 30 months. Both of these procedures can be performed multiple times, but keeping in mind the high rate of cataract formation in phakic patients.

Oral systemic corticosteroid therapy is used when chronic uveitis becomes vision threatening and topical corticosteroids are insufficient or when the underlying systemic disease also requires therapy. Standard initial dosing is prednisone 1mg/kg/day with a taper usually by five to ten mg each week. Patients on high-dose oral corticosteroids should be on histamine-2 receptor blockers or proton pump inhibitors to reduce the risk of gastric and peptic ulcers as side effects from corticosteroids.

Moving away from corticosteroids, topical non-steroidal anti-inflammatory drugs (NSAIDs) can be used to treat post-operative inflammation and cystoid macular edema. Systemic NSAIDs can be used to prevent recurrent or chronic disease, especially idiopathic HLA B-27 associated, recurrent non-granulomatous anterior uveitis. Side effects of prolonged systemic NSAIDs include gastric ulcers, gastrointestinal bleeding, hypertension, nephrotoxicity, and hepatotoxicity. Long-term systemic NSAIDs are contraindicated for the patient in this case report due to his stage three chronic kidney disease.

Immunomodulatory therapy(IMT) is both anti-inflammatory and corticosteroid-sparing and may benefit those with sight threatening non-infectious uveitis or those who are resistant to or intolerant of corticosteroids. Due to potential side effects however, patients will require close monitoring. IMT for uveitis can be separated into four classes: antimetabolites, calcineuron inhibitors, biologic response modifiers, and alkylating agents. Common antimetabolites include methotrexate, azathioprine, and mycophenolate mofetil. All of these drugs work by inhibition of nucleotide synthesis or processing. Calcineurin inhibitors, such as cyclosporine, interrupt T-cell activity and growth by inhibiting calcineurin, which down regulates transcription of interleukin-2. Biologic response modifiers, also known as “biologics”, are typically antibodies used to target specific cytokines within the immune response. TNFα inhibitors, such as infliximab and adalimumab are two of the most widely used biologics for the treatment of uveitis. They block TNFα, a signaling protein that regulates various immune cells. These medications carry risks,

such as latent infection, so it is vital that patients are screened for infection prior to initiating therapy. Other risks include hepatotoxicity, anaphylaxis, demyelinating disease, drug-induced autoimmune disease, and secondary malignancies. Tocilizumab is another biologic. It works by inhibiting IL-6. The last class of immunomodulatory therapy is alkylating agents. These are used in cases of severe or refractory uveitis, or when patients cannot tolerate other medications. Cyclophosphamide and chlorambucil are examples of alkylating agents that work by alkylating nucleotide bases and interfere with DNA replication. Patients on these agents must be monitored weekly or bi-weekly for toxicity and bone marrow suppression. In some cases, combinations of immunomodulatory agents may be used to target inflammation via two different pathways.

New advances are on the horizon and further studies are needed to explore these modalities. Transscleral iontophoresis is a drug delivery system that uses a small electrical current to help diffusion of the drug across the sclera. The benefit of this therapy is that it is non-invasive and has fewer systemic side effects compared to systemic therapy. Additionally, optical coherence tomography angiography (OCTA) is being explored as a non-invasive imaging technique for monitoring disease activity.[17] Visualization of iris neovascularization, quantification of capillary non-perfusion in retinal vasculitis, and identification of retinal neovascularization area few of the possible applications of this technology.

Conclusion:

In conclusion, anterior uveitis is a common clinical diagnosis that is often associated with HLA-B27. The pathogenesis of HLA-B27 associated diseases is still being studied and better understanding will help guide targeted therapies. This subgroup of uveitis has unique characteristics including a non-granulomatous and anterior involvement that is typically acute or recurrent in duration. The diagnostic work-up of patients with uveitis should be guided by clinical characteristics as well as anatomic location, with recommended laboratory and imaging studies based on consensus among the current literature. Treatment should follow a step-wise approach, escalating therapy as needed when the current treatment fails to control inflammation or the patient becomes intolerant to the treatment. The end goal of therapy is to achieve a corticosteroid-free remission while inducing no harm to the patient's clinical condition or quality of life via side effects or complications of the disease. Novel drug delivery systems and OCTA applications are on the horizon and further studies will be needed to evaluate how they fit into recommended algorithm of diagnosis, management, and treatment of HLA-B27 associated uveitis.

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