

Juvenile Idiopathic Arthritis with Associated Bilateral Anterior Uveitis in a Four Year-Old Girl

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Chief complaint: Central posterior synechiae and macular edema in both eyes

History of Present Illness: The patient is a 4 year-old girl who presented to her local eye doctor for routine preschool screening and was found to have central posterior synechiae in both eyes (OU), for which she was started on Atropine 1% OU for 6 weeks. On follow-up, she was found to have macular edema and was referred to pediatric rheumatology for further systemic evaluation with suspicion of inflammatory etiology, and subsequently to pediatric ophthalmology.

Past Ocular History: None

Past Medical History:

- Born at term by repeat C-section after an uncomplicated pregnancy
- History of intermittent labial adhesions

Medications: amoxicillin 400 mg orally, twice daily (BID) for an upper respiratory infection

Allergies: None

Family History: Positive for maternal aunt with psoriasis, otherwise non-contributory.

Social History: Patient lives with her parents. There are no pets in the household.

Review of Systems: Positive for a small, round, recurrent rash on the left forearm. Otherwise, negative in detail, including no joint pain.

Ocular Examination:

Visual Acuity: 20/20 right eye (OD) and 20/25 left eye (OS)

Current refraction: +2.00 sphere OD and OS

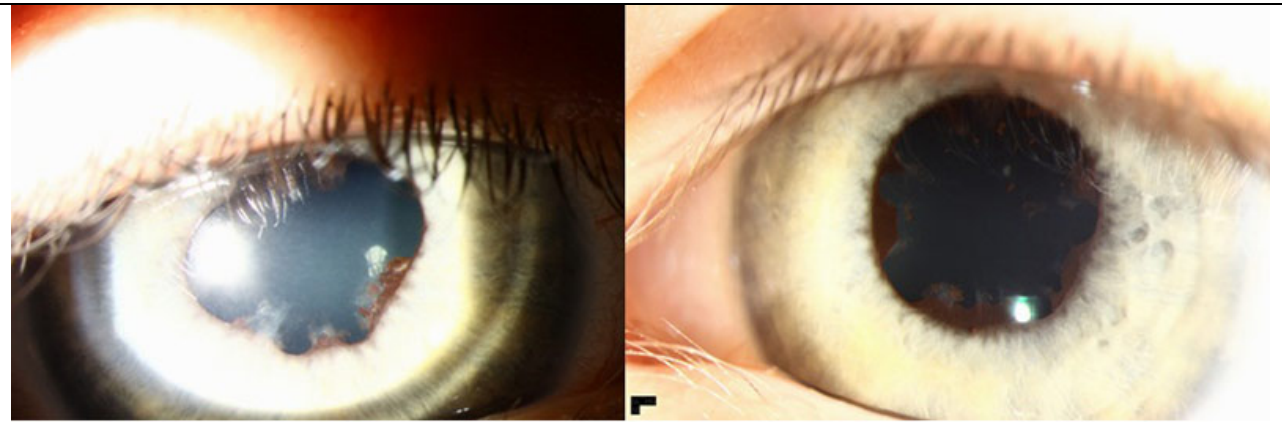
Pupils: 5 mm in dark, 3 mm in light OU without relative afferent pupillary defect

Extraocular movements: Full OU

External: Normal

Slit Lamp Exam: Normal lids and lashes OU, trace injection OU, corneas clear, anterior chambers with 1+ flare and no cell OU, central posterior synechiae OU (Figure 1), lenses show pigment deposits on anterior lens capsule OU

Figure 1: Color slit lamp photographs of central posterior synechiae OU



Dilated Fundus Exam: Bilaterally normal discs, macula, vessels and periphery. No cystoid macular edema (CME) seen.

Musculoskeletal exam: Notable for thickening and fullness of the left ankle, incomplete extension with flexion contraction of right elbow to 70 degrees with thickening felt at medial epicondyle. No pain or warmth noted. Otherwise unremarkable.

Laboratory testing:

ANA	Positive at 1:160, diffuse pattern
Angiotensin-1 converting enzyme	60 U/L (normal 8-52 U/L)
Lyme disease antibody (IgG/IgM)	Negative
Erythrocyte sedimentation rate	14 mm/hr (normal 0-20 mm/hr)
HLA-B27 typing	Negative
Serum IgA	59 mg/dL (normal 27-195 mg/dL)
Serum IgG	667 mg/dL (normal 504-1464 mg/dL)
Urinalysis	Unremarkable

Imaging:

- X-ray of left ankle and right elbow show anterior sail sign on the right elbow
- radiograph consistent with a joint effusion. No synostosis or erosions.
- Optical coherence tomography (OCT): Unable due to patient cooperation

Based on the patient's lack of cells in the anterior chamber, CME on exam and poor cooperation with OCT testing, it was decided to defer topical steroids in lieu of a repeat exam in one month.

One month follow-up exam:

Visual Acuity: 20/25 right eye (OD) and 20/20 left eye (OS)

Intraocular pressure: 8 mmHg OD, 13 mmHg OS by iCare

Current prescription: +2.50 sphere OD, +2.00 +0.50 x 015 OS

Pupils: 5 mm in dark, 3 mm in light OU without relative afferent pupillary defect

Extraocular movements: Full OU

External: Normal

Slit Lamp Exam: Normal lids and lashes OU, conjunctiva clear and quiet OU, corneas show band keratopathy temporally with fine keratic precipitates OU, anterior chambers with 2+ flare and 2+ cell OU, normal iris architecture OU, lenses show pigment deposits on anterior lens capsule OU

Dilated Fundus Exam: Blunted foveal light reflex OD, normal macula OS. Bilaterally normal discs, vessels and periphery.

Optical coherence tomography: Florid CME OD with central macular thickness of 634 microns (Figure 2); central macular thickness OS 330 microns, no intraretinal or subretinal fluid.

The patient was begun on Pred Forte® (prednisolone acetate ophthalmic suspension, USP, 1%) OU every 2 hours while awake, ketorolac OU four times daily and atropine OU at bedtime. Patient was seen by the pediatric rheumatology service later that day, and after a long discussion with the patient's parents, it was decided to begin methotrexate 25 mg subcutaneously weekly with 1 mg of folic acid daily.

Two week follow-up exam in coordination with the Retina service:

Visual Acuity: 20/25 right eye (OD) and 20/30 left eye (OS)

Intraocular pressure: 33 mmHg OD, 27 mmHg OS by iCare

Current prescription: +2.50 sphere OD, +1.75 +0.75 x 018 OS

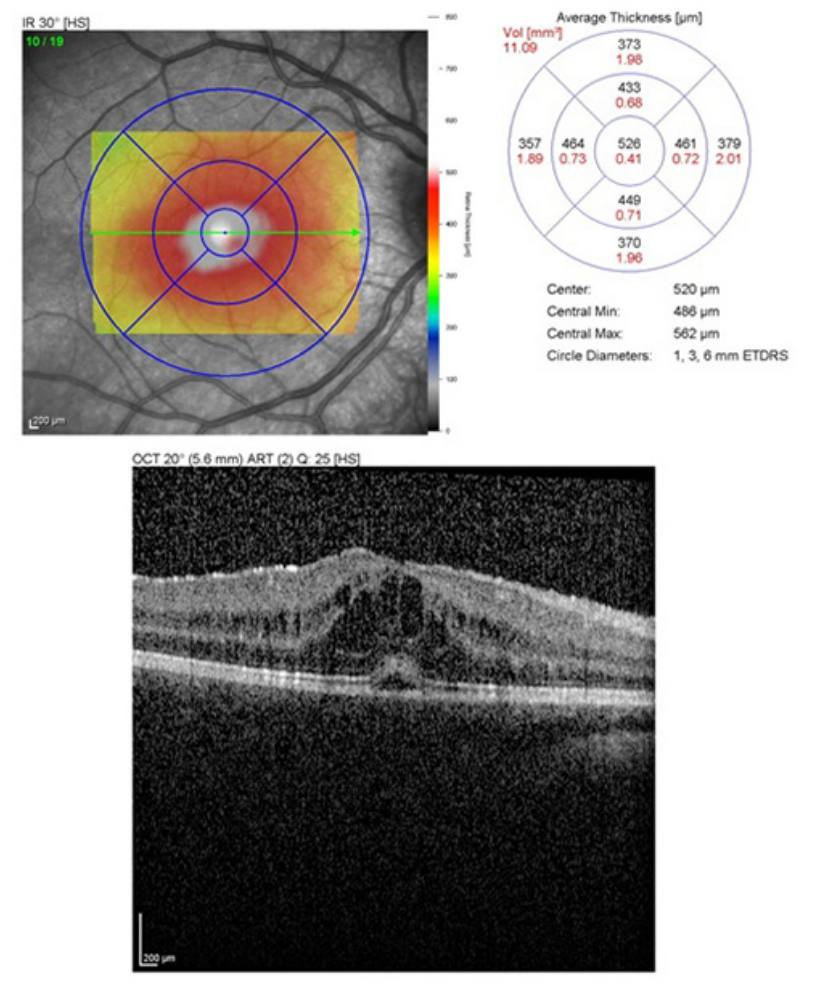
Pupils: 7mm in dark and light OU due to pharmacologic dilation

Extraocular movements: Full OU

External: Normal

Slit Lamp Exam: Normal lids and lashes OU, conjunctiva clear and quiet OU, corneas show early band keratopathy temporally with fine keratic precipitates OU, anterior chamber showed 1+ flare

Figure 2: Heidelberg OCT image showing cystoid macular edema in the right eye.



and no cell OD and trace flare with no cell OS, iris showed multiple posterior synechiae OU, lenses show pigment deposits on anterior lens capsule OU

Dilated Fundus Exam: 1+ vitreous flare without cell OU, bilaterally normal discs, macula, vessels and periphery. No macular edema.

Optical coherence tomography: OD: Central macular thickness 317 microns (was 634 microns) with total resolution of CME (Figure 3); OS: central macular thickness 302 microns (was 330 microns), no CME.

The patient was started on Cosopt® (Dorzolamide and Timolol Ophthalmic) OU twice daily for steroid-induced ocular hypertension, Pred Forte was decreased to every 3 hours OU while awake, ketorolac was continued four times daily in the right eye only, and atropine was stopped.

Three week follow-up exam:

Visual Acuity: 20/30 right eye (OD) and 20/30 left eye (OS)

Intraocular pressure: 13 mmHg OD, 13 mmHg OS by iCare

Current prescription: +2.50 sphere OD, +1.75 +0.75 x 018 OS

Pupils: 5 mm in dark, 3 mm in light OU without relative afferent pupillary defect

Extraocular movements: Full OU

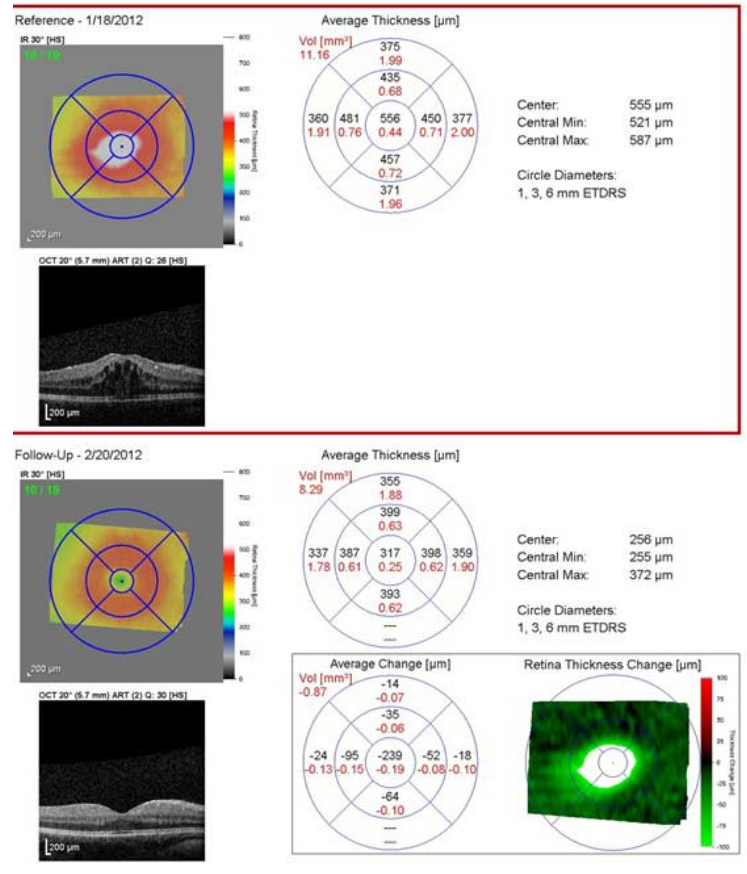
External: Normal

Slit Lamp Exam: Normal lids and lashes OU, conjunctiva clear and quiet OU, cornea clear OD and early band keratopathy OS with interval resolution of fine keratic precipitates OU, anterior chamber showed trace to 1+ flare and no cell OD and trace flare with trace to 1+ cell OS, iris showed multiple posterior synechiae OU, lenses show pigment deposits on anterior lens capsule OU

Dilated Fundus Exam: 1+ vitreous flare without cell OU, bilaterally normal discs, macula, vessels and periphery. No macular edema.

Optical coherence tomography: OD: Central macular thickness 301 microns (was 317 microns) with total resolution of CME; OS: central macular thickness 295 microns (was 302 microns), no CME.

Figure 3: Heidelberg OCT image showing initial OCT with cystoid macular edema (top image) and subsequent resolution of cystoid macular edema (bottom image) in the right eye.



The patient's Pred Forte® was increased back to every 2 hours OU while awake due to recurrence of anterior inflammation in the left eye, and ketorolac and Cosopt® were continued.

On subsequent follow-up exams, the patient had stable inflammation with trace to 1+ flare and no cell OD and 1+ flare and trace cell OS without recurrence of macular edema. The patient's Pred Forte® was decreased to OU four times daily. Four weeks later, patient had stable mild anterior chamber inflammation, and Pred Forte was tapered to OU twice daily, and ketorolac and Cosopt® were continued.

Diagnosis: Juvenile idiopathic arthritis with associated bilateral anterior uveitis

Discussion:

Uveitis is commonly associated with juvenile idiopathic arthritis, most commonly in the oligoarticular category, in which 2-4 joints are involved, within the first 6 months of diagnosis. Additional risk factors include female sex, positive ANA, and negative rheumatoid factor. Unlike uveitis in adults, which often presents with pain, photophobia and redness of the eye, JIA-associated uveitis in children can present with a quiet-appearing eye. Due to the asymptomatic nature, it is important to follow recommended uveitis screening guidelines for children with JIA. After initial ophthalmologic examination at the time of JIA diagnosis, the frequency of follow-up eye exams in patients with JIA is determined by their risk category (Cassidy et al., 2006). High-risk patients, who have positive ANA, are 6 years old or less at onset of joint disease and have had JIA for 4 years or less should be examined every 3 months. Moderate and low risk patients are determined based on a combination of ANA status, age at onset, and duration of disease (Cassidy et al., 2006). Patients with moderate risk should be examined every 6 months, and low risk patients should be examined every 12 months, as shown in Table 1.

Table 1. Frequency of eye exams in patients with JIA, adapted from Cassidy et al., 2006.

Type	ANA	Age at Onset (years)	Duration of Disease (years)	Risk Category	Frequency of Eye Exams
Oligoarthritis or polyarthritis	+	≤ 6	≤ 4	High	3 months
	+	≤ 6	> 4	Moderate	6 months
	+	≤ 6	> 7	Low	12 months
	+	> 6	≤ 4	Moderate	6 months
	+	> 6	> 4	Low	12 months
	-	≤ 6	≤ 4	Moderate	6 months
	-	≤ 6	> 4	Low	12 months
	-	> 6	N/A	Low	12 months
Systemic disease	N/A	N/A	N/A	Low	12 months

Approximately 10% of patients with oligoarticular JIA have uveitis (Kotaniemi et al., 1999), with 37.3% of JIA-associated uveitis patients experiencing complications from the disease or associated

steroid-treatment, such as cataract, posterior synechiae, band keratopathy, glaucoma, or macular edema (listed in decreasing order of incidence) (Sabri et al., 2008). Macular edema was found to occur in 5.6% of 147 children with JIA-associated uveitis, or 3.9% of eyes, as the majority of patients had bilateral uveitis, but less commonly bilateral macular edema (Sabri et al., 2008).

The treatment of JIA-associated chronic uveitis is largely based on clinical course, but basic recommendations exist to guide therapy (Heiligenhaus et al., 2012). Patients presenting with uveitis in the setting of JIA are initially started on topical corticosteroid. If there are prognostic factors of impending vision loss such as poor initial vision, hypotony, glaucoma, cataract, macular edema, or dense vitreous opacities, it is also recommended that systemic corticosteroids are begun, at a dosage of 1-2 mg/kg, and tapering to <0.15 mg/kg within 4 weeks. Oral corticosteroids should be limited to 3 months use secondary to systemic complications, and similarly, topical corticosteroid should be limited to no more than 3 drops per day for chronic use due to risk of cataract and glaucoma. If the uveitis remains active or reactivates within these guidelines, steroid sparing agents should be begun.

Methotrexate, a folate analogue which inhibits a key step in DNA synthesis, is currently the preferred steroid sparing agent in JIA-associated uveitis (Heiligenhaus et al., 2012). Several studies have shown its effectiveness in treating chronic uveitis. Malik et al, 2005, examined the use of low-dose methotrexate in ten children with bilateral chronic anterior and intermediate uveitis. This study found significantly better visual acuity, decrease in anterior chamber inflammation, topical corticosteroid frequency, and oral steroid use than prior to using methotrexate. This study, however, did not include any patients with JIA-associated uveitis. Weiss et al., 1998, reported on seven children with JIA-associated chronic uveitis treated with methotrexate, and 6/7 were found to have a significant reduction in the severity of uveitis, based on the number of cells seen in the anterior chamber. Foeldvari and Wierk, 2005, performed a retrospective chart view of 25 patients with chronic JIA-associated uveitis who were treated with methotrexate. Twenty-one of the 25 patients responded to methotrexate therapy, and in 6 of these patients, methotrexate was discontinued due to continuous remission. There was one case of cystoid macular edema in a 13 year-old patient in Malik et al.'s study, which resolved with methotrexate treatment, although this patient's uveitis was not associated with JIA. There were no cases of macular edema among the JIA-associated uveitis cases treated with methotrexate in the above studies.

Pato et al., 2011, have studied the effect of immunosuppressants and biological therapies in treating posterior autoimmune uveitis and its complications. In this systematic review, they found several studies which have effectively treated macular edema. The agents that were found to be effective include cyclosporine, infliximab, daclizumab, INF-alpha-2a, acetazolamide and methylprednisolone. There was no report of which medications were found to be ineffective in treating macular edema. There were no studies found in which the effect of methotrexate on macular edema associated with posterior uveitis was evaluated.

We present a case in which a 4 year-old girl with oligoarticular JIA and associated chronic uveitis developed a vision threatening complication of macular edema and was successfully treated with methotrexate for her arthritis, and macular edema. The patient was treated with topical corticosteroids and ketorolac for her ocular inflammation, and in conjunction with the methotrexate, she did not need any other therapies for macular edema, such as intravitreal or periocular steroid, which would be difficult to administer in a 4 year-old child without general anesthesia. Interestingly,

she was not begun on oral steroids prior to starting methotrexate, based on the established aggressive course of her disease.

Differential Diagnosis: HLA-B27 associated uveitis, HSV uveitis, Lyme disease uveitis, syphilitic uveitis, tuberculosis uveitis, tubulointerstitial nephritis and uveitis (TINU), idiopathic uveitis.

<p>Signs</p> <p>Anterior chamber cell and flare, often without conjunctival injection</p> <p>Complications include cataract, posterior synechiae, band keratopathy, glaucoma, and macular edema</p>	<p>Risk factors for uveitis</p> <p>Oligoarticular</p> <p>positive ANA</p> <p>negative rheumatoid factor</p> <p>females</p>
<p>Symptoms</p> <p>Often asymptomatic.</p>	<p>Treatment</p> <p>Topical corticosteroids, possibly with oral corticosteroids based on severity and complications</p> <p>With persistent inflammation at maximal recommended treatment, steroid-sparing agents should be begun</p>

Recommended screening: At first diagnosis of JIA, then every 3-12 months, based on risk category, which is determined by ANA, age at onset of disease, and duration of disease, as shown in Table 1, above.

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