

## Diagnostic and Therapeutic Challenge: Pediatric Uveitis and Retinitis

Ashvini K Reddy<sup>1\*</sup>, Christopher T Shah<sup>1</sup>, and Bryn M Burkholder<sup>2</sup>

<sup>1</sup>Department of Ophthalmology, University of Virginia, USA

<sup>2</sup>Department of Ophthalmology Wilmer Eye Hospital, Johns Hopkins, USA

\*Corresponding author: Ashvini K Reddy, MD, 1300 Jefferson Park Avenue, OMS 2860B, Charlottesville, VA 22908, Tel: (434) 924-5653; Fax: (434) 924-5180; E-mail: akr5u@virginia.edu

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### Introduction:

Although children represent only 5% to 10% of all patients in most uveitis clinics, [1,2] familiarity with the diagnosis and management of pediatric uveitis is critical. Children with uveitis may have late presentations, limited ability to communicate symptoms, and examinations limited by cooperation which may create management dilemmas. Outcomes may be influenced by amblyopia and therapeutic limitations (i.e. contraindications to prolonged use of systemic steroids in growing patients) [3,4]. Herein, we describe the clinical course of an 8 year old with evolving uveitis to illustrate diagnostic and therapeutic challenges faced in these settings.

### Case Report

A healthy eight year old Hispanic female was referred for several days of bilateral eye redness. Examination at that time was remarkable for vision of 20/70-OD and 20/100 OS with pinhole acuity of 20/20 OU, absence of afferent pupillary defect, and normal intraocular pressures. Slit lamp examination revealed 2+ conjunctival injection with ciliary flush, diffuse fine keratic precipitates, anterior chambers with 4+ cell and 2+ flare, and posterior synechiae OU. Poor pupillary dilation limited assessment of the peripheral retina, but no retinal lesions were appreciated. On review of systems (ROS), the patient endorsed an upper respiratory infection (negative Rapid Streptococcus Test) three weeks prior but denied fevers, chills, headaches, joint pain, and hematuria. Workup included urinalysis, quantiferon gold, rheumatoid factor, serum lysozyme, Lyme titers, angiotensin converting enzyme, antinuclear antibodies, syphilis IgG, human leukocyte antigen (HLA) B27 including HLA typing (HLA-A2, HLA-B41/B56, HLA-CW1/CW17), complete blood count, serum creatinine, and liver function tests-all of which were normal, except for the presence of white blood cells, red blood cells, and casts in the urine. Given negative ROS and urinalysis findings, the patient was presumptively diagnosed with tubulointerstitial nephritis and uveitis (TINU) syndrome and referred to the nephrology service. She was initially treated with prednisolone acetate (PA) every hour OU and cyclopentolate 2% BID OU. Persistent inflammation despite escalation of therapy to difluprednate QID OU led to initiation of oral prednisone at 1 mg/kg/day.

Two months after presentation, the inflammation had improved, and the posterior synechiae had broken, which allowed for a more complete examination. The peripheral retina was remarkable for granular, peripheral retinitis in both eyes (Figures 1A and 1B). With the new findings of bilateral retinal necrosis in addition to the bilateral anterior uveitis, TINU was felt to be less likely and differential was expanded to include Punctuate Outer Retinal Toxoplasmosis (PORT) and Bilateral Acute Retinal Necrosis (BARN) from a viral infection.

Additional workup was performed, including serologies for toxoplasma, Bartonella, herpes simplex virus (HSV), varicella zoster virus (VZV) titers, and cytomegalovirus (CMV), all of which were non-diagnostic. An anterior chamber paracentesis was recommended and initially deferred by the parents, as the child was very poorly cooperative. The oral prednisone was rapidly tapered, and she was started on oral trimethoprim-sulfamethoxazole 800/160 mg PO BID and valacyclovir 1G PO TID, as per pharmacy's recommendation for a patient of her age and size to cover for infection with HSV, VZV, and toxoplasmosis. After four days of minimal change on valacyclovir and trimethoprim-sulfamethoxazole, the family agreed to an anterior chamber paracentesis, which was performed, and subsequent polymerase chain reaction (PCR) testing for CMV, Toxoplasma, HSV, and VZV were negative. During this time she also had an evaluation by the renal service, including a normal renal ultrasound, and her nephrologists felt that her presentation and repeat urinalysis was not consistent with tubulointerstitial nephritis.

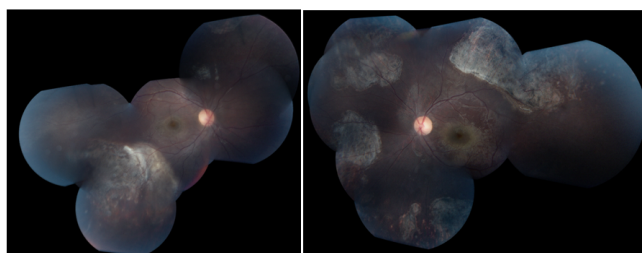


**Figure 1:** Fluorescein angiogram with late sweeps of peripheral retina demonstrating peripheral retinitis without vaso-occlusive changes. A) Right fundus. B) Left fundus.

A week following the paracentesis, the patient returned with decreased vision and pain OU. Examination revealed recurrent anterior chamber inflammation and vitritis with persistent retinitis. The oral prednisone was restarted at 30 mg PO daily, and she was given the first of three weekly intravitreal foscarnet injections to cover for viral infection, including CMV retinitis. In addition, valacyclovir was switched to induction dose valganciclovir 900 mg PO BID. The infectious disease service was consulted, and no evidence of systemic infection or immunocompromise was found. HIV testing and CD4 counts were normal. Flow cytometry for markers of natural killer cell dysfunction were also negative. Given the working diagnosis of CMV retinitis, the trimethoprim-sulfamethoxazole was stopped. She subsequently developed worsening vitritis without worsening retinitis.

Three issues were discussed with the family at this point: (1) the patient had not responded fully to valacyclovir, (2) there was risk of false negative PCR from her aqueous sample, and (3) the patient had some worsening of vitritis when trimethoprim-sulfamethoxazole was discontinued. Given these considerations, the patient was kept on trimethoprim-sulfamethoxazole, valganciclovir, and oral prednisone for eight weeks. At that time, the trimethoprim-sulfamethoxazole was discontinued again without incident, and the prednisone dose was tapered.

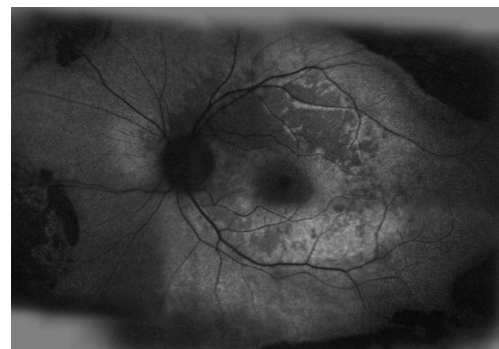
Approximately six months following her initial presentation, the patient's retinitis remained inactive with vision 20/25 OD and 20/60 OS with mild vitreous haze OD and vitreous opacities OS while on prednisone 10 mg PO daily and valganciclovir 450 mg PO BID. Unfortunately, when the prednisone was tapered to 7.5 mg PO, the retinitis returned and progressed. Her prednisone was therefore increased back to 20 mg PO daily. Despite this, the retinitis progressed towards the macula OD, and vitritis worsened OS. She underwent a 25 gauge diagnostic and therapeutic pars plana vitrectomy (PPV) OS with vitreous biopsy and intravitreal injections of foscarnet 2.4 mg/0.1 ml, amphotericin 5 mcg/0.1 ml, and ceftazadime 2.25 mg/0.1 ml. Studies from the vitreous samples were negative for malignancy, Epstein-Barr virus (EBV), HSV, CMV, VZV, and toxoplasmosis. Steroid taper following vitrectomy again led to return of retinitis OD. Stability of her retinitis was ultimately achieved with 40 mg of prednisone PO and valganciclovir 450 mg PO BID. Her course was complicated by considerable weight gain on prednisone, but given the suspicion of a viral etiology, steroid-sparing agents were not recommended. She developed steroid response with ocular hypertension OS which required dorzolamide hydrochloride-timolol maleate BID and brimonidine tartrate BID OS. At last follow-up 9 months following presentation, her vision was 20/25 OU and both retinas were attached with inactive, peripheral necrotic lesions (Figures 2A, 2B and 3).



**Figure 2:** Color fundus photos demonstrating peripheral necrotic lesions with chronic pigmentary changes and borders threatening the macula in both eyes.

## Discussion

Undifferentiated uveitis can be a frustrating condition in adults, and may be even more challenging in children. In a multicenter epidemiologic review of 572 pediatric uveitis patients, the most common diagnosis was idiopathic uveitis (28.8%) followed by juvenile idiopathic arthritis (20.9%) and pars planitis (17.1%) [4]. Infectious uveitis was more likely to present as posterior or panuveitis with a worse visual prognosis [4]. Of the infectious causes of posterior uveitis in all age groups, toxoplasmosis was the most common etiology [1].



**Figure 3:** Autofluorescence montage demonstrating peripheral retinal necrosis as well as retinal pigmentary epithelial changes within the macula and disc.

Children with uveitis may have limited insight into their condition and difficulty cooperating with an examination. In many centers, examinations under anesthesia are not possible or carry additional cost. A specialized anesthesiologist may also be required. Ancillary testing and outpatient procedures, such as intraocular fluid collection and intravitreal injections, require cooperation and induce stress that may be emotionally traumatizing to children. When recalcitrant inflammation necessitates serial examinations and procedures, but disease remains undifferentiated, families of children often express anxiety about many aspects of care.

This case highlights several of the challenges encountered in the management of pediatric uveitis: The initial presentation of bilateral, acute, anterior uveitis in the setting of a positive urinalysis was suspicious for tubulointerstitial nephritis and uveitis. However, TINU rarely causes posterior uveitis, so the development of peripheral retinitis prompted an infectious work-up, including viral serologies [5].

In adult patients, intraocular fluid aspiration is routinely performed in this scenario, but because cooperation limited the ability to perform a diagnostic paracentesis when retinitis was first observed, empiric treatment was initiated with trimethoprim-sulfamethoxazole and valacyclovir to cover for HSV and VZV as well as toxoplasmosis. At this time, the patient had no risk factors for CMV retinitis. Because her inflammation persisted and her ability to cooperate improved, she eventually underwent an anterior chamber paracentesis and was given intravitreal injections of foscarnet. Because inflammation did not subside with valacyclovir, the valacyclovir was changed to valganciclovir to add coverage for CMV though she had a normal CD4 count and no other evidence of immunocompromise.

In our case, inability to taper the steroids despite antibiotic and antiviral coverage prompted vitrectomy in the hope that it would aid in diagnosis and to eliminate the possibility of a masquerading malignancy [6]. Vitreous biopsy ruled out malignancy, and PCR of vitreous for Epstein-Barr virus, HSV, VZV, CMV, and toxoplasmosis was negative, leaving us without a definite etiology. It is worth noting that the sensitivity and specificity of herpesviridae PCR testing are 46% and 98%, respectively, [7] and so the possibility of false negative PCR result exists. Because the patient's clinical examination is so suggestive of CMV retinitis, the patient continues to be treated with valganciclovir and oral prednisone.

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## Conclusion

In summary, undifferentiated pediatric uveitis can present diagnostic and therapeutic challenges to the practicing ophthalmologist, and dilemmas are not uncommon. In some cases, empiric treatment is necessary initially, and management may need to be frequently revised. As with the case described here, the etiology of the inflammation may remain undifferentiated despite extensive laboratory testing, multidisciplinary referrals, and diagnostic surgical procedures.

## Criteria for Authorship

All authors meet the uniform requirements of the Journal of Clinical and Experimental Ophthalmology criteria for authorship.

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