

Case report

Treatment challenges in an atypical presentation of tubulointerstitial nephritis and uveitis (TINU)



Sonny Caplash^a, Sapna Gangaputra^a, Shilpa Kodati^a, Shamir Tuchman^b, Hemalatha Srinivasalu^c, H. Nida Sen^{a,*}

^a Laboratory of Immunology, National Eye Institute, National Institutes of Health, Bethesda, MD, 20814, United States

^b Division of Pediatric Nephrology, Children's National Medical Center, Washington DC, 20010, United States

^c Division of Rheumatology, Children's National Medical Center, Washington DC, 20010, United States

ARTICLE INFO

Keywords:

Immunosuppression
Inflammation
Tubulointerstitial nephritis
Uveitis

ABSTRACT

Purpose: To describe an atypical presentation of Tubulointerstitial Nephritis and Uveitis (TINU), with challenges in treatment course.

Observations: A 12-year-old Hispanic female presented to the National Eye Institute's Uveitis clinic with bilateral blurred vision, red eyes and photophobia, not responsive to topical steroids. On exam, she had bilateral severe panuveitis with areas of subretinal fluid. During her evaluation, she was noted to have elevated serum creatinine. A kidney biopsy confirmed the presence of severe tubulointerstitial nephritis and interstitial fibrosis. She was treated with oral steroids with excellent resolution of symptoms and subretinal fluid. She continued to have anterior segment flares with attempts to taper oral prednisone which lead to treatment with multiple immunomodulatory agents. Associated hypertension and kidney damage complicated the choice of a secondary immunosuppressive agent.

Conclusions and Importance: Although rare, TINU can present as panuveitis with choroidal involvement which may or may not be preceded by tubulointerstitial nephritis. A renal biopsy is required for definitive diagnosis, but abnormal urinalysis or renal function should raise suspicion for TINU.

1. Introduction

Tubulointerstitial Nephritis and Uveitis (TINU) is a rare disease with an estimated prevalence of 0.1%–2.3% of uveitis diagnoses; though it is speculated that this is an underestimation due to the multisystem nature of the clinical presentation precluding prompt diagnosis.¹ TINU was classically characterized in the literature as a disease that affected females (3:1) presenting in adolescence (age range 9–74 years).² However, recent evidence suggests that there is no sex difference.^{3–5} While often idiopathic in etiology, drugs such as non-steroidal anti-inflammatory drugs and certain antibiotics are implicated as a cause of TINU.^{2,6}

TINU is typically characterized by acute onset, bilateral, non-granulomatous, mild anterior uveitis accompanied by tubulointerstitial nephritis, however there have been sporadic reports of TINU presenting with posterior uveitis.^{6,7} Complications of TINU can include posterior synechiae, optic disc swelling and cystoid macular edema. TINU is generally self-limiting, but recurrences have been documented.^{2,4,8} While recurrences of uveitis tend to be rarer in younger patients, they

are more likely to progress to chronic uveitis than older patients.²

There are several systemic diseases that have both renal and uveal involvement and can therefore appear clinically similar to TINU, such as: Sarcoidosis, Behcet's disease, Sjogren's disease, Granulomatosis with polyangiitis, Systemic Lupus Erythematosus and IgA nephropathy.² In TINU, the uveitis can precede, or coincide with the interstitial nephritis.³ The inconsistency of presentation timeline among cases can compound the diagnostic difficulty. We present a challenging and atypical case of TINU in a young Hispanic female with a history concerning for Lyme associated uveitis due to positive IgM, a clinical appearance suggestive of VKH due to exudative detachment and a poor response to standard of care treatment with oral corticosteroid and immunosuppressant medications. We elaborate upon the diagnostic dilemma and multidisciplinary team decision making that helped elucidate the etiology and frame the management.

2. Case history

A 12-year-old Hispanic female and recent immigrant from

* Corresponding author. 10 Center Dr, 10/10N248, Bethesda, MD, 20892, United States.
E-mail address: senh@nei.nih.gov (H.N. Sen).

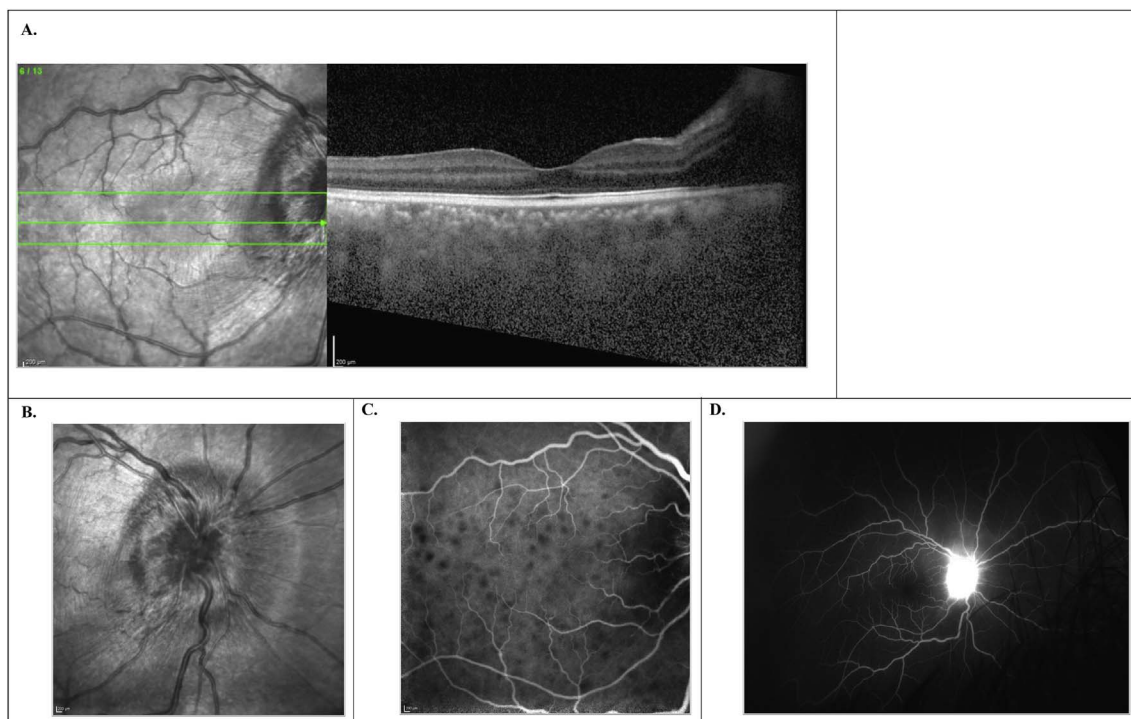


Fig. 1. Right Eye at Presentation.

A. Macula Optical Coherence Tomography (OCT) demonstrates normal foveal contour and thickness. Nasal disc edema can also be noted. B. Infrared imaging (IR) of the optic nerve shows 360-degree disc edema. C. Indocyanine green (ICG) angiography at 5 minutes shows multiple hypofluorescent spots in the choroid. D. Fluorescein angiography (FA) at 10 minutes shows leakage from the optic disc.

Guatemala presented with a three-month history of bilateral uveitis unresponsive to topical steroids. Outside workup for infectious and inflammatory etiology revealed elevated ESR (98 mm/hour) and a positive Lyme serology (23 kDa IgM on Western Blot), despite the fact that the patient had no history of hiking or camping in an endemic area and no history of targetoid rash. The patient was treated with oral doxycycline for 2 months with presumed diagnosis of Lyme associated uveitis with no improvement of ocular inflammation and was referred to our uveitis service for presumed treatment-resistant Lyme uveitis.

Her principal complaint was blurry vision and severe headaches for which she was self-medicating with over the counter Ibuprofen several times daily. On examination, she was afebrile, with normal blood pressure (110/75 mmHg). Her best corrected visual acuity (BCVA) was 20/40 in the right eye and 20/32 in the left eye. The anterior chamber showed 3 + cells and 1 + flare bilaterally. There was 2 + cell and 1 + haze in the vitreous of the right eye and trace cell with no haze in the left eye. Fundus exam showed bilateral asymmetric disc edema and multiple areas of subretinal fluid in the left eye and hypofluorescent choroidal lesions in both eyes on Indocyanine Green Angiography (ICG), suggestive of choroidal inflammation (Figs. 1–2).

An extensive laboratory workup showed: normoglycemic glycosuria and proteinuria on urinalysis; elevated serum beta-2 microglobulin (4.6 mg/L, normal range [0.9–1.7 mg/L]); ESR within normal limits (28 mm/hr); negative autoimmune antibody panel (ANA, anti-dsDNA, RF, anti-CCP); Lyme as well as Syphilis, Tuberculosis, *Bartonella henselae*, Toxoplasmosis and Borrelia studies were all negative. HLA typing indicated HLA A2,33; B15,51, C14,5, DRB1 01,08, DQB1 04,05. Neurology was consulted due to the presence of bilateral disc edema. Opening pressure on lumbar puncture was within normal limits, CSF ELISA and WB were negative for Lyme, and MRI of the orbit and surrounding structures revealed no abnormalities. Review of the patient's previous labs, as ordered by the referring clinician, showed a creatinine of 3.6 mg/dL, however, at presentation to us it was lower at 1.9 mg/dL, though still abnormal.

Clinical evaluation and laboratory work up suggested a differential

diagnosis of incomplete Vogt-Koyanagi-Harada syndrome (VKH) with NSAID overuse that contributed to the elevated serum creatinine versus TINU. The patient began a course of oral and topical corticosteroids which resulted in complete resolution of the disc edema and subretinal fluid. Her serum creatinine continued to trend downward with treatment to 1.3 mg/dL.

Given the presence of persistently elevated creatine and elevated beta-2 microglobulin, a kidney biopsy was performed that showed severe tubulointerstitial fibrosis with tubular atrophy. There was a dense lymphomononuclear interstitial infiltrate composed of small mature lymphocytes admixed with occasional plasma cells with glomerular sparing. No significant eosinophilic component was present. The kidney biopsy was negative for both viral inclusions and interstitial granulomas (Fig. 3). The results confirmed TINU as the diagnosis, and she was restarted on high dose oral prednisone and mycophenolate mofetil. However, she continued to have anterior chamber flares at lower doses of prednisone (< 20mg/day), requiring addition of another immunosuppressive agent. In addition, her serum creatinine continued to increase to a level of 2.3 mg/dL.

A multidisciplinary team consisting of a uveitis specialist, pediatric nephrologist and pediatric rheumatologist were involved in her care to determine the best treatment course. The patient's hypertension and kidney damage limited use of cyclosporin A; addition of an anti-metabolite (mycophenolate mofetil) as corticosteroid-sparing agent resulted in insufficient response and the use of biologics are seldom reported in the management of TINU.⁹ The multidisciplinary team consensus was to begin subcutaneous adalimumab 40mg every 2 weeks. This led to an improvement in the serum creatinine to 1.3 mg/dL allowing the patient to slowly taper her oral prednisone dose while remaining on mycophenolate mofetil. She has remained quiet in both eyes. Her serum creatinine has remained at a stable level of 1.3mg/dL (normal range 0.67–1.17 mg/dL) suggesting chronic irreversible mild kidney damage.

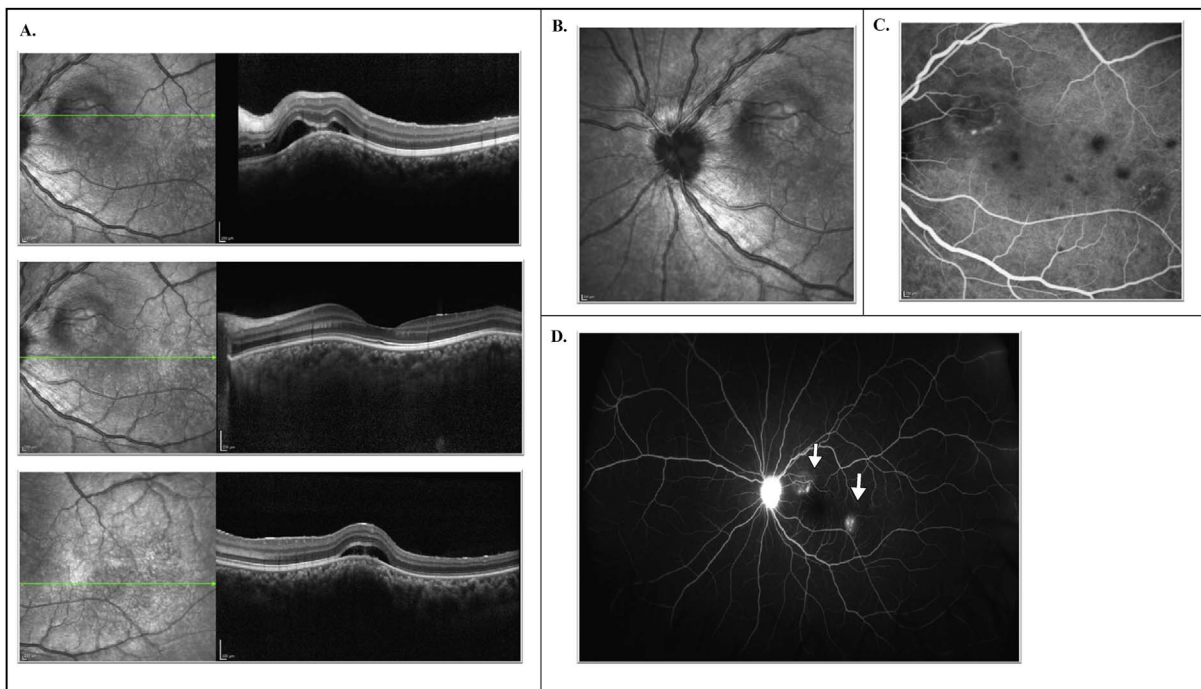


Fig. 2. Left Eye at Presentation.

A. Macula OCT demonstrates normal foveal contour and thickness and multiple pockets of subretinal fluid. B. IR of optic nerve shows disc edema superiorly. C. ICG at 5 minutes shows multiple hypofluorescent spots in the choroid. D. FA at 10 minutes shows leakage from the optic disc and pinpoint areas of fluorescein leakage and pooling.

3. Discussion

This atypical case of TINU presents several relevant teaching points to the current practice of uveitis. The history began with the tentative diagnosis of Lyme-associated uveitis. The diagnosis was based on the presence of 1 band of IgM for Lyme (23kD). The patient's history lacked definitive evidence of a tick bite and the typical targetoid rash. As per the Centers for Disease Control (CDC), a positive IgM Lyme Serology requires the presence of two of the following three bands: 24 kDa, 39 kDa & 41 kDa. Relying on the presence of only one IgM band does not indicate a positive Lyme serology, though it can occur very early after the exposure and needs to be confirmed with repeat testing in 6 weeks.

In addition, presumed Lyme disease with ocular involvement is concerning for neuro-Lyme disease. Treatment regimen as per CDC guidelines for neurologic Lyme consists of one dose of 50–75 mg/kg intravenous ceftriaxone. Therefore, even under a presumed Lyme associated uveitis diagnosis, treatment with oral doxycycline is not recommended.¹⁰ This underscores the importance of strict attention to specific CDC guidelines regarding Lyme diagnosis and treatment.^{11–13}

The clinical appearance of our patient on exam was characterized by diffuse choroiditis and multiple exudative retinal detachments, differentiating this case from typical cases of TINU. Neither posterior involvement nor serous retinal detachments are common features of TINU, however, there have been few reports of TINU presenting with

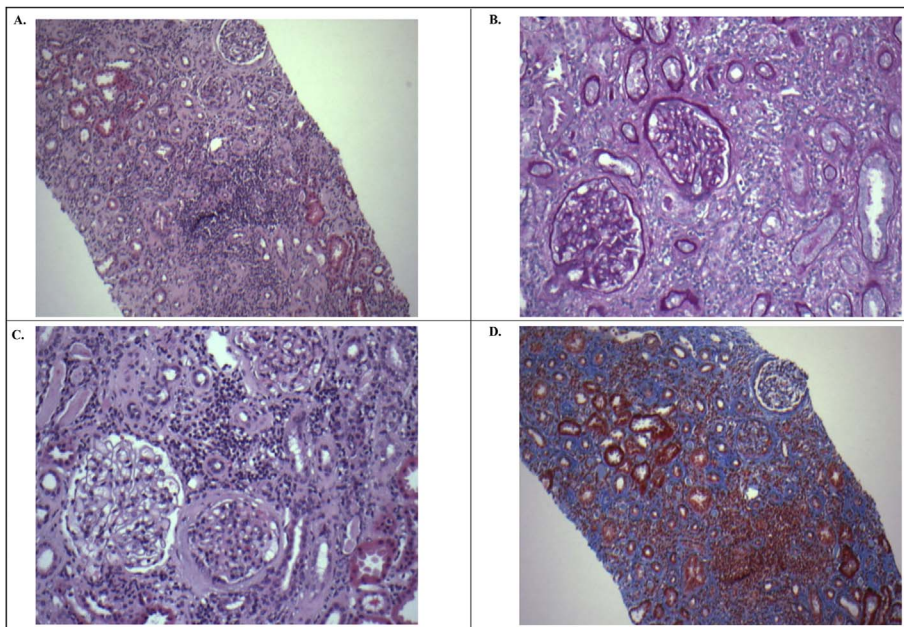


Fig. 3. Kidney Biopsy showing Tubulointerstitial Inflammation.

Hematoxylin & Eosin stained native kidney biopsy revealing no significant proliferative, sclerosing or necrotizing lesions in the glomeruli. The main abnormalities include a patchy dense interstitial lymphomononuclear infiltrate; predominantly composed of small mature lymphocytes admixed with occasional plasma cells. No significant eosinophilic component or granulomatous inflammation is seen. Trichrome staining reveals severe chronic tubulointerstitial disease with tubular atrophy and interstitial fibrosis (blue). Blood vessels are mildly thickened and with no vasculitis. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

posterior uveitis.^{6,7,14,15} Our patient's clinical exam findings were initially suggestive of Vogt-Koyanagi-Harada disease, a multi-system autoimmune disease affecting the visual, integumentary, nervous and auditory systems that commonly affects persons of Asian, Latin or Native American descent. However, the patient did not meet full diagnostic criteria as no extraocular manifestations were observed. In conjunction with these findings, the chronic inflammation with anterior uveitis exacerbations during steroid taper further supported a possible/presumed diagnosis of incomplete VKH.^{16–19}

However, the elevated serum creatinine and elevated urine Beta2 microglobulin did not fit with the diagnosis of VKH and implicated a possible systemic or concurrent pathology impacting renal function. Our differential diagnoses to explain these lab values included IgA nephropathy and TINU, as elevated urinary b2 microglobulin is a critical lab test for suspected TINU.⁵ However, after patient history revealed she had been taking 600mg (11 mg/kg) of Ibuprofen six times a day for headache relief, NSAID associated acute tubular necrosis versus NSAID associated tubulointerstitial nephritis were also included in the differential. The recommended pediatric dosing for Ibuprofen is 10 mg/kg every 6–8 hours, and she well exceeded this dosing. NSAID overuse can cause pre-renal azotemia with minimal histopathologic changes; acute interstitial nephritis, characterized by tubular edema and interstitial inflammation which may be accompanied by proteinuria. Lastly, NSAID use can cause nephrotic syndrome (mainly membranous glomerulopathy or minimal change disease²⁰).

A definitive diagnosis of TINU was confirmed by kidney biopsy. In contrast to the above renal pathologies, the kidney biopsy findings in TINU shows tubulointerstitial edema and a lymphocytic infiltrate that is distinctly different from the glomerular presentation of: Minimal Change Disease, Membranous Nephropathy and IgA-Nephropathy.

TINU is typically responsive to oral corticosteroids. However, patients can have relapses of either their renal disease or uveitis when followed long term.³ Our patient responded well to oral corticosteroids, however we were unable to taper her below 10 mg daily. The addition of mycophenolate mofetil did not help with control of ocular inflammation, leading to a debate regarding which second agent was most suited for her long-term care. Adalimumab (Humira[®]) is currently indicated in the treatment of non-infectious intermediate, posterior and panuveitis in adult patients. Adalimumab is typically given in a range of doses between 20 mg–40 mg subcutaneously, biweekly; most commonly in conjunction with other medications, such as mycophenolate mofetil or methotrexate.²¹ Use of adalimumab in pediatric population is limited to Juvenile Idiopathic Arthritis (JIA) associated uveitis and Crohn's disease. Small studies have shown that adalimumab is a relatively safe and effective treatment in pediatric uveitis.^{21,22} However, adalimumab is not an archetypal choice of immunosuppressive agent for TINU.

An extensive discussion between all members of the multidisciplinary team and the family was performed to explain the limited evidence based knowledge and long-term safety data of biologics for TINU. However, given her recalcitrant inflammation and the lack of other suitable immunosuppressive agents, adalimumab was considered the best option at the time.

This case highlights the need for judicious attention to the non-ocular symptoms and laboratory assessments of patients with uveitis. It also stresses the need for a multidisciplinary team to elucidate an etiology and management plan for these rare multifactorial causes of ocular inflammation, as well as to provide holistic treatment and avoid chronic systemic damage.

Patient consent

The patient's legal guardian consented to publication of the case in writing/orally.

Funding

NEI intramural grant support

Conflicts of interest

The following authors have no financial disclosures: S.C., S.G., S.K., S.T., H.S., H.N.S.

Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Acknowledgements

None.

References

- Okafor LO, Hewins P, Murray PI, Denniston AK. Tubulointerstitial nephritis and uveitis (TINU) syndrome: a systematic review of its epidemiology, demographics and risk factors. *Orphanet J Rare Dis.* 2017;12:128.
- Mandeville JT, Levinson RD, Holland GN. The tubulointerstitial nephritis and uveitis syndrome. *Surv Ophthalmol.* 2001;46:195–208.
- Pakzad-Vaezi K, Pepple KL. Tubulointerstitial nephritis and uveitis. *Curr Opin Ophthalmol.* 2017;28:629–635.
- Legendre M, Devilliers H, Perard L, et al. Clinicopathologic characteristics, treatment, and outcomes of tubulointerstitial nephritis and uveitis syndrome in adults: a national retrospective stroke-compliant study. *Medicine (Baltimore).* 2016;95 e3964.
- Hettinga YM, Scheerlinck LM, Lilien MR, Rothova A, de Boer JH. The value of measuring urinary beta2-microglobulin and serum creatinine for detecting tubulointerstitial nephritis and uveitis syndrome in young patients with uveitis. *JAMA Ophthalmol.* 2015;133:140.
- Lee AR, Sharma S, Mahmoud TH. Tubulointerstitial nephritis and uveitis Syndrome with a primary presentation of acute posterior multifocal placoid pigment epitheliopathy. *Retin Cases Brief Rep.* 2017;11:100–103.
- Ali A, Rosenbaum JT. TINU (tubulointerstitial nephritis uveitis) can be associated with chorioretinal scars. *Ocul Immunol Inflamm.* 2014;22:213–217.
- Goda C, Kotake S, Ichiishi A, Namba K, Kitaichi N, Ohno S. Clinical features in tubulointerstitial nephritis and uveitis (TINU) syndrome. *Am J Ophthalmol.* 2005;140:637–641.
- Hausler U, Guminski B, Helmchen U, Kisters K, Heinz C, Braun J. Tubulointerstitial nephritis with uveitis (TINU) syndrome. A relatively rare rheumatological differential diagnosis with unexplained uveitis. *Z Rheumatol.* 2013;72:393–397.
- Wormser GP, Dattwyler RJ, Shapiro ED, et al. The clinical assessment, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: clinical practice guidelines by the infectious diseases society of America. *Clin Infect Dis.* 2006;43:1089–1134.
- Sanchez E, Vannier E, Wormser GP, Hu LT. Diagnosis, treatment, and prevention of Lyme disease, human granulocytic anaplasmosis, and babesiosis: a review. *J Am Med Assoc.* 2016;315:1767–1777.
- Engstrom SM, Shoop E, Johnson RC. Immunoblot interpretation criteria for serodiagnosis of early Lyme disease. *J Clin Microbiol.* 1995;33:419–427.
- Centers for Disease Control and Prevention. *Two-step Laboratory Testing Process.* 2015; 2015.
- Lecleire-Collet A, Villero F, Vasseneix C, Brasseur G. Tubulointerstitial nephritis and uveitis syndrome (TINU syndrome) with unilateral neuroretinitis: a case report. *Eur J Ophthalmol.* 2004;14:334–337.
- Kim MH, Khanna A. Bilateral exudative retinal detachments in tubulointerstitial nephritis and uveitis syndrome secondary to posterior scleritis. *Retin Cases Brief Rep.* 2007;1:98–100.
- Read RW, Holland GN, Rao NA, et al. Revised diagnostic criteria for Vogt-Koyanagi-Harada disease: report of an international committee on nomenclature. *Am J Ophthalmol.* 2001;131:647–652.
- Burkholder BM. Vogt-Koyanagi-Harada disease. *Curr Opin Ophthalmol.* 2015;26:506–511.
- Read RW, Rao NA, Cunningham ET. Vogt-Koyanagi-Harada disease. *Curr Opin Ophthalmol.* 2000;11:437–442.
- Sakata VM, da Silva FT, Hirata CE, de Carvalho JF, Yamamoto JH. Diagnosis and classification of Vogt-Koyanagi-Harada disease. *Autoimmun Rev.* 2014;13:550–555.
- Singh NP, Ganguli A, Prakash A. Drug-induced kidney diseases. *J Assoc Phys India.* 2003;51:970–979.
- Simonini G, Taddio A, Cattalini M, et al. Prevention of flare recurrences in childhood-refractory chronic uveitis: an open-label comparative study of adalimumab versus infliximab. *Arthritis Care Res (Hoboken).* 2011;63:612–618.
- Castiblanco C, Meese H, Foster CS. Treatment of pediatric uveitis with adalimumab: the MERSI experience. *J AAPOS.* 2016;20:145–147.