Tubulointerstitial Nephritis and Uveitis

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Introduction

Tubulointerstitial nephritis and uveitis (TINU) is characterized by the acute interstitial nephritis (AIN) and uveitis with no known etiology. TINU was first described in 1975 and has a reported prevalence of 1–2%. The disease is more commonly seen in young aged females. Although the exact pathogenesis of TINU is unknown, it is thought to have an autoimmune basis triggered by infections, antibiotics, or NSAIDs. TINU has an established association with HLA-DRB1*01 and HLADQA1*01 and a particularly strong association (RR = 167) with HLA-DRB1*0102. Clinically, patients with TINU present with nonspecific systemic symptoms of fever, malaise, myalgia, and fatigue. About one third of patients present with signs and symptoms of AIN characterized by flank pain, hematuria, sterile pyuria (eosinophiluria), and mild proteinuria. Ocular symptoms in TINU predominantly present as bilateral, nongranulomatous anterior uveitis. The anterior uveitis is sudden in onset and is characterized by pain, redness, and photophobia. On slit lamp examination, fine keratic precipitates, anterior chamber cells, occasionally a high flare, and rarely a hypopyon can be seen. Posterior synechiae can also be visualized. Posterior segment involvement is limited to occasional mild vitreous cells and rare complications of disc and macular edema.

Diagnosing TINU may be challenging because the uveitis may precede the renal symptoms or may even occur up to 14 months after the onset of AIN. Diagnosis of TINU mainly relies on serologic testing for abnormal renal function and ocular manifestation of bilateral sudden-onset anterior uveitis. Laboratory testing abnormalities in TINU patients can include elevated serum creatinine (55–90% of patients) and low-grade proteinuria, microscopic hematuria, and leukocytes by urinalysis. Recently, elevation of β2-microglobulin has emerged as a sensitive biomarker in the diagnosis of TINU, even in the absence of abnormal renal function. In classic drug-associated TINU, the diagnosis is often made on the clinical history within the course of exposure to the drug.

Once a diagnosis of TINU is established after ruling out other differential diagnosis, controlling inflammation and maintaining quiescence are the main therapeutic approaches for TINU patients. Depending on the involvement of the posterior or anterior segment of the eye, topical corticosteroids or systemic corticosteroids might be required to control inflammation. In the long-run, however, 10% of patients might require chronic steroid-sparring immunomodulation therapy (IMT) for the management of the disease.

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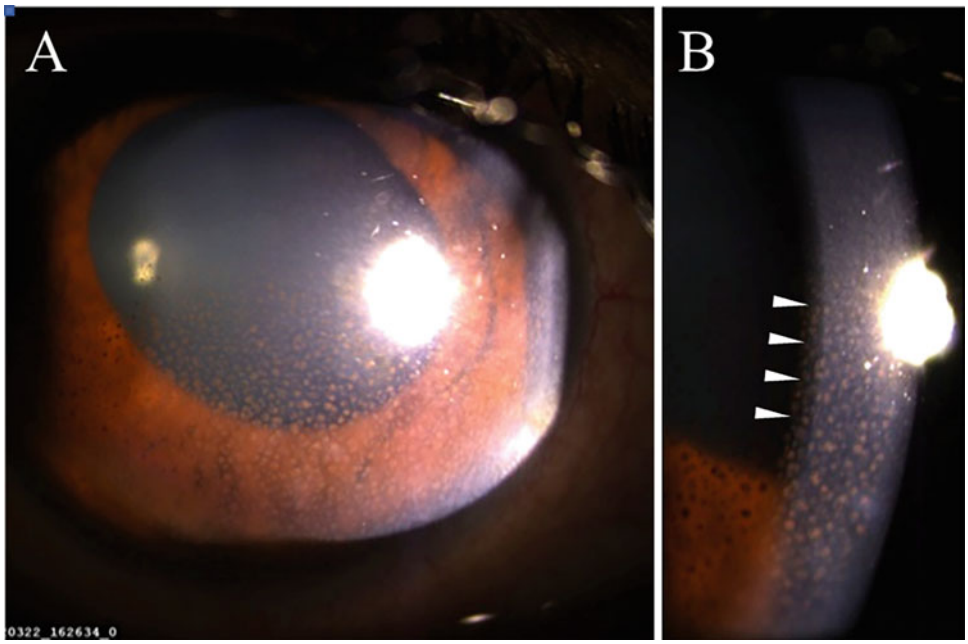

Fig. 1 (**a**) Anterior segment photograph of the right eye showing significant anterior segment inflammation with flare and multiple large pigmented keratic precipitates (KPs) (arrows). (**b**) Pigmented KPs over corneal endothelial surface (arrowheads)

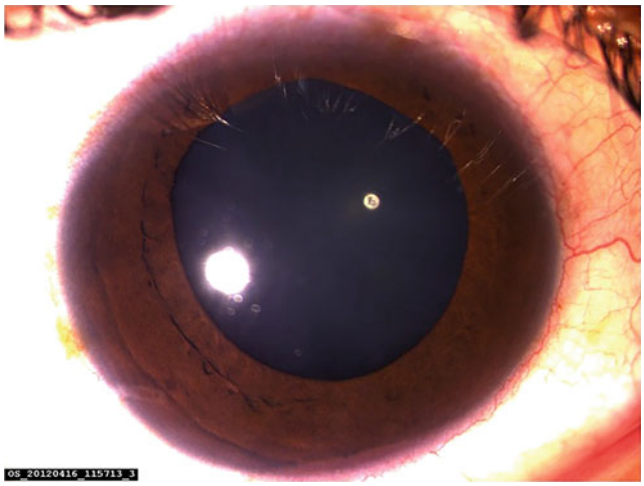

Fig. 2 Anterior segment photograph of the right eye post treatment with topical and systemic steroids showing clear anterior chamber with resolution of the inflammation. No keratic precipitates (KPs) which were present at the initial visit could be seen

Case 1: TINU-Associated Anterior Uveitis

A 24-year-old female was referred to the Uveitis Clinic with complaints of ocular pain and photophobia in both eyes. On review of systems, the patient had a history of mild fever and abdominal pain. The visual acuity was 20/40 in both eyes (OU). Slit lamp examination demonstrated anterior uveitis with 2+ anterior chamber cells and flare in OU. Circumcorneal injection was also noted. There was presence of multiple large pigmented keratic precipitates (KPs) (Fig. 1a and b)

Extensive work-up was performed to rule out etiologies for nongranulomatous anterior uveitis including both infectious and noninfectious etiologies. Chest-x ray, erythrocyte sedimentation rate (ESR), and *Treponema pallidum* hemagglutination test were nonrevealing. Urine examination revealed increased levels of beta-2 microglobulin. A diagnosis of TINU associated uveitis was established and the patient was started on topical corticosteroid as well as a tapering regimen of oral steroids. The patient was asked to return to clinic after 3 months.

At the follow-up visit at 3 months, there was a significant reduction in the patient's symptoms. The visual acuity improved to 20/20 in both eyes. Slit lamp examination revealed significant resolution of inflammation (Fig. 2). She was asked to follow up regularly with nephrology and ophthalmology to periodically assess her renal function and ocular disease activity.

Case 2: TINU-Associated Panuveitis

A 30-year-old male was referred to the Uveitis Clinic with complaints of blurry vision, ocular pain, and photophobia. On review of systems, the patient had a history of fever and weight loss. The visual acuity was 20/160 in right eye (OD) and 20/50 in left eye (OS). Slit lamp examination demonstrated nongranulomatous anterior uveitis with 1+ anterior chamber cells and flare in both eyes (OU). There was presence of fine KPs in OD and posterior synechiae in OU (Fig. 3a and b). Limited dilated fundus examination secondary to limited pupillary dilation revealed 2+ vitreous haze (VH) in OD and 2+ VH in OS (Fig. 4). The optic disc appeared hyperemic in OU. The vessels appeared normal in caliber and contour and peripheral retina was normal.

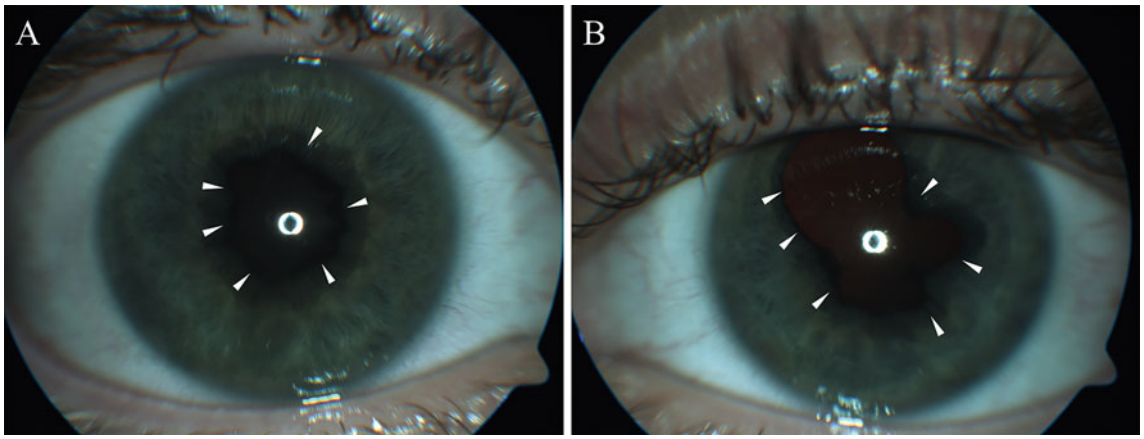

Fig. 3 Anterior segment photograph of the right eye (OD) (**a**) and the left eye (OS) (**b**) showing posterior synechiae (arrowheads) leading to abnormal pupillary shape

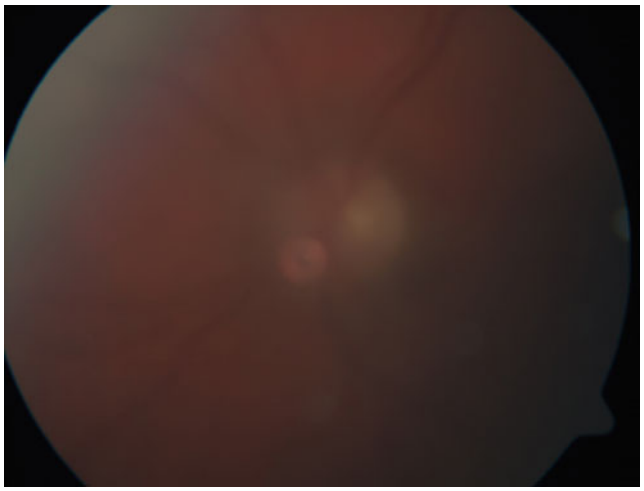

Fig. 4 Color fundus photograph (FP) of the left eye (OS) showing 2+ vitreous haze. There blurriness of the optic disc margins

Fluorescein angiography demonstrated hyperfluorescence of optic disc and foveal leakage in OS in late phase (Fig. 5a and b). No vascular leakage was noted on FA. Spectral-domain optical coherence tomography (SD-OCT) showed increased retinal thickness along with presence of cystic spaces suggestive of macular edema in OU (Fig. 6a and b).

Laboratory evaluations performed revealed negative tuberculin test, *Treponema pallidum* hemagglutination test, normal angiotensin converting enzyme (ACE), and normal chest radiography. However, the patient demonstrated glucosuria without a history of diabetes. Further evaluations for renal function revealed increased levels of β2 microglobulin in urine along with low-grade (1+) proteinuria. A diagnosis of TINU associated panuveitis was established and the patient was started on systemic steroids and a steroid sparing agent. The patient was also instructed to follow up to be monitored for the progression of the disease and response to therapy.

Key Points

- Tubulointerstitial nephritis, though uncommon, should be suspected among patients with bilateral non-granulomatous anterior uveitis with nonspecific systemic symptoms such as fever and myalgias.
- Anterior uveitis in TINU may have nonspecific clinical features of nongranulomatous inflammation such as anterior chamber cells, fine keratic precipitates, and synechiae.
- Investigations such as urinalysis, urine for β-2 microglobulin, a highly sensitive marker for tubular damage, and renal functions in patients with bilateral uveitis with fever and myalgias can be very helpful in making the diagnosis.
- Definitive diagnosis of AIN can only be established by renal biopsy.

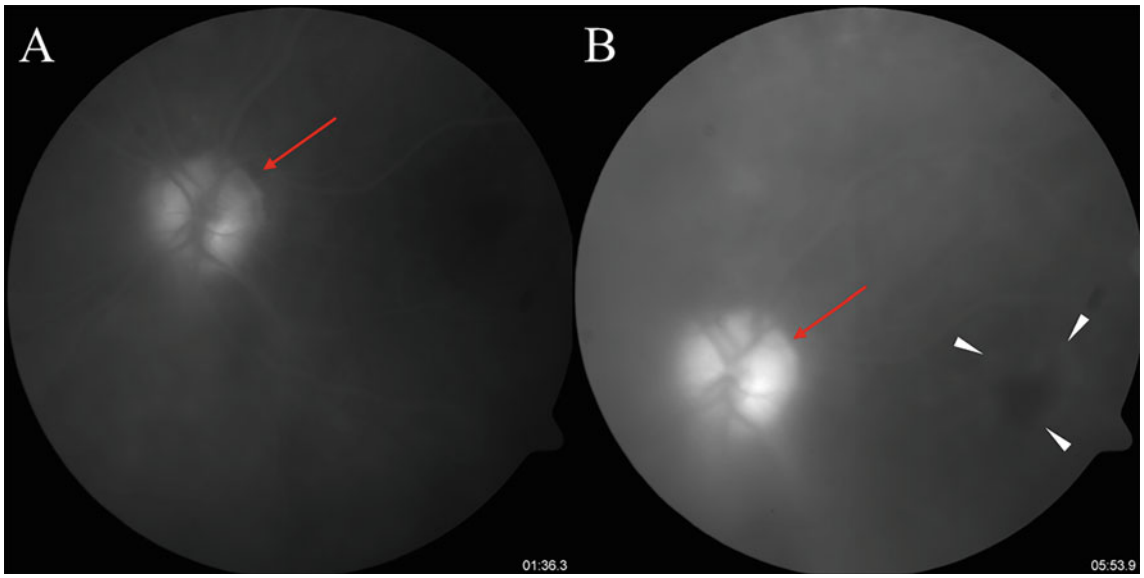

Fig. 5 Fluorescein angiography (FA) of the left eye (OS) shows hyperfluorescence of the optic disc in mid-late (**a**) and late phase (**b**) (red arrows) suggestive of leakage. In addition, there is presence of leakage in the foveal region in the late phase (**b**) (white arrowheads) compatible with macular edema

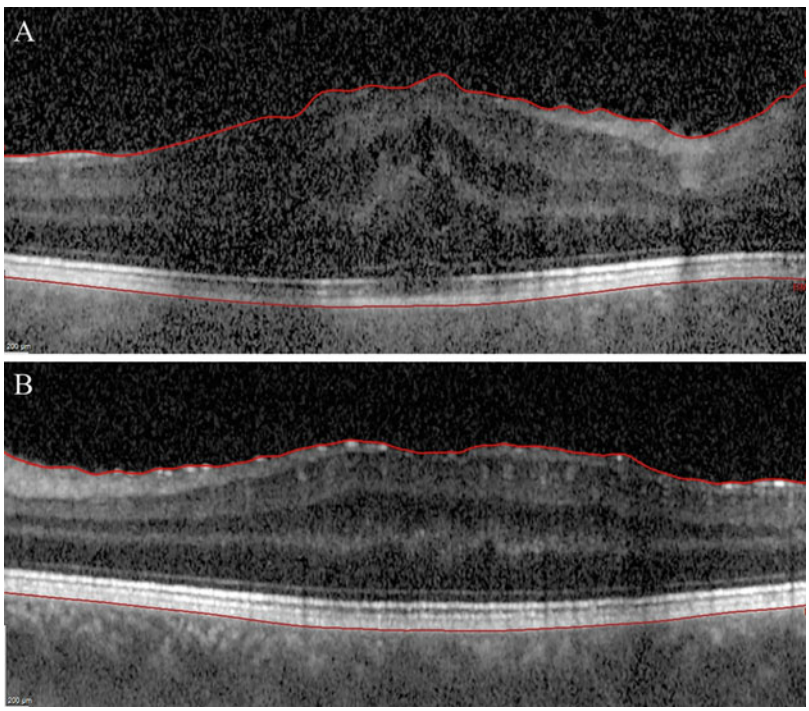

Fig. 6 Spectral domain optical coherence tomography (SD-OCT) scans of OD (**a**) and OS (**b**) shows presence of hyporeflective intraretinal spaces leading to increased retinal thickness suggestive of macular edema

Suggested Reading

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