

TINU syndrome, a case report and literature review

Abstract

Tubulointerstitial nephritis and uveitis (TINU) syndrome is characterized by tubulointerstitial nephritis with sudden-onset of uveitis. Currently, only over 200 cases have been described in the literature. TINU syndrome might be underestimated due to lack of recognition and under-diagnosis. The pathogenesis of TINU syndrome remains unclear, it affects predominantly adolescents. We report a case of an acute renal insufficiency at a 42years old woman whose exploration favors the diagnosis of a TINU syndrome; she was put under cortico-steroids with recovery of a normal renal function at 73ml/min/1.73m². Our message is to enquire specifically for episodes of uveitis in any patient presenting with unexplained acute interstitial nephritis and to keep in mind the diagnosis of TINU syndrome.

Keywords: TINU syndrome, tubulointerstitial nephritis, uveitis, cortico-steroids

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Abbreviations: TINU, tubulo interstitial nephritis and uveitis; AIN, acute interstitial nephritis; KI-6, krebs von den lunge-6

Patients and methods

SA, 40years old women, with uneventful history, admitted on 20/03/2012 at nephrology department for the management of severe renal function impairment discovered fortuitously when chez was assessed for a hypertensive peak two months before her admission, put under amlodipine ambulatory. Physical examination on admission found a conscious patient in good general condition, BP: 110/60mmHg, light mucocutaneous pallor, good apparent hydration state, a febrile with arthralgias at wrists, elbows and knees. Urine dipstick: Prot (+), blood (-) Leuc (-), glu (+), ket (-) PH: 6, density: 1020. The remainder of the physical examination was unremarkable (Table 1).

- a) Blood count: normocytic normochromic anemia (Hb : 10.6g/dl)
- b) Serum protein electrophoresis was normal
- c) Negative serology for hepatitis, HIV and syphil.

Table 1 Blood chemistry

Fasting glycemia	Creatinine	Urea	Natremia	Serum K
6mmol/l	12.1mg/dl	30mmol/l	139meq/l	3.9meq/l
Serum ALB	24H Pu	HbA1c	Serum P	Serum Ca
42g/l	1.13g	4.8%	3.2mg/dl	10.1mg/dl

Imaging

- a. Chest x ray was unremarkable and USG abdomen revealed normal sized kidneys.
- b. Two months later, appearance of a right anterior uveitis and serum creatinine came down to 4.91mg/dl (eGFR MDRD: 10ml/min/1.73m²)
- c. Non contrast enhanced chest and abdomen CT were unremarkable
- d. Immunological tests (ANA, anti-dsDNA antibodies, SSA, SSB, RF, and ANCA) were negative.

Discussion

Variety disease states can cause both uveitis and kidney failures, diagnostics discussed were: Sarcoidosis, Sjogren's, lupus, granulomatosis with polyangeitis (previously Wegener's granulomatosis), infectious diseases (tuberculosis, brucellosis, toxoplasmosis...), and these diagnoses were ruled out by clinical examination, imaging and laboratory finding. The retained diagnosis was TINU syndrome according to Mandeville criteria: acute interstitial nephritis (AIN) diagnosed clinically (abnormal renal function, abnormal urinalysis and, systemic illness lasting two weeks or more) and typical uveitis. Renal biopsy not be done because of the patient refusal.

Management

The patient is put under prednisone to 0.5mg/kg/day (30mg/day) with adjuvant treatment (calcium, vit D, omeprazol) for eight weeks and then gradually tapered then stopped after 12months.

Evolution

Serum creatinine came down to 1.3mg/dl at 6weeks to 0.9mg/dl after 21mounths follow up. (eGFR MDRD: 73ml/min/1.73m²).

Literature review

TINU syndrome is thought to be an autoimmune disease, first described by Dobrin et al.,¹ in 1975; it combines tubule-interstitial nephritis and uveitis. Its incidence is estimated to be 0.2 cases/ year/ MH.² It affects 3 females to 1 male. The median age of onset is 15years (ranging from 9 to 74years). A prevalence of HLA: DQA1* 01, DQB1* 05, HLA- DQB1* 01 (series of 18 patients), DRB1* 0102 HLA was noted.^{3,4} The pathogenesis is incompletely understood. No identifiable risk factors have been found, it has been reported to be associated with infection (e.g. *herpes zoster virus*,⁵ *Chlamydia*,⁶ *Epsteine Barr virus*),⁷ drugs (e.g. the Chinese herb "*Goreisan*"⁸ nonsteroidal anti inflammatory agents and antibiotics), and autoimmune diseases (e.g. primary hyperparathyroidism,⁹ hyperthyroidism,¹⁰ Rheumatoid arthritis,¹¹ lymphoid interstitial lung disease,¹² ankylosing spondylitis,¹³ IgG4-related Auto immune disease),¹⁴ although causality is unclear.

TINU syndrome is mostly postulated to be the result of an

autoimmune process. It may involve both humoral and cellular autoimmunity. In the past, the latter was strengthened because obvious disturbances in cell-mediated immunity were noted in patients with TINU syndrome because of renal interstitial infiltrates are mainly activated T cells, monocytes/macrophages and mast cells, the infiltrated T cells are anergic to skin tests with a very low secretion rate of lymphokines, and patients have general responsiveness to corticosteroids.¹⁵ T cells were considered as playing a major role in the pathogenesis of this disorder.

Although TINU syndrome is also characterized by hyper gammaglobulinemia (IgG), the involvement of humoral immunity was not postulated to play an important role until recently. Recently, auto antibodies directed against renal tubular cells have thrown new light on the role of humoral autoimmunity in TINU syndrome. It is postulated that renal tubular and ciliary body epithelia might share cross-reactive auto antigens since the major characteristics of TINU syndrome are the involvement of the kidneys and eyes, and renal tubular and ciliary body epithelia share some similar functions.

Tenyears ago, Wakaki et al.,¹⁶ found that serum IgG antibodies from a 13-year-old girl with TINU syndrome were Reactive against 125-kDa human kidney protein. Shimazaki et al.,¹⁷ reported that serum from a patient with TINU syndrome could recognize a 125-kDa antigen in both human kidney and retinal protein extracts. However, it is unclear whether the 125-kDa protein identified in both renal and retinal extracts is the same protein.

Abed et al.,¹⁸ demonstrated the presence of auto antibodies recognizing a common auto antigen found in both tubular and uveal cells in the serum of a 15-year-old girl with TINU syndrome. They performed indirect immune fluorescence techniques with the patient's serum, incubating with normal human kidney and normal mouse eye, and showed IgG deposits in tubular epithelial cells and in uveal cells.

Recently, a Chinese group focused on the auto antibodies that could recognize both kidneys and eyes. They further postulated that mCRP might be a target auto antigen in TINU syndrome.¹⁹ The clinical features of TINU syndrome are varied and have been comprehensively reviewed by Mandeville et al.²⁰ The interstitial nephritis precedes the uveitis in 65% of cases but follows ocular manifestations in 21% of cases and develops concurrent to uveitis in 15%. The ocular manifestation is in the form of anterior uveitis in 80% of patients but may also manifest as posterior or pan uveitis. Uveitis may develop up to two months before or up to 14months after onset of systemic symptoms. Uveitis may recur in about 41% and the recurrence may occur up to two years after the first bout, but usually uveitis recurs within three months of discontinuation of steroids. In general, the course of ocular disease is independent from that of the renal disease.²⁰

Systemic symptoms such as fever, weight loss and fatigue predominate.²¹ For renal manifestations, sterile pyuria, hematuria, sub nephritic proteinuria and renal insufficiency have been noted. As for multiple proximal and distal tubular involvement, polyuria, nocturia, aminoaciduria, glucosuria, phosphaturia and acidification defects are commonly seen.²² Renal biopsy is consistent with acute interstitial nephritis. On light microscopy, typical biopsy findings include tubulointerstitial edema and infiltration of inflammatory cells composed mainly of mononuclear cells, such as lymphocytes, plasma cells, and histiocytes. Eosinophils and noncaseating granulomas are frequently seen, with neutrophils also being observed.²³ Glomerular and vascular structures are generally preserved. Findings with immune fluorescence and electron microscopy are also nonspecific.

The diagnosis of TINU syndrome requires the presence of both AIN and uveitis and the exclusion of other known systemic diseases that can cause interstitial nephritis or uveitis. Mandeville et al.,²⁰ has proposed diagnostic criteria for TINU syndrome (Table 2). Diseases which can manifest acute interstitial nephritis along with ocular abnormalities need to be considered in the differential diagnosis of TINU syndrome and include Sjogren's syndrome, sarcoidosis, tuberculosis and toxoplasmosis. AIN should be diagnosed histopathologically or clinically, with onset of bilateral anterior uveitis less than 2months before or no more than 12months after AIN. Since a number of diseases can affect the kidneys and eyes simultaneously, the diagnosis of TINU syndrome should be differentiated from sarcoidosis, Sjogren's syndrome, systemic lupus erythematosus, granulomatosis with polyangeitis, Behcet disease, *Epsteine Barr virus*-associated infectious mononucleosis, tuberculosis, toxoplasmosis, brucellosis, syphilis, and histoplasmosis.²⁴

Table 2 Mandeville criteria

Definite TINU syndrome	AIN diagnosed histopathologically or clinically (complete criteria*) and typical uveitis
Probable TINU syndrome	AIN diagnosed histopathologically and atypical uveitis or AIN diagnosed clinically (incomplete criteria) and typical uveitis
Possible TINU syndrome	AIN diagnosed clinically (incomplete criteria) and atypical uveitis

*The three clinical criteria required to make a clinical diagnosis of AIN are

- i. Abnormal renal function
- ii. Abnormal urinalysis
- iii. A systemic illness lasting two weeks or more.

Urinary β_2 -microglobulin, serum Krebs von den Lunge-6 protein and anti-mCRP auto antibodies are three potential biomarkers of TINU syndrome. The first two have been found to be simultaneously decreased in patients with TINU syndrome after the beginning of treatment and considered to reflect the renal lesion. Urinary β_2 microglobulin level, a marker of interstitial nephritis, was markedly elevated in almost every case tested^{25,26} and may remain elevated for months after the urinalysis and serum creatinine have returned to normal. Krebs von den Lunge-6 (KL-6) is a glycoprotein whose serum concentrations rise in response to various respiratory pathologies.²⁷ Compared to patients with uveitis from other causes, serum KL-6 levels in patients with TINU syndrome were significantly elevated and on renal biopsy the distal tubules of the patients with TINU syndrome stained strongly with anti-KL-6 antibody suggesting that the elevated KL-6 levels reflect the underlying renal lesion.²⁸ Serum KL-6 levels may prove to be a valuable tool in the diagnosis and follow-up of patients with TINU syndrome, especially if studies show a significant difference between patients with TINU syndrome compared with acute interstitial nephritis of other etiology.

Anti-mCRP auto antibodies have been found with elevated titers in both the active phase of tubule interstitial nephritis and right before the relapse of uveitis, which suggests that it might be a potentially useful biomarker for diagnosis and monitoring of disease activity.¹⁹

Renal disease in patients with TINU is usually self-limited and, in most patients, can be expected to spontaneously resolve.²⁹ In a series

of 10 patients, eight of whom had creatinine clearances of less than 70ml/min/1.73m², renal function returned to normal levels within one year in all patients.²⁹ Although seven were administered systemic steroids for uveitis, renal function recovery was independent of such therapy or the relapse of eye disease. There have been no prospective, randomized trials comparing steroid therapy with placebo, or addressing the optimum dose and duration of treatment.

Patients with progressive renal insufficiency are typically treated with prednisone at a dose of 1mg/kg per day (typically between 40 to 60mg/day). Therapy is given for three to six months (with the duration of therapy dependent upon the response), and then slowly tapered. Most patients recover normal renal function. This regimen is similar to (but more prolonged than) therapy in acute interstitial nephritis. However, relapses are more likely to occur in TINU syndrome because of the potential immunological basis of the disease and the lack of a possible culprit agent. Mycophenolate mofetil has been used in a limited number of patients with acute interstitial nephritis and in one reported patient with TINU for the treatment of progressive renal insufficiency.^{30,31}

The prognosis is dependent upon the degree of tubule interstitial fibrosis. Although a few have required renal replacement therapy, even these patients can expect to only temporarily require dialysis.³² Topical and systemic corticosteroids have been used for uveitis with success. However, recurrences and relapses of uveitis are common; infrequently, steroid-sparing immunosuppressive agents, such as cyclosporine, methotrexate, and mycophenolate mofetil are needed. The optimal management of the patient with uveitis requires early referral to and management by an ophthalmologist.

Conclusion

TINU syndrome is a rare cause of AIN, often under diagnosed. It is a diagnosis of exclusion and the evolution seems to be favorable under cortico-steroids. Think to TINU syndrome for any AIN or uveitis of unknown etiology.

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None.

Conflict of interest

The author declares no conflict of interest.

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