CASE REPORT

Tubulointerstitial nephritis and uveitis syndrome in a female adult

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SUMMARY

Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare disease characterised by the association of acute tubulointerstitial nephritis and uveitis. It affects mainly children and young women. Drugs and infections may be precipitating factors. It is a diagnosis of exclusion. The mainstays of treatment are topical and systemic corticosteroids. Prognosis is usually favourable. We report a case of TINU which occurred in our unit. A 37-year-old woman presented with an influenza-like illness, bilateral ocular pain and blurred vision. Ophthalmological evaluation revealed bilateral anterior uveitis and later renal involvement was seen as acute tubulointerstitial nephritis. A diagnosis of TINU was assumed after exclusion of other systemic diseases. She was treated with topical corticosteroids for the uveitis and evolved favourably, with resolution of ocular symptoms and normalisation of serum creatinine and proteinuria. This case highlights the importance of a high degree of clinical suspicion to make the diagnosis of TINU syndrome.

BACKGROUND

Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare disease characterised by the association of both acute tubulointerstitial nephritis (AIN) and uveitis. It was first described in 1975 by Dobrin *et al*¹ and, since then, about 200 cases have been reported from all over the globe and affecting all races.^{2–4} There is a female predominance ranging from 2.5:1 to 5:1.^{5,6} Children and young adults are more commonly affected.^{2–6} The estimated prevalence and incidence are 3.5 cases/million of persons and 0.2 cases/million/year, respectively.^{7,8} Evidence suggests that TINU arises from a confluence of host susceptibility factors and environmental triggers.² It is thought to be an immune mediated process that may be precipitated by drugs such as non-steroidal anti-inflammatory drugs,⁹ Paracetamol+codeine,^{9,10} antibiotics¹¹ or infections,^{12,13} although in many cases no cause is identified.¹⁴ The underlying pathological mechanisms remain unclear, but modified C-reactive peptide has been identified as a possible target auto-antigen in TINU syndrome.¹⁵ The diagnostic criteria include occurrence of tubulointerstitial nephritis and uveitis in the absence of other systemic diseases that can cause either condition, therefore making TINU a diagnosis of exclusion.¹⁴ Treatment is not yet standardised, but topical and systemic corticosteroids are currently the mainstay.^{2,16} Prognosis is usually favourable, but progressive renal failure can occur.²

CASE PRESENTATION

A 37-year-old white, female patient, with medical history of osteopenia and a c-section at age 26, with no known allergies, no regular ambulatory therapy and no family history of kidney or eye disease, presented with fever (tympanic temperature 39°C), chills, headache, malaise and myalgia. Forty-eight hours later she developed bilateral ocular pain and blurred vision. She was evaluated by a general practitioner, who diagnosed her with viral infection and referred her for an ophthalmological evaluation, which revealed conjunctival hyperaemia and bilateral anterior uveitis. Although there were no urinary symptoms reported a urinalysis was performed, which detected non-nephrotic proteinuria. She was medicated with topical prednisolone and referred to our nephrology unit, where she was evaluated 24 hours later.

In our observation, the patient denied consumption of non-steroidal anti-inflammatory drugs, proton pump inhibitors or antibiotics. She had taken two tablets of paracetamol 1g the previous day. The physical examination was unremarkable. The most relevant bloodwork results are shown in table 1.

Chest X-ray was unremarkable. Renal ultrasound showed normal-sized kidneys with maintained parenchymal thickness but a slight increase in cortical echogenicity, with medullary pyramid prominence and reduced corticomedullary differentiation.

INVESTIGATIONS

To investigate the diagnostic hypothesis of TINU syndrome, autoimmune disorder or infectious disease additional evaluation was performed: anti-nuclear antibodies (ANA) were positive (1:160 titre). Anti-neutrophil cytoplasmic antibodies (ANCA), antisoluble nuclear antigen antibodies and anti-dsDNA antibodies were negative. ACE, immunoglobulin, light chain and complement levels were normal, as well as the serum protein electrophoresis. Beta-2 microglobulin levels were slightly increased, both in serum (3.32 mg/L, reference value 1.09–2.53 mg/L) and urine (0.48 mg/L, reference value <0.20 mg/L). Epstein-Barr (EBV) and Cytomegalovirus (CMV) serologies were not compatible with acute infection. Serologies for HIVs 1 and 2, hepatitis B and hepatitis C were negative. Anti-*Treponema pallidum* and anti-*Toxoplasma gondii* antibodies were negative (IgM and IgG). Interferon gamma release assay was negative.

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Table 1 Relevant bloodwork results in the initial nephrology evaluation

	Result	Reference values
Haemoglobin	126 g/L	120–150 g/L
Leucocytes	9.4×10^9 /L	$4.0\text{--}10.0 \times 10^9$ /L
Platelets	265×10^9 /L	$150\text{--}400 \times 10^9$ /L
Glucose	91 mg/dL	74–106 mg/dL
Urea	25 mg/dL	13–43 mg/dL
Creatinine	1.01 mg/dL	0.5–0.9 mg/dL
Estimated glomerular filtration rate (Chronic Kidney Disease Epidemiology Collaboration Equation)	71 mL/min/1.73 m²	>90 mL/min/1.73 m ²
LDH	275 U/L	135–225 mg/dL
Na ⁺	138 mmol/L	136–145 mmol/L
K ⁺	4.37 mmol/L	3.5–5.1 mmol/L
Cl ⁻	98 mmol/L	98–107 mmol/L
C-reactive protein	8.51 mg/dL	<0.5 mg/dL
Erythrocyte sedimentation rate	63 mm/h	<20 mm/h
Urinalysis	Protein ++, Hb +	Negative
Protein to creatinine ratio in spot urine (uPCR)	1849.5 mg/g	<200 mg/g

Values highlighted in bold are outside the reference value.

A kidney biopsy was performed, which revealed an AIN with a predominant lymphocytic infiltrate and noncaseating epithelioid granulomas, without glomerular or vascular changes and negative immunofluorescence (figures 1 and 2).

DIFFERENTIAL DIAGNOSIS

The concomitant presence of bilateral anterior uveitis and granulomatous AIN can be due to systemic diseases such as sarcoidosis, Sjogren syndrome, systemic lupus erythematosus and small vessel vasculitis. However, no clinical and laboratorial features of sarcoidosis were present (no respiratory involvement, no adenopathy and normal serum ACE levels). Likewise, there were no sicca symptoms or positive autoantibodies suggestive of Sjogren syndrome. Systemic lupus erythematosus was ruled

Figure 1 Diffuse interstitial, predominantly mononuclear, inflammatory infiltrate with tubulitis. Some eosinophils are also noted (H&E, magnification $\times 100$).

Figure 2 Periglomerular non-caseating granulomas with multinucleated giant cells (H&E, magnification $\times 100$), with immunohistochemistry showing positive staining for CD68, a macrophage marker (lower right corner).

out as the patient did not fulfil the American College of Rheumatology criteria. The small vessel vasculitis, namely granulomatosis with polyangiitis, can cause uveitis and AIN. However, the negative ANCA antibodies and absence of glomerular and vascular lesions on the renal biopsy make this diagnosis unlikely. Behçet's disease can also cause bilateral anterior uveitis and kidney disease. However, in this case there were no mucous ulcerations or cutaneous lesions. Additionally, these patients seldom undergo kidney biopsies, but those who do more frequently have AA amyloidosis or glomerular and vascular lesions, so it is an improbable diagnosis. IgG4-related disease is a systemic inflammatory disorder that can affect the eye and the kidney and the main renal manifestation is tubulointerstitial nephritis. However, the most common ocular findings are dacryoadenitis and involvement of the orbital soft tissue and extraocular muscles, not uveitis. Additionally, no IgG4-positive plasma cells were identified in renal histology.

The influenza-like illness could be caused by an infectious disease or be related to the TINU syndrome per se. Infectious diseases that can cause unspecific systemic symptoms and granulomatous AIN include EBV and CMV infections, toxoplasmosis, syphilis, tuberculosis, brucellosis and histoplasmosis. These are more common in immunosuppressed patients. In this case, HIV serology was negative; CMV and EBV serologies were compatible with previous infection; anti-*Toxoplasma gondii* and anti-*Treponema pallidum* antibodies were negative; *Brucella* serology was not performed, but there were no risk factors in the medical history and no gastrointestinal involvement; histoplasmosis was deemed unlikely due to the fact that the patient was immunocompetent, had modest serum creatinine elevation and lacked other manifestations of disseminated disease.

After considering and ruling out these diseases a diagnosis of TINU syndrome was assumed.

OUTCOME AND FOLLOW-UP

In the following 2 months the patient evolved favourably, with resolution of ocular symptoms, normalisation of renal function (serum creatinine 0.80 mg/dL) and consistent decrease in proteinuria (uPCR <200 mg/g). No systemic treatment was initiated. Topical prednisolone was tapered and eventually stopped

after 6 months. After 18 months of follow-up she remains clinically stable, asymptomatic and without any signs of recurrent disease (uPCR 54 mg/g, serum creatinine 0.83 mg/dL).

DISCUSSION

TINU syndrome is a rare disease, with an estimated prevalence of 3.5 cases/million of persons and incidence of 0.2 cases/million/year.^{7,8} There is a female predominance and children and young adults are more commonly affected.^{2–6} However, recent data suggest that the prevalence of uveitis in patients with tubulointerstitial nephritis may be higher than currently recognised, particularly in the paediatric population.¹¹

TINU syndrome aetiology and pathophysiological mechanisms are unclear. Drugs and infections have been listed as precipitating factors. The classical presentation is an influenza-like illness, after which the patient is discovered to have azotaemia and/or ocular pain and blurred vision. Most often the kidney manifestations of TINU precede the ophthalmological (65%), although they may appear simultaneously (15%) and the opposite sequence is occasionally noted (20%).^{2,14,17} This asynchrony of eye and kidney involvement in TINU may impede prompt recognition of the syndrome, thus a high degree of clinical suspicion is mandatory when evaluating any young patient presenting with either uveitis or AIN.² In this case the patient presented with a influenza-like illness, which may have corresponded to a viral infection that precipitated the TINU syndrome or be related to the syndrome per se. There was no history of prescription or over-the-counter drug consumption, except for two paracetamol tablets. This drug, in association with codeine, has been associated with TINU syndrome.^{9,10} However, in this case it was taken after the influenza-like manifestations had started and the uveitis and proteinuria had already been identified, so it cannot have been the precipitant factor. It is important to highlight that the patient had no renal symptoms and, if a urinalysis had not been performed, the diagnosis of TINU could have easily been missed.

The renal manifestations of TINU include flank pain, sterile pyuria, proteinuria, haematuria, acute kidney injury, aminoaciduria, glycosuria, phosphaturia and acidification defects. There are no specific serum markers or laboratory abnormalities that suggest TINU. Typically, there is anaemia, eosinophilia, elevated ESR and CRP and slightly abnormal liver function tests. Beta-2 microglobulin and Krebs von den Lunge-6 have been reported to be two potential serological diagnostic markers, but additional investigation is needed.^{6,18} In this report there was elevation of the erythrocyte sedimentation rate and c-reactive protein as well as increased beta-2 microglobulin both in serum and urine.

As previously noted, the hallmark renal lesion of TINU is an interstitial infiltrate composed predominantly of lymphocytes, with varying components of macrophages, plasma cells and often eosinophils. Interstitial oedema may be present early in the course of the disease and fibrosis suggests chronicity. Non-caseating granulomas are frequently seen. Glomerular and vascular structures are usually preserved. Findings in immunofluorescence and electron microscopy are non-specific.^{18–21} The biopsy in this case showed a predominant lymphocytic infiltrate with some plasma cells, eosinophils and non-caseating epithelioid granulomas, without glomerular or vascular changes and negative immunofluorescence. Electron microscopy was not performed.

According to the diagnostic criteria developed by Mandeville *et al*, a definitive diagnosis of TINU is made when typical uveitis (bilateral anterior uveitis with or without intermediate or posterior uveitis) is found 2 months before to 12 months after

histopathologically or clinically diagnosed AIN, in the absence of other systemic disorders with which they are known to be associated.¹⁴ This patient had bilateral anterior uveitis and biopsy-proven AIN diagnosed in an interval of 2 weeks, so she fulfils these criteria. Although clinically diagnosed AIN is mentioned in these criteria as enough to diagnose TINU, we consider that any patient with uveitis and acute kidney injury and/or an active urine sediment should undergo a kidney biopsy to make a definitive diagnosis and to help establish a prognosis.

There are no evidence-based protocols for treating TINU. The recommended treatment for the uveitis consists of topical corticosteroids, which may not be enough if there is involvement of the posterior ocular segment.²² About 80% of reported cases needed treatment with systemic corticosteroids (1–1.5 mg/kg/day of oral prednisolone) and 9% of these progressed to other forms of immunosuppression.¹⁴ The duration of therapy depends on how well and how quickly the patient responds. Some authors suggest at least 12 months of oral therapy to reduce or prevent recurrences.²³ A study with a relatively long follow-up has shown that frequent relapses and recurrences of the uveitis occur despite steroid treatment.²⁴ These are usually responsive to another course of steroids, but infrequently other immunosuppressive agents such as cyclosporine, methotrexate, azathioprine and mycophenolate mofetil may be needed.^{25,26}

In this case, the uveitis responded to topical prednisolone treatment, which was slowly tapered over the course of 6 months. Despite the literature data we decided not to treat this patient with systemic corticosteroids for several reasons: (1) mild renal involvement with almost no scarring of renal tissue; (2) history of osteopenia; (3) quick improvement of proteinuria and normalisation of serum creatinine. She was closely monitored in a nephrology consultation for early recognition of recurrent disease and, after 18 months of follow-up, remains clinically stable and without any sign of recurrent disease.

According to most reports the prognosis of TINU is favourable, but some studies suggest that progressive renal failure can occur.^{6,14,16,22} It appears that older patients and those with more severe renal involvement at presentation have a worse prognosis.¹⁶

In conclusion, this case highlights the importance of a high degree of clinical suspicion and the need for a multidisciplinary approach to make the diagnosis of TINU syndrome. The decision to treat with systemic corticosteroids should be individualised as some patients may not need aggressive treatment.

Learning points

- ▶ Tubulointerstitial nephritis and uveitis syndrome is a rare disease, more frequent in children and young adults and with a female predominance.
- ▶ Drugs and infections can be precipitating factors but its aetiology and pathophysiology remain unclear.
- ▶ The diagnosis implies a high degree of suspicion and is made by the concomitant presence of acute tubulointerstitial nephritis and uveitis in the absence of other systemic diseases.
- ▶ Corticosteroids are the mainstay of treatment. Topical prednisolone should be used to treat the uveitis, but systemic steroids may not be needed in all cases.
- ▶ The prognosis is usually favourable but progressive renal failure can develop.

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