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Take a closer look at TINU syndrome; analysis of a case

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ABSTRACT

Tubulointerstitial nephritis and uveitis syndrome (TINU) combines tubulointerstitial nephritis and uveitis and is a known cause of kidney failure in children and adults. This is a challenging diagnosis since renal and ocular manifestations may not occur simultaneously and may be present in several alternative diagnosis. The authors report the case of a 28-year-old patient with acute kidney injury (AKI) and biopsy-proven acute tubulointerstitial nephritis. Bilateral symptomatic uveitis presented six months after the initial presentation. Physicians in charge of patients with kidney disease attributed to acute tubulointerstitial nephritis must bear in mind the need for ophthalmologic surveillance for at least one year post-diagnosis. Although a diagnosis of exclusion, its incidence may be higher than described. Kidney disease is believed to be self-limited and prognosis still, most patients will require systemic therapy and relapses are common.

Implication for health policy/practice/research/medical education:

This case illustrates the clinical course and diagnostic challenge of patients with tubulointerstitial nephritis and associated ophthalmologic pathology, highlighting the multidisciplinary approach required for an appropriate care.

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Introduction

Tubulointerstitial nephritis and uveitis syndrome (TINU) is an idiopathic cause of tubulointerstitial nephritis and uveitis, can be triggered by drugs or infection, and is characterized by an immune-mediated infiltration of the kidney interstitium with inflammatory cells, namely T-cells (1,2).

Although the underlying mechanisms remain largely unknown, limited data suggest that modified C-reactive protein, an autoantigen common to both the uvea and renal tubular cells, may be involved in the pathogenesis (3). An associated paradoxical suppression of cytokine production and decrease in peripheral immune response may also be relevant to the underlying pathophysiology (4).

It is a rare disease, most common in adolescents and young women (although it has also been reported in older adults). Is generally believed to be self-limited and should be considered in the differential diagnosis of all patients with unexplained acute kidney injury (AKI) or progressive reduction in the glomerular filtration rate (GFR).

The diagnosis is an association of clinical, usually nonspecific symptoms and histological features of tubulointerstitial nephritis and uveitis with no evidence of other systemic or infectious diseases. Laboratory findings are non-specific, and the kidney biopsy may show eosinophils and non-caseating granulomas.

Many patients with TINU syndrome present with late-onset uveitis, and thus, the initial ophthalmologic examination will be negative.

In this report we describe a case of tubulointerstitial nephritis (AIN) and later onset uveitis, detail the diagnostic workup and provide new insights to the treatment of this entity.

Case Presentation

We describe the case of a 28-year-old woman admitted with flank pain. She has a medical history of obesity (body mass index 37.5 kg/m²) and seronegative rheumatoid arthritis (diagnosed two years previously). Immunologic study at that time was positive for antinuclear antibodies,

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and negative for rheumatoid factor, anti-cyclic citrullinated antibodies, HLA B27, and anti-double stranded DNA antibodies. Bone scintigraphy showed an inflammatory pattern compatible with rheumatoid arthritis. The patient was being treated with sulfasalazine, cyclobenzaprime and a vitamin D analog.

She is admitted with a 2-day history of upper gastric pain, nausea, and left flank pain. There were no other associated symptoms, namely macroscopic hematuria, dysuria, other gastrointestinal symptoms, arthralgia, or respiratory symptoms. Vital signs were normal and she was afebrile. Renal murphy sign was negative. Urinalysis showed white blood cells (WBC) and nitrites. The diagnosis of urinary tract infection was assumed and she was started on amoxicillin-clavulanate. At this time no additional laboratory work-up was performed.

She evolves unfavorably and three days later, the patient is admitted to nephrology department with a non-oliguric AKI stage 3 KDIGO (creatinine 12.64 mg/dL) and metabolic acidosis (pH 7.27, HCO₃- 17 mmol/L).

On admission, she was dehydrated. The remaining physical examination was unremarkable. Laboratory tests were relevant for non-hemolytic anemia (hemoglobin; 9.9 g/dL), normal platelets level, raised inflammatory markers (C-reactive protein; 69.9 mg/L), raised serum creatinine and blood urea nitrogen (12.6 mg/dL and 98 mg/dL, respectively), and normal electrolyte panel. Urinalysis showed a pH of 7.5, specific gravity 1.010, no glucosuria, proteins ++, blood +; and urinary sediment with 6 WBC/high power field (HPF), 2 red blood cells (RBC)/HPF (isomorphic), no eosinophils, and a protein-to-creatinine ratio of 1.198 g/g (predominantly non-albumin). Microbiologic work-up was unremarkable (Table 1 - laboratory work-up). The renal ultrasound showed normal sized kidneys, with regular contours, normal cortical echogenicity, normal sinus-parenchyma differentiation, and no signs of obstruction.

The patient showed a gradual and favorable response to fluid and large spectrum antibiotic therapy, with a serum creatinine nadir level of 2.9 mg/dL. Eleven days later the patient was discharged.

Fourteen days later she redeveloped complaints of nausea and vomiting. Laboratory study was meaningful for non-oliguric kidney dysfunction (serum creatinine of 3.7 mg/dL), and microscopic hematuria. Immunologic work-up, serum calcium, angiotensin converting enzyme, chest radiograph and abdominal ultrasound were unremarkable. At this time, a kidney biopsy was performed, revealing signs of AIN, with normal glomeruli and interstitial edema with cellular infiltration, mainly lymphocytes and acute tubular necrosis, with no deposits on immunofluorescence (Figures 1, 2 and 3).

The diagnosis of AIN of unknown etiology was

established with possible culprits including non-steroidal anti-inflammatory agents, antibiotics, and infection. Corticosteroid therapy was started (prednisolone 1 mg/kg/d). The patient evolved favorably with a nadir of serum creatinine of 1.16 mg/dL and a 24-hour urine protein excretion of 122 mg/d.

Six months later, and while on prednisolone tapering, she develops eye complaints – bilateral burning sensation, photophobia, redness, and decreased visual acuity. Ophthalmologic examination was compatible with non-granulomatous anterior uveitis, and topical steroids were added to the existing systemic steroidal therapy (without systemic steroid increment), with improvement in two weeks. Systemic therapy was successfully tapered and discontinued.

Considering the clinical features and laboratorial results, TINU syndrome was integrated as a possible diagnosis. The patient is aware of the possibility of relapses and maintains regular follow-up.

Discussion

We present the case of a young woman with medical history of non-specific inflammatory arthritis, chronically medicated with a known cause of AIN, initially admitted with AKI assumed to be associated with urinary tract infection and dehydration, treated with amoxicillin-clavulanate, piperacillin-tazobactam and fluid therapy, which is readmitted with worsening renal function with a histologic diagnosis of AIN. With this context in mind, more common causes of AIN (aside from TINU) may be assumed.

The majority of patients with uveitis have an immune mediated process. In retrospect, one question that bares in mind is could the inflammatory arthritis, uveitis, and AIN be linked? The differential diagnosis of uveitis associated with a rheumatological component includes; Behçet disease, HLA B27 related ankylosing spondylitis, juvenile idiopathic arthritis associated uveitis, psoriatic arthritis, reactive arthritis, Crohn's disease, lymphoma, sarcoidosis, systemic lupus erythematosus (SLE), syphilis, tuberculosis, Whipple's disease, Lyme disease, adverse drug reaction, TINU, and others.

The absence of other clinical findings, the characteristics of the articular involvement, and the analytical study performed (namely immunologic) helps us delineate our diagnostic work-up. AIN may be present in virtually all of these diagnosis, but other renal diagnosis may be more common (eg, glomerular involvement in SLE) (5).

TINU syndrome is described as the concomitant presentation of acute idiopathic kidney inflammation and bilateral anterior uveitis. Uveitis in TINU is typically sudden onset, bilateral and mostly anterior with a variable amount of vitreous humor inflammation. The disease has

Table 1. Relevant laboratory test results during follow up

	Reference values	1 st Admission	Discharge	2 nd Admission	6 Months (uveitis onset)	1 Year
Hemoglobin (g/dL)	12-15	9.9	11.7	13.9	12.1	13.7
White cell count	4-10	9.1	5.3	6.3	8.4	5.7
Eosinophils ($\times 10^9/L$)	<0.4	0.3	0.1	0.3	0.2	0.1
Platelet count ($\times 10^9/L$)	150-400	321	305	368	354	283
ESR (mm/h)		64				3
Serum creatinine (mg/dL)	0.67-1.17	14.7	2.9	3.7	1.76	1.16
BUN (mg/dL)	7-18.7	115	17	25	18.22	30
CRP (mg/L)	<0.5	137	29	22	<3	<3
HCO ₃ (mEq/L)	22-29	17	22	20	21	23
Sodium (mEq/L)		138	136	137	138	136
Potassium (mEq/L)	3.8-5	4	3.5	3.8	3.7	3.5
Calcium (mg/dL)		9.3	9.4	9.9	9.1	9.3
Albumin (g/dL)	3.5-5	5.7		4.7		4.5
IgG (g/L)	7.51-15.6	19				
Angiotensin converting enzyme (UI/L)	12-68			54		
Urinalysis		6 WBC/HPF 2 RBC/HPF		5 RBC/HPF		3 WBC/HPF 2 RBC/HPF
P/C ratio (g/g creat)		1.198		0.671		0.122
UProt 24H (g)	<300	1.016			1.026	
Protein electrophoresis & Immunofixation		M protein spike not detected				
Autoimmunity		ANCA, ANA, ENA, RF – negative. C3 and C4 – normal				
Serologies		AgHBs, AchBs, AchBc, Ac HIV, Ac HCV - negative				
Microbiologic workup studies		Blood and urine cultures – sterile		Blood and urine cultures – sterile		

ANA: anti-nuclear antibody, ANCA; anti-neutrophil cytoplasmic antibody, BUN: blood urea nitrogen, CRP: C-reactive protein, ENA: extractable nuclear antigen, ESR: erythrocyte sedimentation rate, HCO₃: bicarbonate, HPF: high power field, IgG: immunoglobulin G, P/C ratio: protein/creatinine ratio, RBC: red blood cells, RF: rheumatoid factor, UProt 24h: urine protein excretion collected 24 hours, WBC: white blood cells

an extremely strong association with HLA DRB1*0102.

In addition, patients with TINU are typically systemically ill with fever, myalgias and arthralgias as well as a markedly elevated sedimentation rate (5).

This is a rare condition, ranging from <0.1% to 2% in general healthy population and up to 2.3% in pediatric age. It is believed to have a female predominance, a median age of onset of 15 years, and younger presentation in men (2;6).

A wide range of triggers may be responsible for the development of TINU in a patient with a susceptible genetic background: drugs (including antibiotics and non-steroidal anti-inflammatory drugs), infection,

autoimmune diseases (eg, hypoparathyroidism, hyperthyroidism, IgG4-related disease, and inflammatory arthritis) (6,7).

To help diagnosis, Mandeville published the TINU syndrome diagnostic criteria. It requires histological confirmation of the presence of an AIN and uveitis, with no other systemic disease as a cause. Cases are further categorized as “definite,” “probable,” or “possible” based on the diagnostic criteria for AIN and the clinical characteristics of uveitis (1).

Our patient was classified as having a possible TINU syndrome, as she had histopathological AIN, plus the clinical criteria: abnormal kidney function; abnormal

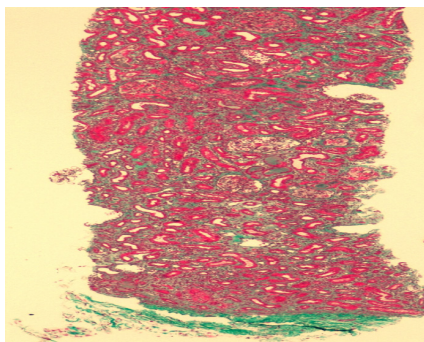


Figure 1. Diffuse tubulointerstitial inflammatory infiltrate in renal fragment. (Masson's trichrome stain, $\times 40$).

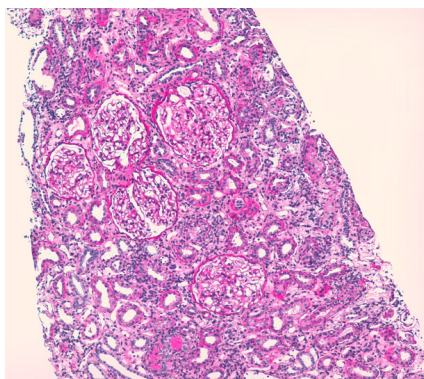


Figure 2. Diffuse interstitial infiltrate with mild tubular atrophy. Normal glomeruli shown. (Periodic acid-Schiff, $\times 200$).

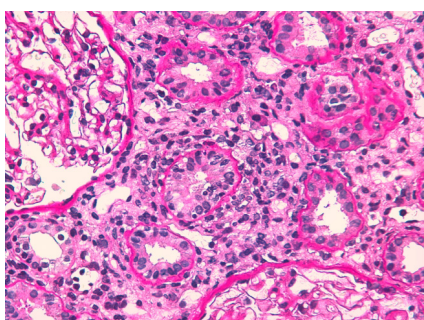


Figure 3. Proximal tubule is shown with invasion of lymphocytes into the tubule ((Periodic acid-Schiff, $\times 400$).

urinalysis and systemic disease lasting ≥ 2 weeks, associated with a typical bilateral uveitis. The urinalysis with WBC, non-dysmorphic hematuria and non-albumin proteinuria are suggestive of renal failure of tubular-interstitial origin.

In our report, bilateral uveitis occurred 6 months after the diagnosis, like 65% of the cases. Eye involvement precedes renal disease in 22% cases. In ophthalmological consult kidney function tests are not performed, thereby, diagnosis of TINU is significantly delayed or unrecognized (1,6).

Most forms of non-infectious uveitis are approached by a treatment algorithm that is not impacted by the cause of the uveitis, with exception to Behçet disease [where a monoclonal antibody that inhibits tumor necrosis factor (TNF) is frequently used] and to anterior uveitis associated with juvenile idiopathic arthritis where methotrexate and/or a TNF inhibitor such as adalimumab has improved the prognosis for this disease markedly (8).

Thereby, uveitis most of the time respond to topical corticosteroids alone. Still, not infrequently, there is a need for systemic use. Since recurrences and relapses are common, there may be a need for steroid-sparing immunosuppressive agents such as cyclosporine, methotrexate, and mycophenolate mofetil (MMF) (1).

Some authors suggest that immediate evaluation of renal involvement might be beneficial in adult patients with bilateral anterior uveitis, especially women, and in presence of systemic constitutional complaints (7). Eye disease may also be masked by high dose of corticosteroids, previously initiated to treat renal disease, thus uveitis commonly occurs with systemic corticosteroid taper or withdrawal (2), like in our patient.

Although kidney disease in patients with TINU is generally believed to be self-limited, most patients will require systemic therapy. Corticosteroids reduce interstitial inflammation and subsequent fibrosis, promoting rapid recovery from renal symptoms and greater improvement in GFR, as compared with no treatment (2). The duration and schedule for tapering of steroid dosage is dependent on how well and how rapidly the patient responds, being usually more prolonged than therapy in other AIN types.

In non-TINU AIN, there are sporadic reports of use and efficacy of MMF, cyclosporine and cyclophosphamide (9). Still, in some cases of biopsy-proven AIN, MMF was used for 13 to 34 months in patients who had responded to corticosteroid therapy but who could not tolerate withdrawal after six months. After addition of MMF, all patients were able to discontinue glucocorticoids (10). Owing to its low prevalence, no standard therapeutic protocols have been established TINU.

The prognosis for most patients is favorable, but in some cases, incomplete recovery with persistent chronic kidney disease or end-stage kidney disease, can occur (2). This may be related with the degree of tubulointerstitial fibrosis at biopsy (10).

In our patient, there was a total recovery of renal function with corticosteroid therapy. Controlling the eye disease can be more challenging as uveitis may persist or relapse even after 10 years (1,2).

Conclusion

In conclusion, the presence of uveitis and AIN should raise clinical suspicion for TINU syndrome. Knowledge

of the management of the disease by nephrologists, rheumatologists and ophthalmologists is essential. It is important to keep in mind that TINU is a diagnosis of exclusion, and its incidence may be higher than described. Ophthalmological screening is recommended all patients with AIN for at least one year after the diagnosis (2).

There are no randomized, controlled trials or large observational studies that inform the treatment of TINU (or general acute interstitial nephritis for that matter). Further randomized, prospective and multicentric studies are necessary for a consensual therapeutic approach.

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Authors' contribution

EC and AC conceived the manuscript; EC undertook the literature searches; EC and AC drafted the manuscript. PLN and APS read and revised the manuscript. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

This case report was conducted based on the World Medical Association Declaration of Helsinki. A written informed consent was obtained from the patient for publication of this report. Besides, ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors, having nothing to declare.

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