CASE REPORT

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Tubulointerstitial nephritis and uveitis syndrome (TINU) – à propos of 2 cases

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ABSTRACT

The authors present two cases of tubulointerstitial nephritis and uveitis syndrome (TINU). TINU is a well-known yet rarely reported oculorenal inflammatory clinical entity. A high level of suspicion is needed to identify this entity. The first case is that of a 24-year-old female presenting with bilateral red eye and ocular pain. Laboratory investigation revealed renal insufficiency (serum creatinine 4.9mg/dL) and kidney biopsy presented tubulointerstitial nephritis. The second case is that of a 69-year-old female initially diagnosed with uveitis who later presented with general symptoms and renal insufficiency (serum creatinine 3.96 mg/dL) and whose kidney biopsy showed a tubulointerstitial nephritis pattern. Both patients were treated with steroids and renal function improved. It may be worth screening for uveitis in all patients with tubulointerstitial nephritis and evaluating renal function in those presenting with apparent idiopathic uveitis.

Key-Words: Immunosuppression, Interstitial nephritis, Steroids, Tubulointerstitial nephritis and uveitis, Uveitis.

BACKGROUND

Acute tubulointerstitial nephritis (ATIN) is an entity with growing incidence in clinical practice[1,2,] responsible for a significant percentage (15-27%) of cases of acute kidney injury (AKI) that undergo renal biopsy[3,4.] It is an inflammatory process of the renal interstitium and tubules, sparing the glomeruli and vasculature. In addition to AKI, patients may present tubular dysfunction. In line with its etiology, ATIN can be broadly classified into 1) drug-induced (D-ATIN), 2) autoimmune/secondary to a systemic disease, or 3) due to other rare causes (such as infection, malignancy or metabolic disorder)[4]. Most studies suggest that drugs are implicated in the majority of biopsy-proven ATIN cases (70–90%), followed by autoimmune diseases, including Sjögren´s syndrome, IgG4-related disease, tubulointerstitial nephritis and uveitis syndrome (TINU) and sarcoidosis[1,5.] However, there is a possibility that some autoimmune-related ATIN are misclassified as D-ATIN when the renal diagnosis is made, due to the absence of systemic manifestations that can present later in the course of the disease[4]. Since the initial presentation may be misleading, a high level of suspicion and close follow-up are mandatory to correctly identify the underlying cause.

TINU is a well-known yet rarely reported[6] oculorenal inflammatory condition in which patients may either be asymptomatic or they may refer nonspecific symptoms (fever, rash, arthralgia, malaise). Synchronous or non-synchronous uveitis (generally bilateral sudden-onset anterior ocular inflammation) and renal disease coexist[7]. Since TINU represents a diagnosis of exclusion, ruling out other systemic disease that may explain both manifestations is essential. The underlying pathological

process remains elusive but treatment with corticosteroids and other immunosuppressive agents seems effective. The authors describe two cases of TINU in different age groups, with different presentations but with similar outcome, while reviewing its epidemiology, pathophysiology, diagnostic criteria, treatment and prognosis.

CASE REPORTS

Case 1

A 24-year-old female patient, originally from Brazil and living in Portugal for the past 2 years, presented with mild fever (37.5-38 °C), chills, myalgia, fatigue and nausea. Symptoms started 2 months before admission, during a trip to Brazil. At that time, she was admitted to the emergency department and discharged with the diagnosis of a common cold. She complained of general discomfort from that moment on. When she returned to Portugal, she presented to the emergency department with visual acuity reduction, red eye and ocular pain and was diagnosed with anterior uveitis. Topical therapy with dexamethasone, cyclopentolate and chloramphenicol was started, and a laboratory investigation of uveitis was performed in the ophthalmology outpatient clinic. She was referred to the emergency department due to serum creatinine elevation of 4.9 mg/dL and was then admitted to the nephrology ward. She had no relevant past medical history apart from tonsillitis during childhood and a self-reported allergy to penicillin. The patient was not under any habitual medication and she denied having taken other medicines besides intra-ocular ones and metamizol.

On admission she referred general indisposition and ocular pain. Diuresis was preserved and the patient denied any change in its pattern or aspect. Signs of neurological impairment were absent and her vital signs were normal. Blood pressure was 110/73 mmHg, pulse 80 bpm regular; she was apyretic and peripheric oxygenation was normal as was respiratory rate. Clinical examination was unremarkable apart from bilateral red eye and pallor. She did not present any sign of hydrosaline overload.

Blood tests revealed normochromic normocytic anemia, with otherwise normal blood count. Her renal function was impaired (urea 49 mg/dL and creatinine 4.3 mg/dL). Ionogram values were normal, as was glucose, and hepatic or cytolysis markers. C-reactive protein was mildly elevated (1.77 mg/dL). Urinalysis showed proteinuria 100mg/dL, erythrocyturia 20/uL and glycosuria 300mg/dL. Urinary creatinine to protein ratio was 0.4. Beta-HCG was negative. Kidney ultra-sound showed normal aspect of both kidneys. Additional investigation was inconclusive including negative ANA, C3 and C4 levels, HIV, Hepatitis A, B and C markers, ASO reaction, ANCA, ECA, anti-GMB and serum electrophoresis. Brucelosis, Coxiella burnetii, Ricketsia conorii and Borrelia infections were excluded. There was past contact with toxoplasma and CMV (IgG positive with IgM negative).

Assuming uveitis (not responding to topical treatment) and possible interstitial nephritis she was started on prednisolone 1mg/kg – 60 mg and a kidney biopsy was performed.

Kidney biopsy showed active chronic tubulointerstitial nephritis (Figures 1 and 2) with no deposits on immunofluorescence and the diagnosis of TINU was assumed.

Patient evolution was favorable with regression of renal dysfunction under prednisolone treatment (slow tapering). She presented a creatinine of 1.3mg/dL and mild glycosuria and leukocyturia after 3 months of treatment.

Figure 1

Optic microscopy. Hematoxylin and eosin staining 10x – interstitium with moderate to intense inflammatory infiltrate (mainly lymphocytes), tubulitis associated lesions and epithelium degenerative changes Glomeruli without significant changes.

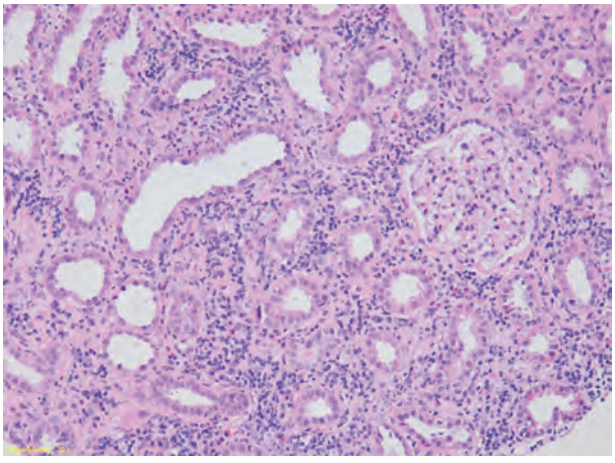
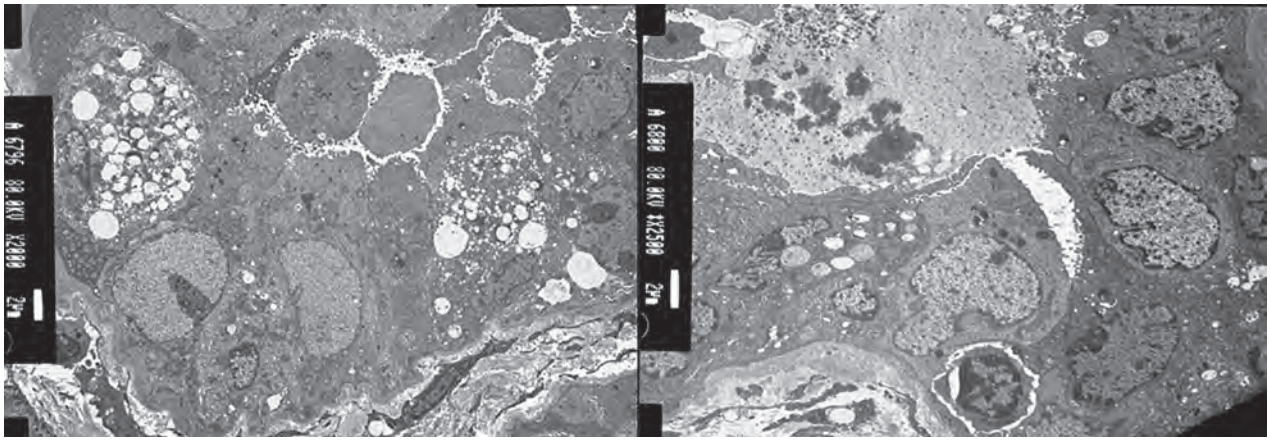


Figure 2

Electronic microscopy 2000x – tubules with epithelium degenerative changes and associated lymphocyte infiltration. Right: Electronic microscopy 2500x – celullar debris within the tubules lumina.



■ Case 2

A 69-year-old woman, with a past history of sporadic consumption of NSAIDs and a 2-month diagnosed hypertension, medicated with an ACEi. Symptoms started 3 months previously, with 3 episodes of painful ocular inflammation (red eye). She consulted an ophthalmologist who confirmed the diagnosis of uveitis, and was medicated with topical steroids. One month later she went to her general practioner, complaining of malaise and anorexia. Blood analysis showed normocytic/normochromic anemia, erythrocyte sedimentation rate 82 seconds, urea 106 mg/dL, Cr 3.96 mg/dL and urinalysis with proteinuria (50 mg/dL) and glycosuria (100 mg/dL). She denied diabetes, hearing loss, arthralgia, photosensitivity or recent infections. Even though the etiology of the renal disease was not known, she was started on systemic steroids referred to the nephrology outpatient clinic.

On our evaluation, blood analysis confirmed the normocytic and normochromic anemia (Hb 8.6 g/dL)

Figure 3

Optic microscopy. Periodic acid–Schiff staining 10x (left) and 20x (right) – interstitium with moderate inflammatory infiltrate (mainly lymphocytes), tubulitis associated lesions and epithelium degenerative changes with cellular debris within the lumina. Proteic non-specific casts.

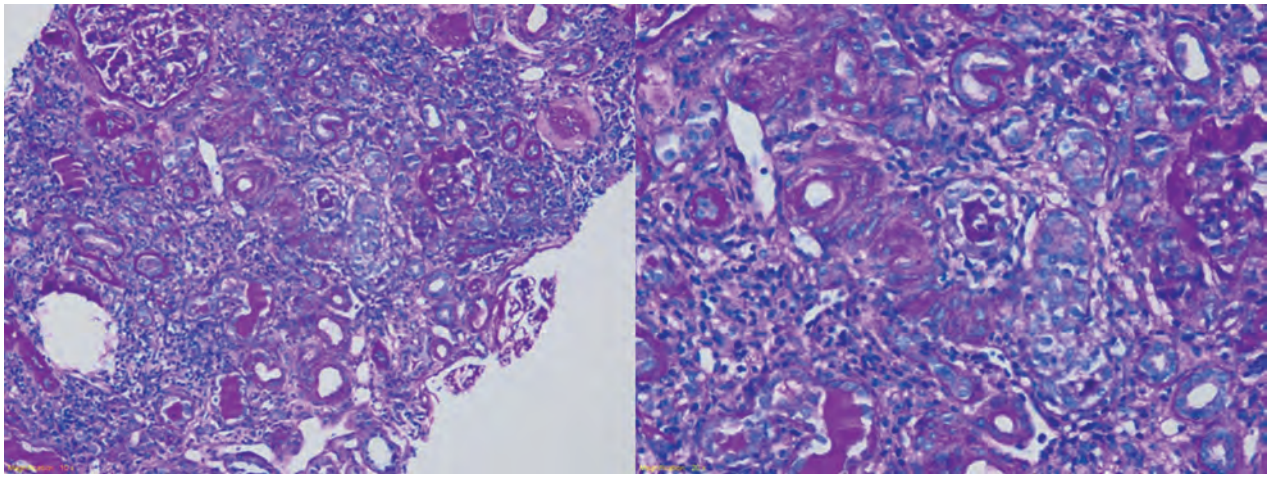
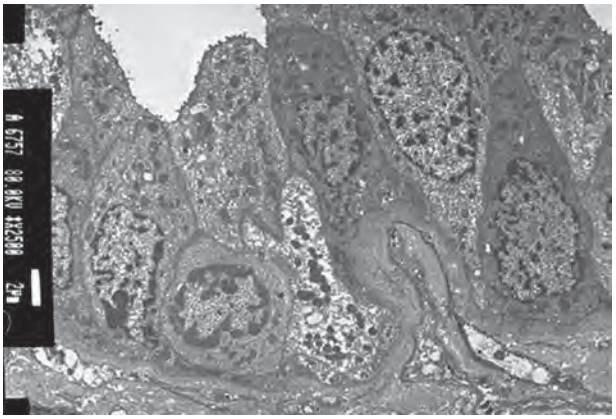


Figure 4

Electronic microscopy 2500x – tubules with epithelium degenerative changes and associated lymphocyte infiltration – tubulitis lesions.



and impaired kidney function (although improving) (Cr 2.8 mg/dL). Diabetes was excluded (HbA1c 5%). The remaining study was unremarkable with neither C3 nor C4 decreased levels and negative ANA, ANCA, ECA, anti-GMB. HIV, Hepatitis A, B and C markers were also negative, as well as ASO reaction. Electrophoresis of serum proteins was normal. Renal ultrasound showed no abnormalities.

Kidney biopsy was then performed and showed chronic tubulointerstitial nephritis with active inflammatory infiltrate rich in lymphocytes and active tubulitis lesions, without deposits on immunofluorescence (Figures 3 and 4).

The diagnosis of TINU was assumed and she was started on prednisolone 1mg/kg.

On follow-up, the episodes of uveitis stopped and the authors verified an improvement of kidney function (Cr 2.8-> 1.9 mg/dL).

DISCUSSION

Epidemiology

TINU was first reported in 1975 by Dobrin et al[8] and since then many cases have been described worldwide. It is predominantly seen in younger age groups, with a slight preponderance in the female gender[9]. Most studies available included pediatric population; hence the reported median age of onset was 15–17 years old[9,10]. However, a French study encompassing older patients encountered a median age of presentation at around 47 years old[11]. Published data suggest an estimated incidence of 1–2 per 10 million population per year[12], a prevalence of 3.5 cases per million[13] and only 0.1–2% of patients attending specialized uveitis centers[9,14]; nonetheless its prevalence may be higher than currently recognized[15.] One prospective study in pediatric patients with biopsy-proven interstitial nephritis identified asymptomatic uveitis in 50% of cases[16] so this entity might be underdiagnosed. TINU may account for 9 to 22% of all cases of ATIN in adults[4.] On the other hand, some uveitis labeled as idiopathic did not undergo further laboratory evaluation to rule out or confirm this entity[15.]

Our hospital serves a population of about 350,000 inhabitants and 2 cases of TINU were identified in the same year, which suggests that indeed its incidence may be higher than described. Both cases occurred in women, with an older age of onset than initially reported but in agreement with more recent series and case reports.

Diagnostic criteria

In 2001, Mandeville and colleagues[9] proposed diagnostic criteria for this entity that include (1) occurrence of tubulointerstitial nephritis (TIN) and (2) uveitis (3) in the absence of other systemic diseases that cause either conditions. Therefore, TINU is considered a diagnosis of exclusion. The urine sediment may present red cells or red cell casts; tubular proteinuria may be detected and a proportion of patients exhibit sterile pyuria. Peripheral blood and urinary eosinophilia are inconsistent findings[7]. Elevated urinary β2-microglobulin was reported in about 87% of cases of TINU, and thus has been suggested as a sensitive and specific non-invasive diagnostic test. However, it is a marker of tubular injury of any etiology and not specific for TINU[6,17,18]. While the type of inflammatory cells infiltrating the renal interstitium are not included in the diagnostic criteria, Legendre et al observed a preponderance of lymphocytes (100% of cases) and plasmocytes (57%)[11]. Although initially defined as anterior, several reports showed a broad range of ocular manifestations (from posterior, intermediate and panuveitis)[11,17,18]. The relationship between clinically apparent tubulitis and uveitis is variable, with several series reporting different predominant sequence: uveitis may precede renal disease in 21–31% of the cases, may be concurrent with nephritis in 15 to 49% and can follow it in 20 to 65%[9,11]. Sarcoidosis, Sjögren´s syndrome,

systemic lupus erythematosus, inflammatory bowel disease and tuberculosis are amongst the pathologies that should be ruled out[6,9,10].

In both cases, the ocular manifestations were typical anterior bilateral uveitis. Tubulointerstitial nephritis was clinically suspected by the concomitant occurrence of renal dysfunction, altered urinalysis (with proteinuria, glycosuria and presence of red cells) and systemic symptoms, later confirmed histologically on kidney biopsy. The interstitial infiltrate was mostly composed of lymphocytes. In case 1, although laboratory evaluation was not initially performed, the authors suspect that nephritis was the presenting feature, based on the presence of systemic symptoms and morphological signs of chronicity in the biopsy specimen. In the second case, the patient had already experienced several episodes of "idiopathic" uveitis before renal dysfunction became apparent. Extensive serological evaluation was performed, excluding other possible causative systemic disorders.

■ Pathophysiology

Thus far, the precise pathophysiology of this syndrome remains to be determined[2,6,18]. Several etiologic factors have been identified, including susceptibility features and environment triggers[19]. Genetic susceptibility associated to various human leucocyte antigens (HLA) has been proposed – HLA-A2[20], HLA-A24[20], HLA--DQA1*01[21], HLA-DQB1*05[21,22,] HLA-DRB1*1[21,22] and HLA-DRB1*0102[23] – but small sample size and heterogeneity between reports preclude robust conclusions[6]. Drugs such as non-steroidal anti-inflammatory agents (NSAID)[24,25,26] and antibiotics[25,26] were the main pharmacological groups associated with the occurrence of TINU. However, a causal relationship has not been proved; these are medicines commonly used in the general population that may simply coexist[7] or patients may take them to treat the prodromal symptoms[19]. Giving the prodromal flu-like symptoms, although with no localizing sign or positive microbial cultures, infectious agents were also considered to have a possible role as external triggers of TINU[7,19].

It is thought to be an immune-mediated process (involving both humoral and cellular responses)[19]. Several findings point to a contribution of humoral immune mechanisms: reports describing the presence of circulating immune complexes[27], transiently reduced C4 concentrations[28], serum from patients with TINU reacting against both the eye and the kidney[29,30], with a possible role for antimonomeric C-reactive protein antibodies[31,32,33], antinuclear antibodies[19,34], antineutrophil cytoplasmic antibody[35] and anti-glomerular basement membrane antibody[36]. Cellular immune mechanisms are elicited by the presence of a predominantly lymphocytic and monocytic interstitial infiltrate and the association with HLA genotypes[19]. A possible model includes a microbial or chemical agent triggering an innate immune response, with production of cytokines and proinflammatory proteins, resulting in indiscriminate tissue damage and exposure of antigenic sites that elicit an autoimmune response. The triggering antigens associate with HLA peptides and interact with T-cell receptors, initiating the adaptive immune response in which antigen-specific T cells are stimulated to proliferate, differentiate, produce cytokines and exert direct cytotoxic effects to the uvea and renal interstitium[19,37,38]. Being a delayed-type hypersensitivity response, a period of 7–10 days is expected between exposure to the triggering agent and organ damage; a shorter period can be seen if preexposure has occurred[39].

Indeed, a flu-like syndrome occurred in case 1 with evidence of organ damage recorded about 2 weeks later – in agreement with the model described above.

■ Treatment

Although comparative studies with control groups are lacking, current accepted treatment in active TIN with progressive renal insufficiency comprises the use of corticosteroids. For uveitis, topical steroids in association with cycloplegic agents are recommended; oral corticoids or other immunosuppressive medication are reserved for refractory cases[11,18,20]. The renal course is thought to be independent from ocular disease as neither the severity nor the prognosis of nephritis is influenced by the presence of uveitis[40,41]. Renal disease relapses in 9% and becomes chronic in 11–32% of cases, with only 5% requiring renal replacement therapy[11,42.] Ocular inflammation may persist for more than 3 months in 14% of cases[43] and recur in 40–50% of patients after corticoid withdrawal[43,44]. So, it seems that maintaining quiescence in the eye can be more difficult than in the kidney but overall, long-term prognosis is favorable for both organ systems[6].

The mainstay of therapy in both cases was oral prednisolone at 1 mg/Kg/day. In case 1, the patient started ocular treatment with topical agents, but considering the lack of response and the presence of active

tubulointerstitial nephritis, systemic corticosteroids were initiated as recommended. The patient presented in case two was initially medicated with topical steroids. Oral corticosteroid (deflazacort) was initiated prior to our evaluation, given the presence of renal impairment. After making the AIN diagnosis (histologically), the switch to prednisolone was made. Even though the follow-up period was short, both patients experienced improved renal function, with no evidence of relapsing uveitis.

CONCLUSION

TINU is a rarely diagnosed syndrome with probable higher frequency than reported. Its clinical recognition may be hindered by the presence of non-specific symptoms, absence of concomitant renal and ocular manifestations and general limited knowledge of the disease. As demonstrated in several studies, it may be worth screening for uveitis in all patients with tubulointerstitial nephritis and evaluating renal function in those presenting with apparent idiopathic uveitis. No randomized controlled trials exist regarding treatment; however observational studies suggest that corticosteroids and other immunosuppressive agents seem effective and this entity has an overall good prognosis. It is thus essential to enhance awareness of general practioners and internists for a correct and timely referral and a optimal articulation between ophthalmologists and nephrologists for both correct diagnosis and treatment.

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