Tubulointerstitial Nephritis and Uveitis (TINU) Syndrome: An Oculo-Renal Disorder to Consider

Síndrome Nefrite Túbulo Intersticial Aguda e Uveíte (TINU): Um Distúrbio Óculo-Renal a ser Considerado

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ABSTRACT

Tubulointerstitial Nephritis and Uveitis (TINU) syndrome is characterized by bilateral anterior uveitis and idiopathic tubulointerstitial nephritis. A 37-year-old female with bilateral anterior uveitis, malaise and fever was evaluated at the Ophthalmology Emergency department. Laboratory investigation revealed an elevated C-reactive protein, a raised erythrocyte sedimentation ratio and a sub-nephrotic proteinuria. Patient was then referred for Nephrology assessment and a renal biopsy showed diffuse tubulointerstitial nephritis. TINU syndrome was assumed. Bilateral anterior uveitis resolved after one week of topical steroid therapy.

This case highlights an under recognized syndrome, occurring in young patients with asymptomatic mild renal disease and chronic or recurrent anterior uveitis. It is important to be aware of this clinical entity since a prompt diagnosis and appropriate treatment can avoid poor renal and visual outcomes.

KEYWORDS: Blood Sedimentation; C-Reactive Protein; Nephritis, Interstitial/diagnosis; Nephritis, Uveitis/diagnosis; Uveitis, Anterior/diagnosis

RESUMO

A síndrome nefrite túbulo-intersticial e uveíte (NTIU) é caracterizada por uveíte anterior bilateral e nefrite tubulointersticial idiopática. Este trabalho descreve o caso de uma mulher de 37 anos que recorreu à urgência de oftalmologia com uveíte anterior bilateral, mal-estar geral e febre. A investigação laboratorial revelou elevação da proteína C reativa e velocidade de sedimentação, bem como, proteinúria subnefrótica. A paciente foi encaminhada para avaliação nefrológica e biópsia renal que mostrou nefrite tubulointersticial difusa. A síndrome NTIU foi diagnosticada. A bilateral resolveu após uma semana de corticoterapia tópica.

Este caso destaca uma síndrome pouco reconhecida, ocorrendo em pacientes jovens com doença renal leve assintomática e uveíte anterior crónica e recorrente. É importante manter suspeição clínica desta entidade, pois um diagnóstico imediato e tratamento adequado podem evitar mau prognóstico visual e renal.

PALAVRAS-CHAVE: Nefrite Intersticial/diagnóstico; Proteína C-Reativa; Sedimentação Sanguínea; Uveíte/diagnóstico; Uveíte Anterior/diagnóstico

INTRODUCTION

Tubulointerstitial nephritis and uveitis (TINU) is a rare cause of uveitis and more commonly presents in children. The condition used to be recognized more by nephrologists than ophthalmologists but recent ophthalmic publications have raised the awareness of this condition.[1] TINU syndrome was first described by Dobrin *et al* in 1975.[2] This syndrome is an immunological abnormality characterized by chronic or recurrent bilateral, simultaneous, mild to moderate anterior uveitis and acute tubulointerstitial nephritis.[3] Other associated ophthalmological manifestations include posterior uveitis, panuveitis, optic nerve head edema or retinal vasculitis.[4]

Pathogenesis of ocular and renal abnormalities are unknown at this point. Nevertheless, common antigens in tubular cells and eyes,[5] modified C reactive protein levels,[6] and IgG4-related systemic disease[7,8] all demonstrated to be related to TINU.[1] Infectious or therapeutic triggers (such as nonsteroidal anti-inflammatory drugs) seem to play a role.[9,10]

Diagnosis depends on ocular and renal findings, mainly tubulointerstitial nephritis (TIN) and anterior uveitis (AU), with no evidence of other systemic or infectious disease. Constitutional symptoms are often very unspecific (fever, headache, malaise and anorexia[11-13] which may delay diagnosis and treatment.[11]

CASE REPORT

A 37-year-old female with unremarkable past medical history was evaluated at the Ophthalmology Emergency department complaining of ocular pain and blurry vision in both eyes. Constitutional symptoms of holocranean headache, chills, malaise, myalgia and fever (39ºC) started two weeks before. She had no urinary symptoms apart from nycturia.

Physical examination was normal except for positive for an axillary temperature of 38.1ºC. Ophthalmological evaluation indicated 20/20 best corrected visual acuities in both eyes. Biomicroscopy revealed bilateral anterior non-granulomatous uveitis with ciliary injection, fine keratic precipitates and anterior chamber cellular reaction (3+). Fundoscopy was normal.

Laboratorial investigation showed an elevated C-reactive protein (8.51 mg/dL) and raised erythrocyte sedimentation rate (63 mm/h). Urinalysis revealed traces of protein (++), haematuria (+), increased occasional urinary proteins (182.2 mg/dL) and elevated urinary protein: creatinine ratio (1210.6 mg/g).

A presumptive diagnosis of TINU was assumed and patient was referred for nephrological assessment. Patient started topical steroid and cycloplegic therapy.

During complementary study, renal echography revealed a minor increase in cortical echogenicity and medullary pyramids prominence, which conditioned loss of parenchymal-sinus discrimination. Further laboratorial investigation showed and elevated serum (3.32 mg/L) and urinary (0.48 mg/L) β2-microglobulin.

Renal biopsy disclosed granulomatous tubulointerstitial nephritis, with moderate chronic inflammatory infiltration, tubular atrophy, mild interstitial fibrosis and periglomerular/peritubular non-necrotizing epithelioid granulomas. Immunofluorescence microscopy was negative. No microorganism was identified by histochemical reaction (Fig.s 1 and 2).[14]

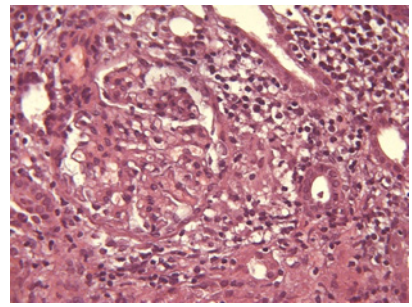

Figure 1 - Renal biopsy specimen 1. This panel shows a high-power image (x400) of a slide prepared from renal biopsy specimen (Hematoxylin and Eosin stain). The optical microscopic study showed diffuse inflammatory infiltration of mononuclear cells in the interstitium, mostly lymphocytes. Mononuclear cells were infiltrating the tubules.

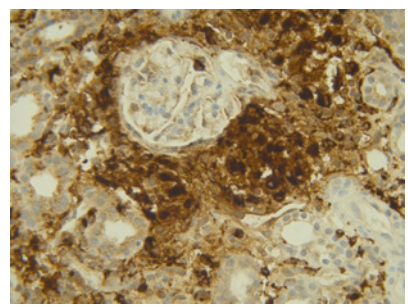

Figure 2 - Renal biopsy specimen 2. This panel shows a high-power image (x400) of a slide prepared from renal biopsy specimen (CD 68 + stain). The optical microscopic study revealed periglomerular and peritubular non-necrotizing epithelioid granulomas.

Differential diagnosis should include infectious uveitis, sarcoidosis, Sjögren syndrome, systemic erythematous lupus, granulomatosis with polyangiitis and Behçet disease since uveitis and nephritis can also co-exist in these cases. Drug related uveitis must be excluded (especially antibiotics and nonsteroidal anti-inflammatory).

Combined treatment with topical steroid and cycloplegic agents is recommended to treat anterior uveitis. When there is no response to topical treatment, systemic steroids or even second-line immunosuppression may have a beneficial effect in controlling the anterior uveitis and improving renal function.[15] However, a previous study compared groups (treated / untreated) to determine whether systemic corticosteroids were effective for TINU syndrome and did not find any significant advantages for systemic steroid treatment.[1] No systemic steroids were prescribed in this case. Our patient clinical improvement and renal function stabilization without systemic therapy.

TINU prognosis depends on immune activity. The nephritis is usually self-limited but the uveitis tends to become recurrent or chronic.[15] In 14% of cases, ocular symptoms persist for more than 3 months[16,17] and uveitis is re-

current in 50% of patients.[3,18] In this case, eight weeks after presentation, under topical therapy, there were no signs of ocular inflammation or renal dysfunction. After a 5-month follow-up, no recurrence was found and the patient remains asymptomatic.

DISCUSSION

TINU is an oculo-renal disorder with a possible autoimmune origin.[19] It seems to primarily affect young females (the median age of onset is 14 years)[9] in a 3:1 female to male ratio. This autoimmune process involves cell-mediated immune responses, autoantibody production and a possible role of HLA molecules.[18] The ocular and renal disturbance suggests a common antigen target in a cross--linked autoimmune reaction.[20] HLA-DQB1*05 was reported to be strongly associated with TINU syndrome[18] and Mandeville *et al* suggested that HLA-A2 and A-24 may also be involved.[9] Reddy *et al*[19] explained that, in otherwise unexplained pediatric panuveitis, selective HLA classe II DNA typing narrows diagnostic possibilities and directs further evaluations.

The main ocular manifestation is bilateral anterior non-granulomatous uveitis, occurring in 80% of patients.[20] Kidney is injured, mostly, by an acute interstitial nephritis.[9] Proximal and/or distal tubular dysfunction are the prominent features of the tubulointerstitial component of the disease. Syndrome constitutional symptoms are unspecific and related to renal disease, including fever, weight loss, fatigue, malaise, anorexia and abdominal pain.

Uveitis can precede (21%), occur concomitantly (15%) or follow (65%) the renal disease.[16,19,20] Mandeville *et al*[9] mentioned that the TIN frequently precedes uveitis by few months. However, in this case, the patient had simultaneous ocular and renal involvement. Since all proposed diagnostic criteria were present[9] (Table 1), TINU syndrome was assumed.

Table 1 – Diagnostic criteria

Typical uveitis, histopathologically confirmed acute interstitial nephritis and the following 3 criteria (excluding any other systemic disease as a cause):
a. Abnormal renal function
b. Abnormal urinalysis
c. Systemic Disease during ≥ 2 week

Laboratory results usually include anaemia, increased ESR, raised C reactive protein, hypergamaglobulinemia and increased urinary ß2 microglobulin.[20] This patient had inflammatory markers elevation (C-reactive protein and ERS), slightly elevated serum and urinary ß2-microglobulin and proteinuria.

TIN histological findings should be investigated for definitive diagnosis but an invasive procedure as a renal biopsy may not be suitable for every patient and should be considered individually.[20] The granulomatous tubulointerstitial nephritis found in this case is consistent with TINU.

CONCLUSION

TINU Syndrome must be considered while managing patients with bilateral, simultaneous AU. TINU is, probably, under recognized in young patients with asymptomatic mild renal disease and otherwise unexplained chronic or recurrent AU. A prompt diagnosis and appropriate treatment can avoid poor renal outcomes. The eye disease may continue for much longer and still require treatment to prevent visual loss.

ETHICAL DISCLOSURES

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Patient Consent: Consent for publication was obtained.

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