Clinical Ophthalmology

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REVIEW

Diagnostic and Management Strategies of Tubulointerstitial Nephritis and Uveitis Syndrome (TINU): Current Perspectives

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Abstract: Tubulointerstitial nephritis and uveitis (TINU) syndrome is a rare autoimmune disease with unclear pathogenesis but probably related to a combination of genetic predisposition and environmental triggers. Diagnosis is challenging due to the asynchronous onset of renal and ocular symptoms, and it is necessary to exclude other causes of nephritis and uveitis. It affects both sexes, with an overall predominance of females and a median age of onset of 15 years. TINU syndrome is characterized by bilateral, non-granulomatous anterior uveitis and tubulointerstitial nephritis, which can cause acute renal failure in severe cases. Several triggers have been identified including concurrent infections, medications, or endocrine diseases. The diagnosis of TINU is mainly based on clinical and analytical findings, and although urinary β2-microglobulin is a useful parameter no specific diagnostic test is available. Current perspectives intend to facilitate its diagnosis identifying susceptibility HLA genotypes, serologic markers and imaging tools to avoid renal biopsy. Treatment options for TINU syndrome include corticosteroids, immunosuppressive agents, and intravenous immunoglobulins, but relapses are frequent, and management can be challenging. The purpose of this review is to provide an updated summary of the diagnostic and treatment strategies of TINU syndrome, helping clinicians recognize and manage this rare autoimmune disorder.

Keywords: TINU, uveitis, nephritis, inflammation

Introduction

The tubulointerstitial nephritis and uveitis (TINU) syndrome is an uncommon disorder characterized by acute tubulointerstitial nephritis and uveitis. It was described in 1975 by Dobrin et al in two patients with acute eosinophilic interstitial nephritis, anterior uveitis, and bone marrow granulomas.[1] TINU syndrome is probably underrecognized because its diagnosis can be challenging. Management is difficult as relapses are very common. The purpose of this article is to offer clinicians an updated summary of the diagnostic and treatment strategies in TINU syndrome.

Epidemiology

Its incidence is unknown, although over the past 40 years case reports and series about TINU syndrome have steadily increased because of its growing recognition among clinicians.[2,3] No geographical or ethnic differences have been reported.[4,5] The median age of onset is 15 years old with patient's ages ranging from 9 to 74.[6–10] It affects both sexes, with an overall predominance of females but a trend towards a male predominance in younger age groups.[4]

Received: 18 May 2023
Accepted: 24 August 2023
Published: 4 September 2023

Etiology

TINU syndrome is probably developed after a confluence of genetic susceptibility and environmental triggers.

HLA Susceptibility

Many studies have recently shown diverse HLA (human leukocyte antigen) typing associations with TINU syndrome, probably according to regional variation in predisposing alleles. The first was described by Mandeville et al in Japanese patients,[4] where correlation was found with HLA-A2 and HLA-A24. Other Japanese series added HLA-DR4.[11] In the United States, HLA-DQA1*01, HLA-DQB1*05 and HLA-DRB1*01 were correlated with TINU,[12] and Mackensen et al correlated the allele HLA-DRB1*0102 with TINU but not interstitial nephritis alone in a European cohort.[13] Our group described a strong presence of HLA-DQB1*05 among TINU patients in Spain and Portugal.[14]

Triggers

Several triggering factors, such as infections or medications, have been postulated. Although in some cases an infectious agent could not be identified in the literature, others were classically associated with one of the following risk factors:

Concurrent infections with Chlamydia trachomatis, Epstein–Barr virus, Mycobacterium tuberculosis, Toxoplasma gondii or Varicella zoster; taking non-steroidal anti-inflammatory drugs (NSAIDs), antibiotics or Chinese herbs; and endocrine diseases such as hypoparathyroidism, hyperthyroidism or systemic autoimmune diseases such as IgG4-related disease and rheumatoid arthritis.[13–24]

Recently, some triggers such as dietary supplements[25] or COVID-19 disease[26] have been described.

Pathophysiology

The specific pathophysiology is unclear but probably involves both humoral and cell-mediated immunity.

The presence of autoantibodies against modified C-reactive protein (mCRP) in renal and ocular tissue suggests the participation of the humoral immunity component in TINU syndrome.[8] According to the literature, these could be a target autoantigen in TINU and predict the onset of uveitis in a patient with acute interstitial nephritis.[27] The reported recurrence of TINU in a patient following kidney transplantation supports this humoral immunity component theory.[28]

The role of cell-mediated immunity implies the different genotypes of HLA-class II, which would make the subject susceptible to a harmless antigen which is common or similar in both the kidney and the eye.[29] In addition, histologic findings in kidney biopsy of TINU patients show predominantly lymphocytic and monocytic interstitial infiltrate which is coherent with this cellular immunity implication and is believed to be the main pathogenic mechanism.[30,31]

Clinical Features

Ocular and renal symptoms are usually asynchronous, nephritis manifesting first in two-thirds of patients. However, uveitis can appear two months before, concurrently, or up to 14 months after renal involvement.[4] Nephritis is usually due to infiltration of the renal interstice by inflammatory cells that, in severe cases, may cause acute renal failure. It is generally mild, resolving sometimes spontaneously and may be asymptomatic or produce nonspecific flu-like symptoms.[32–34] Eye disease may be masked by high dose of corticosteroids initiated for renal disease and occur with systemic corticosteroid withdrawal. Uveitis is usually anterior, acute, non-granulomatous and unilateral at the beginning, progressing to chronic and bilateral. Up to 20% can present vitreous and retinal inflammation. Intraocular complications include posterior synechiae, macular edema, chorioretinal scar, cataracts, and glaucoma.[35,36]

Diagnosis

Diagnosis of TINU syndrome is usually made after excluding other causes of uveitis and nephritis in patients presenting either flu-like symptoms or uveitis. Asynchrony of eye and kidney involvement may preclude prompt recognition of the syndrome; hence, TINU should be suspected in any young patient presenting with either uveitis or TIN, and a detailed clinical history searching for typical symptoms and exposure to triggers should be conducted. Mandeville et al[4] described in 2001 a diagnostic strategy as an attempt to encourage precision in the recognition of TINU based on clinical and analytic findings. Recently the

Standardization of Uveitis Nomencature (SUN) Working Group has proposed the classification criteria for TINU syndrome. They propose that the presence of anterior uveitis and tubulointerstitial nephritis (either confirmed by renal biopsy or abnormal kidney function tests) can be classified as TINU syndrome if syphilis and sarcoidosis have been excluded.[37]

Serologic Tests

At the moment, there are not noninvasive tests of high diagnostic value in TINU. Peripheral blood abnormalities such as normochromic, normocytic anemia, elevated erythrocyte sedimentation rate, hypergammaglobulinemia and elevated CRP are described in TINU.[38] In patients with unexplained acute kidney injury (AKI) (elevated blood urea nitrogen and/or serum creatinine (SCr)) or progressive reduction in glomerular filtration rate (GFR), TIN should be suspected.[39,40] Mucoprotein Krebs von den Lunge-6 (KL-6; encoded by MUC1) was suggested as a serologic marker for TINU,[41] although it was later found elevated in other forms of tubulointerstitial lesions. HLA-DR, DQ class II DNA typing may be useful in cases of relapsing or atypical uveitis where no renal impairment has been studied or identified.[13,42] Having alleles related with TINU syndrome could support the diagnosis in suspected individuals; nevertheless, no genotype–phenotype correlation has been described at the moment.

Urinary Tests

Urinalysis findings are usually non-specific. Tubular dysfunction signs are common, such as glycosuria, aminoaciduria, acidosis (Fanconi Syndrome), and biomarkers of tubular damage such as N-acetylglucosaminidase (NAG) and β2-microglobulin (B2M).[43] The latter has been proposed as a screening measure to investigate for underlying TINU syndrome in patients with uveitis; and a positive correlation between urinary B2M levels and the histological grade of TIN in pediatric patients was reported.[44]

Histologic Confirmation

Diagnosis can be secured only through renal biopsy. Histologic analysis shows interstitial oedema with infiltration of inflammatory cells (T lymphocytes, neutrophils and plasmocytes) and tubular damage with tubule oedema, epithelial degeneration and focal necrosis.[45,46] Glomerular matrix structure, blood vessels and the number of mesangial cells are preserved.[47]

Others

Kawai et al described the diagnostic utility of diffusion-weighted magnetic resonance imaging (DW-MRI) in early stages of renal involvement. It is also a non-invasive tool without exposure to ionizing radiation.[48]

Differential Diagnosis

Ocular involvement and interstitial nephritis can be seen in other diseases which must be considered in the differential diagnosis of TINU syndrome. The most relevant is Sarcoidosis, the differentiation of which can become complicated in the absence of other organs involvement.[15,40] Sarcoid-like noncaseating granulomas have been identified in the eye, kidney and bone marrow of patients with TINU.[49] In addition, up to 10% of sarcoid cases may present without evidence of pulmonary disease and converting enzyme activity may be normal.[50,51] Elevated urinary B2M has been proposed as a differentiative trait in these patients.[52]

Differential diagnosis should also be considered with Sjögren's syndrome, systemic lupus erythematosus, Wegener's granulomatosis, Behçet's syndrome, Juvenile idiopathic arthritis in children and some infectious diseases such as syphilis, tuberculosis, brucellosis, toxoplasmosis and histoplasmosis.[5,53]

Treatment

Although both renal function and uveitis respond to corticosteroid therapy, ocular inflammation tends to be more resistant, chronic and relapsing than renal inflammation.[39]

Uveitis Treatment

Despite topical therapies such as corticosteroids and cycloplegic drops are the first-line treatment for anterior uveitis, it has been shown that up to 80% of TINU patients will need systemic corticosteroid treatment. Moreover, despite the usefulness of systemic corticosteroids at the beginning of the treatment, this therapy is insufficient in the long term in up to 70% of patients with anterior uveitis in the setting of TINU.[34]

The greater severity of recurrences in these patients, as well as the sequelae resulting from such inflammation, often make necessary to start immunomodulation therapy (IMT).[44]

IMT with mycophenolate mofetil (MMF), azathioprine (AZA) or methotrexate (MTX) is used for patients with refractory or insufficient response to corticosteroids, with MTX being the most commonly used.[54] Given the good response and tolerability to IMT, the need for biologics such as adalimumab is rare.[55]

Only after a remission period of at least 12–24 months would it be indicated to withdraw this treatment.[53]

Despite the difficult control of uveitis in TINU syndrome, this disease generally leads to good visual outcomes and few complications (up to 20%) with appropriate management.[4,32]

Renal Treatment

Although the management of renal involvement in TINU is simpler than ocular involvement, complete recovery does not always occur.[46,56]

This makes early treatment with corticosteroid therapy a key predictor of long-term renal function.[7,57]

First-line therapy is oral steroids thought IMT is frequent due to uncontrolled disease; as shown by Legendre et al at 1-year follow-up, in whose study up to 70% of patients progressed to chronic kidney disease and 30% of patients progressed from moderate-to-severe kidney disease despite corticosteroid treatment.[58]

AZA and MMF are the preferred IMT in kidney involvement, but its use is limited to cases of advanced renal involvement or resistance to corticosteroid therapy.[6,44]

Prognosis and Follow-Up

Urine B2M (UB2M) has been shown to be an important parameter in the follow-up and prognosis of TINU, both for its good correlation with uveitis and nephritis, being useful even in subclinical inflammation. As showed by Provencher et al, UB2M may be elevated during periods of uveitis and nephritis activity even when serum creatinine is normal.[59]

It is considered that quarterly ophthalmological screening up to 1 year after the diagnosis of tubulointerstitial nephritis would be useful for the early detection of uveitis and early treatment of TINU, which is key to the prognosis and management of this disease.[7]

Discussion and Conclusion

Diagnosis of TINU syndrome is challenging and requires high level of suspicion because of asynchrony and lack of specificity of eye and kidney disease. Multidisciplinary protocols should be considered in order to increase recognition rates, as urinary B2M quantification in cases of relapsing or bilateral anterior uveitis. Regarding the lack of diagnostic noninvasive tests, recent studies have been identifying serologic markers and susceptibility HLA genotypes which could have a role in the routinary diagnosis in the future. However, further description of HLA genotyping is necessary to understand its regional patterns and improve diagnostic rates.

Funding

No funding received.

Disclosure

Dr Ester Carreño reports DSMB chair from Eyevensis, speaker fees from Allimera, consultancy from Active Biotech and GSK, personal expenses from Novartis, outside the submitted work. The authors declare that there are no other conflicts of interest to disclose.

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