Major review

Tubulointerstitial Nephritis and Uveitis Syndrome: Case report and review of the literature

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ABSTRACT

Purpose: To review the literature on tubulointerstitial nephritis and uveitis (TINU) syndrome, and to report a case of a patient with relapsing polychondritis (RP) and TINU syndrome.

Method: TINU syndrome is a rare oculo-renal inflammatory disorder. It is more common in young women with autoimmune conditions, infections, systemic disease, and previous use of medications. We report the case of a 62-year-old woman with relapsing polychondritis and a 2-year history of acute, recurrent, asymmetric, bilateral, anterior, non-granulomatous uveitis accompanied by tubulointerstital nephritis. The patient was diagnosed with TINU syndrome associated with relapsing polychondritis. No cases of this association have been reported in the literature. The clinical features of TINU syndrome are discussed based on the published works.

Conclusion: TINU is an uncommon syndrome; only about 200 cases have been reported in the literature related to infections, systemic disease, and previous use of medications such as antibiotics and non-steroidal anti-inflammatory drugs. We found that it can be associated with relapsing polychondritis; therefore, it is important to investigate symptoms of this disease since TINU syndrome can co-exist with it.

Key Words: Acute tubulointerstitial nephritis, uveitis, nephropathy, TINU syndrome, relapsing polychondritis.

INTRODUCTION

Tubulointerstitial nephritis and uveitis (TINU) or Dobrin syndrome is a rare oculo-renal inflammatory disorder, characterized by acute tubulointerstitial nephritis and uveitis without a known specific underlying systemic disease.[1]
It can be associated with autoimmune conditions, infections, systemic disease, and previous use of medications.[2] Although there are some reports of TINU syndrome in elderly patients, it generally occurs in children and young adults.[3] Females are affected three times more often than males.[3–5] It affects, approximately, 1–2% of the patients who visit uveitis clinics.[3,4] Generally, renal involvement in TINU is mild, and uveitis tends to recur in some patients.[3]

Genetic markers for TINU were identified by Levinson et al.[6,7] They found that HLA-DQA1*01, HLA-DQB1*05, and HLA-DRB1*01 were highly associated with TINU syndrome in their patient population, and concluded that HLA-DQA1*01/DQB1*05 may be related to risk of development of the disease.[6,7] HLA analysis on patients with isolated bilateral sudden-onset uveitis (TINU subtype) and with isolated tubulointerstitial nephritis (TIN subtype) showed that HLA DRB1*0102 could be related to TINU but not to a TIN subset.[8] Bilateral panuveitis with chorioretinal lesions in pediatric patients was found to be associated with the HLA-DR, DQ class II type, in TINU syndrome.[9]

Mandeville determined the diagnostic criteria for TINU syndrome characterized by the presence of histopathologically confirmed acute interstitial nephritis (AIN) and typical bilateral anterior non-granulomatous uveitis.[2] Clinical manifestations can be nonspecific (fever, abdominal pain, weight loss, fatigue, malaise, anorexia, and headache), and generally, renal involvement is mild.[3] Signs include sterile pyuria, hematuria, and different states of renal failure.[1]

Uveitis may not become apparent for weeks to months after systemic problems have resolved.[1] It may occur 2 months before the presentation of acute interstitial nephritis in approximately one-fifth of patients, but in most cases (65%), nephritis precedes uveitis.[2] It presents as episodes of sudden onset of bilateral anterior non-granulomatous uveitis, and it is chronic or recurrent in about one-half of reported individuals.[1,10]

We present a case of a patient with relapsing polychondritis and TINU syndrome. To our knowledge, this is the first case of TINU syndrome associated with relapsing polychondritis to be reported.

CASE REPORT

A 62-year-old female presented to the uveitis service at the Rosario University in Bogotá, Colombia, with a 2-year history of six acute episodes of conjunctival hyperemia, pain, and myodesopsia in both eyes. She reported also a long-term decrease in visual acuity and, systemically, fatigue, tiredness, rhinitis, cough, dry skin, tinnitus, acute sensorineural hearing loss, and dizziness. She had a history of relapsing polychondritis with positive rheumatoid factor. Previously, in another institution, she had been treated with azathioprine for 3 months without improvement, two doses of infliximab (this was suspended because of deterioration of renal function tests), systemic steroids (prednisolone, deflazacort), topical steroids, mydriatics, and topical cyclosporine.

Laboratory testing showed elevated serum creatinine (1,51 mg/dL) and urea, elevated globular sedimentation velocity (23 mm/h), elevated uric acid, positive rheumatoid factor (80 u/mL, reference value: 40–60 u/mL), elevated β-2 microglobulin in urine, and normal c-reactive protein, ANAS, pANCAS, cANCAS, C3, and C4. Due to her abnormal renal function, she was referred to nephrology for further assessment. Renal biopsy showed tubulointerstital changes, focal segmental glomerulosclerosis, and thin basement membrane disease compatible with TINU syndrome.

This patient was diagnosed with relapsing polychondritis by a rheumatologist due to clear manifestations of inflammatory episodes in cartilaginous tissues such us the external ears, presenting inability to sleep on the affected side; episodes of painful nasal bridge, and laryngotracheobronchial tree symptoms consistent of chronic cough and bronchitis. In addition, she presented episodes of audiovestibular symptoms consistent of suddenly diminished hearing, tinnitus, and vertigo. At the time of consultation in our service she did not present signs of active polychondritis, but the external examination of her ears revealed the beginning of floppy ears (Figure 1). This clinical pictured is in accordance to the episodic nature of RP.

Ocular examination showed best-corrected visual acuity (BCVA) 20/40 in the right eye and 20/25 in the left eye. Pupils were round and reactive to light with no afferent pupillary defect in either eye. Anterior segment examination of the right eye revealed a mild degree of inflammatory cells in the anterior chamber (0.5+), pigment on anterior lens capsule, and posterior subcapsular cataract; the iris had no synechiae (Figure 2). Evaluation of the left eye showed pigment on the anterior lens capsule and nuclear cataract; there was no evidence of inflammatory cells in the anterior chamber or iris synechiae (Figure 3). Intraocular pressures were 12 mmHg in both eyes. Fundus examination was within normal limits.

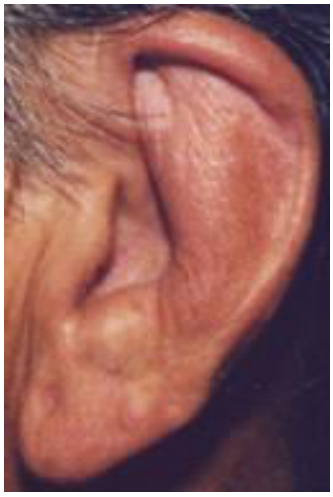

Figure 1.Beginning of deformity of the ears as a consequence of episodic cartilage inflammation.

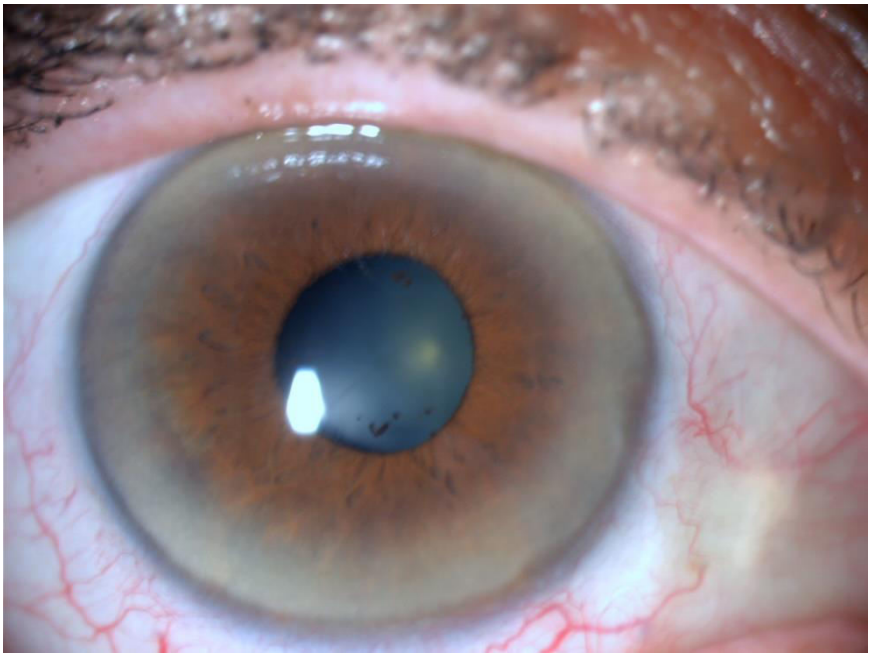

Figure 2. Anterior segment photography of the right eye. The patient presented a mild degree of inflammatory cells in the anterior chamber associated with pigment on the anterior lens capsule and posterior subcapsular cataract.

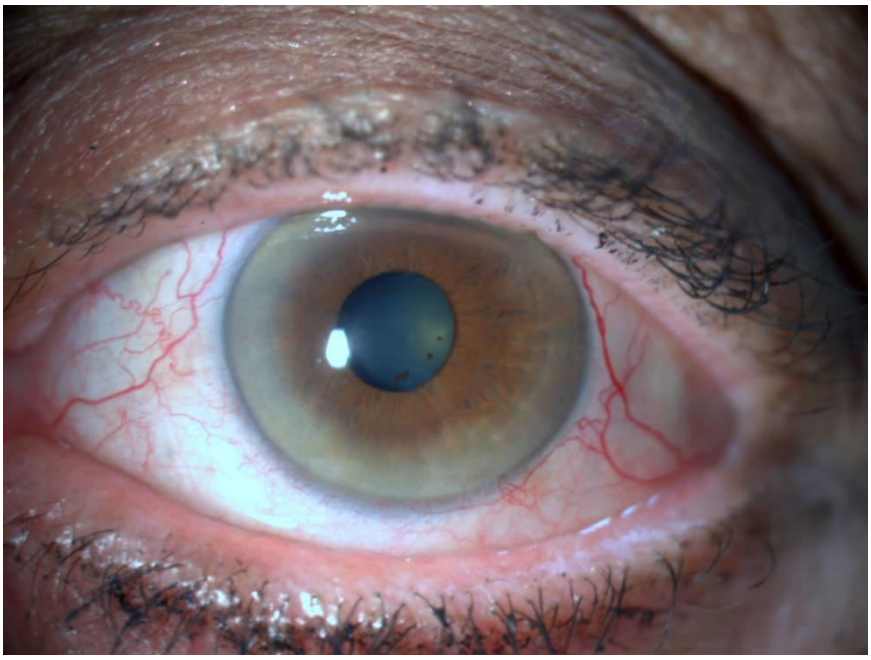

Figure 3. Anterior segment photography of the left eye. There was pigment on the anterior lens capsule and nuclear cataract, with no evidence of inflammatory cells in the anterior chamber or iris synechiae.

EPIDEMIOLOGY

TINU is an uncommon syndrome, first reported and described by Dobrin in 1975.[11] Since then, only about 200 cases have been reported in the literature.[2,12] It generally occurs in young adults, and females are affected three times more often than males.[3,5]
It affects, approximately, 1–2% of the patients who visit uveitis clinics [3,4] and a diagnosis of TINU generally only accounts for 1–2% of all patients attending specialized uveitis centres. [12] In Japan, TINU syndrome is the second most frequent diagnosis in children with uveitis after sarcoidosis and in Europe TINU syndrome has been reported in Spain, France, Belgium, Italy, Poland, Germany, Austria, Switzerland, the Czech Republic, the UK, Serbia, Croatia, and Greece.[13] Generally, renal involvement in TINU is mild, whereas the uveitis tends to recur in some patients.[3] No racial predilection has been identified.[12]

It is possible that ophthalmologists are not diagnosing the disease because the physicians who first evaluate the patient have not considered TINU syndrome. This may be because the presenting symptoms can be nonspecific (fever, abdominal pain), the patient diagnosed as having a “viral syndrome” and the uveitis may not become evident for weeks to months after the systemic problems have resolved. By the time the patient is referred for consultation for the uveitis, evidence of the interstitial nephritis may be difficult to establish.[1]

PATHOLOGY AND PATHOGENESIS

TINU is characterized by idiopathic acute tubulointerstitial nephritis and uveitis.[4]
The pathogenesis of TINU is not clear, but it is thought to be the result of an autoimmune process that might involve humoral and cellular autoimmunity.[14,15]
Reported systemic associations between tubulointerstitial nephritis and uveitis include Fanconi syndrome[16,17] and bilateral optic disc edema.[11] Additionally, there are case reports with no systemic associations as described by Mortajil et al. [4] and Leśniak K et al.[18]

Autoimmune diseases such as rheumatoid arthritis, hyperthyroidism, primary hypoparathyroidism, and Sjögren syndrome have been reported to accompany TINU syndrome.[13] We found no such associations in our case.

Interestingly, renal tubular and ciliary body epithelia share some similar functions, such as those pertaining to electrolyte transporters sensitive to carbonic anhydrase inhibitors[14.] Thus, it is conceivable that they might share cross-reactive autoantigens.[14,19,20] Yin Tang et al.[14] and Li et al.[21] demonstrated for the first time a high prevalence of serum autoantibodies against modified C-reactive protein (anti-mCRP autoantibodies) in patients with TINU syndrome. [14] The results of Ying Tang suggest that mCRP may be one of the common target autoantigens in renal and ocular tissues in patients with TINU syndrome. Plasma C-reactive protein (CRP), a member of the pentraxin family, under certain conditions such as altered pH, high urea concentration, or low calcium concentration, dissociates irreversibly into monomers, also called modified CRP (mCRP). In this study, mCRP autoantibodies were screened by ELISA with purified human C-reactive protein in nine patients with TINU syndrome, and mCRP expression was analyzed by immunohistochemistry in renal biopsy specimens from the nine patients along with 40 from disease controls. The mCRP autoantibodies were detected in all nine patients with TINU syndrome, significantly higher than in the disease controls. The renal histologic score of mCRP in TINU syndrome was significantly higher than that in disease controls. The staining of mCRP and human IgG were co-localized in renal and ocular tissues.[14] These results suggest that mCRP may be one of the common target autoantigens in renal and ocular tissues in patients with TINU syndrome.[14] In comparison with other renal diseases and normal controls, the high prevalence of serum anti-mCRP autoantibodies in TINU syndrome was impressive, especially in the active phase of nephritis.[14]

Otherwise, some studies have described that renal tubulointerstitial infiltrates are primarily composed of activated lymphocytes, among which the helper/inducer T-cell subset is reported to be predominant,[22,23] furthermore, cell-mediated immunity, in particular delayed-type hypersensitivity, could play a large role in TINU syndrome.[24] Most of the studies describing immunohistochemical kidney analysis in TINU patients have demonstrated that interstitium is infiltrated mainly by T-cells together with monocytes/macrophages[25,26] and the case reports of Abed et al.[22] and others have described that the helper/inducer T-cell subset was predominant in renal interstitial infiltration in TINU.[22]

Relapsing polychondritis is a rare autoimmune disorder characterized by episodic, progressive inflammatory destruction of cartilage.[27] The exact etiology and physiopathology of the disease has not been established.[28] It affects cartilaginous structures including ears, nose, tracheobronchial tree, and joints; it can also involve non-cartilaginous tissues rich in proteoglycans such as the eyes, inner ear, heart, blood vessels, and kidney.[27,28] Diagnostic criteria were established by Michet et al.[29] which require the presence of proven inflammation in at least two of three of the auricular, nasal, or laryngotracheal cartilages, or proven inflammation in one of these cartilages plus two other signs, including ocular inflammation, vestibular dysfunction, seronegative inflammatory arthritis, or hearing loss.[28,29]

Our case is consistent with the diagnosis of TINU syndrome and was confirmed histopathologically with renal biopsy associated with typical bilateral uveitis. However, unlike previous reports, our patient had a history of relapsing polychondritis associated with recurrent, asymmetric, bilateral anterior non-granulomatous uveitis episodes in the last two years, with subsequent renal involvement consisting of tubulointerstitial nephritis that did not require dialysis.

Uveitis was treated with topical steroids (prednisolone 1%), topical non-steroidal anti-inflammatory (ketorolac 0.4%) and systemic steroids (deflazacort) in another institution.

Eight months later the patient remained symptomatic with signs of uveitis in both eyes, and consulted again with our service. BCVA was 20/30 in the right eye and 20/40 in the left eye. Subsequently, the uveitis was treated with mycophenolate mofetil. Her renal function and ocular inflammation showed a steady recovery, followed by complete resolution of the uveitis. In the last two years, since the beginning of treatment with mycophenolate mofetil, she has not had any relapses. However in the last optic coherence tomography taken after treatment the patient presented macular edema and epiretinal membrane in both eyes (Figures 4 and 5).

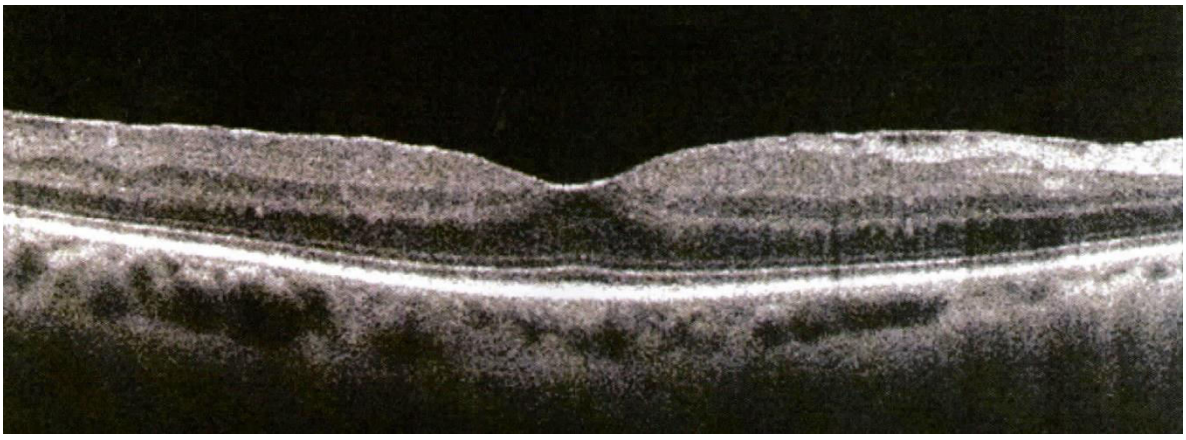

Figure 4: Optical coherence tomography of the right eye with evidence of macular edema and epiretinal membrane.

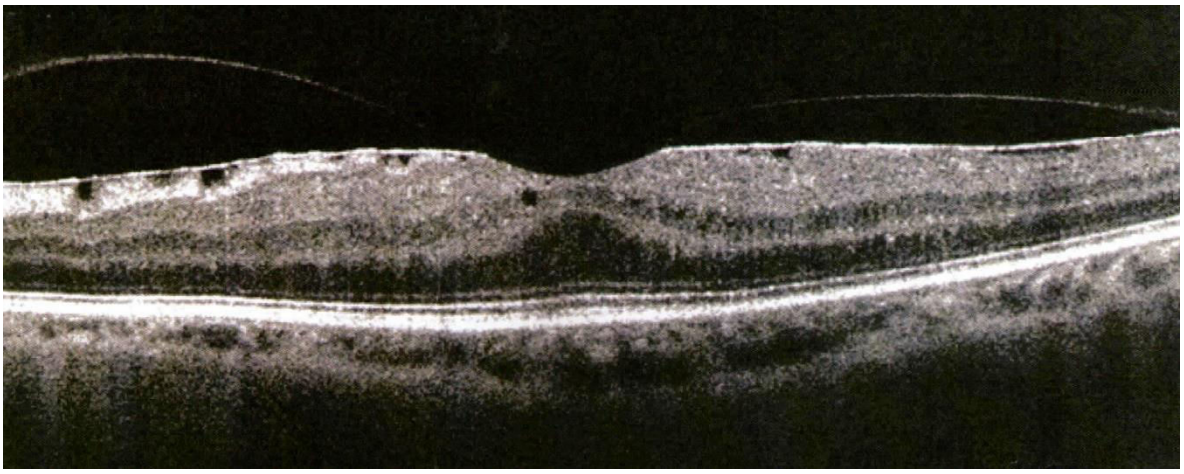

Figure 5: Optical coherence tomography of the left eye with evidence of much marked macular edema and epiretinal membrane.

RISK FACTORS AND ASSOCIATED FACTORS

TINU has been linked with a hypersensitivity reaction, autoimmune conditions, infections, and systemic disease. It has been suggested that non-steroidal anti-inflammatory agents or antibiotics may precipitate TINU syndrome, but this has been difficult to establish.[2,30]

Mackensen et al. reported a retrospective case series of 33 patients with TINU syndrome.[12] Seven patients had been taking occasional ibuprofen within approximately 2 to 6 weeks of the time of disease onset. Two other patients were taking other non-steroidal anti-inflammatory drugs. Only two individuals had been taking antibiotics: one, erythromycin, and the other, co-trimoxazole and amoxicillin–clavulanic acid. Nevertheless, it was not possible to establish a causal relationship between the medication used and TINU syndrome in any of the patients.[12]
On the other hand, Suzuki et al.[31] reported a case of a 58-year-old man with fever and arthralgia. His clinical course and marked ciliary hyperemia allowed suspected tubulointestinal nephritis and uveitis (TINU) syndrome, which was confirmed ophthalmologically and by renal biopsy. Results of a drug-induced lymphocyte-stimulating test were positive for the Chinese herb “Goreisan.” This was the first case in which the use of “Goreisan” was causally related to TINU syndrome.[31]

CLINICAL SPECTRUM

General symptoms like fever (53%), weight loss (47%), general weakness and malaise (44%), nausea, asthenia, myalgia, headache, emesis, and anorexia (28%) may be presenting signs.[3] The classic triad consists of inflammatory syndrome, nephritis, and uveitis.[5] Anemia may be present, and the erythrocyte sedimentation rate may be markedly elevated.[1] In our case, the patient referred with cough, dry skin, fatigue, tiredness, tinnitus, acute sensorineural hearing loss, and dizziness. Concomitant

autoimmune disease could be present in one-third of patients with RP.[32] In our patient, the rheumatoid factor (RF) was slightly positive: 80 u/mL (reference value: 40–60 u/mL), which is not common in RP in which seronegative inflammatory arthritis is characteristic. Moreover, rheumatoid arthritis (RA) was ruled out, having taken into account that her physical and radiological evidence did not correspond to RA. In addition, anti-cyclic citrullinated peptide (anti-CCP) titer was negative. The presences of anti-CCP antibodies are typically elevated in RA but not in relapsing polychondritis.

Ocular effects seen with uveitis are limited to the anterior chamber in 80% of cases; both eyes are affected in 77% of cases. The uveitis tends to be bilateral, anterior, and non-granulomatous, but cases of unilateral or granulomatous uveitis and involvement of the intermediate or posterior segment and panuveitis have been reported.[13] The uveitis is most often symptomatic, with pain and photophobia.[1] In most cases, nephritis precedes uveitis, however in 21% of cases uveitis is present before nephritis and in 15%, the two conditions occur simultaneously.[2] Retinal vasculitis with retinal vascular sheathing has been reported in two patients, intraretinal hemorrhages and exudates in three patients, focal chorioretinitis in two patients, and multifocal choroiditis in one patient.[1] Symptoms associated with interstitial nephritis are flank pain, pyuria, hematuria, and proteinuria. Renal failure could occur and may be acute or/and chronic.[3]
On slit lamp examination, fine keratic precipitates, anterior chamber cells, sometimes a high flare even fibrin and, rarely, a hypopyon, are seen. Posterior synechiae may have formed already at first presentation and the posterior segment of the eye is not involved except for mild vitreous cells and possibly complications of anterior uveitis as disk edema and/or macular edema.[12] Also, nodular escleritis may be part of the possible spectrum of ocular inflammation occurring as part of the TINU syndrome as described by Ebenezer et al. in their case report.[33]
On the other hand, chorioretinal lesions have rarely been described as part of the spectrum of TINU.[2,34] Amro, Ali et al.[35] reported four patients with presumed TINU and inferior chorioretinal scars.[35] However, because only one of the patients had biopsy proven TINU, they were not able to conclude on the basis of the report alone that TINU is definitely associated with chorioretinal lesions.[35]

DIAGNOSIS

While diagnostic criteria of TINU syndrome have been published, it is important to take into consideration that not every patient will be diagnosed at the time of presentation, and not every patient will have a renal biopsy to make the diagnosis of interstitial nephritis, or present with the typical bilateral anterior uveitis.[1] Once the physician suspects TINU syndrome according to the clinical presentation, urinalysis, including microscopic examination of the urinary sediment, should be included in the work-up of all pediatric uveitis patients. The presence of glycosuria, proteinuria, aminoaciduria, or microscopic hematuria necessitates evaluation by a nephrologist. Twenty-four hour urine collection for proteins, β-2 microglobulin, and N-acetyl-b-D-glucosaminidase aid in the

diagnosis. Renal biopsy demonstrates necrosis of renal tubule epithelium. Interstitial edema, and CD4 positive lymphocytic infiltrates are the hallmark features.[5,36]

Genetic markers for TINU have been related to the risk of development of the syndrome and of some subsets of the disease. Some of these markers are: HLA-DRB1*01, HLA DRB1*0102, HLA-DQA1*01, and HLA-DQB1*05.[6–9]

Definite TINU syndrome is diagnosed when acute interstitial nephritis is firmly established and the patient has bilateral anterior uveitis of sudden onset, which is the most common ocular presentation in reported cases, and well-established acute interstitial nephritis.[1] For definite TINU syndrome, acute interstitial nephritis is diagnosed either by histologic examination of renal biopsy specimens, or by all three of the following criteria for AIN: 1) abnormal renal function, usually mildly elevated creatinine or creatinine clearance, 2) abnormal findings on urinalysis consistent with AIN, and 3) history of acute systemic illness lasting for at least 2 weeks, characterized by the typical signs, symptoms, and laboratory findings.[1]

Differential diagnosis of TINU syndrome includes other causes of nephropathy and uveitis, such as poststreptococcal glomerulonephritis, systemic lupus erythematous, Wegener's granulomatosis, sarcoidosis, juvenile idiopathic arthritis, IgA nephropathy, Sjögren syndrome, Adamantiades-Behcet disease, syphilis, tuberculosis, brucellosis, and leptospirosis.[5]

TREATMENT

Once the diagnosis of TINU is made, immediate steroid therapy is necessary together with a collaborative approach to treatment by an internist and an ophthalmologist.[3] Tubulointerstitial nephritis can resolve spontaneously and dialysis therapy is not usually required.[37] Treatment for auricular or nasal chondritis or peripheral arthritis without other significant organ involvement in relapsing polychondritis includes low-dose corticosteroids; other more severe disease manifestations may require treatment with high-dose corticosteroids or other immunosuppressive agents.[28]

In reported cases of TINU syndrome, uveitis was chronic or recurrent in about half of the individuals; treatment has included the use of systemic steroids, topical steroids, and mydriatics. In our patient, it was important to establish systemic treatment to control not only tubulointerstitial nephritis and uveitis, but also underlying relapsing polychondritis with antimetabolites and other corticosteroid-sparing immunomodulatory agents in order to avoid potential complications such as cataracts, glaucoma, and macular edema.[38] Our patient presented an adequate systemic response to immunomodulatory treatment with mycophenolate mofetil.

PROGNOSIS

In TINU syndrome, uveitis tends to persist or relapse in 50% of patients, and is characterized by severe inflammation with a high prevalence of posterior segment involvement.[6,13] In a retrospective case series of 1,985 patients with uveitis, individuals with TINU represented 1.7% of all patients with uveitis (*n* = 33).[12] The course of the disease was persistent over a median of 7 months (range, 1–147), after which the inflammation resolved in five patients (15%) (1, 8, 12 and 24 months). The other 28 patients were still active at the last follow-up or were followed up by their primary ophthalmologist.[12] The beneficial effect of systemic steroids for treatment is well established but a relapse may occur following discontinuation of the steroids and may require immunosuppressive drugs because of frequent recurrences; for this reason immunotherapy with methotrexate, cyclosporine A, and azathioprine has been suggested.[39,40.] Our patient required additional treatment, initially with azathioprine, and then with mycophenolate mofetil, due to relapses of anterior uveitis despite the treatment with systemic steroids. Our patient was treated in another institution without systemic therapy during for 8 months, and she had persistent inflammation, developing epiretinal membrane and macular edema. TINU syndrome generally has a favorable prognosis and renal dysfunctions tend to be self-limiting.

CONCLUSION

TINU syndrome is an unusual disease that has been related to a hypersensitivity reaction; it can be connected to autoimmune conditions, infections, systemic disease, and previous use of medications such as antibiotics and non-steroidal anti-inflammatory drugs.[11.] Previous cases have not been associated with relapsing polychondritis; it is important to investigate the presence of symptoms of this disease since TINU syndrome can co-exist with it.

DECLARATION OF INTEREST

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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