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TINU Syndrome: Two case reports and review of literature

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ABSTRACT

Inflammation of renal interstitium along with uvea involvement sets out the two components of tubulointerstitial nephritis and uveitis (TINU) syndrome. Though classically described as occurring in young females, it can affect a broad spectrum of patients.

Both renal and eye disease could be asymptomatic and/or appear with an important delay. Renal disease gives rise to non-specific flu-like symptoms, often self-limited with therapeutic and with good prognosis. Eye-disease emerge mainly as a sudden-onset bilateral anterior uveitis and has a tendency for a chronic course, even under treatment.

The syndrome was firstly thought to affect 2% of uveitis patients. Today, the challenging clinical features and the limited recognition are enlightened, and it is believed to be an under-diagnosed illness. It is thus imperative to have a high clinical suspicion for TINU.

We describe and analyze two clinical cases of TINU syndrome with different initial clinical manifestations and over one-year of follow-up.

Keywords: TINU, uveitis, nefritis, inflammation, auto-immunity

RESUMO

A inflamação do interstício renal, juntamente com o atingimento da úvea, estabelece os dois componentes da síndrome de nefrite tubulointersticial e uveíte (TINU). Embora classicamente descrita como ocorrendo em mulheres jovens, a síndrome pode afetar um amplo espectro de doentes.

Tanto a doença renal como a ocular podem ser assintomáticas e/ou aparecer com um atraso importante. A doença renal dá origem a sintomas constitucionais inespecíficos semelhantes a uma síndrome gripal, muitas vezes autolimitados e com bom prognóstico. A doença ocular surge principalmente como uma uveíte anterior bilateral de início súbito e tem uma tendência para um curso crónico, mesmo sob tratamento.

Os dados clássicos indicam que a síndrome afeta 2% dos doentes com uveíte. Atualmente, reconhecem-se as características clínicas complexas da doença, acreditando-se que seja sub-diagnosticada. É, portanto, imperativo ter uma alta suspeita clínica para TINU.

Neste trabalho são descritos e analisados dois casos clínicos da síndrome TINU com diferentes manifestações clínicas iniciais e com mais de um ano de acompanhamento.

Palavras-chave: TINU, uveíte, nefrite, inflamação, auto-imunidade

O Trabalho final exprime a opinião do autor e não da FML.

ÍNDICE

I. DEFINITION AND EPIDEMIOLOGY

In 1975 Dobrin et al. described for the first time the concomitant presentation of an acute idiopathic kidney inflammation accompanied by an anterior uveitis of unknown cause.[1] Today, around 300 cases of tubulointerstitial nephritis and uveitis (TINU) syndrome are reported in medical literature.[2]

This syndrome has classically a female predominance and a median age of onset of 15 years,[3] with males having a likely earlier age of onset.[3-4] However, this gender effect appears weaker than initially proposed and its occurrence in middle-aged people has also been reported.[3,5–7] TINU syndrome has been described to occur in most ethnic groups, and no geographic nor racial predilection has to date been defined.

Up to 2% of patients attending specialized uveitis centers are diagnosed with TINU,[3,4,9] and it accounts to nearly one-third (32%) of children and adolescents under 20 years-old with typical sudden-onset anterior uveitis.[4] However, and as it will be later discussed, it is often deemed to be an under recognized disorder.

II. RISK FACTORS

TINU has been suggested to derive from the interplay of host vulnerability factors and environmental triggers.

II.I. FAMILY AND HLA

The genetic predisposition of TINU is one of the most curious aspects of the disease and it is being highlighted, with clinical reports on monozygotic twins[10,11], siblings[12–14] and a mother and her son[15] diagnosed years apart, without a likely common environmental influence.

As with other autoimmune diseases, the investigation for genetic susceptibility markers has been centered on HLA genes. The human leukocyte antigens (HLA) system is the major histocompatibility complex (MHC) in humans. It consists of cell-surface proteins produced by genes located on chromosome 6 that are responsible for the regulation of the immune response. Specific HLA associations with TINU have lately been researched, the first one led by Mandeville et al. regarding the HLA-A2 and -A24 antigens in Japanese patients with TINU (75%).[3] These were however subsequently identified as also common in healthy

Japanese subjects, and thus not relevant.[7] Levinson et al. found in 2003 the link to HLA-DQA1*01, HLA-DQB1*05, and HLA-DRB1*01. The strongest association was for the HLA-DRB*0102 allele (a subtype of HLA-DRB1*01), which was present in 72% (13/18) of a TINU patients population, with an estimated relative risk (RR) of 167.1[16] that was further revised to 46.3.[17] In this latter study, Mackensen et al. show that the HLA-DRB*0102 allele occurs in increased frequency in one cohort of European patients with isolated sudden-onset bilateral anterior uveitis (typical of TINU), but not in another group with isolated tubulointerstitial nephritis. This could provide evidence that these risk alleles might be most relevant for the uveitic component of TINU, particularly in younger patients.[17] In the uveitis group was also described an association with HLA-DRB1*01 (RR = 4.0), which had not been shown in the earlier TINU cohort.

In paediatric patients with panuveitis with or without known accompanying renal disease the frequency of TINU risk alleles (HLA-DRB1*01-HLADQB1*05 haplotype) was also reported to be higher (RR = 9.96) than in general North American population.[14] A study conducted in a Finnish population with TINU did not show associations with the formerly described by Levinson "TINU susceptibility" alleles,[18] perhaps because they are not common in Finland.[5] Instead, this study revealed the association with the haplotypes DQA1*04:01 (RR = 4.0), DQA1*01:04 (RR = 6.1) and DRB1*14 (RR = 8.2) alleles.[18]

Several other small studies and case reports referring association to the alleles cited above and even others have been published.[5] The discrepancy between studies may reflect a regional variation in predisposing alleles. Hitherto, there is no determined susceptibility genotype across populations.

II.II. DRUGS AND INFECTIONS

TINU appears to be an immune mediated process, in most cases idiopathic, that may be precipitated by drugs or infections.[3,18,19] There is currently no well-established scientific evidence of a causal relationship between drugs or infections and TINU. Most studies in this field are retrospective, a substantial proportion of the suggested risk factors are common in the general population and may even coexist.[5]

The most commonly associated infections originate in the respiratory tract.[3] Prior infections with agents such as EBV,[20–23] *Chlamydia trachomatis*,[24] *Mycoplasma tuberculosis*,[25,26] *Toxoplasma gondii*,[27] and VZV reactivation[28] have been related.

Non-steroidal anti-inflammatory (NSAIDs) agents and antibiotics are the main drug groups that have been involved,[3,4,20] with other less well-known drugs, such as Chinese herbs,[29] also reported. It is postulated that uveitis in TINU syndrome may be induced pharmacologically by pathogenic mechanisms distinct from the ones responsible for drug-induced isolated uveitis, since they appear to have different causative agents.[5,30] Likewise, the well-recognized NSAIDs-induced isolated tubulointerstitial nephritis (TIN) appears to be distinct from TINU, as it presents with heavy proteinuria and it has no apparent association with uveitis.[31]

II.III. OTHERS

Autoimmune disorders such as rheumatoid arthritis, hyperthyroidism, parathyroidism and Sjögren syndrome have been implicated to follow TINU. It remains unclear whether these occurrences are merely coincidental or result of shared inappropriate immune responses.[3]

III. PATHOGENESIS

The exact immunopathology of TINU syndrome has so far not been clarified. The current proposal estimates that an environmental factor (such as drugs of infections) may trigger a autoimmune cascade in a susceptible genetic background. Both cellular and humoral immunity are thought to be involved in the disease development.

Cellular immunity is believed to be a key-feature in the pathogenesis of TINU. HLA-class II (such as HLA-RB1*0102) expressed on antigen-presenting cells is a crucial informant in the early phases of cellular immunity, presenting processed exogenous antigens to CD4+ helper T cells. It is therefore conceivable that a specific class II subtype might modify the immunity response to a pathogen, making a subject susceptible to a normally harmless antigen.[17] Although none has as yet been discovered, a shared or similar antigen may explain the involvement of both organs.[14] Furthermore, kidney analysis in TINU patients provides evidence of tubulointerstitial infiltrates composed primarily of helper/inducer T-cells subset,[32–35] indicating that T-cell mediated immunity, in particular delayed-type hypersensitivity, could play a large role in this disorder.[36] FOXP3+ T regulatory lymphocytes are central to the maintenance of self-tolerance and tissue homeostasis by suppressing pathological and physiological immune responses.[37] Its quantitative and/or functional impairment results in a diminished ability to suppress effector

T cell proliferation and has been implicated in many autoimmune diseases and malignancies. These cells have been recently found in kidney biopsies samples from paediatric TINU and TIN patients.[38] When compared to patients with isolated TIN or TINU with uveitis lasting <3 months, CD4+ and/or FOXP3+ T-cells have been shown to be present in a smaller amount in patients with TINU with chronic uveitis. This may indicate a different pathogenesis for these conditions. T-reg activation may thus be restrained in TINU patients with chronic uveitis, leading to a persistent inflammatory response and to the chronicity of the clinical condition.[38]

The role of humoral immunity was firstly suggested by the identification of autoreactive antibodies in patients with TINU syndrome against a 125-kD antigen in both renal and uveal cells.[32,39] Tan et al. have shown later the presence of autoantibodies against modified C-reactive protein (mCRP), a dissociated monomer of the acute phase reactant pentamer (C-reactive protein), in renal and ocular tissue of TINU patients.[40] In comparison with other renal autoimmune diseases and normal controls, they noted a significantly higher prevalence of serum anti-mCRP autoantibodies in TINU syndrome, especially in the active phase of nephritis. These results suggest that anti-mCRP may be one of the common target autoantigens in both tissues, having disease-specific relevance.[40] However, it has not been proved whether this autoantibodies are pathogenic in this disease, since they could merely arise from a chronic inflammation with formation of acute phase reactants, as documented in lupus nephritis.[41] Moreover, it has been defined that in patients with acute interstitial nephritis, elevated anti-mCRP antibodies were predictive of subsequent uveitis development.[42] This is in line with the clinical evidence suggesting that the kidney may be the primary target of a sequential process, possibly leading to an inflammatory cascade with secondary effects on the eye. Regarding the humoral immunity, it is also to note the recurrence of TINU in a patient following a kidney transplantation, suggesting that the target renal antigen might be a wild-type endogenous protein.[43]

IV. CLINIC

The renal and ocular symptoms have often an asynchronous presentation.[44] In most cases (65%), the uveitis follows the interstitial nephritis with an average delay of 3 months, although up to 14 months has been noted. In 20% of patients, the eye disease can also precede the kidney illness and, in a minority (15%), they both have a concurrent onset.[3,45]

IV.I. RENAL DISEASE: SYMPTOMS AND SIGNS

Tubulointerstitial nephritis is a frequent cause of acute kidney injury (AKI) and a potentially life-threatening condition. It is characterised by an immune-mediated infiltration of the kidney interstitium by inflammatory cells. In TINU syndrome, renal involvement is generally mild, resolving sometimes spontaneously, and there is a correlation between the patient's advanced age and the severity of renal disease.[3,45]

Patients may be asymptomatic or present with prolonged non-specific constitutional symptoms, classically associated with a hypersensitivity reaction, which can be mistaken for a "flu-like syndrome". These include weight loss, malaise, fever, rash, arthralgia or abdominal/flank tenderness/pain. Among them, fever is the most frequent and less than 10% develop the classic triad of fever together with rash and arthralgia.[45,46] Polyuria and nocturia have also been reported in up to 8% of cases.[3,45]

IV.II. OCULAR DISEASE: SYMPTOMS AND SIGNS

Non-infectious uveitis accounts for one of the main causes of preventable, irreversible vision loss. [47] TINU's uveitis develops between 2 months prior to 12 months after the onset of TIN,[3] but the ocular symptoms are also not always present.[4,49] Asymptomatic uveitis in TINU syndrome may be under recognized, with prospective studies identifying it in up to 50% of the patients. [2,50] This may be especially important in young children, in which uveitis frequently causes few or no symptoms. Even in more severe cases, parents may not be aware of any visual impairment until the development of severe complications. [47]

Unlike other inflammatory eye diseases, the TINU-related uveitis is often symptomatic.[47,51] Most patients experience a bilateral sudden-onset non-granulomatous anterior uveitis, presenting with typical symptoms of redness, pain and photophobia. Ocular manifestations are described as bilateral in about 80% of cases.[52] The uveitis is initially located in one eye, with the median time for second-eye involvement being one week.[4] Posterior uveitis or panuveitis can also be part of the clinical picture, occurring in up to 20% of patients, although it is thought to be underappreciated as a manifestation of TINU.[2,3] There are also a few reports of confirmed TINU with granulomatous anterior uveitis.[53,54]

Other symptoms that may also arise are eyelid oedema and rapidly progressive loss of vision. Signs include presence of conjunctival and perilimbal injection, small pupils with

sluggish or no light reaction.[55] Nodular scleritis may be part of the possible spectrum of ocular inflammation. [56]

Considering the relative broad spectrum of eye manifestations, examination of both the vitreous and fundus should be an integral part of ophthalmologic examination. Slit-lamp examination reveals anterior chamber cells and flare, fine keratic precipitates and vitreous cells. Recurring and/or prolonged inflammatory cases can be accompanied by mutton-fat keratic precipitates (granulomatous inflammation), fibrin deposition, anterior (iridocorneal) or posterior (iridolenticular) synechiae and hypopyon.[6,57] Although not typically affected, posterior involvement manifestations comprise intraretinal haemorrhages or retinal vascular sheathing, cotton wool spots, dilated retinal vessels, disk and macular oedema, focal and multifocal choroiditis and choroidal neovascularization.[55,58- 60]

V. DIAGNOSTIC

TINU syndrome remains a diagnosis of exclusion. Other disease entities known to cause both of these disorders must first be excluded.[3,22] TINU is usually diagnosed in either of two initial contexts: an azotaemia of unknown origin, conceivably related to a flu-like illness, or a spectrum of ophthalmologic symptoms, namely visual impairment, burning and/or red eyes.[31] This diagnostic should be promptly suspected in young patients presenting with either uveitis or tubulointerstitial nephritis. After the suspicion, definite diagnostic is only confirmed through renal histopathology.

V.I. LABORATORY EVALUATIONS

The classic triad of TINU consists of nephritis and uveitis together with an inflammatory syndrome that may lead to peripheral blood abnormalities, such as normochromic, normocytic anaemia, elevated erythrocyte sedimentation rate, hypergammaglobulinaemia and elevated CRP.[61] An inconsistent feature is the development of peripheral blood eosinophilia.[5]

The renal disease (tubulointerstitial nephritis) is difficult to diagnose based on clinical examination alone. As result of tenuous clinical manifestations, the diagnostic of TIN may be challenging and sometimes only achieved through abnormal laboratory findings. Unlike the classic drug-related TIN, the renal disease in TINU's syndrome usually lack a well-defined triggering event, and there are no specific cutaneous, hematologic or urinary

correlates.[31] In patients with unexplained acute kidney injury (elevated blood urea nitrogen and/or creatinine) or progressive reduction in glomerular filtration rate (GFR), TIN should be suspected.[5] An hyperkalemic, hyperchloremic metabolic acidosis out of proportion to the renal dysfunction can occur.[46]

TIN affects primarily the renal interstitium and the tubular wall without prominent glomerular or vascular involvement.[34] Urinalysis abnormalities reflect this, yet the findings are usually nonspecific. Microscopic examination of the urinary sediment may be bland or denoted by sub-nephrotic proteinuria, microscopic haematuria, sterile pyuria and aminoaciduria.[3,39] Because glomerular pathology is not significant, high albuminuria levels are usually not seen, but tubular proteinuria may be detectable.[5] Although not evaluated in routine laboratory tests, urinary eosinophilia may also be observable.[5] Evidence of proximal tubular dysfunction is common, such as normoglycemic glycosuria and Fanconi syndrome (glycosuria, aminoaciduria, acidosis).[3,31,45]

Biomarkers of kidney tubular damage, such as urinary N-acetylglucosaminidase (NAG) and β2-Microglobulin (B2M) are helpful suggesting the diagnostic and are commonly found in TINU. B2M is a small globular protein filtered at the glomerulus and reabsorbed at the proximal tubule, representing a very sensitive marker for tubular damage.[4] In patients with uveitis, the positive predictive value of increased serum creatinine and urinary B2M levels has been reported to be 100% and the negative predictive value of 97% for detecting associated TIN.[52] Urinary B2M levels have therefore been proposed as a screening measure for patients with uveitis, to help on assessment of TINU syndrome.[4] A correlation between urinary B2M levels and the histologic grade of TIN in 10 paediatric patients has been shown.[34]

Despite this, it is noteworthy that there is also evidence of subclinical forms of biopsy-confirmed TINU syndrome in Japanese patients with normal renal function.[8] Endocrine abnormalities of the thyroid and parathyroid glands could be associated. Therefore, thyroid stimulating hormone testing is recommended in newly diagnosed patients.[61]

V.II. KIDNEY BIOPSY

The typical histopathological findings on renal biopsy are the only way of proving the definitive diagnostic of tubulointerstitial nephritis (TIN), and thus TINU syndrome.[8,50,62] TIN is characterised histologically by interstitial oedema with infiltration of inflammatory cell (predominantly T lymphocytes along with neutrophils and plasmatocytes) and tubular

damage with tubule oedema, epithelial degeneration and focal necrosis. Granuloma formation is uncommon. Conversely, the normal structure of glomerular matrix, blood vessels and the number of mesangial cells is preserved.[6,63]

Nonetheless, it should be noted that TIN remains a clinical diagnosis, with suggestive clinical signs, such as low-molecular-weight (LMW) proteinuria (elevated α1 or β2-Microglobulin). As an invasive procedure, kidney biopsy causes discomfort and pain, and may not be suitable for all the patients. In patients suspected of having TINU syndrome with normal serum renal parameters, the biopsy is not recommended. It should be appraised on individual basis and considered with uncommon features of TIN, unidentifiable offending agent, severe renal dysfunction, renal disease relapse, or prior to starting treatment.[55,8,64]

V.III. FLUORESCEIN ANGIOGRAPHY

Fluorescein angiography is valuable in assessing the extent of retinal involvement, since the retina may be involved without any apparent manifestations on funduscopic examination. A common finding is the leakage of fluorescent dye from the optic disks and central-to-peripheral microvessels, on degrees ranging from limited to the peripheral fundus to cystoid macular oedema. Retinal capillary leakage is consistent with blood-retina barrier disruption.[6,39,59]

V.IV. HLA TYPING

Renal symptomatology is often a cause of late referral to specialized centres. HLA-DRB1*0102 allele might provide a time-independent marker, useful to suggest the diagnosis of TINU. Therefore, HLA-DR, DQ class II DNA typing may help narrowing the differential diagnosis and defining a need for further medical assessment in both typical TINU's uveitis and in some atypical cases, such as paediatric patients with panuveitis.[14,17] This may be particularly important in patients without evident renal disease, where the alleles detection could target the patients who would require additional evaluation of renal function. The sensitivity and specificity of this test seem to be relative good in North American and European patients.[14]

V.V. DIFFERENTIAL DIAGNOSTIC

Ocular and renal inflammation overlap can occur in other systemic illnesses, notably sarcoidosis, Sjögren's syndrome, systemic lupus erythematosus (SLE), granulomatous polyangiitis, Behçet's disease, tuberculosis (TB) and syphilis.[3,5,65] The typical uveitis

subtypes, median age of onset, and other characteristic systemic symptoms and signs can be promptly distinguishable. A complete review of systems and clinical examination should guide the serologic and imagiologic testing for these conditions.[55,65]

Sarcoidosis can be particularly similar to TINU's syndrome, with Ali et al. even hypothesizing about a common pathogenesis.[66] The distinction may be particularly challenging in the paediatric population where the typical pulmonary manifestations may not arise.[65] Sarcoidosis is typically a prolonged systemic granulomatous disease, where eye and kidney can be affected. The eye is commonly implicated, presenting with acute anterior bilateral uveitis or panuveitis with chorioretinal lesions. Kidney involvement is less frequent, with 20% having granulomatous interstitial nephritis, with elevated urinary B2-microglobulin levels.[54,67,68] Granulomas are the exception in TINU disease. Nevertheless, the syndrome can have an associated granulomatous disease, with reports of granulomas in the eye, bone marrow and liver. In challenging cases, such as in granulomatous uveitis (suggestive of sarcoidosis), a renal biopsy may clarify the diagnosis, as the granulomas are rare in patients with isolated interstitial nephritis, including TINU. However, there are sometimes grey areas where even the histological findings do not confirm a diagnosis. It is thus important to keep in mind that TINU is a diagnostic of exclusion. [3,46,65]

V.VI. CRITERIA AND PROBLEMS IN DIAGNOSIS

Mandeville and associates described in 2001 the evaluation criteria for TINU syndrome. Alongside the typical uveitis, clinical diagnosis was based on three components as follows: 1. Abnormal serum renal function (increased serum creatinine or decreased creatinine clearance); 2. Abnormal urinalysis: increased β2-Microglobulin, low-grade proteinuria, presence of urinary eosinophils, pyuria or haematuria without infection, urinary white cell casts, or normoglycemic glycosuria; and 3. A systemic illness lasting ≥2 weeks, characterized by a combination of the following symptoms and laboratory findings: (a) Signs and symptoms: fever, weight loss, anorexia, malaise, fatigue, rash, abdominal or flank pain, arthralgia, or myalgia; and (b) Laboratory findings such as the evidence of anaemia, abnormal liver function, eosinophilia, or a erythrocyte sedimentation rate >40 mm/h.[3]

TINU is thought to be an under recognized syndrome due to a combination of absence and/or asynchronicity of the ocular and renal symptomatology. This might be particularly important in paediatric population. More frequently, renal symptoms arise first, and kidney function tests may be altered before the ocular inflammation, which can be difficult to

diagnose and treat in the early stages. The subsequent uveitis may cause few or no symptoms and, when arising, may be late in onset and the link with the renal disease may be missed. The 'idiopathic' tubulointerstitial nephritis diagnostic may thus be incorrectly established. TINU syndrome is thought to be a rare cause of ATIN.[39] The highest prevalence of uveitis related with TIN in a retrospective case study was 46%, reaching 84% in a prospective study conducted in the same population submitted to regular slit-lamp examination, and may be higher with longer follow-up time, due to late-onset presentation of ocular inflammation.[2,18,19,50]

On the other hand, mild renal disease may be hard to detect, since it can exhibit nonspecific symptoms or may not become symptomatic. Diagnostic tests regarding renal involvement are therefore either not obtained or not performed at the time of presentation of uveitis.[3,58] Even when assessed, renal investigations may already be normalized, given the self-limiting nature of the kidney disease. This naturally delays or hinders the diagnosis of TINU and it is responsible for cases labelled as 'idiopathic' uveitis. Even when both diseases cause symptoms, they may not be synchronous, and the connection between them may be missed.[5]

VI. TREATMENT AND PROGNOSTIC

Long-term follow-up of TINU's syndrome is to date still insufficiently studied. The long-term outcomes with treatment are generally good for both eye and kidney, but TIN and uveitis have been thought to have independent courses and severities.[3,48,55,69,70] As a rare disease, its treatment is not standardized. During the active phase, both ocular inflammation and renal function respond readily to corticosteroid treatment, but the eye-disease control can be more challenging. The uveitis has been reported to persist or relapse even after 10 years, whereas the renal disease is often self-limited.[4,44,71]

Topical corticosteroids and cycloplegic agents are the first-line treatment for anterior uveitis. However, in the acute phase of TINU's anterior uveitis, up to 80% of patients will require systemic corticotherapy. [3,54] In other uveitis subtypes, systemic steroid therapy is the preferential initial treatment. [3,54,65] Earlier short-follow publications reported high rates of spontaneous resolution with corticosteroids, with only 10% of refractory patients. [3] More recently it has been shown that in 70% of TINU patients systemic steroid therapy does not seem to be sufficient to prevent recurrences of uveitis. [54,55]

Younger age has been identified as a risk factor for developing chronic uveitis lasting >3 months. Ocular inflammation recurs in up to 50% of patients after corticosteroid withdrawal and relapses are generally often more severe than the initial event.[3,34,54,71] Immunomodulation therapy (IMT) drugs are the second-line treatment, including methotrexate, cyclosporine, azathioprine or mycophenolate mofetil. [22] In the series of Sobolewska et. al, it has been shown that, with adequate prolonged IMT treatment, the control of the ocular disease may be achieved with improved recurrence-free period.[22,54] They reported a median treatment duration of 29.5 months (range: 13-40 months) in most patients (70% (6/9)) over a follow-up period of 4.5 years (range: 24-133 months).[54] IMT therapy could be therefore considered in steroid-resistant cases or to lessen undesirable steroid-related adverse effects. This treatment should seek to maintain quiescence for at least 12-24 months before withdrawal.[65]

Despite the difficult control, TINU's uveitis carries a good prognosis for visual acuity, with an average vision of 20/25, that rarely decreases below 20/40. [2,4] Ocular complications occur in 20% and include posterior synechiae (the most common), optic disc oedema, cystoid macular oedema, cataracts, elevated intraocular pressure or chorioretinal scarring. [3,4,8,54,55] Some complications are strongly associated with systemic and topical corticosteroids, particularly cataracts and elevated intraocular pressure. [14,55]

Most TINU patients are treated with systemic therapies for the renal disease, even in the absence of ocular indication. Earlier studies suggested that renal disease in TINU is self-limiting, spontaneously or after steroid treatment, with persistent renal dysfunction only in about 10% of patients.[44] Later there have been reports in the development of end-stage renal failure in patients with TIN not treated with systemic steroid therapy,[72] and histological changes of acute kidney inflammation in biopsy-samples despite systemic prednisone treatment, even 6-9 months after the diagnosis of TINU.[33,73] Even minimal tissue damages might lead to chronic kidney disease and hypertension,[17] and although unusual, severe TINU may lead to chronic dialysis and kidney transplantation.[3,4,70] Moreover, it should be stressed that systemic corticosteroids for treatment of TIN do not seem to prevent or reduce the occurrence of later uveitis. [2,74,75]

Management of TINU has not yet been sufficiently researched, due to the rarity of this disorder and variabilities regarding primary endpoints and patient age group.[65] The course and severity of both the nephritis and uveitis and their treatment should be managed by ophthalmologist together with nephrologists. Because the tubular dysfunction may persist

regardless of treatment, it is recommended during the follow-up of renal disease urinalysis and quantitation of LMW protein excretion even in patients with normal serum creatinine concentration. [2]

Considering that the uveitis symptoms may be inconspicuous and delayed in onset, ophthalmologic screening is warranted for all patients with isolated TIN for at least 1 year after the diagnosis, starting with 3-month intervals.[2,50] On the other hand, in patients with typical TINU's bilateral sudden-onset anterior uveitis, renal disease should also be ruled out. Although the transient renal findings may already be normalized, urinary B2M levels and serum creatinine have been proposed as a screening measure, with positive and negative predictive values of 100% and 97%, respectively.[4,52] This is particularly important when a renal biopsy is not indicated. [2,3,52]

VII. CASE REPORTS

VII.I. CASE 1

A 18-year-old previously healthy woman sought medical assistance for general malaise with tiredness, nausea, vomiting and weight loss lasting for several weeks. Blood tests were normal despite elevated serum creatinine (2.8 mg/dL) and erythrocyte sedimentation rate (90 mm/h), and she was admitted for medical management. The urinalysis showed a proteinuria of 400 mg/24h without urinary eosinophils. Her medical history was unremarkable, and as regular medications, she was taking ibuprofen due to intense dysmenorrhea during her menstrual periods. Clinical assessment did not reveal signs of recent infection, skin rash, arthralgia, arthritis, muscular pain, photosensitivity or alopecia. Viral serologies, antistreptolysin O test, and further autoimmunity tests were all negative. Angiotensin-converting enzyme (ACE) levels were normal. During the hospitalisation, urine output remained stable, with progressive improvement of renal function. Kidney echographic findings were normal, and chest-abdominal-pelvic computed tomography was unremarkable, with no visible mediastinal lymph nodes. At the time of medical discharge, the kidney function showed creatinine level of 1.8 mg/dL and BUN of 45 mg/dL.

One month later, the patient experienced right red painful eye and reduced visual acuity, and acute anterior uveitis was identified. Kidney biopsy could confirm the tubulointerstitial nephritis, and TINU diagnostic was established. The patient was treated with oral

prednisone. Upon adequate clinical response and normalisation of kidney function after 1 month of treatment, steroids were slowly tapered off, with a rapid recurrence of the ocular inflammation. Without systemic therapy, the patient had recurrent bilateral acute anterior uveitis, treated with intensive topical steroids and cycloplegia. Due to the uveitis relapse with difficult control of the eye disease, the institution of systemic therapy was discussed with nephrology colleagues and treatment with oral methotrexate was started up to a dose of 17.5 mg/week. After one year of surveillance for eye and kidney disease and acceptable treatment tolerability, the patient remains asymptomatic with no signs of active inflammation.

VII.I. CASE 2

A 12-year-old girl presented in emergency department for right eye redness and photophobia. On the slit-lamp examination, fine keratic precipitates and posterior synechiae were observed. The fundus assessment did not disclose any abnormality. Right acute anterior non-granulomatous uveitis was diagnosed, and the patient was treated with topical prednisolone and cyclopentolate. The physical examination was normal, with no signs of recent infection, nor signs of joint swelling, joint stiffness or gastrointestinal symptoms. She had started oral contraceptives 5 months before and reported fatigue and anorexia in the past month.

In routine a medical check-up 1 month before, the blood tests showed a normocytic normochromic anaemia (Hb 11.3, MCV 83, MCH 27.6) with low serum iron (32 μg/dL), normal creatinine levels (1.18 mg/dL), with thyroid function and further laboratory assessment unremarkable. She was then medicated with iron supplementation. After one week of topical treatment, the patient experienced a worsening of the uveitis, with bilateral involvement. A new blood panel reveals hypergammaglobulinemia, increase in creatinine concentration (1.38 mg/dL), with normal BUN, C-reactive protein 0.3 mg/dL, and normal liver enzymes. ACE level was normal. Antinuclear antibodies were negative. Serologies for HIV, hepatitis and syphilis were also negative. Urinalysis revealed proteinuria, glycosuria, leukocyturia, haematuria, and high levels of urinary B2M (12.51 mg/dL). Both eye and kidney involvements were identified clinically, and TINU syndrome was thus diagnosed. The renal histopathological findings confirmed this diagnostic. Because of incomplete response to topical treatment, systemic treatment with prednisone 20 mg/day was initiated and later due to incomplete response to oral steroids, methotrexate up to 17.5 mg/week was started, with excellent response and quiescence of ocular involvement. . At the end of the

second month, laboratory findings were normal, the patient was asymptomatic, and the systemic steroids could be gradually tapered off. The patient remains under over 10 months of methotrexate treatment with no further complications.

VIII. DISCUSSION

We observed two cases of TINU with different initial clinical presentations. Regarding gender and the age of the patients, both are in line with the classical epidemiological features of the syndrome.

The nonspecific symptoms typical of renal involvement appeared firstly in both cases, though with different manifestations and intensities. Constitutional flu-like symptoms were the initial motive for referral in the first case. The delay between the occurrence of renal and eye symptoms was of 2 months and 1 month in the first and second case, respectively. As described in the literature, also both of our patients experienced a first episode of unilateral acute anterior uveitis, the second-eye being rapidly involved with the persistence of the inflammation.

The diagnostic establishment was challenging in both cases. In the first one, the general nonspecific manifestations together with the urinalysis alterations could point towards an idiopathic tubulointerstitial nephritis, since no triggering infective agent could be identified, and the patient had no known genetic nor systemic inflammatory conditions associated. The eye involvement developed subsequently with the typical bilateral acute anterior uveitis, and a kidney biopsy could finally confirm TINU. The second patient presented with an episode of a non-infectious right acute anterior uveitis with no identifiable cause. Given the recent initiation of a contraceptive treatment, a drug-related uveitis could be a possibility. Nonetheless, this remains a diagnosis of exclusion, since a link is not possible to ascertain. The general symptoms were initially related the microcytic hypochromic anaemia on treatment, with no evident connection with the uveitis. TIN-related systemic symptoms were therefore not pronounced, and recognition of kidney involvement was only possible in view of the laboratory abnormalities, with the typical high concentrations of creatinine and B2M. TINU diagnosis was confirmed in a kidney biopsy. Sarcoidosis was an important differential diagnosis in both patients, but absence of granulomas and normal ACE levels could rule out this disorder.

With regards to treatment, in the first case one month of systemic steroids could control eye and kidney involvement. On therapy discontinuation, uveitis relapses are more severe than the initial condition and with difficult management under topical-steroids alone. Methotrexate was introduced, and disease control is accomplished for one year of follow-up. In case 2, the approach to treatment was different. To the initial isolated anterior uveitis topical steroids are administered, without success. Persistent uveitis justified further assessment and TINU syndrome was diagnosed. Systemic steroids plus methotrexate were instituted, and after two-month steroid treatment could be tapered. Treatment with methotrexate allow control of the disease for over 10 months.

In both cases, the progression of the syndrome was typical with the reported previously in several studies. Whereas the renal disease had a rapid regression under steroid systemic therapy, the progression of uveitis lead to the need for treatment extension with IMT. Analysing the two different treatment options, for the same duration of systemic therapy (i.e., one month), the relapsed uveitis was easier to manage in the case where combined-therapy with corticosteroids and methotrexate was started early in the treatment course. Thus, it could be hypothesized that an initial tight disease control could be beneficial for these patients.

IX. CONCLUSION

Our cases reflect the wide range of presenting symptoms that TINU patients may undergo and highlight the complexity of this diagnosis. Both patients presented with typical eye-kidney disease courses and the treatment response was similar to the formerly reported in the literature and detailed in this review. It is important to bear in mind the under-recognition of TINU syndrome, as its prevalence and importance might be much higher than initially thought. A high-grade clinical suspicion is crucial, with important attention to the cases "labelled" as idiopathic tubulointerstitial nephritis or idiopathic uveitis. These patients should be surveilled to the occurrence of subsequential eye or renal disease, respectively.

X. RESUMO

A Síndrome TINU (Nefrite Tubulointersticial e Uveíte) foi descrita primeiramente em 1975 e descreve o atingimento inflamatório do olho e do rim.

Classicamente, destacou-se na epidemiologia uma predominância feminina, com os primeiros sintomas a surgir numa média de idade de 15 anos. Apesar disto, hoje sabe-se que esta síndrome pode ocorrer em ambos os sexos, e pode atingir qualquer idade, sem apresentar especial predileção ética, geográfica ou racial. O diagnóstico de TINU é determinado em cerca de 2% dos doentes que recorrem a centros especializados de uveíte, e esta doença é responsável por até um terço das crianças e adolescentes com idade inferior a 20 anos com a típica uveíte anterior de início súbito.

Como fatores de risco destacam-se, por um lado, a suscetibilidade genética e, por outro, agentes externos. A predisposição genética é um dos aspetos mais interessantes da doença, estando reportados casos em gémeos homozigóticos, irmãos e numa mãe e no seu filho. A investigação de marcadores genéticos de suscetibilidade tem-se centrado nos genes do complexo HLA, destacando-se os HLA-DQA1*01, HLA-DQB1*05 e HLA-DRB1*01. A associação mais forte foi com o alelo HLA-DRB*0102, que se mostrou presente em 72% (13/18) de uma população de doentes com TINU. Outros estudos com amostras menores revelaram associações para os alelos supra-mencionados e ainda outros, havendo uma discrepância entre estudos que poderá ser justificada por uma variação regional nos alelos predisponentes. Os fármacos e infeções poderão ter um papel importante, ao precipitar o processo imune, apesar de não haver, até agora, uma relação causal estabelecida entre estes dois fatores e a síndrome. As infeções mais frequentemente associadas originam-se no tracto respiratório, e têm como agentes principais EBV, *Chlamydia trachomatis*, *Mycoplasma tuberculosis*, *Toxoplasma gondii*, e VZV. Relativamente aos fármacos, os anti-inflamatórios não esteroides (AINEs) e os antibióticos são os principais grupos envolvidos.

A fisiopatologia da síndrome TINU continua por ser esclarecida. A proposta actual estima que um fator ambiental possa suscitar uma cascata autoimune num indivíduo com o fundo genético suscetível. A imunidade celular tem sido implicada como mecanismo de doença, principalmente através dos HLA-classe II, que exibem um papel crucial numa fase precoce da resposta imune, apresentando os antigénios exógenos processados a células T CD4+. Assim, um determinado subtipo de HLA-classe II poderia modificar a resposta imune para um patogénio, tornando um sujeito suscetível a um antigénio normalmente inofensivo. Para

além disto, a histopatologia renal evidencia infiltrados tubulointersticiais de subtipos de células T helper/inducer, indicando que a imunidade mediada por células T poderá ter um papel importante neste processo. A imunidade humoral também tem sido implicada na patologia da síndrome, nomeadamente pela elevada quantidade de anticorpos séricos contra a proteína C-modificada (anti-mCRP) em doentes com TINU, relativamente com outras doenças autoimunes renais e indivíduos saudáveis. Além disto, foi determinado que, em doentes com nefrite intersticial aguda, um título elevado de anticorpos anti-mCRP pode ser preditivo do desenvolvimento posterior de uveíte. Isto está de acordo com a proposta que sugere que o rim poderá ser o alvo primordial de um processo sequencial, que possivelmente levará a uma cascada inflamatória com efeitos secundários no olho.

Os sintomas renais e oculares têm, habitualmente, uma apresentação assíncrona, surgindo primeiramente a nefrite intersticial e, posteriormente, a uveíte, num intervalo médio de 3 meses. A nefrite tubulointersticial é uma causa frequente de lesão renal aguda e uma condição possivelmente letal. Na síndrome TINU, o envolvimento renal é geralmente moderado, e os doentes podem apresentar-se assintomáticos ou com uma clínica inespecífica de sintomas constitucionais semelhantes a um quadro gripal como febre, perda ponderal, artralgia e dor abdominal. A uveíte poderá ser assintomática até 50% dos doentes com TINU, particularmente em crianças. Caracteristicamente, esta é anterior, bilateral, de início súbito e não granulomatosa, tendo como sintomas habituais olho vermelho, dor e fotofobia. Como sinais, destacam-se a presença de hiperémia conjuntival e perilímbica e miose sem reação à luz. As manifestações oculares poderão ser variadas, pelo que o exame oftalmológico integral não deve ser dispensado. O exame à lâmpada de fenda revela caracteristicamente células na câmara anterior e *flare*, finos precipitados queráticos e células vítreas. Apesar de raro, o envolvimento posterior é possível e estão descritos vasculopatia com hemorragias, enfartes algodonosos, edema macular e do disco, coroidite e neovascularização coroideia.

A síndrome TINU é um diagnóstico de exclusão, que normalmente é realizado ou num contexto de uma azotémia de origem desconhecida ou num espectro de sintomas oftalmológicos, como diminuição da acuidade visual, olho vermelho ou dor ocular. A investigação laboratorial poderá apresentar anomalias subsequentes da síndrome inflamatória sistémica, como uma anemia normocítica normocrómica, velocidade de sedimentação elevada, hipergamaglobulinémia e elevação da proteína C reactiva. Pela patologia intersticial renal, o exame sedimentar da urina pode demonstrar uma proteinúria nefrótica, hematúria microscópica, piúria estéril e aminacidúria. Biomarcadores de dano

tubular renal, como a N-acetilglucosaminidase (NAG) e a β2-Microglobulina (B2M) poderão ser úteis na suspeita do diagnóstico e são comummente encontrados na TINU. A B2M urinária demonstrou ter elevados valores preditivos negativos e positivos na deteção da doença renal em doentes com uveíte, e tem sido proposta como um método de rastreio em indivíduos com uveíte.

A biópsia renal é o único exame que permite assegurar o diagnóstico de TINU. Histologicamente, caracteriza-se por edema intersticial com células inflamatórias e dano tubular com edema tubular, degeneração epitelial e necrose focal. Pelo facto de ser um exame invasivo, a realização da biópsia renal deverá ser ponderada caso a caso.

O diagnóstico diferencial realiza-se com doenças com manifestações oculo-renais, como a sarcoidose, o lúpus eritematoso sistémico, poliangeíte granulomatosa, tuberculose e sífilis. As características da uveíte, a idade de início e outros sinais e sintomas sistémicos específicos podem prontamente distinguir estas patologias. Uma revisão de sintomas completa e um exame clínico devem guiar os testes serológicos e imagiológicos posteriores. Os critérios de diagnóstico da síndrome TINU foram descritos por Mandeville em 2001, e incluem a uveíte característica, alterações da função renal, alterações das análises urinárias, sinais e sintomas de doença sistémica e achados laboratoriais de síndrome inflamatório.

Pelo facto de as doenças renal e ocular poderem ser assíncronas e/ou assintomáticas, admite-se que a TINU seja uma síndrome sub-diagnosticada, fazendo possivelmente parte dos diagnósticos incorretamente estabelecidos de nefrite intersticial idiopática e uveíte anterior idiopática, especialmente numa faixa etária mais jovem.

O seguimento a longo prazo da TINU continua não totalmente conhecido e o tratamento não suficientemente bem estudado. Apesar de o prognóstico ser geralmente bom para ambos os órgãos, a doença renal e a doença ocular parecem ter cursos e severidades independentes, com a uveíte tendencialmente a ser de um controlo mais complexo e a doença renal frequentemente auto-limitada. Na uveíte anterior no contexto de TINU, o tratamento com corticoide tópico exclusivo não é suficiente em 80% dos doentes, muitas vezes sendo necessário corticoterapia sistémica. Após suspensão do tratamento sistémico, a uveíte tende a recorrer em 50% dos doentes, sendo as recidivas normalmente mais graves que o evento inicial. Os fármacos imunomoduladores são o tratamento de segunda-linha, e incluem o metotrexato, a ciclosporina, azatioprina e o micofenolato de mofetil. Este tratamento pode ser considerado em casos resistentes aos corticosteroides e para evitar os efeitos adversos

relacionados com os corticoides. As complicações oculares ocorrem em 20% dos doentes e incluem sinéquias posterior, edema do disco óptico, edema macular cistoide e cataratas.

A doença renal pode igualmente requerer terapêutica sistémica com corticosteroides, já que mesmo danos teciduais mínimos podem levar a doença renal crónica e hipertensão.

O curso e a severidade da TINU e do seu tratamento devem ser geridos em conjunto por oftalmologistas e nefrologistas. No que respeita o seguimento, é recomendado a realização de análises urinárias e quantificação da excreção urinária de proteínas de baixo peso molecular. O rastreio oftalmológico é também aconselhado a todos os doentes com nefrite tubulointerstecial isolada, até um ano depois do diagnóstico.

No caso clínico 1, uma doente de 18 anos recorreu a cuidados médicos por alteração do estado geral com cansaço progressivo, náusea, vómitos e perda de peso durante várias semanas. Laboratorialmente, determinou-se uma elevação da creatinina sérica (2.8 mg/dL) e da velocidade de sedimentação (90 mm/h), com uma proteinúria de 400 mg/24h. A doente não apresentava quaisquer sintomas reumáticos e a serologias viral e estudo de auto-imunidade foram negativos. Os exames de imagem e os níveis de enzima conversora da angiotensina revelaram-se também normais. Um mês mais tarde, surgiram sintomas oftalmológicos com dor ocular e diminuição da acuidade visual, e o diagnóstico de uveíte anterior foi estabelecido. Verificou-se refractariedade ao tratamento inicial com prednisolona oral, com múltiplas recidivas da inflamação ocular, pelo que um tratamento com metotrexato oral foi iniciado, com boa tolerância e sem recorrência de sintomas sob 1 ano de tratamento.

No caso clínico 2, uma criança de 12 anos apresentou-se com vermelhidão ocular e fotofobia. O exame oftalmológico à lampa de fenda mostrou finos precipitados queráticos e sinéquia posterior, pelo que o diagnóstico de uveíte anterior aguda não granulomatosa foi determinado. Em avaliação analítica realizada 1 mês antes, uma anemia normocítica normocrómica teria sido diagnosticada. Após exclusão de outros diagnósticos, a biópsia renal permitiu estabelecer o diagnóstico de TINU. Tal como no caso anterior, foi iniciado tratamento com com metotrexato, com regressão da inflamação ocular e sem outras complicações adicionais.

Os casos clínicos apresentados refletem a ampla gama de sintomas que os pacientes com TINU podem manifestar e destacam a complexidade deste diagnóstico. Ambos os pacientes

apresentaram cursos típicos de doença *olho-rim* e a resposta ao tratamento foi semelhante à anteriormente relatada na literatura e detalhada nesta revisão. É importante ter em mente o sub-reconhecimento da síndrome TINU, pois sua prevalência e importância podem ser muito mais elevadas do que inicialmente se sabia. Um alto ídice de suspeição é fundamental, especialmente nos casos interpretados como nefrite tubulointersticial idiopática ou uveíte idiopática. Estes doentes devem ser vigiados para a ocorrência de doença visual ou renal subsequente, respetivamente.

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