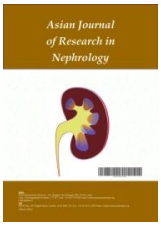

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# Tubulo Interstitial Nephritis and Uveitis Syndrome (TINU): Study of 5 Cases

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***Authors' contributions***

*This work was carried out in collaboration among all authors. Author SM designed the 5 cases. Author AD wrote the manuscript. Authors AD and MB managed the analyses of the 5 cases. All authors read and approved the final manuscript.*

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## ABSTRACT

Tubulo interstitial nephritis and uveitis syndrome (TINU) is a rare disease characterized by association of intraocular inflammation and nephritis. We report study of 5 cases of TINU syndrome collected retrospectively in the internal medicine departments from 1996 to 2012.
We found female predominance with female / male sex ratio at 4/1 and median age at 36.4 years. Uveitis was the first manifestation of the disease in all cases. 3 patients had systemic signs. All the patients had renal failure with proteinuria. Aseptic pyuria was noticed in 4 patients, microscopic hematuria in 2 patients and glucosuria without diabetes in one patient. All patients presented an elevated erythrocyte sedimentation rate. 3 patients had normochromic normocytic anemia and 2 patients had elevated level of gamma globulinemia. Kidney biopsy was performed in all patients. It showed acute interstitial nephritis in 1 case and chronic interstitial nephritis in 4 cases with segmental and focal glomerulosclerosis in 1 patient. All patients received oral corticosteroids. They were stopped in 3 cases and maintained in two cases. Residual renal failure was noticed in one case and one patient presented sequelae uveitis. One recurrence of uveitis was observed during progress after 2 years and a half. Progress was favorable. 3 patients had a good prognosis and the 2 others had an intermediate prognosis.

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TINU syndrome should be considered in the presence of any uveitis associated with renal impairment. Multidisciplinary management is recommended for early diagnosis and effective treatment

*Keywords: Uveitis; tubulo interstitial nephritis; corticosteroids; immunosuppressant.*

## 1. INTRODUCTION

Tubulo interstitial nephritis and uveitis syndrome (TINU) is a rare disease characterized by the combination of intraocular inflammation and nephritis [1]. Its frequency wasn't well known. It was under-diagnosed and the incidence could be higher because it could account for some cases of idiopathic uveitis [2]. Immune mediated process was proposed and it could be related to drug, infection and other factors [3]. It was considered as diagnosis of exclusion. In this manuscript, we describe epidemiological, clinical and biological features of our series including 5 cases of TINU syndrome. We report the treatment prescribed and progress of our patients.

## 2. PATIENTS AND METHODS

This is a retrospective study in which we report 5 cases diagnosed TINU syndrome observed in our department of internal medicine between 1996 and 2012. The diagnosis of TINU syndrome requires the combination of acute tubulointerstitial nephritis and uveitis after ruling out any other diseases that could lead to kidney and eye damage. Diagnosis can be definitive, probable or possible. Criteria are based on the level of evidence for tubulointerstitial nephritis and the nature of the uveitis. Complete remission of TINU syndrome is defined by the recovery of normal renal function and improvement of visual acuity to at least 8/10.

For each patient, we collected interview data (onset of symptoms: systemic signs and ocular signs, the treatment received and the response…), clinical findings (ophthalmological examination: uveitis and its laterality/ visual acuity/ ocular tonometry/ intensity of cellular inflammatory reaction / the intensity of hyalitis and other ocular signs associated as well as complications such as neovascularizations, ocular hypertension, synechiae and macular edema), biological results (creatinine, ionogram, examination of urine sediment, 24-hour proteinuria, sedimentation rate, blood count and formula, electrophoresis of proteins, phosphocalcic balance, hepatic test, serologies of toxoplasmosis, cytomegalovirus, Epstein-Barr virus, hepatitis B and C virus, syphilis and herpes virus, HLA typing, anticardiolipin antibodies, rheumatoid factor, antinuclear antibodies, native anti-DNA antibodies, anti-cytoplasmic antibodies of neutrophils, cryoglobulinemia), kidney biopsy data, the treatment (the molecule, dose, duration and type of administration) and the progress of patients (ocular relapse, biological inflammatory syndrome, renal function ).

## 3. RESULTS

There has been a female predominance in our reported cases with female / male sex-ratio at 4/1. The median age of onset of the disease was 36.4 years, ranging from 15 to 55 years. 2 patients were 15 years old. Any past medical history was noticed in our patients. The most common initial symptom was ocular symptoms observed in 4 cases consisting in eye pain and redness. Digestive disorders like abdominal pain and vomiting were present in 3 cases. Weight loss and asthenia were present in 2 cases. Arthralgias and myalgias were present in one case. Ocular and renal diseases were simultaneous in the five cases. Patients suffered from decreased visual acuity in all cases and eye redness with pain in 4 cases. Ophthalmologic examination found anterior and intermediate uveitis in 3 cases and anterior uveitis in 2 other case. Uveitis was unilateral in one case and bilateral in the 4 other cases. It showed keratic precipitates in 3 patients, an inflammatory Tyndall of the anterior chamber in 2 cases, hyalitis in 3 patients and an epiretinal membrane in one case. Ocular complications have also been observed. These were posterior synechiae, papillary edema and macular fold in 1 case each. Physical examination revealed high blood pressure in one patient. Biological analysis found renal failure in all cases (median creatinine level: 215 umol/L), inflammatory biological syndrome (Median Erythrocyte Sedimentation Rate: 94 mm at the first hour) in all cases, elevated level of gamma globulinemia in 3 cases and anemia in 3 other cases. Urinary analysis revealed proteinuria more than 0,5 g/24 hours ranging from 0,6 g/24 hours to 0,9 g/24 hours in 4 cases,

sterile pyuria in 4 cases, hematuria in 2 cases, and glucosuria without diabetes in one case. Calcemia, serum phosphorus, liver function analysis and angiotensin converting enzyme rate were normal in all cases.

Viral, fungal and bacterial investigations (Cytomegalovirus, Epstein-Barr virus, hepatitis B and C virus, herpes simplex virus, syphilis, toxoplasmosis and tuberculosis) were all negative. Rheumatoid factor, anti-nuclear antibodies were also negative. HLA-B27 was negative in all cases. Chest X-ray was normal in all cases. Renal ultrasound was normal in 4 cases and revealed inverted cortico-medullary differentiation in the other case. Salivary gland biopsy practiced in 3 cases was normal. Kidney biopsy practiced in all cases revealed chronic interstitial nephritis in 4 cases and acute interstitial nephritis in one case. Focal and segmental glomerulosclerosis was observed in one case and glomeruli were normal in the other cases. Granulomas were absent. Immunofluorescence was negative. Diagnosis of TINU syndrome was retained in all cases. All patients received pulses of methyl prednisolone (1 g) relayed by high doses of prednisone (1mg/ Kg/ day) for six weeks followed by a taper until 10 mg a day. This treatment was associated with ocular corticosteroid and mydriatic eye drops in all cases. Corticosteroids were stopped in 3 cases after period of treatment ranging from 6 months to 44 months. In the two other cases, corticosteroids were maintained. Renal function improved in 4 cases and residual renal failure was noticed in one case. Uveitis disappeared in 4 cases and one patient presented sequelae uveitis. One recurrence of uveitis was observed during progress after 2 years and a half.

## 4. DISCUSSION

Tubulo interstitial nephritis and uveitis (TINU) syndrome is a rare disease characterized by ocular and renal inflammation described at the first time by Dobrin in 1975 [4]. In 2001, a large review in the literature including 133 cases was established proposing diagnostic criteria of this rare entity [3].

Its true frequency wasn't well known. It represents less than 2% of uveitis followed in hospitals [5], 8% of uveitis in children [6] and approximately 4.7% of acute tubule interstitial nephritis [7]. Many factors other than age were included genetic or/and environmental factors, diagnostic criteria used, and the recognition of this entity [8].

The median age was 36.4 years in our study, with extremes ranging from 15 to 55 years. Two patients had 15 years old. In the review of H. Mandeville [3] the prevalence of TINU syndrome is more important in younger people but could affect elders. In other studies, the prevalence varied up to 2.3% in pediatric population [8].

In our study, we found a clear female predominance with a female / male sex ratio at 4/1. Female preponderance was noticed in the majority of series. However, recently, it has been noticed that TINU syndrome was affecting men more frequently. Since 1990, the proportions increased from 18% to 34% [7-8].

Clinical manifestations during TINU syndrome are stereotypical. It included non specific signs and manifestations related to ocular and renal disease. Ocular disease and renal involvement progressed independently. In most cases, uveitis is delayed compared to kidney damage occurring after average 3 months and could exceed in some cases 14 months [3]. Rarely, it was contemporary or precedes kidney damage [2, 9, 10] like in our cases where we noticed both involvements occurred simultaneously.

Ocular involvement was usually bilateral anterior uveitis in 80% of the cases [3]. However, it can be posterior with hyalitis [6,11]. In the Mackensen series [1] concerning 33 patients, all patients presented bilateral anterior uveitis. Thirteen patients (40%) had unilateral uveitis that bilateralized 1 to 16 weeks later. In a recent review reported by David Amaro, the most common anatomical form of eye inflammation was bilateral anterior uveitis. TINU syndrome accounts for approximately 1%-2% of uveitis [2]. In our study, uveitis was the mode of revelation of the disease. It was bilateral in 4 patients. Isolated anterior uveitis was found in 2 patients. The other 3 cases presented anterior and intermediate uveitis.

Systemic signs that can be observed where deteriorated general state (weight loss, anorexia, and fever), abdominal pain, nausea, vomiting, arthralgia and myalgia [12-13]. Uveitis may develop up to two months before or up to 14 months after onset of systemic symptoms [14]. In Mandeville's review [3], impairment of the general state was described in about half of the cases. Fever was noticed in 53%, weight loss in

47% and asthenia in 44% and anorexia in third of the cases. In our study, 2 patients presented deterioration of the general state (asthenia, anorexia, weight loss). Other signs can also be seen, but more rarely, polyuria, generalized lymphadenopathy, rash and dyspeptic disorders [3].

Biological findings mostly observed were inflammatory biological syndrome, normo chromic normocytic inflammatory anemia and hypergammaglobulinemia. Erythrocyte sedimentation rate was accelerated in 89% with high level of gamma globulinemia in 83% and normochromic normocytic anemia in 96% in the review of Mandeville [3]. These findings were concordant to our study, in which all patients presented accelerate erythrocyte sedimentation rate with an average of 94.8 mm in the first hour; normochromic normocytic anemia was observed in 3 patients (60%).

Acute kidney failure with elevated serum creatinine was observed between 90 % to 100% of cases [3,13,15] like our study. Abnormal urinary analyses were present with different frequency. Mandeville found moderate proteinuria in 86%, hematuria in 42%, sterile pyuria in 55%, glucosuria without diabetes in 47% and eosinophiluria in 3%. High level of β2-microglobulin in the urine was present in all cases. Vohra and Al [6] reported hematuria in 50% of cases proteinuria and glucosuria in 75%. In the study of Sanchez [16] a moderate proteinuria was observed in all patients and glycosuria without diabetes was noticed in 66%. In a study of 12 patients [17], proteinuria was reported in 42% of cases, glucosuria without diabetes in 58%, high β2-microglobulinuria in 92% and sterile pyuria in all cases. In our study, proteinuria was present in 80% (average of proteinuria at 0,69g /24 hours), sterile pyuria in 80 of cases, microscopic hematuria in 40% and glucosuria in 20% of cases.

Treatment was based on oral corticosteroids at a dose of 1 mg / kg / day, preceded by 3 pulses of methylprednisolone in all cases of our study. This systemic treatment was associated with local treatment based on corticosteroid and mydriatic eye drops.

Progress showed ocular recurrence in one patient and sequelae synechiae in another case. Only one patient presented a moderate residual renal failure (serum creatinine level at 140µmol / l). Most cases reported revealed the efficiency of corticosteroids with resolution of uveitis and renal function but, more recently, it has been shown that in 70% of patients with TINU, systemic corticosteroid therapy does not seem to be sufficient to prevent recurrences of uveitis [18-19]. On the other hand, with steroids, renal relapses are much less frequent than uveitis relapses but reactivation of nephritis is documented with steroid tapering [20-22]. In Mandeville review [3], 15 patients (11%) had renal failure and 5 patients (3.8%) needed hemodialysis. In a study of 6 cases [16]; we noticed recuperation of normal renal function in all cases. In a study guided by Legendre [23], concerning 10 cases, 40% had ophthalmic recurrences, 10% presented signs of chronic tubulopathy without renal failure, and 10% had moderate renal failure.

Prognosis is generally good. In our study, 3 patients had good prognosis (visual acuity at 10/10 and mean serum creatinine at 85 µmol /L). The two other cases, had an intermediate prognosis (one had visual acuity at 10/10 and serum creatinine at 140µmol /L, the other had visual acuity at 5/10 and serum creatinine at 82 µmol /L).

## 5. CONCLUSION

The pathogenisis of TINU syndrome remained poorly understood. Most of clinical studies were small in size and retrospective. Eye and renal disease were independent in evolution. Disease relapses may be underestimated due to the short follow-up time in most studies. Even corticosteroids therapy, long-term reports showed important frequency of refractory uveitis. Further prospective large studies help to understand the disease and the efficacy of treatments.

## CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the author(s).

## ETHICAL APPROVAL

It is not applicable.

## COMPETING INTERESTS

Authors have declared that no competing interests exist.

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