Scientific Research Publishing

Open Journal of Nephrology, 2021, 11, 21-33
https://www.scirp.org/journal/ojneph
ISSN Online: 2164-2869
ISSN Print: 2164-2842

Nephritis Syndrome Tubulo-Intertitial and Uveitis (Tinu Syndrome): About 2 Cases

Hiba El Oury[1], Fatim-Zahra Jabrane[1], Kenza Bouyad[2]

[1]Université mohammed VI des sciences de la santé, Casablanca, Maroc
[2]Université Hassan II, faculté de médecine et de pharmacie, Casablanca, Maroc
Email: aida_eloury@yahoo.fr

How to cite this paper: El Oury, H., Jabrane, F.-Z. and Bouyad, K. (2021) Nephritis Syndrome Tubulo-Intertitial and Uveitis (Tinu Syndrome): About 2 Cases. *Open Journal of Nephrology*, **11**, 21-33.
https://doi.org/10.4236/ojneph.2021.111003

Received: November 18, 2020
Accepted: February 23, 2021
Published: February 26, 2021

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Abstract

Introduction: Tubular and interstitial nephropathy syndrome with uveitis or TINU syndrome is a rare association. **Patients and methods:** We have listed cases in which the clinical-biological picture and histology were consistent with this syndrome. **Results:** Two cases were retained: These were two female patients whose mean age at diagnosis was 16 years. The inaugural symptoms were bilateral anterior uveitis in two cases. The time to onset of renal signs: was 4 to 2 weeks months. Acute kidney failure was reported in both cases with a mean creatinine of 36.4 mg/l. An average proteinuria of 1.1 g/24 h associated with aseptic leukocyturia in one case/2 and glycosuria normoglycemic in 1 case/2. Non inflammatory syndrome specific with inflammatory anemia is reported in both cases. Kidney puncture biopsy confirmed the diagnosis with nephropathy diffuse polymorphic tubulointerstitial and immunofluorescence negative in both cases. Oral corticosteroid therapy (1 mg/kg per day) was started for 4 to 6 months. Both patients received initial local corticosteroid therapy for uveitis. The outcome was favorable under treatment with remission complete. Kidney function recovered after 6 months with an average serum creatinine of 6 mg/l. **Discussion:** The incidence of TINU syndrome appears to be underestimated in the literature. It is believed to be an autoimmune disease. The positive diagnosis is based on clinical, biological and histological. An etiological investigation in search of disease systemic is necessary before making the diagnosis. There is no codified treatment. The prognosis is favorable in the majority of cases. **Conclusion:** Investigation of renal function is necessary for any patient.

Keywords

Nephritis Syndrome Tubulo-Intertitial, Uveitis, Tinu Syndrome

1. Introduction

TINU syndrome was first described in 1975 by Dobrin [1]. This syndrome is characterized by the association of acute tubulointerstitial involvement and uveitis, most often anterior and bilateral, apart from any systemic disease likely to cause this symptomatology [2]. Its incidence would be underestimated, only 200 cases have been reported during the last forty years [3]. The pathophysiology is still poorly understood; it may be an autoimmune disorder secondary to environmental, drug or infectious triggering factors [2]. The prognosis in the majority of cases is favorable [4]. There is no standardized treatment, but the majority of cases have been treated with corticosteroid therapy and/or immunosuppressant [4].

2. Material and Method

We have identified two clinical cases of tinu syndrome in the pediatric rheumatology department at the children's hospital at the Ibn Rochd Casablanca University Hospital.

CLINICAL CASE N˚1:

Young girl, 15 years old, with no particular pathological history. Accepted for the aetiological assessment of bilateral anterior uveitis developing in a context of deterioration of the general condition with weight loss estimated at 12 kg over the space of 2 months. Interrogation did not reveal any recent infectious episode, nor medication, oral aphthosis or arthralgia. The clinical examination noted the presence on the urine dipstick of 2 protein crosses. The para-clinical examination revealed an inflammatory syndrome with a sedimentation rate of 110 mm, a normochromium normocytic anemia at 9.6 g/dl of hemoglobin, severe acute renal failure at 56 mg/l, *i.e.* a glomerular filtration rate. At 15 ml/min/1.73 m^2 with a preserved diuresis, proteinuria for 24 h at 1 g/24 h, cytobacteriological examination of the urine does not reveal leukocyturia, hematuria or glycosuria. The abdominopelvic ultrasound was unremarkable. An etiological assessment looking for tuberculosis, toxoplasmosis, sarcoidosis, acute systemic lupus erythematosus, Sjogren, behçet was negative. A renal puncture biopsy for diagnostic, therapeutic and etiological purposes was performed in the aftermaths were simple. Renal biopsy revealed an inflammatory mononuclear infiltrate made up of interstitial lymphoplasmacytic cells without vascular or glomerular lesions. Immunofluorescence negative. The patient received 3 boluses of methyl prednisolone followed by oral corticosteroid therapy. The evolution was marked by improvement in the clinical and biological state with normalization of renal function, negativation of 24-hour proteinuria and regression of uveitis after 5 weeks.

CLINICAL CASE N 2:

16-year-old girl, with no particular pathological history. Hospitalized for the aetiological assessment of a bilateral anterior uveitis progressing for 4 weeks in a context of apyrexia and maintenance of general condition. The examination did

not reveal any recent infectious episode or drug intake, oral aphthosis or arthralgia. The clinical examination was unremarkable. The urine dipstick notes the presence of normoglycemic glycosuria. On the biological assessment, an inflammatory syndrome with an accelerated sedimentation rate, a negative C reactive protein, a normochromic normocytic anemia at 8.8 g/dl of hemoglobin. Acute renal failure with sustained diuresis with plasma creatinine at 16.8 mg/l, *i.e.* a glomerular filtration rate of 43 ml/min/1.73 m^2. On cytobacteriological examination, amicrobial leukocyturia is noted, with normoglycemic glycosuria. The 24-hour proteinuria is 1.2 g/24 h. The kidney ultrasound was normal. The etiologic infectious (tuberculosis, toxoplasmosis) and autoimmune assessment for sarcoidosis, systemic lupus erythematosus, Sjogren was negative. At the renal puncture biopsy we find an interstitial lymphoplasmacytic infiltrate with interstitial fibrosis, without glomerular lesion, nor vascular without granuloma, the immunofluorescence was negative. The patient received oral corticosteroid therapy at a dose of 1 mg/kg/day with a good clinical-biological evolution: regression of uveitis and improvement of renal function with normalization of renal function after 6 weeks with negativation of the 24 h proteinuria (Table 1)

3. Results

These are two female patients. Average age at diagnosis was 16 years. The inaugural symptoms were bilateral anterior uveitis in both cases. The time to discovery of renal signs compared to uveitis: is 4 weeks to 2 months. Acute renal failure

Table 1. Sociodemographics and clinical charactersitics and the participants.

	Case 1	Case 2
Age	15	16
gender	Girl	Girl
Pathological history	no	no
Context	Bilateral anterior uveitis Deterioration of the general condition	bilateral anterior uveitis apyrexia and maintenance of general condition
Clinical sign	urine dipstick of 2 protein crosses	normoglycemic glycosuria
Physical sign	negative	negative
Kidney ultrasound	Normal	Normal.
Etiological assessement	negative	negative
Renal puncture biopsy	inflammatory mononuclear infiltrate made up of interstitial lymphoplasmacytic cells without vascular or glomerular lesions. Immunofluorescence negative.	interstitial lymphoplasmacytic infiltrate with interstitial fibrosis, without glomerular lesion, nor vascular without granuloma, the immunofluorescence was negative.
Treatement	oral corticosteroid therapy at a dose of 1 mg/kg/day	oral corticosteroid therapy at a dose of 1 mg/kg/day
Evolution	good clinical-biological evolution: regression of uveitis and improvement of renal function with normalization of renal function after 6 weeks with negativation of the 24 h proteinuria.	good clinical-biological evolution: regression of uveitis and improvement of renal function with normalization of renal function after 6 weeks with negativation of the 24 h proteinuria.
Observation period	6 months	6 months

with retained urine output was reported in both cases with a mean creatinine of 36.4 mg/l. A mean proteinuria of 1.1 g/24 h associated with aseptic leukocyturia in 1 case/2 and normoglycemic glycosuria in 1 case/2. A non-specific inflammatory syndrome with inflammatory anemia is found in both cases. At the renal puncture-biopsy, we find an inflammatory interstitial infiltrate mononuclear lymphoplasmacytic without granuloma, with interstitial fibrosis in 1/2 cases. The immunofluorescence was negative in both cases. Oral corticosteroid therapy (1 mg/kg per day) was started for 3 to 6 months in both patients. Local treatment with corticosteroids for uveitis was given in both patients. The outcome was favorable under treatment with complete recovery of renal function between 4 - 6 weeks and remission of uveitis.

4. Discussion

4.1. Epidemiology

1) Prevalence and incidence:

The first case of TINU syndrome was described in 19751 in two adolescent girls. Since 200 cases have been reported over the last forty years, worldwide [5] [6], in pediatric and ophthalmological journals as clinical cases or series of cases. The incidence and prevalence of TINU syndrome are reportedly underestimated. It is believed to be the cause of less than 2% of uveitis cases in ophthalmology units [7] [8] and less than 15% of cases of acute tubulo-intestinal nephritis in nephropediatric departments [5].

2) Demographic factors:

Age:

The TINU syndrome is more described in the pediatric population: In an important review of the literature, concerning 133 cases, Mandeville found a median age of 15 years (9 years - 74 years) 2. These results are similar to the study by Mackensen reporting a median age of 15 years (6 years - 64 years) [7] and to a Japanese study conducted by Goda [9]. However, other cases have been reported at older ages [10].

Gender:

According to Mandeville *et al.*, there is a female predominance at 74% (98/133) confirmed by the Mackensen study at 60%. But the percentage of male patients increased (from 18% before 1990 to 34% after 1990) [11]. It has been suggested that gender might affect age: according to Mandeville the median age is 14 years for males versus 17 years for females [2], also for Mackensen with a median age of 15 for male versus 40 years old for females [7].

Ethnicity:

Ethnic predisposition 2 has not been described.

4.2. Physiopathology

The pathophysiology of TINU syndrome remains incompletely understood.

All of the elements reported in the medical literature revive the hypothesis of

an autoimmune cell and humoral mediated disease following a triggering factor in a patient with a predisposing genetic background.

1) Triggering factors:

Drug intake is most often found as a triggering factor, particularly after taking non-steroidal anti-inflammatory drugs or antibiotics [12].

Occasional associations have been described with: infectious pathologies such as Epstein Barr virus [13], chlamydiae [14] And autoimmune diseases such as primary hyperparathyroidism, hyperthyroidism, or rheumatoid arthritis.

2) Genetic predisposition:

Several studies have reported a genetic predisposition to tinu syndrom.

Levinson *et al.* noted the association of TINU syndrome with the HLA-DQA1 * 01, DQB1 * 05 alleles and particularly strongly with the HL-DRB1 * 0102 allele in 72% of cases 15. A case of a monozygous twin developed TINU syndrome at two-year intervals, confirming the role of genetics in this syndrome [15] [16].

3) Physio pathogenesis:

The pathophysiology of TINU syndrome remains unknown. Several cases described have hypothesized that it is a cellular and humoral autoimmune process [4]. At Humoral-mediated immunity in TINU syndrome: There is a little evidence in the literature that points to the presence of a humoral mediated reaction. Polyclonal hypergammaglobulinemia and a non-specific biological inflammatory syndrome are found in the majority of cases of TINU syndrome [17] [18]. In 1985, evidence of circulating immune complexes in a patient [17]. In 2001, CONZ *et al.* noted the decrease in the level of complement C4 in the blood in a 48-year-old patient who presented with TINU syndrome [19]. Wakaki *et al.* isolated serum IgG immunoglobulins directed against a kidney protein in a 13-year-old girl with TINU syndrome [20]. Abed *et al.*, in a 15-year-old patient, demonstrated the presence of IgG autoantibodies directed towards antigens common to renal tubular cells and uveal cells present in the ciliary bodies and the iris [21]. In 2011, in a Chinese study in Beijing, autoantibodies directed against the mCRP protein (modified C Reactive Protein) present without tubular cells and uveal cells have been found in the blood of patients with TINU syndrome [22]. The case of recurrence of TINU syndrome in a patient after renal transplantation [23] The pathogenic role of anti-tubular basement membrane antibodies in the kidney and in the serum remains to be demonstrated. b. Cell mediated immunity: Cellular immunity is central in the pathophysiology of TINU syndrome [24]. Demonstrated during renal biopsies by the presence of an interstitial infiltrate made up of monocytes and lymphocytes and seen in association with specific HLA genotypes. In uveitis and interstitial nephritis, there is an inflammatory immunological process following the interaction of antigen, T lymphocyte and cytokines: • The suspect antigen binds to the Toll-like receptor present on the surface of the antigen presenting cell (APC) • Triggering of the innate immune response, release of cytokines and pro-inflammatory proteins responsible for tissue damage which leads to exposure and modification of antigen sites with escape from the mechanism of tolerance and induction of an auto-immune re-

sponse against auto-antigens. • Triggering of an acquired immune response by the activation of T lymphocytes by the antigen-HLA complex (major histocompatibility complex), differentiation of T lymphocytes, formation of cytotoxic T lymphocytes, release of cytotoxins, recruitment of B lymphocytes, activation and differentiation in plasma cells and autoantibody release with tissue damage (Figure 1).

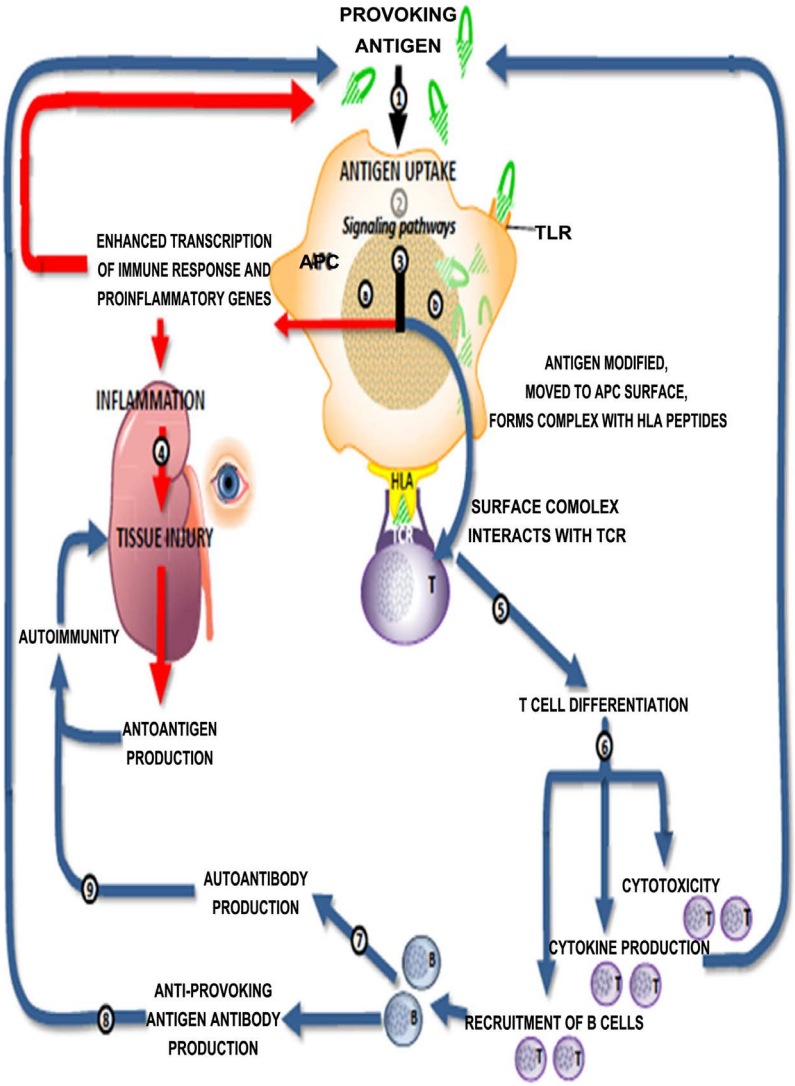

Figure 1. Diagram illustrating the pathogenesis of tubulo nephritis interstitial and uveitis in tinu syndrome [4]. (1) Triggering antigen binds to its receptor Toll-like ligand on the surface of the antigen presenting cell. (2) Activation of signaling. (3) 2 processes result: (a) innate immunity in red, (b) acquired immunity in blue (4) innate immunity: the antigen presenting cells encode pro-inflammatory proteins and cytokines inducing lesions tissue and self-antigen formation (5) acquired immunity: T lymphocyte receptors recognize the Ag HLA complex, activation of T lymphocytes: recruitment of B lymphocytes, production of cytokines, direct cyto toxicity of T lymphocytes. (6) Antibody production. (7) Humoral and cellular response of the acquired immune response. (8) Antibody directed against the triggering antigen. (9) Tissue damage which leads to exposure and modification of the sites antigens with escape from the mechanism of tolerance and induction of an autoimmune response against autoantigens

4.3. Circumstance of Discovery

1) General Events:

Alteration of the general condition with asthenia, weight loss, arthralgia, fever. b. Renal manifestations: Renal involvement is most often initial in 65% following a flu-like syndrome. vs. Ocular manifestations: • Red eye, red, blurred vision, photophobia. • "Ocular involvement may be initial in 20%. May appear at the time of diagnosis of renal failure Delayed a few months or even a year after diagnosis of renal failure.

2) Clinical:

Renal and extrarenal manifestations are summarized **Table 2**.

- Renal impairment:

Acute or subacute renal failure, of varying severity, is found in 2/3 of patients with a serum creatinine level of 184 µmol/l at the time of diagnosis.

Signs typical of tubulointestinal renal impairment, an active urine sediment we can find an active urinary sediment: leukocyturia, hematuria, tubular proteinuria. ➢ A proximal tubular dysfunction such as normoglycemic glycosuria is frequent [9] [25] [26] [27], as was found in case N 2 or type of fanconi [28] [29] [30] [31].

➢ Distal tubular dysfunction, type polyuria [32] or distal tubular acidosis type 1 have also been reported. An increase in urinary excretion of markers of tubular renal damage to the type of beta 2 microglobulin, N-acetyl glucosaminidase (NAG) could be a diagnostic marker according to Goda and his collaborators who noted the increase in urinary excretion in 11 patients/12.

Another KL-6 marker, human glycoprotein, whose serum concentration is high in respiratory pathologies, used in monitoring the activity of sarcoidosis, was found to be significantly elevated in the blood of patients with TINU syndrome, by Kase and his collaborators [33].

- Ocular involvement:

In the TINU syndrome: "Uveitis is most often bilateral and anterior2, but can be intermediate [34] [35] or posterior [36]. All compartments of the uvea can be affected: choroid with chorioretinitis [37], choroidal neovascularization [38], optic nerve edema [39], macular edema [40] [41], sclerochoroiditis [42] c. Extrarenal and extra ocular involvement: Since it is an autoimmune phenomenon, inflammation can affect other organs: ➢ Thyroid: Hashimoto thyroiditis or Hyperthyroidism [40] [43] [44] Ear: Hearing loss and vestibular damage [44] [45] ➢ Lungs: Alveolar pulmonary involvement [27] Joints: Arthritis [44] Localized or diffuse lymphadenopathy [17].

3) Renal histology:

Renal Biopsy Puncture makes it possible to make a positive diagnosis of renal involvement in TINU syndrome. Anatomopathological characteristics (**Figure 2**) ➢ Interstitial edema ➢ Marked interstitial inflammatory infiltrate - Peri-tubular - T lymphocytes - Monocytes-macrophages ➢ Eosinophils ➢ Granuloma ➢ Tubular abnormalities (necrosis) to varying degrees ➢ Fibrosis possible - Initially sparse at the cortico-medullary junction [46] [47] [48].

Table 2. Renal and extrarenal manifestations of TINU. 1.

Box 1. Diagnostic Criteria for TINU

Background: The major prerequisite for making the diagnosis is the presence of both AIN and uveitis, in the absence of other systemic disorders with which they are known to be associated. Depending on the strength of the respective diagnoses of AIN and uveitis, it is recommended to further categorize cases as "definite," "probable," or "possible."

Definite TINU syndrome

- AIN diagnosed histopathologically or clinically (complete criteria) and typical uveitis

Probable TINU syndrome

- AIN diagnosed histopathologically and atypical uveitis or
- AIN diagnosed clinically (incomplete criteria) and typical uveitis

Possible TINU syndrome

- AIN diagnosed clinically (incomplete criteria) and atypical uveitis

Defining Criteria for AIN

- Histopathologic diagnosis: kidney biopsy consistent with TIN
- Clinical diagnosis: the presence of the following criteria (a case is considered to have "complete criteria" if the 3 factors listed below are present; "incomplete criteria" if <3 factors listed below are present):
  1. Abnormal kidney function (elevated serum creatinine or decreased creatinine clearance)
  2. Abnormal urinalysis: increased B2M (reference range, 0-0.3 μg/mL), low-grade proteinuria (a level below that seen in patients with nephrotic syndrome [≤2+ on a semiquantitative test, or a spot UPCR of 3 g/g, or 3.0 g/d in an adult or 3.5 g/1.73 m^2/d in a child]), urinary eosinophils, pyuria or hematuria without infection, urinary white blood cell casts, or normoglycemic glucosuria
  3. A systemic illness lasting 2 wk, 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, arthralgias, or myalgias
     b. Laboratory findings: evidence of anemia, abnormal liver function, eosinophilia, or Westergren erythrocyte sedimentation rate 40 mm/h

Defining Characteristics for Uveitis

- Typical
  1. Bilateral anterior uveitis with or without intermediate uveitis or posterior uveitis
  2. Onset of uveitis 2 mo before or 12 mo after AIN
- Atypical
  1. Unilateral anterior uveitis or intermediate uveitis or posterior uveitis or a combination of these categories
  2. Onset of uveitis 2 mo before or 12 mo after AIN

Note: Adapted from the diagnostic criteria for TINU as developed by Mandeville et al[7] with permission of the copyright holder (Elsevier Science Inc).
Abbreviations: AIN, acute interstitial nephritis; B2M, β_2-microglobulin; TIN, tubulointerstitial nephritis; TINU, tubulointerstitial nephritis and uveitis; UPCR, urinary protein-creatinine ratio.

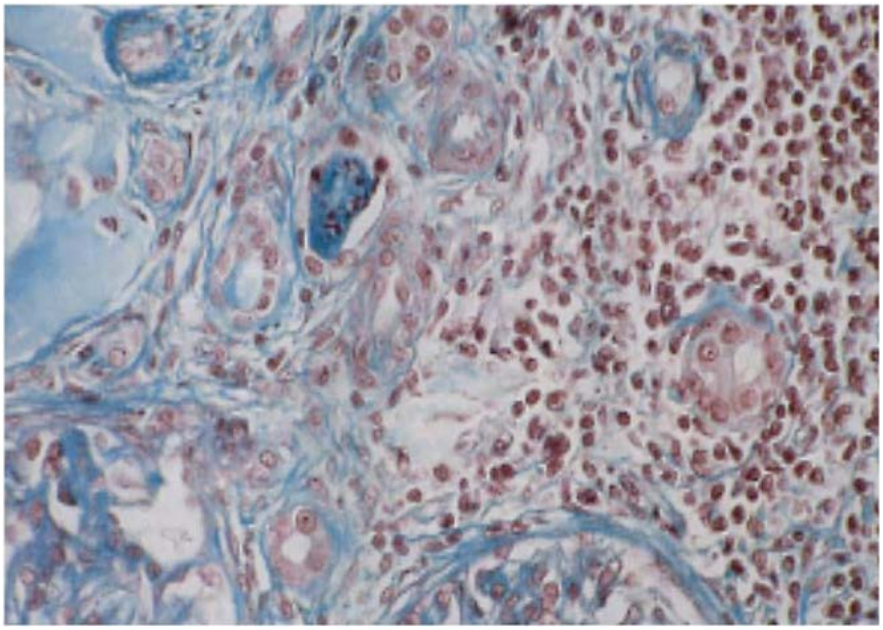

Figure 2. Renal biopsy of a young girl with TINU syndrome.

4.4. Treatment

There is no standardized treatment for TINU syndrome.

1) Treatment of renal impairment:

Corticosteroids are the basic treatment.

Indicated in renal failure.

Oral corticosteroid therapy based on prednisone or prednisoslone.

Dose of 1 - 1.5 mg/kg/day [49] [50].

The duration and reduction of corticosteroid therapy depend on the type and speed of response of the patient.

Some cases have reported the use of immunosuppressants: Cyclophosphamide or mycophenolate mofetil [51] [52].

Other cases reported complete and spontaneous remission of renal involvement without treatment [53].

2) Treatment of uveitis:

Local corticosteroid therapy more or less oral corticosteroids.

In case of resistance to corticosteroids/use of immunosuppressants: Cyclophosphamide, Cyclosporine, Methotrexate, Mycophenolate Mofetil [53].

4.5. Evolution and Prognosis

1) Renal prognosis:

In general, tubulointertial nephritis progresses to spontaneous remission or under corticosteroid treatment. Some cases have reported recurrence of renal damage and persistence of end-stage chronic renal failure with the use of extrarenal cleaning. The renal prognosis depends on the severity of the tubulointertitial fibrosis

2) Ocular prognosis:

In general, there is a remission following treatment. However, relapses of uveitis are frequent and can be prevented by prolonged local treatment with corticosteroids or by immunosuppressive therapy based on methotrexate, cyclosporine A or azathioprine [54].

5. Conclusion

The incidence of TINU syndrome is on the rise, the epidemiology may change with greater involvement in the elderly and in males. It is an autoimmune disease promoted by triggers and genetic predisposition. There are diagnostic markers such as B2 microglobulin and KL-6 which may provide benefit in the future. You have to think about the different differential diagnoses before choosing the diagnosis of UTI. Collaboration between ophthalmologist, pediatric nephropologist and nephrologist is essential for a better.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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