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CASE REPORT

Clinical manifestations of adult tubulointerstitial nephritis and uveitis (TINU) syndrome

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Abstract To describe the clinical manifestations and response to therapy of adult patients with tubulointerstitial nephritis and uveitis (TINU) syndrome and to provide suggested work-up and treatment. We retrospectively examined medical records of all adult patients suffering from TINU at Soroka University Medical Center (SUMC) over the past 15 years. Characteristics of ocular and nephrologic manifestations were investigated with particular attention given to age, presenting signs and symptoms, treatment and course of disease. Five adult patients (median age 44 years) were diagnosed with TINU syndrome and followed from 1991–2006 at SUMC**.** As renal involvement was present at initial evaluation in all patients, they were all treated with steroids. They all suffered from moderate to severe ocular inflammation and most of them relapsed; they also suffered from TINU-related non-specific symptoms. The uveitis in our adult patients was more severe than previously reported. Renal failure and TINU-related non-specific symptoms were observed in all patients and led to the diagnosis of TINU and to systemic therapy which is more aggressive than the usual therapy for uvetis. Thus, early suspicion and diagnosis of TINU may help to direct the appropriate therapy for the degree of uveitis observed in these patients.

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Introduction

The tubulointerstitial nephritis and uveitis (TINU) syndrome is a distinct entity that consists of acute transient interstitial nephritis (ATIN) and uveitis. This syndrome has been increasingly recognized in recent years since it was first described in 1975 [1].

Uveitis in TINU is usually diagnosed early in the course of the disease, but the renal involvement might be overlooked because of its late appearance or due to unimpressive clinical presentation, especially in adults where the disease is less frequent. To the best of our knowledge a study focusing on adult TINU patients has not been published to date.

In this study we describe the adult TINU patients treated at Soroka University Medical Center (SUMC) over a 15 year period. Younger patients treated in this institution over the same period are not discussed in this manuscript. Clinical and laboratory findings and response to therapy are described, and suggestions are made for work-up of renal involvement especially in patients with bilateral anterior uveitis. This retrospective study is based on a review of medical records with particular attention given to age,

presenting signs and symptoms, and course of disease.

Methods

Our cohort of patients comprised all adult patients from the ophthalmology and nephrology clinics at Soroka University Medical Center (SUMC) who were diagnosed with TINU from 1991–2006 and who were subsequently followed up. All patients met the diagnostic criteria for TINU syndrome described by Mandeville et al. [2].

The diagnosis of TINU syndrome requires the documentation of ATIN and uveitis, without evidence of other systemic disease or infection that could cause both renal and ocular inflammation.

We retrospectively examined all their medical records. The main outcome measures were the characteristics of the ocular and nephrologic manifestations of adult TINU syndrome patients. Particular attention was given to age, presenting signs and symptoms, treatment and course of disease.

Investigation included detailed ophthalmologic examinations, urinalysis, complete blood count, erythrocyte sedimentation rate (ESR), serum electrolytes, plasma urea and creatinine, 24-h urine collection for creatinine and protein, serum electrolytes, plasma proteins, ANA, RF, CRF, complement levels, and chest X-ray. Renal biopsy was performed in all patients. Scoring of inflammation of uveitis was assessed using the guidelines of the International Ocular Inflammation Society [3].

Demographic, historical and clinical information of the study patients was compared to patients with TINU syndrome described in the medical literature.

Results

Five adult patients with TINU syndrome were diagnosed and followed from 1991–2006 at SUMC. Detailed data of patients is given in Table 1.

There were four females and one male with an age range of 18–64 years (median age 44 years). In all patients renal involvement was present at initial evaluation. Two of the patients presented with bilateral anterior uveitis and renal involvement was found in the initial work-up. The other three patients had no ocular symptoms at presentation and were initially diagnosed with renal failure and ATIN, while uveitis followed the diagnosis of ATIN by 1.5–6 months.

All patients suffered from TINU-related non-specific symptoms including flu-like symptoms, low-grade fever, nausea or arthralgia, for a few weeks to a few months prior to initial evaluation. A variable degree of elevated ESR was observed in all patients.

Renal involvement varied between moderate renal dysfunction (serum creatinine $\sim$2 mg/dl) in two patients to severe renal dysfunction (serum creatinine $\sim$3.7–5 mg/dl) in the other three patients. The latter three were those that presented with ATIN and no ocular symptoms.

Bilateral anterior segment involvement was observed in all patients in the initial ophthalmologic evaluation, and the posterior segment was also involved in the relapse of one patient. The uveitis relapsed in three of the patients a few months after remission and cessation of steroid therapy and required resumption of steroids, with the addition of immunosuppressive therapy including cyclosporine or azathioprine in two patients. Two patients, including a recently-diagnosed patient with 1 year of follow-up, did not relapse. In relation to severity of ocular disease, all patients suffered moderate to severe inflammation (grade 2–4 uveitic response), and four out of five had keratic precipitates (KPs) and posterior synechia.

Case 1

A 43-year-old man presented with bilateral ocular pain lasting for several days, and over the previous 3 months he had also suffered a “flu-like” illness consisting of malaise, fatigue and low-grade fever. Ophthalmic examination revealed bilateral moderate anterior uveitic response with posterior synechia (PS) and no KPs or posterior segment involvement. Bilateral anterior uveitis was diagnosed and a topical ocular treatment using steroids and cycloplegia were initiated. Due to the constitutional complaints accompanying the uveitis, a uveitic work-up was performed, which revealed impaired renal function, mild proteinuria and mildly elevated ESR (Table 1). A renal biopsy showed severe acute and chronic tubulointerstitial nephritis with marked tubular atrophy and

Table 1 Patient data

Data		Case 1	Case 2	Case 3	Case 4	Case 5
Clinical data	Age at diagnosis (years)	43	64	57	44	18
	Gender	Male	Female	Female	Female	Female
	Presenting symptoms	Bilateral ocular pain	Bilateral ocular pain	Nausea, vomiting, anorexia lasting for a few weeks	Nausea, non-specific constitutional complaints	Non-specific constitutional complaints
	Other concomitant symptoms	Low-grade fever, malaise, fatigue lasting for a few months)	Arthralgia, non-specific constitutional complaints, for a few months	None	None	None
	Elapsing time between two diagnosis	Simultaneously	Simultaneously	5 months	6 weeks	5 months
	Past medical history	Negative	Arterial hypertension	Asthma, arterial hypertension	Negative	Negative
	Blood pressure	130/80	125/77	130/80	100/80	100/60
Preceding diagnosis		Anterior uveitis	ATIN	Anterior uveitis	ATIN	ATIN
Blood (at presentation	ESR (mm/h)	40	89	60	115	60
	Creatinine (mg/dl)	2.1	1.75	5.0	4.7	3.7
	Urea (mg/dl)	57	70	120	78	51
	Hb (g/dl)	12.5	12.4	10.6	10.2	8.3
	Leukocytes/mm^3	14,700	11,280	14,080	8,900	5,450
	Albumin	3.8	4.0	4.3	4.7	4.2
Ocular findings	BCVA at presentation	OD 20/20	OD 20/20	OD 20/40	OD 20/30	OD 20/40
		OS 20/20	OS 20/40	OS 20/40	OS 20/20	OS 20/30
	Uveitic response at presentation	OU flare +3 cells +3	OD flare +2 cells +2, KPs, OS flare +4 cells +4, KPs	OU flare +2 cells +2, KPs	OU flare +2 cells +2	OU flare +3 cells +3, KPs
	Posterior synechia at presentation	Mild (resolved)	OS moderate (resolved)	Moderate (resolved)	None	Moderate (resolved)
	Intraocular pressure at presentation	Normal	Normal	Normal	Normal	Normal
	Secondary cataract	None	None	Mild posterior subcapsular cataract	None	Mild posterior subcapsular cataract
	Posterior segment involvement	None	None	Posterior uveitis, chorioretinitis	None	OU optic disc edema

Table 1 continued

Data		Case 1	Case 2	Case 3	Case 4	Case 5
Histopathology of kidney		Severe interstitial nephritis	Interstitial nephritis	Interstitial nephritis	Severe interstitial nephritis	Severe interstitial nephritis
Treatment	Initial systemic treatment	Systemic steroids	Systemic steroids	Systemic steroids	Systemic steroids	Systemic steroids
	Response to initial treatment	Initial remission, relapse 4 months following cessation	Remission	Initial remission, relapse 2 months following cessation	No remission, uveitis develops	Initial remission, uveitis develops 2 weeks following cessation
	Alternate systemic treatment	Cyclosporine A	Not needed	Systemic steroids	Azathioprine stopped due to impaired liver function tests	Systemic steroids
	Response to alternative treatment	Full remission		Full remission, followed by a second relapse, nine months later	Full remission following reinstitution of steroids	Mild chronic uveitis, full resolution.
Follow-up	Follow-up period (years)	5	2	7	9	6
	Last visual acuity	OD 20/30	OD 20/20	OD 20/20	OD 20/30	OD 20/30
		OS 20/30	OS 20/20	OS 20/20	OS 20/30	OS 20/30
	Last renal function	Creatinine: 1.05	Creatinine: 0.99	Creatinine: 1.33	Creatinine: 1.12	Creatinine: 1.10
		Urea: 40	Urea: 43	Urea: 43	Urea: 41	Urea: 38

fibrosis. The patient received oral prednisone (1 mg/kg) for 6 months, which led to remission of the ocular findings and normalization of the renal function tests. Four months following cessation of the steroid treatment, a relapse of the uveitis and worsening of the renal function were observed. The patient received treatment with cyclosporine A for 6 months with complete remission of the uveitis, and normalization of the renal function tests and urinalysis again. The syndrome has not recurred during 7 years of follow-up.

Case 2

A 64-year-old woman with a history of hypertension presented with bilateral ocular pain lasting for several days, and she had also experienced arthralgia and non-specific constitutional complaints over the previous 3 months. Ophthalmic examination revealed decreased best-corrected visual acuity (BCVA) of 20/40 OS. In the right eye there were small KPs and a moderate anterior uveitic response and no PS or posterior uveitis. In the left eye the uveitis response was more marked, with ciliary injection, KPs and a severe reaction in the anterior chamber with fibrin formation and PS. There was no posterior segment involvement. Intraocular pressure (IOP) was normal bilaterally. Bilateral anterior uveitis was diagnosed and a topical ocular treatment using steroids and cycloplegia were initiated. Uveitic work-up revealed renal dysfunction, mild proteinuria, glycosuria, and elevated ESR (Table 1). Renal biopsy showed severe tubulointerstitial nephritis. The patient received oral prednisone for 2 months, followed by slow tapering of the dosage, with complete remission of the ocular findings and normalization of the renal function tests. During her follow-up of 1 year, there was no relapse.

Case 3

A 57-year-old woman with a history of asthma and hypertension, presented with nausea, vomiting and anorexia lasting for several months. Initial laboratory results showed severely impaired renal function and a moderately elevated ESR. Renal biopsy showed tubulointerstitial nephritis. There were no ocular complaints at that time. She was treated with oral prednisone for 4 months, with marked improvement of renal function and mild residual renal failure. Five months following the diagnosis of ATIN the patient started complaining of bilateral ocular pain and impaired visual acuity. Ophthalmic examination revealed BCVA of 20/40 OU, a bilateral moderate anterior uveitic response, multiple small KPs and PS OD. Bilateral anterior uveitis was diagnosed and a topical ocular treatment using steroids and cycloplegia were initiated with full remission. Seven months following the onset of the disease a relapse of the uveitis accompanied by worsening of the renal function were observed. The uveitis included a moderate reaction in the anterior chamber, small KPs and white infiltrates in the periphery of the vitreous body, OU. Systemic and topical steroids were re-initiated for 2 months with full remission of the ocular findings and improvement of the renal function. Nine months later the patient suffered another relapse of bilateral uveitis, including posterior uveitis, manifested as vitreal cells and multiple white intra- and sub-retinal exudates, without associated renal function deterioration, which responded completely to a course of steroids. The disease did not recur during more than 5 years of follow-up. The patient subsequently expired from carcinoma of colon.

Case 4

A 44-year-old woman presented with several weeks history of nausea and non-specific constitutional complaints. Initial laboratory results showed impaired renal function and a markedly elevated ESR. Renal biopsy showed severe tubulointerstitial nephritis with mild to moderate fibrosis. There were no ocular complaints at that time. The patient was started on systemic steroids but renal function, though improving, still remained impaired. Six weeks following the diagnosis of ATIN the patient started complaining of ocular pain and impaired visual acuity. Ophthalmic examination revealed decreased BCVA of 20/30 OD and a bilateral moderate anterior uveitic response. A topical ocular treatment, including steroids and cycloplegia was initiated. The systemic steroid treatment was replaced with oral azathioprine. The patient could not complete the full course of treatment due to impaired liver function tests secondary to the azathioprine. Steroid therapy was resumed for 12 months and the uveitis and impaired renal function resolved. The disease has not recurred since then, during 5 years of follow-up.

Case 5

An 18-year-old woman presented with non-specific constitutional complaints. Initial work-up revealed normochromic normocytic anemia, impaired renal function and small kidneys on ultrasound examination. A renal biopsy showed severe tubulointerstitial nephritis. There were no ocular complaints. The patient was started on systemic steroids with a good response. The steroids were discontinued after 5 months of treatment but 2 weeks later the patient started suffering from bilateral ocular pain, redness and photophobia. Ophthalmic examination revealed BCVA of 20/30 OD and 20/40 OS, bilateral severe anterior uveitic response, KPs, extensive PS and bilateral disc edema. Bilateral anterior uveitis was diagnosed and topical ocular treatment using steroids and cycloplegia was initiated in conjunction with re-institution of systemic steroids. Due to the findings of disc edema, pseudotumor cerebri secondary to steroid treatment was suspected but ruled out by normal cerebral computed tomography and normal opening pressure on lumbar puncture. There was no relapse of the nephritis. Systemic steroids were administered for an additional 5 months with slow tapering resulting in slow resolution of the anterior uveitis and disc edema. There was no relapse during follow-up of 7 years.

Discussion

TINU syndrome appears most commonly in the prepubertal age group, the median age of patients being 15 years (range 9–74 years) with a 3:1 female-to-male predominance [2]. The incidence of TINU syndrome is 0.2 cases per million population (pmp) per year [4]. Mackensen et al. [5] found that individuals with TINU represent only 1.7% of all patients with uveitis; however, TINU was diagnosed in 10% of patients presenting with bilateral sudden-onset anterior uveitis and in 32% of patients who were $<$20 years of age. Creatinine levels were more likely to be elevated in patients $>$40 years of age.

As TINU presents in up to two-thirds of patients with non-specific symptoms and signs [2], its diagnosis may be delayed, especially in adults. The diagnosis of TINU syndrome necessitates the exclusion of other causes of interstitial nephritis associated with uveitis, such as tuberculosis, histoplasmosis, infectious mononucleosis, toxoplasmosis, brucellosis, systemic lupus erythematosus, sarcoidosis and Wegener's granulomatosis.

Uveitis in TINU syndrome is bilateral in about 80% of patients and is usually anterior. It most commonly presents with eye pain and redness, occurring in almost 80% of patients with uveitis [2]. Less common are blurred vision and photophobia and about 3% of patients with uveitis are asymptomatic. The most common ocular findings are anterior chamber flare and cells occurring in all patients, conjunctival injection in about 70% of patients and KPs in 13% [2]. Uveitis in TINU syndrome may cause severe complications in approximately 20% of patients, the most common being posterior synechia in about 70% of patients, optic disc swelling in 25%, cataract in 20% and secondary glaucoma in 20% [2]. Permanent severe visual loss has not been reported.

ATIN is a common renal pathology that may be associated with a variety of infections and drugs or may develop without an identified cause. It can be associated with fever, rash and non-specific symptoms, but frequently is asymptomatic. Laboratory investigation reveals impaired renal function, eosinophilia and eosinophiluria, non-nephrotic range proteinuria, hematuria, and sterile pyuria. Definitive diagnosis is made by kidney biopsy demonstrating inflammation and edema of the interstitium. The treatment for ATIN primarily consists of eliminating the source of the antigen, when known. The beneficial effect of systemic steroids is well established but a relapse may occur following discontinuation of the steroids and may require immunosuppressive drugs. Early recognition and appropriate therapy usually lead to an excellent prognosis, but the disease can sometimes progress to end-stage renal disease (ESRD).

This study focuses on adult patients with TINU who were diagnosed and followed up at SUMC for 15 years. We tried to compare our small group of patients to the large survey of Mandeville et al. who reviewed 133 published cases of TINU [2]. In contrast to our patients (median age 44 years) most of the patients in that report were young (median age 15 years); however, similar to that review, our patients had a high female-to-male ratio. Although we only had a small number of patients, some characteristics common to these specific patients may be relevant to diagnosis and therapy.

Table 2 Patient characteristics compared with previously published data

		Study sample ($n = 5$)	Goda[4] ($n = 12$)	Mandeville[2] ($n = 133$)
Patient characteristics	Median age (years)		42 (10–56)	15 (9–74)
	Female	80%	83%	74%
Uveitis characteristics	Uveitis at presentation	35%	100%	58%
	Anterior uveitis	80%	44%	80%
	Intermediate, posterior panuveitis	20%	56%	20%
	Unilateral/alternating	0%	0%	23%
	Bilateral	100%	100%	77%
	Single episode	20%	6%	48%
	Recurrent/chronic	80%	94%	52%

In our series, the ocular findings preceded (20%), developed concurrently with (15%), or followed (65%) the onset of intersititial nephritis with a median onset of ocular symptoms one month following the onset of systemic symptoms. In Mandeville's review 58% of patients suffered bilateral uveitis at initial presentation of ocular involvement. In 52% the uveitis had a chronic course or recurred.

In another recent article focusing on the clinical features of TINU syndrome [6], where uveitis was the presenting symptom in all patients, 92% presented with bilateral uveitis and systemic features were present in only 33%. The uveitis and renal failure were initially mild (up to +2 reaction in the anterior chamber and serum creatinine 1.1–1.2 μmol/l). Recurrence or exacerbation of the uveitis occurred in 50% and was characterized by a more severe inflammation with a higher prevalence of posterior segment involvement [7].

All our patients suffered from bilateral uveitis from the onset of ocular involvement and in comparison to Mandeville's review, it seems that the uveitis in our adult patients was more severe, with KPs and posterior synechia appearing in four out of five. All of the patients presented here suffered from renal dysfunction at presentation and those presenting initially with renal involvement without ocular features, had a higher preliminary degree of renal failure compared to those presenting with uveitis concurrently with renal involvement. Three of our patients experienced a relapse and a fourth did not respond to systemic steroid treatment and needed additional immunosuppressive therapy.

Levinson et al. [7] described TINU patients who were primarily older subjects and found significant differences in demographic and disease characteristics between the study patients and the patients described in previous publications (Table 2).

Since the initial therapy of uveitis without ATIN usually consists of topical therapy alone, without systemic steroid or immunosuppressive therapy, early diagnosis of renal involvement is essential for ensuring appropriate therapy and improving renal outcome and prognosis. We suggest that the immediate evaluation of renal involvement might be beneficial in adult patients suffering from bilateral anterior uveitis, especially women, and in the presence of systemic constitutional complaints. Early diagnosis of TINU by assessing renal involvement, especially in patients with uveitis characteristic for TINU (bilateral and anterior), may be helpful in limiting renal damage due to earlier initiation of systemic therapy.

In the 20% of patients where ocular findings precede renal involvement, performing periodic renal evaluation might be useful for early detection and treatment of nephritis thus improving renal prognosis.

Another objective emphasizing the need for early diagnosis is the fact that all of our patients had at least a moderate uveitic response and three of our four long-term followed-up patients relapsed after cessation of systemic therapy. This may suggest that in addition to limiting renal damage, early diagnosis of TINU by assessing renal involvement may be helpful in directing more appropriate therapy for the relatively severe uveitis observed in TINU patients as compared to idiopathic uveitis patients. Furthermore, because inflammation was more severe in exacerbated or recurrent uveitis, in instances where uveitis is refractory to local therapy, systemic corticosteroids

should be considered as early as possible. This observation was also noted in Goda's series of patients [6].

In conclusion, our small group of adult TINU patients was characterized by initial significant renal involvement and bilateral anterior involvement with high severity of disease and high relapse rate in spite of initial systemic therapy. We propose that in the subset of adult uveitis patients, especially females, presenting with bilateral anterior involvement with or without constitutional symptoms, evaluation of renal involvement may have a beneficial effect on diagnosis, therapy and prognosis. We believe ophthalmologists play an important role in the initial discovery of patients with TINU syndrome.

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