Pediatr Nephrol (2018) 33:287–293
DOI 10.1007/s00467-017-3796-z

ORIGINAL ARTICLE

FOXP3$^+$ T cells are present in kidney biopsy samples in children with tubulointerstitial nephritis and uveitis syndrome

Sari H. Rytkönen[1] · Petri Kulmala[1,2] · Helena Autio-Harmainen[3] · Pekka Arikoski[4] · Kira Endén[5,6] · Janne Kataja[7] · Tuomo Karttunen[3] · Matti Nuutinen[1] · Timo Jahnukainen[6]

Received: 2 June 2017 / Revised: 10 August 2017 / Accepted: 24 August 2017 / Published online: 11 September 2017

Abstract
Background Tubulointerstitial nephritis (TIN) is an inflammatory disease of unknown pathogenesis. To evaluate a possible role of regulatory T cells (Tregs) in the pathophysiology of TIN with (TINU) and without uveitis, we investigated the presence and quantity of FOXP3$^+$ T regulatory lymphocytes in diagnostic kidney biopsies from pediatric patients.
Methods A total of 33 patients (14 TIN and 19 TINU) were enrolled. The quantity of CD4$^+$, FOXP3$^+$ and double-positive T cells in formalin-fixed kidney biopsies was determined using double label immunohistochemistry with anti-human CD4 and FOXP3 antibodies.
Results FOXP3 staining was successful in all 33 patients. In patients with chronic uveitis, the density of FOXP3$^+$ cells was significantly lower (p = 0.046) than in TIN patients without uveitis or with uveitis lasting <3 months. CD4$^+$ staining was successful in 23 patients. The density of all lymphocytes (CD4$^+$, CD4$^+$FOXP3$^+$ and FOXP3$^+$ cells) was significantly lower (p = 0.023) in patients with chronic uveitis than in other patients.
Conclusions FOXP3$^+$ T cells are present in kidney biopsy samples from TIN and TINU patients. In patients with chronic uveitis, the density of FOXP3$^+$ T cells is significantly lower than in other patients, suggesting a different pathomechanism for these clinical conditions.

Keywords Tubulointerstitial nephritis · Regulatory T cell · Child · Biopsy · Uveitis · FOXP3

✉ Sari H. Rytkönen
sari.rytkonen@fimnet.fi

1 PEDEGO Research Unit and Medical Research Center (MRC) Oulu, University of Oulu and Oulu University Hospital, Box 23, 90029 OYS, Oulu, Finland

2 Biomedicine Research Unit, Clinical Microbiology and Immunology, University of Oulu, Oulu, Finland

3 Cancer and Translational Medicine Research Unit, University of Oulu, and Department of Pathology, Oulu University Hospital, Box 50, 90029 OYS, Oulu, Finland

4 Department of Pediatrics, University of Eastern-Finland and Kuopio University Hospital, Box 100, 70029 KYS, Kuopio, Finland

5 Department of Pediatrics, Tampere University Hospital, Box 2000, 33521 TAYS, Tampere, Finland

6 Department of Pediatric Nephrology and Transplantation, Children's Hospital, Helsinki University Hospital and Helsinki University, Stenbäckinkatu 11, Box 281, 00029, Helsinki, Finland

7 Pediatric and Adolescent Medicine, Turku University Hospital, Box 51, 20520 TYKS, Turku, Finland

Introduction

Tubulointerstitial nephritis (TIN) is an inflammatory process affecting primarily the renal interstitium and the tubular wall without significant glomerular or vascular involvement [1]. In some cases, renal symptoms are accompanied by uveal inflammation (TINU syndrome) [2]. TIN has been reported to cause approximately 7% of acute kidney injuries (AKI) in the pediatric population [3]. In the adult population, TIN accounts approximately for 1.5–11% of all diagnostic renal biopsies [4].

Tubulointerstitial nephritis may be caused by various viruses and bacterial infections and by numerous drugs [5]. However, especially in children and adolescents, the pathomechanism of TIN remains unknown. The diagnosis of TIN is based on histological findings in renal biopsy. Typically, there are T-cell infiltrations, plasma cells, and eosinophils in the renal interstitium and tubular walls [6]. Immunofluorescence usually remains negative, suggesting

that TIN is not an antibody-mediated disease. Both TIN and TINU syndrome have been shown to be enriched in patients with certain HLA type, potentially reflecting underlying autoimmune mechanisms [7–9].

Naturally occurring $CD4^+CD25^+$ regulatory T cells (nTregs) actively suppress pathological and physiological immune responses. These cells contribute to the maintenance of immunological self-tolerance and immune homeostasis by inhibiting the activation, proliferation, and function of other lymphocytes in physiological or pathological immune responses [10]. Tregs constantly express the x-linked transcription factor forkhead box protein 3 (FOXP3), which is the major regulator of the development, homeostasis, and function of regulatory T lymphocytes [11].

Regulatory T cells have been shown to be important in many different immunological conditions such as renal allograft rejection [12, 13] and in many autoimmune diseases such as systemic lupus erythematosus (SLE), multiple sclerosis (MS), ankylosing spondylitis (AS) [14], and in glomerulonephritis (GN) [15, 16]. Mutations in the FOXP3 gene lead to dysfunctional Treg cells causing immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX), which accompanies severe autoimmune diseases, e.g., diabetes, inflammatory bowel disease, allergy, and various forms of renal injury [17].

The data regarding the expression of $FOXP3^+$ T helper cells in renal biopsy samples is restricted to a few study reports [18, 19]. In the present study, we aimed to evaluate the presence of these cells in the kidney biopsy samples of pediatric TIN patients. We also studied whether the expression of $FOXP3^+$ T cells differs between the patients with TIN and TINU patients with or without chronic uveitis.

Materials and methods

In this nationwide study, all pediatric patients (age < 16 years of age) diagnosed with biopsy-proven idiopathic TIN between 2001 and 2014 were enrolled. All except 6 patients had participated in our previous studies. All TIN diagnoses were based on kidney biopsies, which were performed before any treatment was given. All patients had meticulous work-up to exclude possible underlying conditions, such as respiratory infections, sarcoidosis, connective tissue disorder, or lymphoma. Also, patients with suspected self-limiting, drug-induced TIN were excluded [2, 20, 21]. A total of 42 patients from five university hospitals in Finland were found, and stored biopsy material was available from 33 patients. Nineteen patients (58%) had uveitis (TINU syndrome) and 14 (42%) of them had chronic uveitis. The median age at the time of diagnosis was 12.7 (9.4–14.4) years (Table 1). In 10 (30%) cases immunohistochemical double-staining for both $CD4^+$ and $FOXP3^+$ could not be done owing to insufficient biopsy material,

Table 1 Patient demographics and key laboratory findings at the time of the diagnostic biopsy. The data are presented for all patients and depend on the presence and chronicity of uveitis

	All patients $n = 33$	TIN $n = 14$	TINU $n = 19$	p value	TINU with chronic uveitis $n = 14$	No chronic uveitis[a] $n = 19$	p value	TINU without chronic uveitis $n = 5$[b]
Male gender, (%)	17 (52)	7 (50)	10 (53)		8 (57)	9 (47)		2 (40)
Age, years	12.7 (9.4–14.4)	11.4 (8.5–12.2)	12.7 (12.1–14.3)	0.358	13.2 (12.1–14.4)	11.8 (8.8–12.3)	0.679	13.2 (10.9–15.0)
CRP, mg/L	14.0 (3.0–60.0)	34.0 (4.0–74.0)	13.0 (3.0–53.0)	0.286	13.0 (3.0–53.0)	23.0 (3.0–60.0)	0.650	8.4 (2.5–48.5)
P-Crea, μmol/L	143.0 (108.0–259.0)	254.0 (102.0–332.0)	128.0 (103.0–169.0)	0.012	127.0 (92.0–205.0)	139.0 (103.0–263.0)	0.186	128.0 (99.0–132.0)
U-β2MG, mg/L	20.0 (3.4–48.0)	14.8 (2.3–20.6)	34.0 (12.6–47.0)	0.220	20.0 (3.4–47.0)	20.6 (3.2–42.0)	0.650	38.0 (11.2–69.7)
ESR, mm/h	95.0 (39.0–116.0)	104.0 (94.0–113.0)	73.0 (29–106)	0.010	64.0 (25.0–92.0)	105.0 (92.0–114.0)	0.039	95.0 (29.0–110.0)
GFR, ml/min/1.73 m^2	53.0 (28.0–78.0)	31.0 (22.0–97.0)	61.0 (47.0–80.0)	0.014	62.0 (47.0–91.0)	45.0 (27.0–72.0)	0.077	65.4 (45.5–77.5)

Chronic uveitis was defined as uveitis that had lasted more than 3 months despite of treatment and/or with relapse within 3 months after discontinuing treatment

Reported values are median values and 25th and 75th percentiles are in brackets, except where stated otherwise

TIN tubulointerstitial nephritis, *TINU* tubulointerstitial nephritis with uveitis syndrome, *CRP* C-reactive protein, *P-Crea* plasma creatinine concentration, *U-β2MG* urine beta-2-microglobulin concentration, *ESR* erythrocyte sedimentation rate, *GFR* glomerular filtration rate

[a] Including patients with TIN and TINU syndrome without chronic uveitis

[b] There were no statistical differences between TINU patients without chronic uveitis compared with other subgroups

disorientation of the sample on the slide or poor quality of the staining. Consequently, double staining of both CD4+ and FOXP3+ cells was successful in 23 patients.

All patients were followed up by a pediatric nephrologist and an ophthalmologist for at least 1 year after the diagnosis of TIN. Uveitis was classified according to standardization of uveitis nomenclature (SUN) criteria. Chronic uveitis was defined as uveitis that had lasted more than 3 months despite treatment and/or with relapse within 3 months after discontinuing treatment.

Laboratory samples were taken at the time of the diagnostic kidney biopsy. Plasma creatinine (P-Crea), C-reactive protein (CRP), blood erythrocyte sedimentation rate (ESR), and urinary excretion of low molecular weight (LMW) proteinuria by measuring β-2-microglobulin (β-2-MG) were analyzed from each patient. Glomerular filtration rate (GFR) was measured either by Cr-EDTA or by iohexol clearance. Estimated GFR was calculated using bedside Schwartz formula.

Immunohistochemistry

Kidney biopsies were routinely formalin-fixed and embedded in paraffin blocks after biopsy. As part of this study, paraffin blocks were cut to 2.5-μm sections. The second phase was antigen retrieval with Tris-EDTA (pH 9) in a microwave. The quantities of $CD4^+$, $FOXP3^+$, and $CD4^+FOXP3^+$ double-positive T cells were determined with double-label immunohistochemistry using anti-human CD4 (Novacastra ™ Product Code NCL-L-CD4–368 with 1:50 dilution) and FOXP3 (Abcam, 236A/E7 with 1:100 dilution) antibodies. Immunostainings were performed using Dako REAL™ EnVision ™ Detection System (Dako code K5007). For $CD4^+$ cells DAB-peroxidase substrate was used from the same kit. For FOXP3, Vector SG substrate kit (catalog number SK-4700 by Vector laboratories) was used (Fig. 1).

The areal density of positive cells was determined with high magnification (×40 objective) and a graticule corresponding field size of 0.063 mm^2. Cells were counted in five random fields and the mean value was calculated. The quality of the $CD4^+$ and $FOXP3^+$ stainings was confirmed using a positive control sample from tonsillar tissue. In addition to the kidney biopsy, samples from the 33 TIN patients, 25 kidney biopsy samples from Henoch–Schönlein nephritis (HSP) patients were stained as control samples (Fig. 1).

Statistical analysis

We used IBM SPSS Statistics version 22 for statistical analysis. Owing to the skewed distribution of each measured continuous variable, we used Mann–Whitney *U* test to compare the results of TIN and TINU patients with or without chronic uveitis. A two-tailed p value <0.05 was considered to indicate statistical significance.

Results

General findings

The demographic data of the patients are presented in Table 1. In TIN patients, ESR and P-Crea were significantly higher ($p = 0.010$ and $p = 0.012$) and GFR was significantly lower ($p = 0.014$) than in TINU patients at the time of diagnosis. Furthermore, in patients with chronic uveitis, ESR was significantly higher ($p = 0.039$) than in patients without chronic uveitis (Table 1).

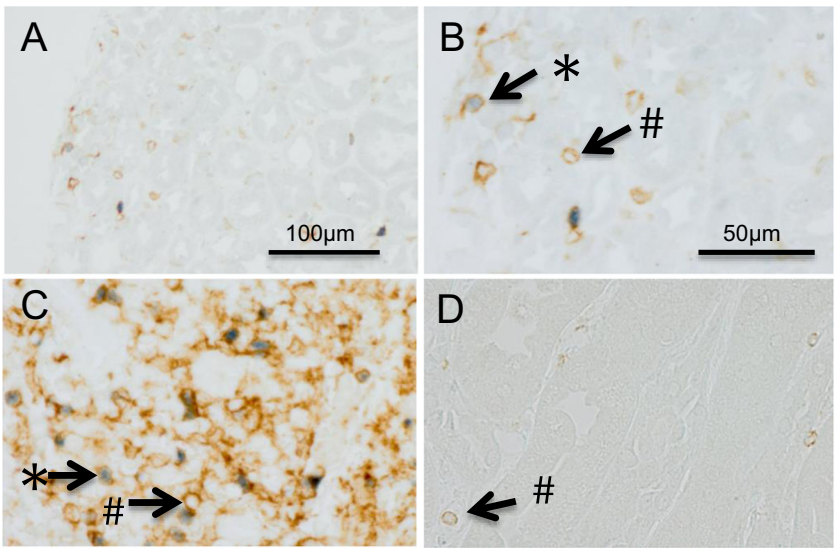

Fig. 1 Immunohistochemical staining of $CD4^+$ and $FOXP3^+$. **a** Renal biopsy from a TINU patient with chronic uveitis, x20 magnification. **b** Same specimen with ×40 magnification. **c** Control tonsillar tissue, x40 magnification. **d** Renal biopsy sample from a HSP patient, x40 magnification. *TINU* tubulointerstitial nephritis and uveitis syndrome, *HSP* Henoch–Schönlein purpura. *Asterisk* double positive $CD4^+FOXP3^+$ cell; *hash*$CD4^+$ cell

Immunohistochemistry

Immunohistochemical staining for FOXP3 was successful in all 33 patients. The cell densities are presented in Table 2 separately for TIN patients, for patients with TINU, for patients with TINU and chronic uveitis, and for patients with TINU without chronic uveitis. In patients with chronic uveitis, the density of $FOXP3^+$ T cells was significantly lower ($p = 0.046$) than in TIN patients without uveitis or uveitis lasting <3 months (Table 2, Fig. 2).

$CD4^+$ staining was successful in 23 (70%) patients. The age and gender distribution of these 23 patients did not differ significantly from the total study population. The prevalence of uveitis (52%, $n = 12$) and chronic uveitis (35%, $n = 8$) were also comparable with the original population (data not shown). The results from the double staining experiments are shown in Table 2 and Fig. 2. The overall density of lymphocytes was significantly lower ($p = 0.023$) in patients with chronic uveitis compared with other patients.

Immunohistochemical stainings performed on 25 kidney biopsy samples from HSP patients were all successful. In all 25 HSP samples the density of $CD4^+$ and $FOXP3^+$ and double positive cells were almost nonexistent (Fig. 1).

Discussion

A rare condition with various etiologies, TIN/TINU syndrome is of unknown immunopathology [22]. In the present study, we have demonstrated, to our knowledge for the first time, that $FOXP3^+$ T cells are present in kidney biopsy samples from pediatric TIN patients. We also showed some evidence for a significantly lower density of $CD4^+$ and/or $FOXP3^+$ T cells in TINU patients with chronic uveitis compared with other patients. It may well be that the immune response in patients with chronic TINU is different from other patients, leading to a prolonged inflammatory process.

Renal biopsies of TIN patients typically show the presence of T lymphocytes and other mononuclear cells, and occasionally eosinophils [6]. The pathomechanism in TIN is therefore suggested to be antigen-driven molecular mimicking leading to autoimmune-type disease [23]. A recent study by Cheng et al. has shown evidence about an increased number of dendritic cells in kidney biopsy samples from TIN patients and from patients with lupus nephritis (LN) when compared with samples from minimal change disease patients [24]. In the present study, we found $CD4^+FOXP3^+$ T cells, i.e., potential Tregs, in the biopsy samples from TIN patients. Interestingly, in patients with chronic uveitis indicating persistent autoimmune response, the density of these cells was lower than in patients with other forms of TIN. It may well be that in these patients Treg activation is for some reason dampened, which leads to prolonged inflammatory response and the chronic form of the

Table 2 Lymphocyte densities in all patients, in patients with tubulointerstitial nephritis (TIN) and tubulointerstitial nephritis with uveitis (TINU) syndrome, depending on the presence and chronicity of uveitis

	All patients $n = 33^b/23^c$	TIN $n = 14^b/11^c$	TINU $n = 19^b/12^c$	*p* value	TINU with chronic uveitis $n = 14^b/8^c$	TINU without chronic uveitis $n = 5^b/4^c$	All patients without chronic uveitis $n = 19^b/15^c$	*p* value chronic uveitis vs nonchronic uveitis
All $FOXP3^+$ / mm^2 $n = 33$	240 (134–448)	283 (131–432)	230 (141–422)	0.76	187 (134–240)	502 (381–512)	381 (211–502)	0.046
All cells /mm^2 a $n = 23$	583 (362–1,261)	1,181 (446–1,280)	520 (362–658)	0.375	464 (282–556)	1,192 (583–1,974)	1,181 (522–1,389)	0.023
$CD4^+FOXP3^+$ /mm^2 $n = 23$	141 (67–272)	211 (82–296)	104 (62–197)	0.413	93 (62–157)	248 (83–440)	211 (82–350)	0.131
$CD4^+$ /mm^2 $n = 23$	333 (138–560)	333 (170–654)	312 (139–402)	0.833	312 (123–373)	764 (160–373)	333 (160–890)	0.325

Chronic uveitis was defined as uveitis that had lasted more than 3 months despite treatment and/or with relapse within 3 months after discontinuing treatment

Reported values are median values and 25th and 75th percentiles are in brackets

[a] $CD4^+$, $CD4^+$ $FOXP3^+$, and $FOXP3^+$ cells

[b] All patients with successful $FOXP3^+$ staining

[c] All patients with successful double staining

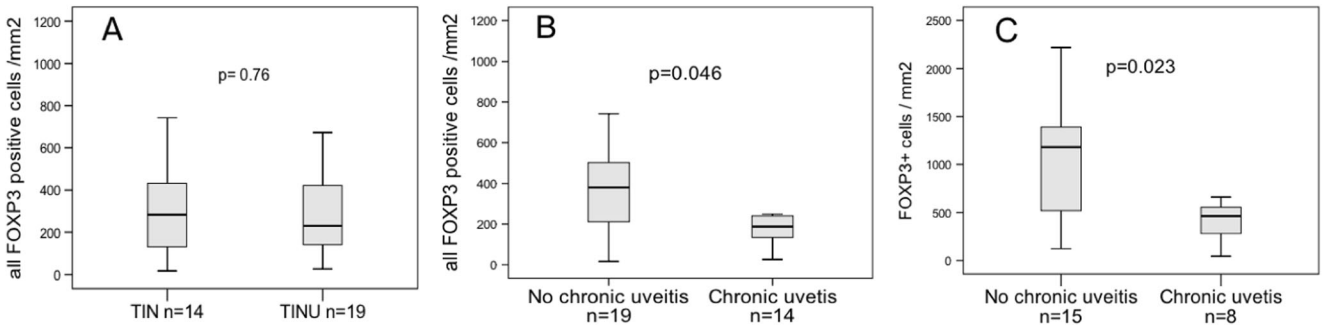

Fig. 2 Comparison of FOXP3+ and/or CD4+ cell density between TIN, tubulointerstitial nephritis and uveitis syndrome (TINU) and patients with or without chronic uveitis. **a** Difference in all FOXP3$^+$ cells between TIN and TINU patients, n = 33. **b** Difference in all FOXP3$^+$ cells between patients with and without chronic uveitis, n = 33. **c** Difference between all cells (CD4$^+$FOXP3$^+$, CD4$^+$, and FOXP3$^+$ cells) between patients with and without chronic uveitis, n = 23. *TIN* tubulointerstitial nephritis, *TINU* tubulointerstitial nephritis and uveitis syndrome. Chronic uveitis was defined as uveitis that had lasted more than 3 months despite treatment and/or with relapse within 3 months after discontinuing treatment. Each boxplot presents the median and the 25th and 75th centiles; error bars represent the smallest and the largest values

disease. For comparison, the density of CD4$^+$ and FOXP3$^+$ cells were almost non-existing in our biopsy samples from HSP patients, which is in line with previous studies [25, 26].

No previous data regarding Tregs in TINU patients have been published. However, it has been shown that the quantity of FOXP3$^+$ T cells in kidney transplants correlates positively with long-term graft function. Patients with no chronic damage in biopsy had a significantly higher percentage of CD3$^+$/FOXP3$^+$T cells than patients with any chronic histological damage [12, 13]. Moreover, it has been shown that the number of FOPX3$^+$ T cells within the entire CD4$^+$ T cell population is significantly higher in patients with subclinical or mild rejection than in patients with acute rejection, and it correlates negatively with graft function at the time of biopsy [27], suggesting that Tregs might reduce interstitial inflammation. Polymorphisms in the FOXP3 gene and in genes coding various cytokines have been shown to cause an altered inflammatory response, which may result in autoimmune disease [28].

The potential role of Tregs in other autoimmune kidney diseases has been studied in both murine and human models. In anti-neutrophil cytoplasmic antibody (ANCA) -associated vasculitis (AAV), the findings from human studies are conflicting regarding the amount of circulating Tregs, but there is evidence that FOXP3$^+$ Tregs are functionally impaired, with diminished capability to suppress effector T cell (Teff) proliferation [29–34]. There are several reports about the reduced quantity and function of Treg cells in SLE patients. Xing et al. demonstrated decreased frequency of CD4$^+$CD25$^+$FOXP3$^+$ Treg cells in peripheral blood with lupus nephritis (LN) compared with SLE patients without nephritis [35]. In the study by Afeltra et al., the ratio of FOXP3$^+$/CD3$^+$ cells was significantly lower in lupus nephritis class IV than in lupus nephritis class V, patients with nephroangiosclerosis, and 6 patients with acute TIN used as control patients [19].

The major limitation of the present study is the relatively low number of patients. However, TIN is a rare disease and this is by far one of the largest studies available in the literature. In addition, all patients were studied and followed up by a pediatric nephrologist and ophthalmologist using the same protocol [21]. This meticulous work-up guarantees that the study population represents patients with idiopathic TIN or TINU with or without chronic uveitis. In addition, based on our results, we are not able to draw any conclusions about the mechanism of uveitis in this patient cohort. However, several other autoimmune diseases that are accompanied by uveitis, e.g., ankylosing spondylitis [36], juvenile idiopathic arthritis [37], and SLE [38] have been shown to have impaired Treg production or function.

Conclusions

To the best of our knowledge, this is the first report comparing the presence of FOXP3$^+$ T cells in biopsy samples from patients with TINU and patients with TINU and chronic uveitis. FOXP3$^+$ T cells could be found in all patients; however, in patients with chronic uveitis the density of Tregs was significantly lower than in other patients. This may indicate a different pathomechanism behind these clinical conditions, implying that in TINU patients with chronic uveitis, the pathomechanism may be of autoimmune origin. Because of the relatively low number of patients, replication studies with larger patient cohorts are needed.

Acknowledgements We would like to thank Mrs Heli Ylisuutari for her excellent contribution to the preparation and execution of the immunohistochemical stainings.

Funding This study has been supported by the Foundation for Pediatric Research, Finnish Medical Foundation, the Sigrid Juselius Foundation, and the Alma and K.A. Snellman Foundation, Oulu, Finland.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Statement of human rights The study adhered to the tenets of the Declaration of Helsinki and the study protocol was approved by the ethics committee. All participants and/or their parents gave their informed consent to the study.

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