Measurement of urinary biomarkers in a case of tubulointerstitial nephritis and uveitis syndrome during glucocorticoid treatment

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Abstract

Tubulointerstitial nephritis and uveitis (TINU) is a rare syndrome in which idiopathic interstitial nephritis coexists with chronic recurrent uveitis. This syndrome often represents systemic disorders such as arthralgia, rash, prolonged fever, anaemia and ocular symptoms that require medication including glucocorticoid administration. Recently, novel urinary biomarkers, such as kidney injury molecule-1, neutrophil gelatinase-associated lipocalin and liver-type fatty acid-binding protein, were shown to be associated with tubulointerstitial damage and were elevated in interstitial nephritis. We evaluated these urinary biomarkers in a case of TINU syndrome before and during treatment and found that their levels were elevated at onset and decreased during treatment, especially NGAL. We conclude that these urinary biomarkers are useful to evaluate and predict prognosis in interstitial nephritis.

Keywords Kidney injury molecule-1 · Liver-type fatty acid-binding protein · Neutrophil gelatinase-associated lipocalin · Urinary biomarkers · Tubulointerstitial nephritis and uveitis syndrome

Introduction

Tubulointerstitial nephritis and uveitis (TINU) syndrome was first described in 1975 by Dobrin et al. as acute idiopathic interstitial nephritis combined with simultaneous uveitis [1]. It predominantly affects adolescent girls, and onset may be associated with the administration of antibiotics or non-steroidal anti-inflammatory drugs [2].

Renal involvement in TINU syndrome is usually self-limiting in several cases [3]; however, when systemic symptoms such as prolonged fever, body weight loss and anaemia of chronic disorders become intolerable, oral glucocorticoid treatment may be required. Meanwhile, elderly patients with TINU often do not recover spontaneously, especially those with renal insufficiency [4], and it is important to monitor treatment, including glucocorticoids, during drug tapering.

Recently, novel urinary biomarkers including neutrophil gelatinase-associated lipocalin (NGAL or lipocalin 2), kidney injury molecule-1 (Kim-1) and liver-type fatty

acid-binding protein (L-FABP) were identified to monitor chronic kidney disease progression and diagnose acute kidney injury.

We evaluated kidney injury by measuring traditional and novel urinary biomarkers in a young girl with TINU syndrome before and during glucocorticoid treatment and to assess their usefulness for the prediction of renal prognosis in TINU.

Case study

A 12-year-old girl was admitted to our hospital with fever, respiratory symptoms and malaise. She was diagnosed with bacterial bronchiolitis and administration of antibiotics (ceftriaxone and clindamycin) and acetaminophen as antipyretic improved her respiratory symptoms after 2 weeks of hospitalization. However, low-grade fever and anorexia did not improve and white blood cell count increased (8400/ μ L). Hemoglobin was 9.1 g/dL without iron deficiency. Serum creatinine (Cr) was 1.44 mg/dL and cystatin C was 2.02 mg/dL, indicating slight renal insufficiency. C-reactive protein was elevated (4.48 mg/dL). Anti-Sjögren's syndrome-related antigen A (anti-SS-A), anti-SS-B, anti-DNA and antinuclear antibodies were

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all negative. Serum monoclonal immunoglobulin was not detectable. Although urinary protein was negative (9 mg/dL), urinary beta 2-microglobulin was highly elevated (22,100 µg/L) and *N*-acetyl-β-D-glucosaminidase was also increased (12.6 U/L). Abdominal computed tomography revealed bilateral renal enlargement with a smooth surface, but hydronephropathy was not noted. Because there was a possibility of interstitial nephritis, subcutaneous renal biopsy was performed. Renal biopsy revealed leukocyte influx, predominantly comprising lymphocytes and a few plasma cells, in the renal interstitium (Fig. 1). Atrophic epithelial tubular cells and interstitial fibrosis were also observed, without glomerular lesions. Kim-1 expression was detected in the damaged proximal tubules (Fig. 1) via immunohistochemical analysis. Non-granulomatous anterior uveitis was also confirmed by the ophthalmologist, and she was diagnosed with TINU syndrome. Systemic illness apart from renal disorder persisted; therefore, oral administration of 50 mg/day prednisolone was initiated.

Prolonged fever, elevated inflammation and renal impairment were resolved within 4 weeks. Novel urinary biomarkers including L-FABP, NGAL and Kim-1, and the traditional proximal tubular damage biomarker, beta-2 microglobulin, were elevated (54.02, 1.25, 4.71 and 718 µg/g Cr, respectively). Each value was examined before and during treatment, as shown in Fig. 2.

Glucocorticoid treatment was gradually tapered and discontinued over 24 weeks, and the levels of all four biomarkers decreased. The level of traditional proximal tubular damage biomarker, urinary beta-2 microglobulin did not improve even after 2 weeks of treatment; however, urinary L-FABP and Kim-1 fluctuated after 8 weeks of treatment compared with the other biomarkers. Meanwhile, after

Fig. 1 Diffuse interstitial cellular infiltration of kidney (Haematoxylin and eosin staining, magnification 100×)

Fig. 2 Changes in urinary biomarker levels before and during glucocorticoid treatment. The levels of all the four biomarkers decreased, and urinary NGAL decreased rapidly compared with the other three biomarkers. Urinary L-FABP decreased gradually, and KIM-1 fluctuated after 8 weeks. *NGAL* Neutrophil gelatinase-associated lipocalin, *KIM-1* kidney injury molecule-1, *Beta2-MG* microglobulin, *L-FABP* liver-type fatty acid-binding protein

2 weeks, urinary NGAL levels decreased by less than 20% compared with that before treatment and were extremely low in the following process (Fig. 3).

Fig. 3 The clinical course of our case indicates clinical symptoms and the changes of laboratory data. *CTRX* Ceftriaxone, *CLDM* clindamycin, *BW* body weight, *P.O.PSL* per os prednisolone, *S-Cys C* serum cystatin C, *S-Cr* serum creatinine, *Hb* haemoglobin, *CRP* C-reactive protein

Materials and methods

Urine specimens were obtained at the onset of the syndrome and every 2–4 weeks for a total of 24 weeks. Urinary NGAL concentration was measured using a Human NGAL ELISA Kit 036RUO (BioPorto Diagnostics, Copenhagen, Denmark) according to the manufacturer's instruction. Urinary Kim-1 was measured using previously described methods [5]. Urinary L-FABP was measured using the BML, Inc. (Tokyo, Japan) latex agglutination coagulating method. The level of each urinary biomarker was normalised to the urinary Cr of the same urine specimen and was expressed as micrograms per gram of Cr.

Immunohistochemical staining for Kim-1 was performed on 6- μ m renal frozen sections of optimal cutting temperature compound embedded using the avidin–biotin complex method with human TIM-1/KIM-1/HAVCR biotinylated antibody (BAF1750) (R&D System, Minneapolis, USA) [5].

Discussion

To diagnose tubulointerstitial inflammation within TINU syndrome, renal biopsy is occasionally performed to predict the outcome of renal disorder, or to differentiate from IgG4-related disease, acute tubular necrosis, rheumatic disease and other illnesses which could result in acute kidney injury. Typical renal biopsy findings include interstitial oedema with active interstitial inflammation, mainly consisting of plasma cells, lymphocytes and eosinophils [6]. However, the degree of pathological changes to cell infiltration or interstitial fibrosis is not associated with renal prognosis in adults [7]. Furthermore, renal biopsy is highly invasive and cannot be performed easily or repeatedly. In contrast, urinary biomarkers are non-invasive and can be repeatedly examined to evaluate disease activity or therapeutic effects. Mandaville et al. reviewed 133 patients with TINU syndrome and suggested three possible criteria to diagnose, including urinary findings without renal biopsy, renal impairment in adult TINU often leads to chronic renal disease [4], and the prediction of renal outcome, is therefore, important.

Altered levels of urinary biomarkers in some cases of interstitial nephritis have already been reported [9]. These include urinary MCP-1 levels correlating with acute phase inflammation in renal specimens and elevated urinary NGAL levels compared with healthy controls. We also chose novel biomarkers to evaluate interstitial nephritis and its progress. To our knowledge, our study is the first to describe novel biomarkers in TINU syndrome during glucocorticoid treatment.

During acute renal failure and renal parenchymal inflammation in humans, NGAL protein accumulates in the renal proximal and distal tubules [10]. The major sites of NGAL production in inflammation include monocytes/macrophages, neutrophils and tubular epithelial cells [11]. Similar to our results, Kuwabara et al. reported that urinary NGAL showed the largest fold increase and the quickest response to treatment compared with other traditional urinary biomarkers in interstitial nephritis [12].

Kim-1 exhibits homology to hepatitis A virus cell receptor 1 and is up-regulated in the urine after kidney injury [13]. Urinary Kim-1 expression and Kim-1-positive tubules are associated with macrophage aggregates and pre-fibrotic areas with increased expression of alpha-smooth actin, a marker of interstitial fibrosis [14]. After renal injury, damaged tubule epithelial cells express Kim-1 and assume the characteristics of endogenous phagocytes [15], indicating that Kim-1 may be associated with not only the acute inflammatory phase, but also the healing phase. In our study, Kim-1 fluctuated slightly after substantial resolution of inflammation, indicating that Kim-1 may contribute to repairing the interstitial tissue during this phase.

L-FABP, found in the cytoplasm of human proximal tubules, has a high affinity and capacity to bind long-chain fatty acid oxidation products, and may have a protective effect on damaged proximal tubules [16]. In hospitalised patients with acute kidney injury, urinary L-FABP levels were associated with renal outcome or requirement for renal replacement therapy [17]. Tanaka et al. used an adenine-induced renal injury mouse model and reported that urinary L-FABP concentration was positively correlated with interstitial fibrosis and macrophage infiltration but urinary NAG and albumin were not [18]. In our study, urinary L-FABP levels decreased gradually compared with other biomarkers and may not indicate precise activity in this syndrome.

In conclusion, NGAL may be the most sensitive biomarker in TINU syndrome during glucocorticoid treatment. However, since our patient is a single case, it is not known whether the same phenomenon can be seen in other TINU cases. Furthermore, as there has been very little research into novel urinary biomarkers in interstitial nephritis, the optimum method to evaluate disease progression and renal outcome in TINU is not well understood and further studies are required.

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Research involving human participants and informed consent Informed consent was obtained from all individual participants including in this case report.

Ethical standards All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

References

1. Dobrin RS, Vernier RL, Fish AL. Acute eosinophilic interstitial nephritis and renal failure with bone marrow-lymph node granulomas and anterior uveitis. A new syndrome. *Am J Med.* 1975;59:325–33.
2. Vohra S, Eddy A, Levin AV, Taylor G, Laxer RM. Tubulointerstitial nephritis and uveitis in children and adolescents. *Pediatr Nephrol.* 1999;13:426–32.
3. Takemura T, Okada M, Hino S, et al. Course and outcome of Tubulointerstitial nephritis and uveitis syndrome. *Am J Kid Dis.* 1999;34:1016–21.
4. Li C, Su T, Chu R, Li X, Yang L. Tubulointerstitial nephritis with uveitis in Chinese adults. *Clin J Am Nephrol.* 2014;9:21–8.
5. Nozaki Y, Kinoshita K, Yano T, et al. Estimation of kidney injury molecule-1 (Kim-1) in patients with lupus nephritis. *Lupus.* 2014;23:769–77.
6. Sinnamoni KT, Courtney AE, Harron C, O'Rourke DM, Mullan RN. Tubulointerstitial nephritis and uveitis (TINU) syndrome: epidemiology, diagnosis and management. *NDT Plus.* 2008;1:112–6.
7. Legendre M, Devilliers H, Perad L, et al. Clinicopathologic characteristics, treatment, and outcomes of tubulointerstitial nephritis and uveitis syndrome in adults: a national retrospective stroke-compliant study. *Medicine (Baltimore).* 2016;95:e3964.
8. Mandeville JT, Levinson RD, Holland GN. The tubulointerstitial nephritis and uveitis syndrome. *Surv Ophthalmol.* 2001;46:195–208.
9. Yu Wu L, Yang T, Su C, Wang G, Liu Xiao-mei, Li. Pathological significance of panel of urinary biomarkers in patients with drug-induced tubulointerstitial nephritis. *Clin J Am Soc Nephrol.* 2010;5:1954–59.
10. Mori K, Nakao K. Neutrophil gelatinase-associated lipocalin as the real-time indicator of active kidney damage. *Kidney Int.* 2007;71:967–70.
11. Cowland JB, Sorensen OE, Sehested M, Borregaard N. Neutrophil gelatinase-associated lipocalin is up-regulated in human epithelial cells by IL-1 beta, but not by TNF-alpha. *J Immunol.* 2003;171:6630–39.
12. Kuwabara T, Mori K, Mukoyama M, et al. Urinary neutrophil gelatinase-associated lipocalin levels reflect damage to glomeruli, proximal tubules, and distal nephrons. *Kidney Int.* 2009;75:285–94.
13. Ichimura T, Joseph V, Boncentre, Veronique, Bailly, et al. Kidney injury molecule-1, a putative epithelial cell adhesion molecule containing a novel immunoglobulin domain, is up-regulated in renal cells after injury. *J Biol Chem.* 1998;273:4135–42.
14. van Timmeren MM, van den Heuvel MC, Bailly V, Bakker SJL, van Goor H, Stegeman CA. Tubular kidney injury molecule-1 (KIM-1) in human renal disease. *J Pathol.* 2007;212:209–17.
15. Ichimura T, Asselton EJ, Humphreys BD, Gunaratnam L, Duffield JS, Bonventre JV. Kidney injury molecule-1 is a phosphatidylserine receptor that confers a phagocytic phenotype on epithelial cells. *J Clin Invest.* 2008;118:1657–68.
16. Kamijo-Ikemori A, Sugaya T, Obama A, et al. Liver-type fatty acid-binding protein attenuates renal injury induced by unilateral ureteral obstruction. *Am J Pathol.* 2006;169:1107–17.
17. Ferguson MA, Vaidya VS, Waikar SS, et al. Urinary liver-type fatty acid protein predicts adverse outcomes in acute kidney injury. *Kidney Int.* 2010;77:708–14.
18. Tanaka T, Doi K, Maeda-Mamiya R, et al. Urinary L-type fatty acid-binding protein can reflect renal tubulointerstitial injury. *Am J Pathol.* 2009;174:1203–11.