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Behçet's Disease with Extremely High Levels of Urinary β2-Microglobulin after Non-Steroidal Anti-Inflammatory Drug Treatment

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Behçet's disease is an inflammatory disease which manifests itself as various symptoms, such as uveitis, oral and genital aphthae, erythema nodosa, gastro-intestinal ulcerations and encephalopathy. Among the manifestations, renal dysfunction is reported in some percentage of the patients with this disorder. We experienced a middle-aged male with Behçet's disease who showed an extremely high level of urinary β2-microglulin, which is one of the markers of renal dysfunction, despite normal serum creatinine levels. The patient was on non-steroidal anti-inflammatory drug (NSAID) therapy for 7 weeks, and this could have affected his renal dysfunction. The present report suggests that renal injury should not be underestimated in patients with Behçet's disease, especially in patients using NSAIDs.

Keyword: Behçet's disease; β2-microglobulin; creatinine; non-steroidal anti-inflammatory drug; renal dysfunction
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Introduction

Behçet's disease was first described in 1937 by a Turkish dermatologist, Hulsi Behçet, after whom the disease was named (Adil et al. 2020). The major manifestations of this disorder include oral and genital aphthae, erythema nodosum, and uveitis. Less common manifestations are arthritis, thrombophlebitis, deep vein thrombosis, aortitis, encephalopathy, and gastro-intestinal ulcerations. Additionally, renal dysfunction has been reported as a complication of Behçet's disease. Although Akpolat et al. (2002) reported that renal involvement in Behçet's disease is more frequent than has been recognized in previous studies, very few studies have indicated renal dysfunction in Behçet's disease thus far (Zheng et al. 2015; Ozel et al 2016; Leonard et al. 2018). Furthermore, non-steroidal anti-inflammatory drugs (NSAIDs), which are one of the therapeutic medicines for Behçet's disease, are well known to have renal toxicity (Adams et al. 1986). Urinary β2-microglobulin is a common marker of renal dysfunction (Argyropoulos et al. 2017), particularly tubulointerstitial nephritis (Statius van Eps and Schardijn 1984), and may be an important marker of the kidney involvement in Behçet's disease. We report a patient with Behçet's disease, who showed extremely high levels of urinary β2-microglobulin, indicating that renal dysfunction should be carefully monitored in patients with Behçet's disease.

Case Presentation

A 43-year-old man visited our hospital for a rash, fever, and joint pain for two months. His past medical history included hypertension, hypercholesterolemia, and migraine. Before he visited the hospital, he was prescribed with naproxen (NSAID) for 7 weeks and levofloxacin (antibiotic) for a few days because of a sore throat, cough, and joint pain at a local clinic. His symptoms did not improve with these medications. His highest body temperature was 40.7°C. During the clinical course, reverse transcription-polymerase chain reaction testing for severe acute respiratory syndrome coronavirus 2 was negative twice. At admis-

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sion he presented with oral aphthae, bilateral joint pain in the knees and ankles, erythema nodosum, skin pustules, headache, and fever. Fortunately, no uveitis was observed. The vital signs at admission were a body temperature of 37.8°C, blood pressure of 148/83 mmHg, a regular heart rate of 100 beats per min and a regular respiration rate of 24 breaths per min. The results of blood and urinary analyses on admission are presented in the Table 1. Remarkably abnormal data include C-reactive protein (CRP) of 12.06 mg/dL, serum amyloid A (SAA) of 1,940 μg/mL (reference range: 0.0-8.0), erythrocyte sedimentation rate (ESR; 1 h) of 41 mm/h, and ESR (2 h) of 52 mm/2h, and urinary red blood cells (RBC) of > 100/high power field (hpf). A skin biopsy from the lower limb revealed neutrophil infiltration in adipose tissue, indicating the presence of erythema nodosa (Fig. 1). The summary of these findings led to the diagnosis of Behçet's disease.

The high level of urinary β2-microglobulin of 14,800 μg/L (reference range: 200-300) detected in the urine was surprising, particularly because the serum creatinine levels were normal. After admission, the NSAID was ceased and colchicine was administered, and the urinary β2-microglobulin level went down to 139 μg/L. The urinalysis also showed that both the urine occult blood and protein were decreased from (1+) and (3+) to (+/−) and (+/−), respectively, along the clinical time course. This led to the speculation that tubulointerstitial nephritis had developed secondary to NSAID use along with the constitutional

Table 1. The results of blood and urinary analyses.

		On admission	Reference range
Blood analysis	White blood cells (10^3/mL)	3.1	3.3-8.6
	Neutrophils (%)	78.9	47-70
	Eosinophils (%)	0	1-5
	Basophils (%)	0	0-1
	Lymphocytes (%)	12	20-40
	Monocytes (%)	8.9	1-10
	Red blood cells (10^6/mL)	5.02	4.35-5.55
	Hemoglobin (g/dL)	14.8	13.7-16.8
	Hematocrit (%)	45	40.7-50.1
	Platelets (10^3/mL)	477	317-353
	Blood urea nitrogen (mg/dL)	10	3.7-7.8
	Serum creatinine (mg/dL)	0.9	0.65-1.07
	eGFR (mL/min/1.73m^2)	74	90 <
	Aspartate aminotransferase (U/L)	41	13-30
	Alanine aminotransferase (U/L)	101	10-42
	γ-glutamyl transpeptidase (U/L)	70	13-64
	Sodium (mmol/L)	140	138-145
	Potassium (mmol/L)	4.6	3.6-4.8
	Cloride (mmol/L)	99	101-108
	Calcium (mg/dL)	9.7	8.8-10.4
	C-reactive protein (mg/dL)	12.06	0.00-0.14
	Serum amyloid A (mg/L)	1,940	0-8.0
	ESR 1h (mm)	41	2-10
	ESR 2h (mm)	52	5-25
	IgG (mg/dL)	886	861-1747
	IgA (mg/dL)	318	93-393
	IgM (mg/dL)	41	33-183
	Rheumatoid factor (IU/mL)	14	0-15
	Ani-nuclear antibody	× 40	0-39
Urinary analysis	Glucose	negative	negative
	Protein (mg/dL)	56	0-15
	pH	5.5	4.5-7.5
	Red blood cells (/hpf)	> 100	< 1
	White blood cells (/hpf)	< 1	1-4
	Epithelial cast (/hpf)	< 1	5-9

renal dysfunction caused by Behçet's disease (Fig. 2).

The patient was treated with colchicine (1 mg/day), and his oral aphthae, fever, and joint pain dramatically improved. In addition, his CRP decreased to 0.54 mg/dL resulting in discharge from the hospital. Written consent was obtained from the patient for publication. This report was approved by the ethical board of Tohoku Medical and Pharmaceutical University.

Discussion

Renal dysfunction is reported to be more common in Behçet's disease than previously indicated (Akpolat et al. 2002; Zheng et al. 2015; Ozel et al. 2016; Leonard et al 2018). Renal involvement in Behçet's disease is reported to result from renal amyloidosis, IgA nephropathy, crescentic glomerulonephritis, or focal segmental glomerulosclerosis (Leonard et al. 2018). In these conditions, amyloidosis is considered to be an important prognostic factor affecting survival (Akpolat et al. 2002). Contrastingly, renal biopsy in 5 patients with Behçet's disease resulted in one minor glomerular lesion, one mild mesangial proliferative glomerulonephritis and one chronic tubular-interstitial nephropathy, and two IgA nephropathy (Zheng et al. 2015). Because the serum IgA was not significantly high in the present case (318 mg/dL) and the urinary β2-microglobulin levels are not extremely high in common IgA nephropathy, which is a primary glomerular disease, it is considered that IgA nephropathy is not highly likely in this case. In addition, we consider that allergic interstitial nephritis is also unlikely in this case because eosinophilia was not observed (eosinophils 0%). The extremely high level of urinary β2-microglobulin was obtained at a few days after the administration of levofloxacin, in other words, the duration of the administration of naproxen was much longer than that of levofloxacin. Therefore, we consider that tubulointerstitial nephritis is caused by the NSAID more likely than by levofloxacin. On the other hand, naproxen was discontinued on the 3rd day after the admission and urinary β2-microglobulin drastically decreased after the administration of colchicine. Thus, it is considered that the increase in urinary β2-microglobulin was induced by both the administration of NSAID and Behçet's disease itself. It was also reported that the renin-angiotensin-aldosterone

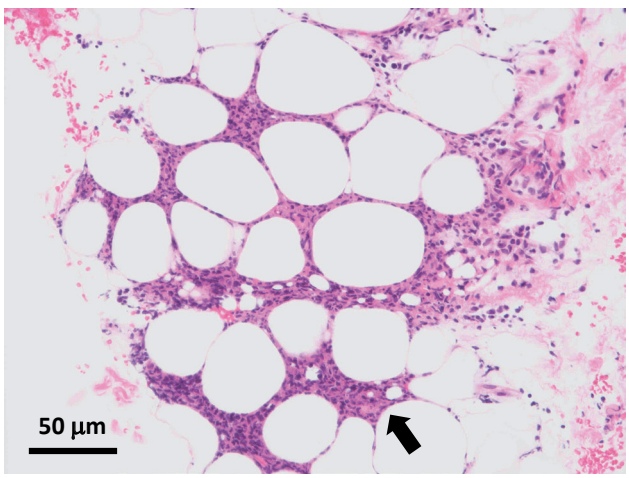

Fig. 1. A photomicrograph of skin biopsy from the lower limb. The photomicrograph shows neutrophil infiltration in adipose tissue (indicated by the arrow), indicating the presence of erythema nodosa.

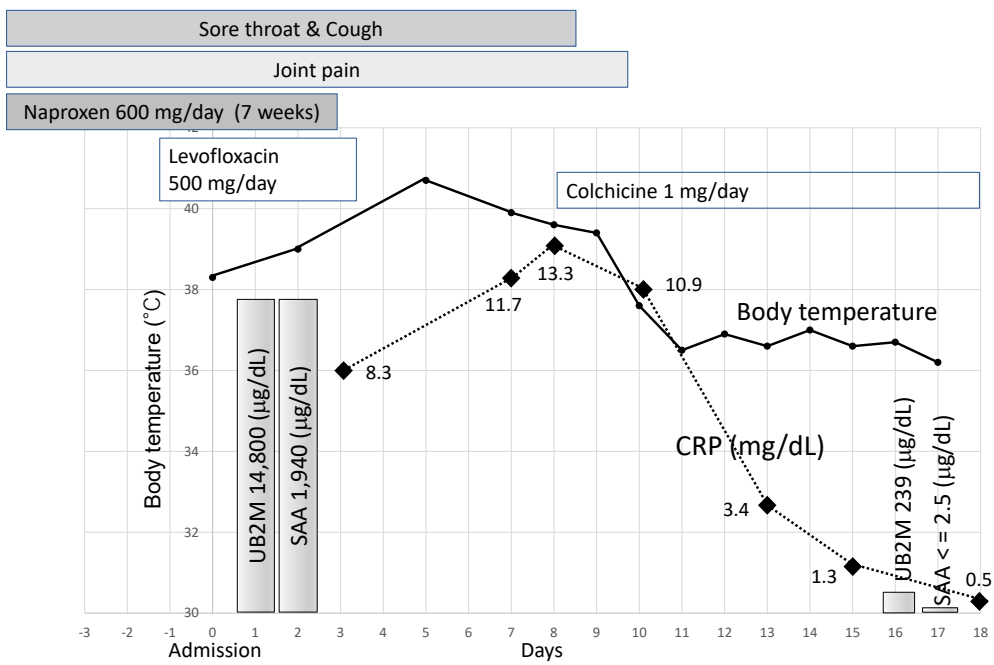

Fig. 2. Clinical time course of the patient.
It includes major symptoms, body temperature, C-reactive protein (CRP), urinary β macroglobulin (UBMG), serum amyloid A (SAA) and medications.

cascade was activated in Behçet's disease by the vascular changes, including renal artery constriction and decreased renal blood flow (Ozel et al. 2016).

*β*2-microglobulin, a low molecular weight protein, is thought to maintain serum albumin levels, and aid in albumin reuptake from tubular fluid through the neonatal Fc receptor (Argyropoulos et al. 2017). In addition, *β*2-microglobulin is an important molecule in evaluating the re-absorptive capacity of the renal proximal tubule (Statius van Eps and Schardijn 1984). Because proximal tubular dysfunction with disturbance of tubular reabsorption is characterized by elevated urinary *β*2-microglobulin, this molecule is viewed as a predictor of renal function and clinical outcomes (Provencher et al. 2018). Contrastingly, some nephrologists support *β*2-microglobulin as a marker of tubular pathology and glomerular dysfunction because serum *β*2-microglobulin levels and glomerular filtration rate exhibit some positive correlation (Shea et al. 1981; Argyropoulos et al. 2017). Sahin et al. (2004) reported that renal injury, based on urinary *β*2-microglobulin levels and albuminuria, was more frequent in Behçet's disease patients than has been recognized. The frequency of microalbuminuria and abnormal urinary *β*2-microglobulin excretion tended to be higher among Behçet's disease patients. Therefore, microalbuminuria and abnormal urinary *β*2-microglobulin excretion could be sensitive markers of renal dysfunction. Renal function in Behçet's disease patients could also be affected by NSAID use, as demonstrated in this case, although the effect of NSAID on urinary *β*2-microglobulin has not been precisely documented.

In conclusion, routine screening tests with urinalysis including urinary *β*2-microglobulin and microalbumin, in addition to serum creatinine, should be recommended for the early diagnosis of renal dysfunction in patients with Behçet's disease especially in patients prescribed with NSAID. We consider that drug-induced nephrotoxicity in most cases is supposed to be associated with urinary markers, which are useful to detect abnormality in the early stage. Moreover, this report indicates that colchicine may be a beneficial treatment in these Behçet's disease patients with renal dysfunction.

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Conflict of Interest

The authors declare no conflict of interest.

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