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Rapid Clinical Improvement of Multicentric Castleman Disease (MCD) with Renal Involvement Following Treatment with Tocilizumab: AA Amyloidosis as a Possible Renal Involvement of MCD

Jumpei Temmoku,[1] Tomomi Sasajima,[2] Takeshi Kuroda,[3] Yuya Sumichika,[1] Kenji Saito,[1] Shuhei Yoshida,[1] Haruki Matsumoto,[1] Yuya Fujita,[1] Naoki Matsuoka,[1] Tomoyuki Asano,[1] Shuzo Sato,[1] Toshiyuki Yamada,[4] Yuko Hashimoto[5] and Kiyoshi Migita[1]

[1]Department of Rheumatology, Fukushima Medical University School of Medicine, Fukushima, Fukushima, Japan
[2]Department of Rheumatology, Fukushima Rosai Hospital, Iwaki, Fukushima, Japan
[3]Department of Rheumatology and Nephrology, Niigata University Graduate School of Medical and Dental Sciences, Niigata, Niigata, Japan
[4]Department of Clinical Laboratory Medicine, Jichi Medical University, Shimotsuke, Tochigi, Japan
[5]Department of Pathology, Fukushima Medical University School of Medicine, Fukushima, Fukushima, Japan

Castleman disease (CD) is a lymphoproliferative disorder that manifests as hypergammaglobulinemia and severe inflammation with multiorgan involvement. However, renal involvement has been infrequently described in CD. We present a case of a 63-year-old Japanese male patient with multicentric CD (MCD) in whom kidney involvement, including impaired renal function and massive proteinuria, is present. He had a 2-year history of inflammatory arthritis and was referred to our clinic with newly developed proteinuria, renal dysfunction, and elevated levels of acute-phase proteins. Abdominal computed tomography scan revealed hepatosplenomegaly, including mesenteric and inguinal lymph node enlargements. The patient underwent inguinal lymph node resection. Excisional biopsy of the inguinal lymph node showed multiple lymphoid follicles and expansion of interfollicular areas by marked plasmacytosis consistent with mixed type CD. The patient was diagnosed with human herpes virus 8-negative MCD according to the international diagnostic criteria for CD. Diagnostic renal biopsy was not performed following the medical viewpoint. Tocilizumab (TCZ) treatment was highly effective in reducing proteinuria and stabilizing renal function, as well as improving other clinical symptoms. The patient responded to TCZ treatment, and the renal involvement was rapidly improved. Our preliminary immunohistochemical analysis indicated AA amyloid deposits in urinary epithelial cells suggesting a possible renal involvement of AA amyloidosis. TCZ could potentially be one of the therapeutic options in patients with MCD with renal involvement.

Keywords: Castleman disease; renal involvement; tocilizumab
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Introduction

Castleman disease (CD) is clinically classified as unicentric CD in which the lesion is localized in only one region, and multicentric CD (MCD) in which the lesions are present in multiple regions (Waterston and Bower 2004; Li et al. 2019). Unicentric CD is localized in limited tissues and typically not accompanied by systemic symptoms. Resection of the affected lymph node is the gold standard for treating patients with unicentric CD. In contrast, MCD manifests with systemic symptoms, including fever, weight loss, anemia, hypergammaglobulinemia, and elevated levels of acute-phase reactants (Liu et al. 2016). MCD is often associated with human herpes virus 8 infection (Parravicini

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Correspondence: Kiyoshi Migita, M.D. Ph.D., Department of Rheumatology, Fukushima Medical University School of Medicine, 1 Hikarigaoka, Fukushima, Fukushima 960-1295, Japan.
e-mail: migita@fmu.ac.jp

et al. 2000); however, a significant proportion of Japanese patients have no known viral etiology (Murakami et al. 2020). Interleukin-6 (IL-6) has been identified as a target for MCD therapy because dysregulated overproduction of IL-6 has been implicated in the pathogenesis of MCD. Tocilizumab (TCZ), a humanized anti-human IL-6 receptor monoclonal antibody, has been reported to be effective in treating MCD (Nishimoto et al. 2000, 2005).

The majority of patients with MCD clinically presented with systemic manifestations, such as fever, peripheral lymphadenopathy, splenomegaly, polyclonal hypergammaglobulinemia, anemia, and thrombocytopenia (Liu et al. 2016). Although renal complications in MCD are infrequently reported, renal involvement can be accompanied in patients with MCD (El Karoui et al. 2011; Landeiro et al. 2021). Here, we present a case of MCD in whom kidney involvement was successfully managed by TCZ treatment. Although renal biopsy could not be performed due to the patient's inability to hold his breath, immunohistochemical analysis suspected amyloid A (AA) depositions in urinary sediments. We presented the effects of anti-IL-6 receptor monoclonal antibody, TCZ, on this patient with MCT with renal involvement.

Case Presentation

A 63-year-old Japanese man was admitted to our hospital for further examination of the increased levels of acute-phase reactants with renal involvement, including proteinuria and renal dysfunction. At the age of 61, the patient had been diagnosed with inflammatory arthritis based on his articular symptoms with increased levels of C-reactive protein (CRP) and hypergammaglobulinemia. He was treated with low-dose prednisolone and adalimumab (anti-human tumor necrosis factor-α monoclonal antibody). However, his arthritis was not completely resolved, and the increased CRP levels had been sustained. His serum creatinine (s-Cr) level increased from 0.74 to 1.34 mg/dL. He was also suspected of generalized lymphadenopathy and hepatosplenomegaly, and referred to our hospital for further examinations.

The patient's height was 170 cm, and his body weight was 64 kg. His blood pressure, pulse rate, and body temperature were 129/83 mmHg, 95 beats/min, and 36.2°C, respectively. He occasionally experienced night sweats. Physical examination revealed diffuse lymphadenopathy, an enlarged spleen, and papulae on the body trunk. The laboratory data are presented in Table 1. The following were the laboratory findings: white cell count, 11,800/μL; hemoglobin, 9.1 g/dL; platelet count, 46.9 × $10^4/\mu$L; serum aspartate aminotransferase, 82 IU/L; alanine aminotransferase, 82 IU/L; total protein, 9.3 g/dL; albumin, 2.2; s-Cr, 1.79 mg/dL; PT-INR (prothrombin time-international normalized ratio), 1.26; APTT (activated partial thromboplastin time), 39.9 seconds (reference range, 26.9-38.1); fibrinogen, 476 mg/dL; CRP, 10.99 mg/dL (reference range, < 0.3); serum immunoglobulin (Ig)G, 3,633 mg/dL (reference range, 870-1,700); IgA, 1,431 mg/dL (reference range, 93-393); IgM, 41 mg/dL (reference range, 33-183); C3, 158 mg/dL (reference range, 73-138); and serum IL-6, 54.6 pg/mL (reference range, < 4.0). Autoantibodies, including antinuclear antibody, anti-double stranded-DNA (anti-ds-DNA), anti-Sm, anti-SSA, proteinase 3-anti-neutrophil cytoplasmic antibody (PR3-ANCA), and myeloperoxidase-ANCA (MPO-ANCA) were all negative. Although serum levels of IL-6 were elevated, M-protein was not noted in serum immunoelectrophoresis. Serum PCR for human herpesvirus-8 (HHV-8) were negative. Urinary protein excretion was 1.96 g daily.

Computed tomography scan revealed an intracortical, retroperitoneal tumor mass in his upper abdomen and enlarged inguinal lymph nodes (Fig. 1A, B). Pathological examination of the resected inguinal lymph node revealed the germinal center atrophy and interfollicular space enlargement with increased plasma cells (Fig. 2A, B). Immunohistochemistry against immunoglobulin light chains did not reveal monoclonality of kappa or lambda light chains. Few IgG4-positive cells were observed, and the IgG4/IgG ratio was < 0.05. These pathological findings were consistent with a diagnosis of MCD. Tissue biopsies of the duodenum and descending colon revealed no AA amyloid deposition by Congo red staining (Fig. 3). Based on the patient's symptoms and laboratory findings, he was diagnosed with idiopathic MCD according to the diagnostic criteria (van Rhee et al. 2018).

Renal biopsy is a significant procedure for identifying renal pathologies, including renal amyloidosis, which require immediate and appropriate treatment. However, it was difficult to perform due to the patient's inability to hold his breath. He was treated with intravenous TCZ (8 mg/kg, every 2 weeks). After treatment with TCZ, the patient's elevated levels of CRP or serum AA (SAA) returned to normal levels, and anemia and polyclonal gammopathy improved (Fig. 4). Furthermore, his urinary protein level reduced from 1.35 to 0.31 g/gCr. Finally, we evaluated whether AA amyloid depositions can be detected in urinary sediments. Seven ml of fresh urine before TCZ treatment was centrifuged at 1,500 r.p.m. for 10 min. The resultant pellet was re-suspended in 150 μl of phosphate-buffered saline (PBS) and 1-2 drops of the cell suspension was placed on a slide in the central area by cyto-centrifuge using cytospin (Cytospin 3, Shandon, UK). The cytosides were fixed in acetone for 5 min. The sample was incubated with the primary rat anti-AA monoclonal antibody (Yamada et al. 1997) at 1:100 dilution for 60 min. After washing, the slides were incubated with the secondary antibody (HRP-conjugated goat-anti-rat IgG) for 30 min followed by a final PBS washing step. The reactions were colored using 3,3′-diaminobenzidine (DAB). Positively stained tubular epithelial cells were suspected (Fig. 5). To determine the origin of these epithelia cell isolated from urinary sediments, we evaluated the expressions of the epithelial cell markers, using anti-Megalin (Motoyoshi et al. 2008) or

Table 1. Laboratory findings on admission.

Peripheral blood		Serological tests	
Red blood cells	3.30×10^6 /μL (3.86-4.92)	C-reactive protein	10.99 mg/dL (< 0.30)
Hemoglobin	9.1 g/dL (11.6-14.8)	IgG	3,633 mg/dL (870-1700)
Hematocrit	28.7% (35.1-44.4)	IgA	1,431 mg/dL (93-393)
Platelets	46.9×10^4 /μL (15.8-34.8)	IgM	41 mg/dL (33-183)
White blood cells	11.8×10^3/μL (3.3-8.6)	IgG4	265.6 mg/dL (11-121)
Neutrophil	78% (44-74)	C3	158 mg/dL (73-138)
Eosinophil	3% (0-6)	C4	31 mg/dL (11-31)
Monocytes	4% (1-14)	ANA	< 80 (< 80)
Lymphocytes	15% (20-50)	RF	7 IU/mL (0-15)
Basophil	0% (0-1)	Anti-ds-DNA Abs	2.1 U/mL (< 9.9)
Blood chemistry		Anti-SSA Abs	1.1 U/mL (< 6.9)
Total protein	9.3 g/dL (6.6-8.1)	Anti-SSB Abs	0.6 U/mL (< 6.9)
Total bilirubin	0.3 mg/dL (0.4-1.5)	MPO-ANCA	0.2 EU (0-3.5)
Albumin	2.2 g/dL (4.1-5.1)	PR3-ANCA	0.6 EU (0-2)
Aspartate aminotransferase	82 IU/L (13-30)	sIL-2R	1,105 U/mL (121-613)
Alanine aminotransferase	82 IU/L (10-42)	T-SPOT	negative
Lactate dehydrogenase	204 IU/L (124-222)	HHV-8-DNA (PCR)	$< 2.0 \times 10^2$
γ-Glutamyl transpeptidase	228 IU/L (13-64)	Interleukin-6	54.6 pg/mL (< 4.0)
Alkaline phosphatase	477 IU/L (106-322)	VEGF	563 pg/mL (143.1-658.8)
Creatine kinase	21 U/L (59-248)	Urinalysis	
Blood urea nitrogen	28 mg/dL (8-20)	pH	6
Creatinine	1.79 mg/dL (0.65-1.07)	Specific gravity	1.01
Sodium	124 mEq/L (138-145)	Protein	(2+)
Potassium	4.2 mEq/L (3.6-4.8)	Protein/creatinine	1.96 g/g creatinine
Chlorine	89 mEq/L (101-108)	Occult blood	(3+)
Glucose	101 mg/dL (73-109)	Bacteria	(-)
HbA1c	5.7% (4.9-6.0)	Red blood cells	> 100/HPF
Coagulation tests		White blood cells	10-19/HPF
PT-INR	1.26 (0.90-1.15)	Hyaline casts	50-99/WF
APTT	39.9 seconds (26.9-38.1)	Granular casts	20-29/WF
D-dimer	1.1 μg/mL (0-1.0)	β2-microglobulin	1.43 μg/ml
Fibrinogen	476 mg/dL (200-400)	N-acetyl-β-D-glucosaminidase	13.0 U/L

Reference values are shown in parentheses.
HbA1c, hemoglobin A1c; PT-INR, prothrombin time-international normalized ratio; APTT, activated partial thromboplastin time; Ig, immunoglobulin; C3, complement 3; C4, complement 4; ANA, anti-nuclear antibodies; RF, rheumatoid factor; Abs, antibodies; anti-ds-DNA, anti-double stranded-DNA; MPO-ANCA, myeloperoxidase-anti-neutrophil cytoplasmic antibodies; PR3-ANCA, proteinase 3-anti-neutrophil cytoplasmic antibodies; sIL-2R, soluble interleukin-2 receptor; T-SPOT, T-cell spot of tuberculosis test; HHV-8, human herpesvirus-8; VEGF, vascular endothelial growth factor; HPF, high-power field; WF, whole field.

anti-epithelial membrane antigen (EMA) antibodies (Helbert et al. 2001), in the urinary sediments isolated from a patient with active lupus nephritis. Although AA staining was not detected, Megalin and EMA were expressed in the epithelial cells isolated from the urinary sediments, suggesting that these cells originated from the proximal or distal renal tubular epithelial cells (Fig. 6).

Discussion

MCD is characterized by multiple regions of lymphadenopathy and systemic inflammatory symptoms, as well as organ dysfunction due to the overproduction of IL-6, which induces the elevations of acute-phase proteins, including SAA (Margeli et al. 2005; Liu et al. 2016). IL-6 is a pleiotropic cytokine that plays a pivotal role in the pathogenesis of idiopathic MCD. TCZ is an anti-human IL-6 receptor monoclonal antibody that blocks IL-6-mediated trans-signaling. TCZ improves the symptoms and biochemical abnormalities noted in MCD by inhibiting IL-6 (Song et al. 2010). MCD is characterized by systemic symptoms, including fever, weight loss, anemia, hypergammaglobulinemia, and hypoalbuminemia (Liu et al. 2016). Moreover, renal involvement can be implicated in patients with MCD. MCD-associated renal involvement is highly heterogeneous, including mesangial proliferative glomerulonephritis (El Karoui et al. 2011). Among these renal

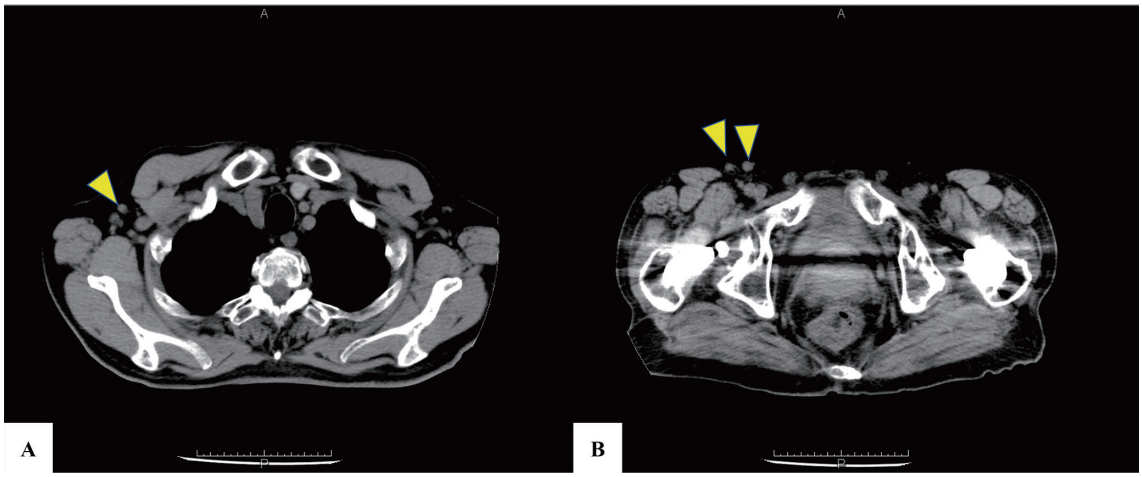

Fig. 1. Computed tomography (CT) findings on admission.
Chest and abdominal axial CT findings show swollen right axillary lymph nodes (A), and right inguinal lymph nodes (B).

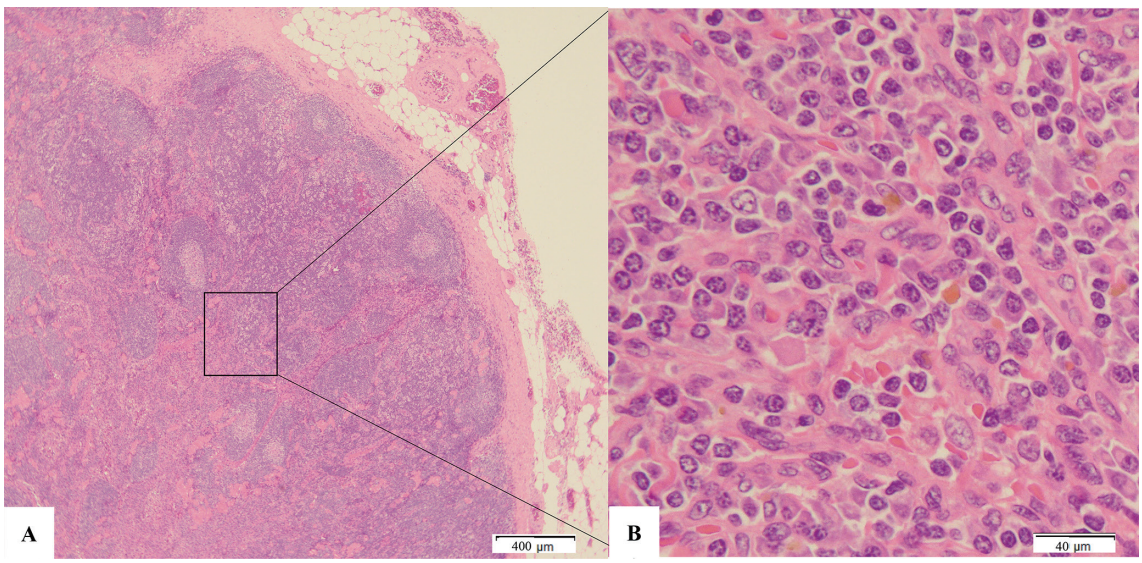

Fig. 2. Pathological findings of the resected right inguinal lymph node.
(A) Hematoxilin and eosin staining specimen shows marked atrophy of germinal center and relatively enlargement of mantle zone (× 40, bar = 400 μm). (B) Numerous plasma cells infiltration and hyper vascularity were observed in developed interfollicular space (× 400, bar = 40 μm).

manifestations, AA amyloidosis is the most serious renal complication (Lachmann et al. 2002; Bernabei et al. 2020). Amyloidosis is a systemic disorder characterized by the pathological accumulation of insoluble AA amyloid fibrils in the extracellular space of various tissues and organs leading to organ dysfunction (Papa and Lachmann 2018). AA amyloidosis is caused by the overproduction of the acute-phase protein, SAA, induced by inflammatory cytokines, such as IL-6 (Westermark et al. 2015).

We present the effects of an anti-IL-6 receptor monoclonal antibody, TCZ, on a Japanese patient with MCD associated with moderate renal manifestations. In this case, TCZ treatment was promising in reducing proteinuria and stabilizing renal function. Pathological evaluations for the kidneys are needed considering the significance of precise diagnosis and prognosis prediction (Lefaucheur et al. 2009). Renal biopsy is an important procedure for identifying renal pathologies, including renal amyloidosis, which require immediate and appropriate treatment (Bernabei et al. 2020); however, it could not be performed due to the inability of the patient to hold his breath.

The misfolded amyloid protein results in the generation of AA amyloid fibrils. Using electron microscopy and Congo red staining, the fibrils showed a characteristic appearance (Dember 2006). Previous studies have reported that amyloid fibrils are demonstrated in urinary sediments using electron microscopy in a patient with primary amyloidosis, indicating that this non-invasive method can be valuable in patients suspected with amyloidosis in whom renal biopsy cannot be performed (Shemer et al. 1979). We

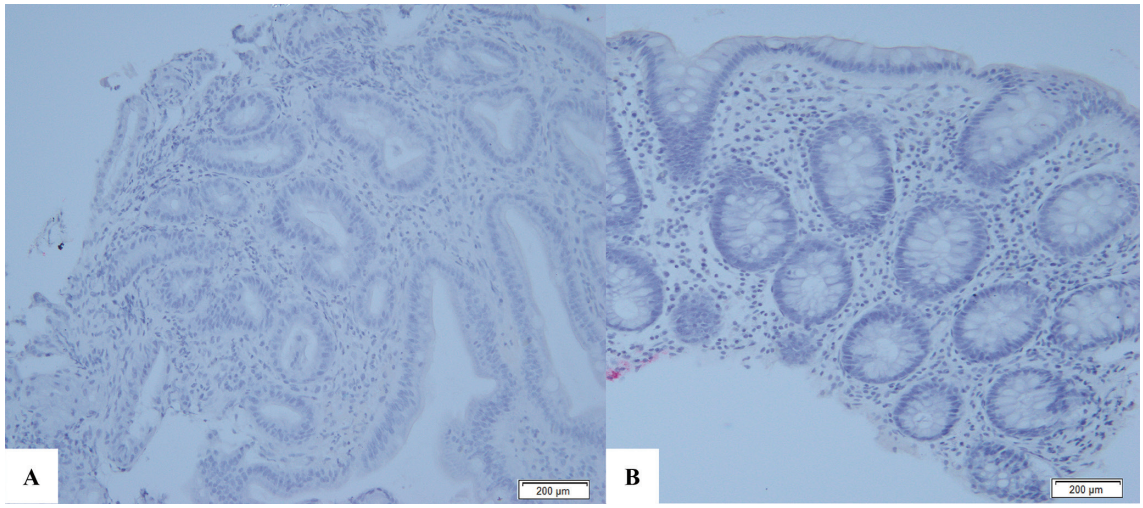

Fig. 3. Congo red staining of the mucosa in duodenum (A) and descending colon (B). There are no AA amyloid deposition using Congo red staining (× 200).

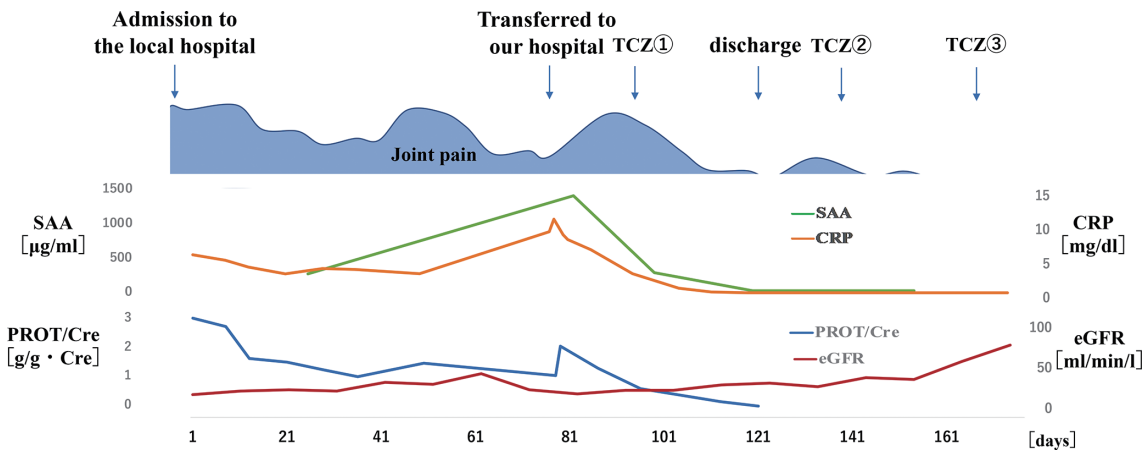

Fig. 4. Clinical course of 63-year-old Japanese male patient with multicentric Castleman disease (MCD). After treatment with TCZ, the patient's elevated levels of CRP or SAA returned to normal levels, and renal dysfunction improved. TCZ, tocilizumab; SAA, serum amyloid A; CRP, C-reactive protein; Prot/Cre, protein/creatinine ratio; eGFR, estimated glomerular filtration rate.

evaluated urinary sediments, and AA amyloid depositions in the epithelial cells isolated from the urine were suspected. Our preliminary evaluation of the urinary sediments suspected the presence of AA amyloid depositions in the tubular epithelial cells.

AA amyloidosis can lead to multiorgan dysfunction, including impaired renal function and proteinuria. Histological regression of amyloidosis in renal biopsy has rarely been reported in the literature; however, resolution of nephrotic syndrome has been demonstrated in MCD complicated with renal AA amyloidosis (Komaba et al. 2008; Iijima et al. 2015). It can be suggested that reversal of renal involvement could be attributable to the termination of acute-phase reactants, including SAA, as well as regression in amyloid deposition by blocking IL-6-mediated signals using TCZ. The presence of a close relationship between elevated IL-6 levels and SAA protein deposition suggests that IL-6 is critical for the development of AA amyloidosis in CD. In the mouse model of MCD, it was demonstrated that proteinuria was decreased following the reduction of circulating IL-6 levels (Suthaus et al. 2012; Ueda et al. 2013). In the clinical setting, IL-6 blockade has also been reported to decrease proteinuria in patients with AA amyloidosis (Lane et al. 2015). The management of AA amyloid kidney disease is primarily focused on targeting inflammatory cytokines, including IL-6, to stabilize GFR, reduce proteinuria, and delay potential progression to kidney failure (Thorne et al. 2022). IL-6-targeting agents, such as TCZ, may be promising in blocking IL-6 signaling and SAA-reducing effects in MCD. However, in the present case, amyloid deposition could not be evaluated using renal biopsy. A literature review of 64 cases with MCD revealed amyloidosis as the main pathological findings in kidney biopsy (39.1%) as well as other glomerular lesions, including thrombotic microangiopathy (TMA) or membranous proliferative glomerulonephritis were demonstrated (Xu et

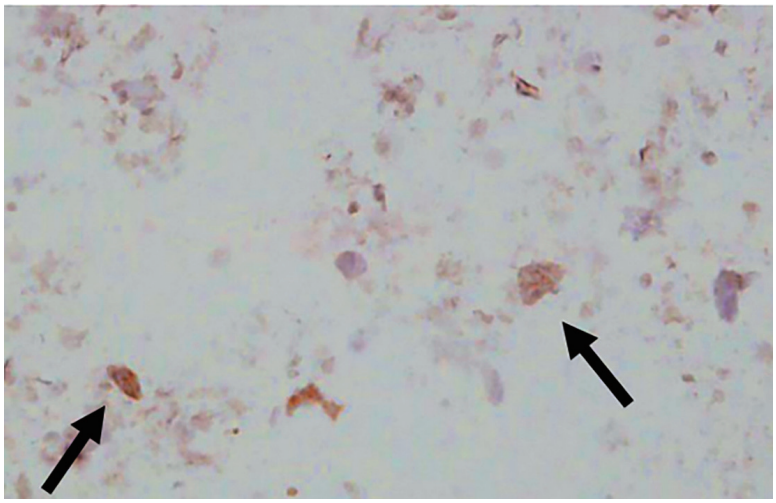

Fig. 5. AA amyloid staining using urine sediments.
Urine sediments were prepared using cytospin onto poly-l-lysine-coated slide and stained with rat anti-human AA monoclonal antibody (Yamada et al. 1997) at 1:100 dilution for 60 min. After washing with phosphate-buffered saline (PBS), secondary antibody (HRP-labeled goat anti-rat IgG, Dako, Santa Clara, CA, USA) was added for 30 min. The secondary antibody was visualized with hydrogen peroxide substrate and the 3,3′-diaminobenzidine tetrahydrochloride chromogen, which produces a brown precipitate readily detected by light microscopy. Slides were counterstained with hematoxylin and eosin. Positively stained tubular epithelial cells were suspected (× 400).

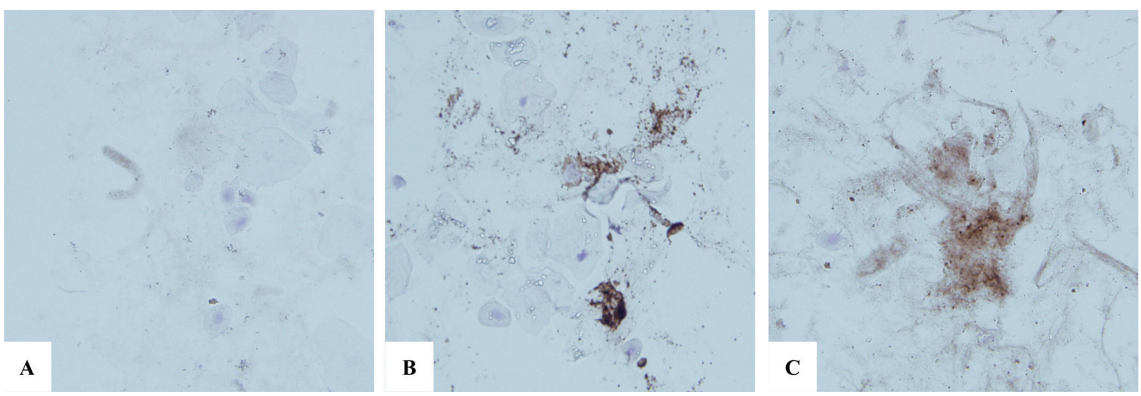

Fig. 6. Megalin and epithelial membrane antigen (EMA) expressions in urine sediments isolated from a patient with active lupus nephritis.
Urine sediments were prepared using cytospin onto poly-l-lysine-coated slide and stained with rat anti-human AA monoclonal antibody (A), anti-human Megalin antibody (B) (rabbit polyclonal antibody ab76969, abcam, Cambridge, UK) at 1:500 dilution, and anti-epithelial membrane antigen (EMA) antibody (C) (mouse monoclonal antibody, E29 Dako) at 1:100 dilution for 60 min. After washing with PBS, secondary antibodies (HRP-labeled goat anti-rat, rabbit or mouse IgG, Dako) were added for 30 min. The secondary antibody was visualized with hydrogen peroxide substrate and the 3,3′-diaminobenzidine tetrahydrochloride chromogen, which produces a brown precipitate readily detected by light microscopy. Slides were counterstained with hematoxylin and eosin.

al. 2012; Saiki et al. 2021). Additionally, clinical improvements of these glomerular lesions were demonstrated in TCZ-treated patients (Tosaki et al. 2021). Therefore, it is possible that in addition to AA amyloidosis these glomerular lesions may contribute to the renal manifestations seen in the present case.

In conclusion, the present case report showed that the blockade of IL-6 using TCZ was therapeutically effective for various MCD-associated renal manifestations, as well as improving other clinical symptoms related to MCD. These findings support the notion that IL-6 plays, either directly or indirectly, a central role in the pathogenesis of various MCD-related renal diseases.

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Conflict of Interest

The authors declare no conflict of interest.

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