Case Report

Interleukin-6 receptor inhibition with tocilizumab in various renal involvements associated with multicentric Castleman’s disease: a report of three cases

Hirotaka Komaba1, Takashi Nakazawa2, Yutaka Yamaguchi3, Shunichi Kumagai2 and Masafumi Fukagawa1

1Division of Nephrology and Kidney Center, 2Department of Clinical Pathology and Immunology, Kobe University School of Medicine, Kobe and 3Department of Pathology, Kashiwa Hospital, The Jikei University School of Medicine, Chiba, Japan

Abstract

Multicentric Castleman’s disease (MCD) is an inflammatory lymphoproliferative disorder characterized by polyclonal hypergammopathy and dysregulated overproduction of interleukin-6 (IL-6). A variety of renal involvements infrequently arise in patients with MCD. However, there is no established treatment for MCD and its associated renal involvements. We present the effects of an anti-IL-6 receptor monoclonal antibody, tocilizumab, on three patients with MCD associated with various renal manifestations. In all three patients, tocilizumab treatment was very effective in reducing proteinuria and stabilizing renal function, as well as improving other clinical symptoms. These findings indicate the pathological significance of IL-6 in renal involvements associated with MCD, and the potential use of tocilizumab in its treatment.

Keywords: anti-interleukin-6 receptor antibody; interleukin-6; multicentric Castleman’s disease; tocilizumab

Introduction

Castleman’s disease (CD), also known as angiofollicular lymph node hyperplasia, is an uncommon lymphoproliferative disorder characterized by benign lymphadenopathy and polyclonal hypergammopathy [1]. A multicentric form of CD (MCD) manifests systemically as fever, weight loss, anaemia, hypergammaglobulinaemia and hypoalbuminaemia. In addition, a variety of renal involvements infrequently arise in patients with MCD. However, there is no established treatment for MCD and its associated renal involvements.

Case reports

Patient 1

A 46-year-old man was admitted to our hospital because of general fatigue, and generalized lymphadenopathy. Seven years before admission, he had visited a local hospital because of tender, enlarged lymph nodes in the right inguinal region, for which surgical resection was performed. However, there was no improvement of the symptoms, and he was referred to our hospital for further investigation. On admission, the serum creatinine level was 0.65 mg/dL, blood urea nitrogen was 10 mg/dL, haemoglobin was 10.8 g/dL, total serum protein was 11.0 g/dL, serum albumin was 2.0 g/dL, and C-reactive protein (CRP) was 8.8 mg/dL. Urine analysis showed microhaematuria and proteinuria of 1.0 g/24 h. Serum protein electrophoresis results showed a polyclonal gammopathy with an increased level of IgG of 6070 mg/dL (IgG1, 62%; IgG2, 23%; IgG3, 4% and IgG4, 11%). Serum IL-6 was markedly elevated to 23.8 pg/mL. Collagen vascular disease workup was negative. We re-examined the specimens of the lymph nodes sent from the local hospital, which was compatible with the mixed type of CD.

The renal biopsy showed a slightly thickened glomerular basement membrane with a bubbly appearance, as observed by periodic acid–Schiff–methenamine silver staining (Figure 1A). There was also a mild increase in mesangial matrix and cellularity. There was focal interstitial nephritis...
with infiltration of plasma cells and lymphocytes. Of note, the perirenal adipose capsule was dominated by massive infiltration of plasma cells and lymphocytes, showing follicle-like lymphoid strictures with interfollicular neovascularization (Figure 1B). An immunofluorescence study showed IgG2 deposits along the capillary wall (Figure 1C). Electron microscopy showed numerous scattered subepithelial and intramembranous deposits (Figure 1D). These findings were consistent with membranous nephropathy (MN) associated with renal and perirenal plasma cell infiltration.

He was treated with prednisolone 30 mg/day, but his symptoms and biochemical abnormalities were not improved. We, therefore, started intravenous tocilizumab 8 mg/kg every 2 weeks. After 2 months of treatment, anaemia, hypoaalbuminaemia, elevation of CRP and polyclonal gammopathy were all improved. Furthermore, his urine protein level decreased to <0.5 g/24 h (Figure 2). Prednisolone therapy could be discontinued without exacerbation. He has been doing well with slight proteinuria and stable renal function.

Patient 2
A 53-year-old man was admitted to our hospital for evaluation of anaemia and generalized lymphadenopathy. He had been diagnosed with diabetes mellitus 5 years ago, which was well managed with glibenclamide. On admission, the serum creatinine level was 1.47 mg/dL, blood urea nitrogen was 19 mg/dL, haemoglobin was 9.5 g/dL, total serum protein was 12.9 g/dL, serum albumin was 1.7 g/dL and CRP was 13.7 mg/dL. Urine analysis showed microhaematuria and proteinuria of 2.6 g/24 h. Serum protein electrophoresis results showed a polyclonal gammopathy with an increased level of IgG of 8680 mg/dL. Serum IL-6 was markedly elevated to 62.2 pg/mL. Collagen vascular disease workup was negative. There was no evidence of diabetic retinopathy or neuropathy. Histological findings of the right inguinal enlarged lymph nodes were compatible with the plasma cell type of CD.

The renal biopsy showed 10 glomeruli, 3 of which exhibited global sclerosis. The remaining glomeruli showed diffuse mesangial stalk thickening and hyalinosis of both afferent and efferent arterioles. There was patchy infiltration of plasma cells and lymphocytes in the interstitium (Figure 1E). The immunofluorescence study showed no significant staining of glomeruli. Electron-dense deposits were absent. The biopsy findings were compatible with interstitial nephritis associated with plasma cell infiltration, superimposed on pre-existing early diabetic glomerulosclerosis.

He was treated with 8 mg/kg tocilizumab intravenously every 2 weeks without concomitant immunosuppression.
Within 3 months of treatment, his anaemia, hypoalbuminaemia, inflammation and polyclonal gammapathy were all improved. Furthermore, serum creatinine and proteinuria decreased to 1.12 mg/dL and 0.4 g/24 h, respectively (Figure 2). He has been free of symptoms with stabilized renal function for 1 year while maintained on tocilizumab treatment.

**Patient 3**

A 54-year-old woman was admitted to our hospital because of general fatigue, chronic inflammation and generalized lymphadenopathy over 10 years. On admission, the serum creatinine level was 1.00 mg/dL, blood urea nitrogen was 16 mg/dL, haemoglobin was 10.0 g/dL, total serum protein was 10.1 g/dL, serum albumin was 3.0 g/dL and CRP was 5.9 mg/dL. Urine analysis showed microhaematuria and proteinuria of 1.7 g/24 h. Serum protein electrophoresis results showed a polyclonal gammapathy with an increased level of IgG of 4800 mg/dL. The antinuclear antibody was positive at 1/80. Serum IL-6 was elevated to 20.4 pg/mL. Histological findings of the left inguinal lymph nodes were compatible with the plasma cell type of CD. The renal biopsy showed marked amyloid deposits in the glomeruli and vascular walls (Figure 1F). The immunofluorescence study showed no significant staining of glomeruli.

She was treated with prednisolone 15–20 mg/day as an outpatient, but biochemical abnormalities, including proteinuria, were not improved. She was then treated with 8 mg/kg tocilizumab intravenously every 2 weeks. Surprisingly, she achieved complete remission only after 1 month of tocilizumab treatment. Within 3 months of treatment, her anaemia, hypoalbuminaemia, inflammation and polyclonal gammapathy were improved. Renal function remained stable (Figure 2). Prednisolone therapy was discontinued without exacerbation. She has been free of symptoms, with stabilized renal function.

**Discussion**

Renal histopathological lesions associated with CD are very heterogeneous, including mesangial proliferative glomerulonephritis [4], membranoproliferative glomerulonephritis...
Here, we report three patients with various MCD-related renal diseases, i.e., MN, interstitial nephritis with plasma cell infiltration and renal amyloidosis. Our experience with tocilizumab treatment and recent insight into the pathological roles of IL-6 led to the hypothesis that this cytokine also contributes, either directly or indirectly, to the development of various renal involvements.

The direct action of IL-6 on renal involvements has been suggested in experimental studies. IL-6 regulates mesangial cell growth in an autocrine manner [8], and IL-6 transgenic mice develop mesangial proliferative glomerulonephritis and plasma cell infiltration [9]. These findings suggest that IL-6 plays a central role in these types of nephritis. In addition, overproduction of IL-6 may also induce plasma cells to infiltrate the kidneys, thereby leading to interstitial nephritis. A longstanding overproduction of the serum amyloid A protein induced by IL-6 may result in renal amyloidosis. Furthermore, excessive expression of IL-6 also causes the production of vascular endothelial growth factor (VEGF). The pathogenic role of VEGF in renal involvements remains unknown [5]; however, given that tight regulation of VEGF signalling is critical for maintenance of the glomerular filtration barrier, local or systemic VEGF overproduction seems causative rather than protective.

Other pathogenic factors associated with IL-6 overproduction, such as polyclonal hypergammopathy and a variety of autoantibodies, may also be involved in the pathogenesis of CD-related renal diseases. In this regard, the distribution pattern of IgG subclasses in MN is interesting; it has been shown to be biased towards IgG4 in idiopathic MN and IgG3 in lupus-related MN [10]. In our case of MN associated with MCD (Patient 1), IgG2 was the only positive subclass in the glomeruli, despite its low circulating level. Although the pathogenic role of IgG2 is unknown, this finding may suggest that our case of MN is a manifestation secondary to MCD, rather than a coincidental occurrence of idiopathic MN.

The present case studies showed that blockade of IL-6 by tocilizumab was therapeutically effective for various renal involvements associated with MCD, 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. Of note, Patient 3, who had severe renal amyloidosis, achieved complete remission of proteinuria only after 1 month of treatment. Because insoluble amyloid depositions were unlikely to be cleared in such a short time, we surmise that IL-6R inhibition may have directly restored glomerular capillary permeability, resulting in remission of proteinuria. Indeed, complete remission of nephrotic syndrome can be achieved after the removal of localized CD but without histological regression in renal amyloidosis [7].

In conclusion, tocilizumab is a very promising treatment for various renal involvements associated with MCD. This study also indicated the pathological significance of IL-6 in various renal involvements in CD. The response to tocilizumab for other renal diseases is also of interest. Further clinical studies are needed to better evaluate the role of tocilizumab in the treatment of renal diseases associated with IL-6 overproduction.

Acknowledgements. The authors thank Dr G. Tsuji, Dr H. Hayashi, Dr A. Abe and Dr N. Yamana for thoughtful discussions, and all colleagues who recorded medical information and performed renal biopsies.

Conflict of interest statement. None declared.

References

1. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymph node hyperplasia resembling thymoma. Cancer 1956; 9: 822–830
2. Nishimoto N, Kishimoto T. Interleukin 6: from bench to bedside. Nat Clin Pract Rheumatol 2006; 2: 619–626
3. Nishimoto N, Kanakura Y, Aozasa K et al. Humanised anti-interleukin-6 receptor antibody treatment of multicentric Castlemans disease. Blood 2005; 106: 2627–2632
4. Lui SL, Chan KW, Li FK et al. Castleman’s disease and mesangial proliferative glomerulonephritis: the role of interleukin-6. Nephron 1998; 78: 323–327
5. Seida A, Wada J, Morita Y et al. Multicentric Castleman’s disease associated with glomerular microangiopathy and MPGN-like lesion: does vascular endothelial cell-derived growth factor play causative or protective roles in renal injury? Am J Kidney Dis 2004; 43: E3–E9
6. Frokjaer Thomsen O, Ladefoged J. Castleman’s disease with renal infiltration by polyclonal plasma cells. Clin Nephrol 1998; 49: 328–330
7. Keven K, Nergizoglu G, Ates K. Remission of nephrotic syndrome after removal of localized Castelman’s disease. Am J Kidney Dis 2000; 35: 1207–1211
8. Ruef C, Budde K, Lacy J et al. Interleukin 6 is an autocrine growth factor for mesangial cells. Kidney Int 1990; 38: 249–257
9. Brandt SJ, Bodine DM, Dunbar CE et al. Dysregulated interleukin 6 expression produces a syndrome resembling Castleman’s disease in mice. J Clin Invest 1990; 86: 592–599
10. Haas M. IgG subclass deposits in glomeruli of lupus and nonlupus membranous nephropathies. Am J Kidney Dis 1994; 23: 358–364

Received for publication: 13.9.08
Accepted in revised form: 16.9.08