CASE REPORT

Successful Treatment of a Mesangial Proliferative Glomerulonephritis with Interstitial Nephritis Associated with Castleman’s Disease by an Anti-interleukin-6 Receptor Antibody (Tocilizumab)

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Abstract

We report a case of mesangial proliferative glomerulonephritis with interstitial nephritis associated with multicentric Castleman’s disease (MCD) successfully treated with an anti-interleukin-6 receptor antibody (tocilizumab). This mesangial proliferative glomerulonephritis with interstitial nephritis was resistant to methylprednisolone treatment; however, it was markedly improved with tocilizumab, which was administered intravenously at a dose of 8 mg/kg every 2 weeks. These results suggest that tocilizumab is effective for the treatment of mesangial proliferative glomerulonephritis with interstitial nephritis associated with MCD.

Key words: multicentric Castleman’s disease, mesangial proliferative glomerulonephritis, interstitial nephritis, tocilizumab

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Introduction

Castleman’s disease (CD), or angiofollicular lymph node hyperplasia, is a nonmalignant lymphoproliferative disorder (1). Clinically, CD can be categorized into two types: unicentric (UCD) and multicentric (MCD) (2). Histologically, it is classified into three variants: hyaline vascular type seen in 90% of CD, plasma cell type and a mixed type (2). MCD is usually associated with plasma cell type and mixed type (2). Renal complications are uncommon in MCD; however, they show various lesions including minimal change disease, membranous nephropathy, membranoproliferative glomerulonephritis, mesangial proliferative glomerulonephritis, thrombotic microangiopathy, interstitial nephritis and amyloidosis (3-7). Excess IL-6 production by hyperplastic lymph nodes is thought to play a central role in the pathogenesis of MCD and manifestations including renal complications (8). Several studies have reported that an anti-interleukin-6 receptor antibody (tocilizumab) is effective for MCD including several types of renal complications (5, 9); however, the effect of tocilizumab on mesangial proliferative glomerulonephritis with interstitial nephritis remains to be determined.

Case Report

A 57-year-old man exhibited anemia and mild reticular opacity of bilateral lung fields on chest radiography in a medical checkup. Upon further examination at a hospital, blood analysis showed that the C-reactive protein (CRP) level was increased to 8.7 mg/dL, hemoglobin (Hb) level was decreased to 9.2 g/dL, blood urea nitrogen (BUN) level was increased to 22 mg/dL and creatinine (Cr) level was increased to 2.4 mg/dL. Urinalysis showed proteinuria (2+) and hematuria (+), and urinary sediments showed red blood cells (10-15/field). Mild linear and reticular opacity on bilateral lung fields and enlargement of the cervical, supraclavicular, axillary, hilar, mediastinal and inguinal lymph nodes were detected by computed tomography. No neurological

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abnormality was detected. Serum protein electrophoresis results showed a polyclonal gammopathy with an increased level of IgG of 5,686 mg/dL. Plasma interleukin-6 (IL-6) level was markedly increased to 25.9 pg/mL. Plasma anti-β2 microglobulin (β2 MG, 3,578 μg/L).

Plasma IL-6 level increased to 1,270 pg/mL at 2 months and decreased to 597 pg/mL at 5 months after tocilizumab treatment. The overproduction of IL-6 in germinal centers of the hyperplastic lymph node was thought to contribute to the development of mesangial proliferative glomerulonephritis associated with MCD (8). IL-6 is reported to act directly on cultured mesangial cell growth (10). In addition, IL-6 transgenic mice have been shown to develop mesangial proliferative glomerulonephritis and plasma cell infiltration (11). These results suggested that overproduction of IL-6 contributed to both mesangial proliferative glomerulonephritis and interstitial nephritis with the infiltration of plasma cells. Although we estimated renal disease activity on the basis of observation by light microscopy, the investigation of immunoperoxidase staining in infiltrated plasma cells and vascular endothelial growth factor (VEGF) level in plasma, infiltrated plasma cells and glomeruli, which were reported to be associated with disease activity, might have provided more information if they had been performed (12, 13). Since no neurological abnormality was detected, we diagnosed the present case as not categorized in POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal-protein and skin changes) syndrome, which was defined as abnormal plasma cell proliferation and polyneuropathy (14).

In a review, Xu et al. stated that amyloidosis, thrombotic microangiopathy and membranoproliferative glomerulonephritis were observed at high levels (10-55%) as renal diseases associated with MCD (7). They also stated that mesangial proliferative glomerulonephritis, interstitial nephritis and membranous nephropathy were less commonly observed (<10%) renal diseases associated with MCD (7). Tocilizumab was reported to be effective for MCD including several renal complications (5, 9). Komaba et al. reported that tocilizumab was also effective for membranous nephropathy, interstitial nephropathy and amyloidosis associated with MCD (5). The results of the present case study suggested that tocilizumab was also effective for mesangial proliferative glomerulonephritis and interstitial nephritis associated with MCD was diagnosed on the basis of renal histological analysis. Although the patient showed remission in clinical symptoms, lung disease, lymphadenopathy and in biochemical abnormalities such as CRP level, Hb level and polyclonal gammopathy, we decided to continue with tocilizumab for mesangial proliferative glomerulonephritis with interstitial nephritis associated with MCD. Two months after renal biopsy, renal functions were improved as follows: Cr level, 1.1 mg/dL; urine occult blood (-); proteinuria, 0.1 g/day; urine NGA level, 10 U/L; and urine β2 MG, 3,578 μg/L. Plasma IL-6 level increased to 1,270 pg/mL at 2 months and decreased to 597 pg/mL at 5 months after tocilizumab treatment.

Discussion

We showed a therapeutic effect of tocilizumab for mesangial proliferative glomerulonephritis with interstitial nephritis associated with MCD, which was resistant to methylprednisolone treatment. The overproduction of IL-6 in germinal centers of the hyperplastic lymph node was thought to contribute to the development of mesangial proliferative glomerulonephritis associated with MCD (8). IL-6 is reported to act directly on cultured mesangial cell growth (10). In addition, IL-6 transgenic mice have been shown to develop mesangial proliferative glomerulonephritis and plasma cell infiltration (11). These results suggested that overproduction of IL-6 contributed to both mesangial proliferative glomerulonephritis and interstitial nephritis with the infiltration of plasma cells. Although we estimated renal disease activity on the basis of observation by light microscopy, the investigation of immunoperoxidase staining in infiltrated plasma cells and vascular endothelial growth factor (VEGF) level in plasma, infiltrated plasma cells and glomeruli, which were reported to be associated with disease activity, might have provided more information if they had been performed (12, 13). Since no neurological abnormality was detected, we diagnosed the present case as not categorized in POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal-protein and skin changes) syndrome, which was defined as abnormal plasma cell proliferation and polyneuropathy (14).
with MCD because, in addition to hematuria and proteinuria, tubular interstitial damage markers such as urine NAG and β2 MG level were decreased by tocilizumab treatment. Komaba et al. reported that the urinary protein level was reduced in association with a decreased level of CRP at one month after tocilizumab treatment in a case of membranous nephropathy, interstitial nephritis and amyloidosis associated with MCD (5). In the present case study, renal complications started to improve at 3 months after tocilizumab treatment, although clinical symptoms, lymphadenopathy and other laboratory values such as CRP level, Hb level and polyclonal gammopathy were improved at 1 week after start of tocilizumab treatment. This delayed response of renal complications of MCD in this case may be explained by the fact that mesangial proliferative glomerulonephritis with interstitial nephritis associated with MCD may need comparatively long-term treatment to improve with tocilizumab treatment compared with membranous nephropathy, interstitial nephropathy and amyloidosis. The plasma IL-6 level increased and subsequently decreased after tocilizumab treatment in this patient. Nishimoto et al. reported that increase in IL-6 with tocilizumab treatment in MCD may explain that IL-6 receptor (IL-6R)-mediated consumption of IL-6 was inhibited by the unavailability of complex of tocilizumab and IL-6R (15). They also reported that the decrease in IL-6 during tocilizumab treatment may therefore indicate disease remission (15). These lines of evidence suggested that the time course of plasma IL-6 level in the present patient demonstrated the effectiveness of tocilizumab and it may be a good marker for monitoring the effect of tocilizumab treatment for mesangial proliferative glomerulonephritis with interstitial nephritis associated with MCD. Although the long-term side effects of tocilizumab are not fully understood, it may affect the immune system leading to the development of infection (16). Therefore, further careful and long-term observations will be necessary to evaluate the treatment effects and side effects of tocilizumab for renal complications associated with MCD.

In conclusion, tocilizumab was effective for mesangial proliferative glomerulonephritis with interstitial nephritis associated with MCD.

The authors state that they have no Conflict of Interest (COI).

References

4. Lui SL, Chan KW, Li FK, Cheng IK, Chan TM. Castleman’s dis-


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http://www.naika.or.jp/imindex.html