Annals of Hematology (2019) 98:1995–1997
https://doi.org/10.1007/s00277-019-03616-y

LETTER TO THE EDITOR

Tocilizumab for focal segmental glomerulosclerosis secondary to multicentric Castleman's disease

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Received: 14 December 2018 / Accepted: 14 January 2019 / Published online: 13 February 2019

Dear Editor,

Multicentric Castleman's disease (MCD) is a lymphoproliferative disorder accompanying systemic symptoms and multi-organ dysfunction by excessive interleukin (IL)-6 [1]. Focal segmental glomerulosclerosis (FSGS) is an uncommon complication of MCD and no consensus has been achieved on its treatment [2]. Although pharmacological IL-6 blockade by tocilizumab is highly effective for MCD [1], its effect against FSGS secondary to MCD is unknown. Herein, we report a first case of FSGS secondary to MCD successfully treated by tocilizumab.

A 41-year-old Japanese man diagnosed with MCD by inguinal lymph node biopsy had been observed without therapy because of mild symptoms. He was negative for HIV. HHV-8 status was not evaluated because of the extreme rarity of HHV-8-associated MCD in Japan [3].

Anemia had progressed slowly from year to year, and 23 years later, when he was 63 years old, his hemoglobin level decreased to 5.3 g/dl. At this time, urinary protein to creatinine ratio (UPCR) had increased to 5.4 g/gCr. Oral prednisolone at 1 mg/kg was administered and proteinuria was controlled at 0.5–1 g/gCr thereafter. Hemoglobin levels were maintained at 9–10 g/dl. However, his eGFR decreased to below 40 ml/min/1.73 m^2. To achieve better control of proteinuria, tocilizumab at a dose of 8 mg/kg was administered every 2 weeks. His residual symptoms had disappeared and UPCR diminished to 0.15 g/gCr. CRP levels decreased from 10–12 to 1–3 mg/dl and deterioration of renal function was stopped.

Three years later, proteinuria recurred and UPCR reached 3.6 g/gCr, while other markers such as CRP and hemoglobin levels remained unchanged. Renal biopsy was performed for further evaluation. The histological examination of the kidney demonstrated segmental sclerosis in 1 of 22 glomeruli and basement membrane adhesion in 2 of 22 glomeruli (Fig. 1). Immunofluorescence staining demonstrated mild deposition of IgM. The electron microscopic examination showed diffuse foot process effacement but no electron dense deposits. No amyloid fibril was observed. Based on these findings, he was diagnosed with FSGS.

Just before renal biopsy, we increased the frequency of tocilizumab from twice to three times a month, which gradually lowered his UPCR levels. His CRP levels were also lowered from 1–2 mg/dl to below 1 mg/dl. Accordingly, UPCR levels continued to decrease to reach 0.8 g/gCr 4 months after intensification of tocilizumab therapy and have been stable thereafter.

Recently, activation of the JAK2/STAT3 pathway by IL-6 was identified as a potential injurious factor in primary FSGS [4] and could be a potential therapeutic target [5]. In this case, tocilizumab in every 2 weeks seems to suppress IL-6 signaling pathway enough to alleviate symptoms, but insufficient to completely normalize inflammatory state, represented by sustained elevated levels of CRP, given that CRP is a sensitive biomarker reflecting IL-6 levels. We speculate that this insufficient IL-6 inhibition exposed his kidneys to residual pathologically activated IL-6/JAK2/STAT3 signaling for those long periods, which might contribute to the development of

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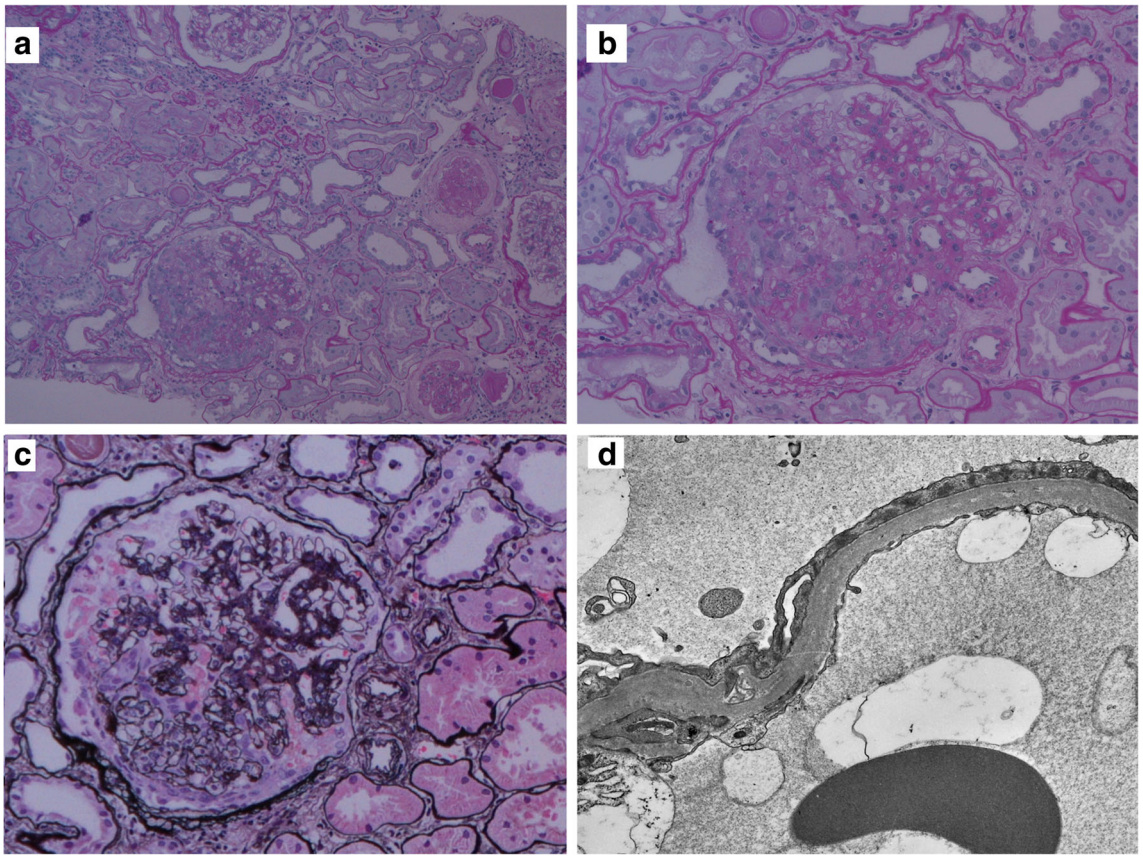

Fig. 1 Findings of renal biopsy. **a**–**c** Light microscope: glomeruli with segmental sclerosing lesion and epithelial hyperplasia, mesangial proliferation without spike formation, and extracapillary proliferation accompanied by rupture of glomerular basement membrane were observed. Periodic acid-Schiff (PAS) stain, × 100 (**a**) and × 200 (**b**) magnification. **c** Periodic acid-silver methenamine (PAM) stain, × 200 magnification. **d** Electron microscope: diffuse foot process effacement was observed but electron dense deposits were absent

FSGS. Considering that intensification of tocilizumab treatment lowered UPCR levels in concordance with CRP levels, tocilizumab could be a potential therapeutic agent against FSGS secondary to MCD.

Compliance with ethical standards

Full informed consent was obtained from the patient in this report for the treatment. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of interest Kazuhiro Toyama has the following financial relationship to disclose. Honoraria (lecture fee) from Chugai Pharmaceutical Co., Ltd. (tocilizumab). Masaomi Nangaku has the following financial relationships to disclose. Honoraria (lecture fee) and research funding from Chugai Pharmaceutical Co., Ltd. (tocilizumab). Mineo Kurokawa has the following financial relationship to disclose. Research funding from Chugai Pharmaceutical Co., Ltd. (tocilizumab). The other authors (Drs K.E., Y.M., J.T., H.N., K.H., M.H.) declared that they had no relevant financial relationships to disclose.

References

1. Fajgenbaum DC, Uldrick TS, Bagg A, Frank D, Wu D, Srkalovic G, Simpson D, Liu AY, Menke D, Chandrakasan S, Lechowicz MJ, Wong RS, Pierson S, Paessler M, Rossi JF, Ide M, Ruth J, Croglio M, Suarez A, Krymskaya V, Chadburn A, Colleoni G, Nasta S, Jayanthan R, Nabel CS, Casper C, Dispenzieri A, Fossa A, Kelleher D, Kurzrock R, Voorhees P, Dogan A, Yoshizaki K, van Rhee F, Oksenhendler E, Jaffe ES, Elenitoba-Johnson KS, Lim MS (2017) International, evidence-based consensus diagnostic criteria for HHV-8-negative/idiopathic multicentric Castleman disease. Blood 129(12):1646–1657. https://doi.org/10.1182/blood-2016-10-746933
2. Yuan XG, Hu W, Chen FF, Huang BF, Zhao XY (2011) Renal complications of Castleman's disease: report of two cases and analysis of 75 cases. Clin Exp Nephrol 15(6):921–926. https://doi.org/10.1007/s10157-011-0499-9
3. Kawabata H, Kadowaki N, Nishikori M, Kitawaki T, Kondo T, Ishikawa T, Yoshifuji H, Yamakawa N, Imura Y, Mimori T, Matsumura Y, Miyachi Y, Matsubara T, Yanagita M, Haga H, Takaori-Kondo A (2013) Clinical features and treatment of

multicentric castleman's disease : a retrospective study of 21 Japanese patients at a single institute. J Clin Exp Hematop 53(1): 69–77

4. Estrada CC, Paladugu P, Guo Y, Pace J, Revelo MP, Salant DJ, Shankland SJ, D'Agati VD, Mehrotra A, Cardona S, Bialkowska AB, Yang VW, He JC, Mallipattu SK (2018) Kruppel-like factor 4 is a negative regulator of STAT3-induced glomerular epithelial cell proliferation. JCI Insight 3(12). https://doi.org/10.1172/jci.insight.98214
5. Savin VJ, Sharma M, Zhou J, Gennochi D, Fields T, Sharma R, McCarthy ET, Srivastava T, Domen J, Tormo A, Gauchat JF (2015) Renal and hematological effects of CLCF-1, a B-cell-stimulating cytokine of the IL-6 family. J Immunol Res 2015: 714964. https://doi.org/10.1155/2015/714964