Successful autologous stem cell transplantation for light-chain proximal tubulopathy with severe kidney injury.

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1. Introduction

Monoclonal gammopathy is associated with various types of renal injuries, such as light chain cast nephropathy (LCPT), AL amyloidosis, and monoclonal immunoglobulin deposition disease, recently recognized as monoclonal gammopathy of renal significance (MGRS). LCPT is a rare type of MGRS, with approximately only 150–200 cases reported in the literature [1–6]. In LCPT, monoclonal light chains secreted by abnormal plasma cells accumulate in the proximal tubular cells and cause proximal tubular dysfunction, which is clinically characterized by tubular acidosis, normoglycemic glycosuria, aminoaciduria, and hypophosphatemia, collectively called Fanconi syndrome [7].

Diagnosis of LCPT is confirmed by findings of renal biopsy and the presence of specific histological features, including cytoplasmic monoclonal light chain inclusions and an increased number of lysosomes in the proximal tubular cells, which are sometimes only detectable by electron microscopy [8]. In addition, the coexistence of LCPT and other paraprotein-related kidney disease has been reported [9–11], which makes the diagnosis more difficult. LCPT often presents as a slowly progressive renal impairment; however, some patients develop end-stage kidney disease or aggressive multiple myeloma [7]. Although the treatment strategy for MGRS has not yet been established due to the rarity and lack of familiarity of this entity, several studies have shown that improvement in renal function can be achieved with hematologic response to chemotherapy, commonly bortezomib for plasma cell dyscrasia, and rituximab for B cell lymphoproliferative disease. Some case reports and case series have shown that chemotherapy directed at multiple myeloma is also effective for LCPT [1–4], but only a few case reports have described its clinical course, and the optimal treatment strategy remains unknown.

Herein, we describe the case of a patient with LCPT and severe kidney injury who received bortezomib-based chemotherapy and autologous stem cell transplantation (ASCT). This case report illustrates new insight into the optimal treatment strategy for LCPT in the future.

2. Case report

A 64-year-old Japanese man with a history of hypertension, gastric cancer, and mild thrombocytopenia had renal dysfunction (Creatinine 1.5 mg/dL) and hypokalemia 3 years prior and was referred to our nephrologist because of progressive renal impairment and proximal tubular dysfunction. His laboratory data are shown in Table 1. Urinalysis revealed massive proteinuria (2+, 3.6 g/day) without hematuria and the test results for Bence Jones protein were positive. Urinary beta-2 microglobulin (β-2MG) level was markedly elevated to 92,279 ng/mL. Serum potassium and uric acid level was 4.4 mEq/L (under oral potassium supplementation) and 1.9 mg/dL, respectively. The serum creatinine level was 2.81 mg/dL (eGFR 18.7 mL/min/1.73m^2). Serum protein electrophoresis showed an M-spike with monoclonal immunoglobulin (Ig)G-ϰ and elevated free light chain (FLC)- ϰ level (56.7 mg/dL).

Concerning the renal tubular function, the fractional excretion (FE) of uric acid (FEUA; normal range 4–14%) and potassium (normal range 10–20%) was 50% and 37.5%, respectively, and the tubular reabsorption of phosphate (TURP; normal range 60–90%) was 59%.

A bone marrow examination showed normocellular marrow with 5% plasma cells exhibiting κ light chain clonality. Cytogenic analysis using the G-banding technique showed a normal karyotype, and metaphase fluorescence *in situ* hybridization revealed a 1q gain of 3% (three copies) without any other high-risk chromosomal abnormalities, including t(4;14)(p16;q32), t(14;16)(q32;q23), or deletion(17p).

Renal biopsy and immunofluorescence analysis revealed that none of the glomeruli showed histological abnormalities, including amyloid or immunocomplex deposition. However, the κ light chain was positive in the proximal renal tubules, and electron microscopy revealed light chain proximal tubulopathy-specific crystals in the proximal tubular epithelial cells (Figure 1).

[^{18}F]Fluorodeoxyglucose positron emission tomography-computed tomography ([^{18}F]FDG PET/CT) scan revealed no additional renal signs of light chain deposition disease or bone lesions suggestive of multiple myeloma.

The clinical course of the patient is shown in Figure 2. Following an established diagnosis of LCPT with monoclonal gammopathy of undetermined significance, bortezomib 1.5 mg/m^2, cyclophosphamide 300 mg/m^2, and dexamethasone 40 mg (VCd) were administered on days 1, 8, 15, 22. After four treatment cycles, serum κ light chain, and creatinine improved to 24.9 mg/L (pretreatment; 567 mg/L), and 1.87 mg/dL respectively. Improvements in the renal function prompted us to initiate ASCT, and the patient underwent peripheral blood stem cell mobilization with granulocyte colony-stimulating factor (G-CSF) and plerixafor. Subsequently, he received a high dose of melphalan (140 mg/m^2) followed by ASCT and achieved successful engraftment without serious complications. One month after ASCT, he achieved a stringent complete response, and serum creatinine level decreased from 3.32 mg/dL to 1.85 mg/dL. In addition, proximal tubular function improved, as evidenced by a reduction in FEUA, elevation of TURP, and resolution of urinary glucose. The patient no longer needed potassium or bicarbonate supplementation. His renal function remained stable for 6 months after ASCT.

3. Discussion

This is the first case that described the clinical course of ASCT for LCPT with severe kidney injury and the improvement in renal function in detail.

LCPT is a rare subtype of MGRS, and the treatment strategy remains controversial as well as the other types. Previous studies did not support the use of chemotherapy such as alkylating agents because of its ineffectiveness in improving renal function and adverse effects such as secondary malignancy [5]. However, as new drugs for multiple myeloma have become available, 11 case reports and 4 case series have shown the efficacy of chemotherapy, particularly bortezomib-based regimens and ASCT to improve renal and tubular function [12-22] (summarized in Tables 2 and 3). Although these studies comprised a small case series, and the definition of the renal outcome was variable, all reports showed that chemotherapy improved renal function or delayed the progression to end-stage kidney disease, compared with that in the non-chemotherapy group (Table 2). In addition, they reported an improvement in renal tubular function, characterized by the resolution of proteinuria or urinary glucose and elevation of serum phosphate and uric acid levels (Table 2). Although we cannot precisely assess the efficacy of different treatments owing to the small size and heterogeneity of the series, a combination of chemotherapy and ASCT tends to achieve a better renal or proximal tubular function than chemotherapy alone [1,2]. These data suggest that renal and tubular functional improvements can be achieved by reducing the secretion of free light chains by abnormal plasma cells. Although emerging evidence suggests that organ response rate may be improved by negative minimal residual disease in AL amyloidosis, the most common type of MGRS [23], no data are available on whether the complete eradication of abnormal plasma cells is beneficial for the kidneys or delays the progression to multiple myeloma in patients with LCPT.

Recently, daratumumab, an anti-CD38 monoclonal antibody, has been commonly administered for multiple myeloma and AL amyloidosis. Since most of the case reports are published before the approval of daratumumab, the administration of daratumumab for LCPT is limited to only 2 cases, complicated with AL amyloidosis or crystal-storing histiocytosis respectively. [9,11] Both are efficacious and CD38 monoclonal antibody seems to be a promising therapeutic alternative for LCPT.

It is noteworthy that the renal function improved in our case despite severe initial kidney injury, compared to the extent of renal injury in the previous case reports (Table 3). Although most previous reports include eGFR above 30 mL/min/1.73m^2 or creatinine below 2.0 mg/dL, renal injury progressed to eGFR 15.4 mL/min/1.73m^2 (creatinine 3.31 mg/dL) at the initiation of treatment in our case. We found only two cases of LCPT with severe kidney injury, one of which showed no improvement of renal function [22], and the other showed remarkable improvement as well as in our case [19]. These data imply that we should aggressively consider the diagnosis by renal biopsy and chemotherapy for LCPT even with severe kidney impairment.

Our study limitation is the uncertainty of whether the addition of ASCT leads to better clinical outcomes. Although the role of ASCT is not established in LCPT, we decided to perform ASCT considering that the patient responded well to chemotherapy with rapid improvement in renal function.

In conclusion, a combination of bortezomib-based chemotherapy and ASCT could effectively treat LCPT and successfully improve the renal function in this patient. Therefore, hematologists should be familiar with LCPT as a differential diagnosis for renal impairment with monoclonal gammopathy of undetermined significance and multiple myeloma and should consider chemotherapy even with severe renal injury. However, data on the best treatment strategy and long-term prognosis are still lacking. Larger prospective studies are needed to support our results and determine the optimal treatment strategy for LCPT.

References

1. Stokes MB, Valeri AM, Herlitz L, et al. Light chain proximal tubulopathy: clinical and pathologic characteristics in the modern treatment era. *J Am Soc Nephrol.* 2016;27(5):1555-1565. doi:*10.1681/ASN.2015020185*
2. Vignon M, Javaugue V, Alexander MP, et al. Current anti-myeloma therapies in renal manifestations of monoclonal light chain-associated Fanconi syndrome: a retrospective series of 49 patients.*Leukemia.* 2017;31(1):123-129. doi:*10.1038/leu.2016.195*
3. Wu X, Zhang L, Feng J, et al. Bortezomib-based chemotherapy can improve renal and tubular functions in patients with light chain-associated Fanconi syndrome. *Ann Hematol.*2019;98(5):1095-1100. doi:*10.1007/s00277-018-3572-6*
4. Chen Z, Li J, Shi X, et al. Clinicopathological characteristics and long-term prognosis of monoclonal immunoglobulin light chain associated Fanconi syndrome. *Ther Adv Hematol.*2021;12:2040620720983127. doi:*10.1177/2040620720983127*
5. Liu Y, Zhu T, Xu L, Qin Y, Zhuang J. A single-center case series of eight patients with the rare plasma cell dyscrasia of acquired Fanconi syndrome secondary to monoclonal gammopathy. *Leuk Lymphoma.*2015;56(11):3124-3128. doi:*10.3109/10428194.2015.1025392*
6. Ma CX, Lacy MQ, Rompala JF, et al. Acquired Fanconi syndrome is an indolent disorder in the absence of overt multiple myeloma.*Blood.* 2004;104(1):40-42. doi:*10.1182/blood-2003-10-3400*
7. Sirac C, Batuman V, Sanders PW. The proximal tubule toxicity of immunoglobulin light chains. *Kidney Int Rep.*2021;6(5):1225-1231. doi:*10.1016/j.ekir.2021.02.026*
8. Sugimoto Y, Fujimoto M, Machida H, Nagaharu K, Murata T, Tsukada T. Light chain proximal tubulopathy diagnosed solely by electron microscopy of a renal biopsy specimen in a patient with monoclonal gammopathy of undetermined significance. *Int J Hematol.*2021;114(3):303-304. doi:*10.1007/s12185-021-03193-9*
9. Feurstein S, Zoller J, Schwab C, et al. Concurrent light chain amyloidosis and proximal tubulopathy: insights into different aggregation behavior-A case report. *EJHaem.*2022;3(4):1377-1380. doi:*10.1002/jha2.555*
10. Chopra R, Santana de Roberts R, Batal I, Batra S, Jim B. Light chain proximal tubulopathy with cast

nephropathy in monoclonal gammopathy of renal significance. *BMJ Case Rep.* 2020;13(6):e234361. doi:*10.1136/bcr-2020-234361*

11. Qin AB, Yu XJ, Zheng XZ, Wang SX, Zhou FD, Zhao MH. Lessons for the clinical nephrologist: a rare case with MGRS characterized by combined crystalline light chain proximal tubulopathy and crystal-storing histiocytosis responding to daratumumab. *J Nephrol.*2023;36(4):1203-1207. doi:*10.1007/s40620-023-01584-1*
12. Ino A, Yamaguchi K, Taneda S, et al. Proximal tubulopathy with fibrillary inclusions: a rare manifestation of lymphoma-associated monoclonal gammopathy of renal significance (MGRS). *Kidney Med.*2019;1(6):397-401. doi:*10.1016/j.xkme.2019.07.013*
13. Ugai T, Tsuda K, Sugihara H, et al. Renal Fanconi syndrome associated with monoclonal κ free light chain in a patient with Waldenström macroglobulinemia. *Br J Haematol.* 2013;162(1):1. doi:*10.1111/bjh.12398*
14. Mathur M, Chacko B, Vankalakunti M, Patil C. Fanconi syndrome due to light chain proximal tubulopathy in a patient with multiple myeloma.*Saudi J Kidney Dis Transpl.* 2016;27(4):805-807. doi:*10.4103/1319-2442.185268*
15. Chung EYM, McIlroy K, Fung C, Seshan SV, Moran S, Coleman PL. Glomerular, mesangial, and tubular cytoplasmic fibrillary inclusions in a patient with light-chain proximal tubulopathy. *Nephron.*2020;144(4):190-194. doi:*10.1159/000505029*
16. Li MN, Zhao L, Li XH, et al. Autologous peripheral blood stem cell transplantation combined with bortezomib and dexamethasone for the treatment of light chain proximal tubulopathy: a case report.*Zhonghua Xue Ye Xue Za Zhi.* 2019;40(8):703. [Article in Chinese] doi:*10.3760/cma.j.issn.0253-2727.2019.08.019*
17. Li F, Xie X, Sun L, Zhang Z, Chen J, Wang X. Non-crystalline light chain proximal tubulopathy associated with monoclonal gammopathy of renal significance: a case report and review of the literature. *Clin Nephrol.* 2023;99(1):32-40. doi:*10.5414/CN110883*
18. Gutiérrez-Peredo GB, Filho JCBO, Montaño-Castellón I, Gutiérrez-Peredo AJ, Crusoé EQ, Gusmao-Flores D. Lambda light chain-induced monoclonal gammopathy of renal significance, manifesting with Fanconi syndrome and osteomalacia. *BMC Nephrol.* 2022;23(1):278. doi:*10.1186/s12882-022-02901-9*
19. Tsuyuki T, Uramatsu T, Shimizu M, et al. Improvement of light chain proximal tubulopathy without crystals in IgGλ-type monoclonal gammopathy of undetermined significance using bortezomib and dexamethasone: a case report. *Intern Med.* 2023. doi:*10.2169/internalmedicine.1835-23*
20. Kawamoto S, Hidaka Y, Kaneko Y, et al. Remission of light chain proximal tubulopathy in IgG λ-type multiple myeloma by lenalidomide and dexamethasone therapy. *CEN Case Rep.* 2019;8(3):159-165. doi:*10.1007/s13730-019-00382-8*
21. Ikeda D, Matsue K. Non-crystalline light chain proximal tubulopathy without renal Fanconi syndrome in a patient with IgD-λ multiple myeloma. *Br J Haematol.* 2022;196(2):261. doi:*10.1111/bjh.17785*
22. Kishi S, Obata F, Miki H, et al. Lambda light chain non-crystalline proximal tubulopathy with IgD lambda myeloma. *Intern Med.*2018;57(24):3597-3602. doi:*10.2169/internalmedicine.1323-18*
23. Palladini G, Paiva B, Wechalekar A, et al. Minimal residual disease negativity by next-generation flow cytometry is associated with improved organ response in AL amyloidosis. *Blood Cancer J.*2021;11(2):34. doi:*10.1038/s41408-021-00428-0*

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