C3 Glomerulonephritis Along With Light Chain Tubular Reabsorption in Multiple Myeloma: A Case Report

Junhui Xu
Peking University First Hospital

Xiaojuan Yu
Peking University First Hospital

Suxia Wang
Peking University First Hospital

Miao Yan
Peking University First Hospital

Mangju Wang
Peking University First Hospital

Jinping Ou
Peking University First Hospital

Lihong Wang
Peking University First Hospital

Huihui Liu
Peking University First Hospital

Xinan Cen (cenxn@bjmu.edu.cn)
Peking University First Hospital

Case report

Keywords: Multiple myeloma, C3 glomerulonephritis, autologous stem cell transplantation, light chain tubular reabsorption.

DOI: https://doi.org/10.21203/rs.3.rs-76646/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

**Background:** Multiple myeloma has different kinds of renal injuries. C3 glomerulonephritis (C3GN) is characterized by abnormal deposition of complement C3 in the glomeruli due to abnormal activation of the alternative pathway of complement system. The association between C3GN and multiple myeloma had been well established. However, the mild renal injury of C3GN in the multiple myeloma patients with high level of light chain had not been reported.

**Case presentation:** A 55 years old Chinese man presented with proteinuria. Combined with immunofixation electrophoresis, bone marrow biopsy and renal biopsy, this patient was diagnosed with IgA type multiple myeloma accompanied by C3GN and light chain tubular reabsorption. Although he had a higher level of lamda serum free light chain, the renal injury of this patient was mild. After treated with 4 courses of BD, one course of PAD and autologous stem cell transplantation, he achieved a very good partial hematologic response with stable renal function.

**Conclusions:** In multiple myeloma, the condition for light chain to result in renal impairment of C3GN is that the light chain reaches a certain level and lasts for a long time. Early diagnosis and early intensive treatment are extremely important for the prognosis of such patients.

Background

Multiple myeloma is characterized by abnormal proliferation of bone marrow plasma cells accompanied by excessive production of monoclonal immunoglobulin or light chain (M protein) leading to osteolytic lesions, hypercalcemia, anemia and kidney damage. Multiple myeloma has different kinds of renal injuries[1], including cast nephropathy, amyloidosis, proliferative glomerulonephritis with monoclonal immunoglobulin deposits, immunotactoid glomerulopathy, brisnary glomerulonephritis and light chain proximal glomerulopathy.

C3GN is characterized by abnormal deposition of complement C3 in the glomeruli due to abnormal activation of the alternative pathway of complement system[2]. It is worth noting that the most common abnormal factors which result in C3GN are autoimmune factors such as C3 nephritic factor, complement H factor antibody, properdin and genetic variations such as mutations of complement genes, coding for the components of the C3 convertase, for C3, Factor B, Factor H, CFHR5 (Complement Factor H Related Protein 5) and copy number variations in the CFHR gene. However, C3GN also had been described in some cases of multiple myeloma [3–6]. The association between C3GN and multiple myeloma had been well established. The light chain acted as a mini-autoantibody bind within the complement regulator region of factor H, resulting in the continuous activation of the alternative pathway of complement system which resulted in C3GN[7]. However, the mild renal injury of C3GN in the multiple myeloma patients with high level of light chain had not been reported.

Case Presentation
A 55 year-old Chinese man presented to our center with three months history of proteinuria and bilateral eyelid edema from Aug. 15, 2017. This patient did not have any other significant comorbidities. His complete blood count was normal. Urinalysis showed microscopic hematuria with RBC 20–30/HP and proteinuria fluctuating between negative and microscale with 24 h urinary protein quantity (0.13 g/24 h). The biochemical test showed that kidney function and serum electrolytes were normal and total protein was obviously decreased along with hypoalbuminemia and normal immunoglobulin. The quantitative detection of immunoglobulin subclasses showed that Immunoglobulin A was significantly elevated, whereas Immunoglobulin G and Immunoglobulin M were both decreased. Urine kappa light chain was normal and urine lamda light chain was significantly increased (571 mg/L, normal range < 5.1 mg/L). In addition, serum free lamda light chain level was greatly elevated (8050 mg/L, normal range 5.71–26.3 mg/L), whereas serum free kappa light chain level was normal. M protein was detected by serum protein electrophoresis, and IgA-lamda-type monoclonal immunoglobulin band was identified by immunofixation electrophoresis. Furthermore, the bone marrow biopsy showed that his BMPC (bone marrow plasma cell) was 42.5%. The level of β2-Microglobulin was slightly raised. Based on the above, we believed that this patient had IgA-lamda-type multiple myeloma (D-S: stage I group A; ISS: stage II), even though bone lesions were not founded.

In order to clarify the cause of renal injury in this patient, we performed a renal biopsy on this patient in Nov. 21, 2017. Immunofluorescence microscopy showed that granular C3 deposited in the mesangial area (Fig. 1A). Kappa light chain staining was negative (Fig. 1B). Granular deposition of the lamda light chain was exhibited in the renal tubular epithelium (Fig. 1C). Under the light microscopy, glomerular mesangial cell hyperplasia was noted (Fig. 1D). Mild segmental hyperplasia of the stroma with a small amount of eosinophil deposition, granular degeneration of renal tubular epithelium and renal interstitium with small focal lymphocytes and monocytes infiltrating were also detected. Additionally, electron microscopy identified the dense deposits in the mesangial areas (Fig. 1E). Abnormal lysosomes in the cytoplasm of proximal tubular epithelial cells were also noted (Fig. 1F). He had marked hypocomplementemia with reductions in complement C3, but the complement C4 was normal. In addition, we found that the patient's C3 nephritic factor, complement factor H antibody, complement factor H concentration and vWF-cleaving protease (ADMAMTS13) activity were also normal.

Above all, this patient was diagnosed C3GN along with light chain tubular reabsorption resulted from multiple myeloma. The treatment effect of this patient was very good response with BD (Bortezomib plus dexamethasone) for 4 courses. In Apr. 19, 2018, this patient's disease had relapsed. Then, he was treated with one course of PAD (Bortezomib plus doxorubicin and dexamethasone) and BEAM (BCNU, etoposide, cytarabine and melphalan) pretreatment protocol along with the autologous stem cell transplantation in Jul. 11, 2019. He achieved a very good partial response again with stable renal function. The timeline of kidney function, proteinuria, C3, serum lamda light free chain and urine lamda light chain in relation to treatment was showed in Fig. 2 and Table 1. After that, this patient went to another hospital to accept the treatment. Unfortunately, this patient was dead of cardiovascular disease in May 13, 2020.
Table 1
The timeline of kidney function, 24 h UTP, C3, serum lamda light free chain and urine lamda light chain in relation to treatment.

| Time              | Scr (mmol/L) | 24hUTP (g/24 h) | C3 (g/L) | Serum lamda light free chain (g/L) | Urine lamda light chain (g/L) |
|-------------------|--------------|-----------------|----------|-----------------------------------|-----------------------------|
| 2017.11.15 BD     | 0.0606       | 0.13            | 0.047    | 8.05                              | 0.517                       |
| 2017.12.26 BD     | 0.0541       | 0.09            | 0.058    | 5.05                              | 0.005                       |
| 2018.01.22 BD     | 0.0563       | 0.14            | 0.632    | 3.11                              | 0.005                       |
| 2018.02.20 BD     | 0.0581       | 0.16            | 0.661    | 1.55                              | 0.005                       |
| 2018.04.10 CTX    | 0.0605       | 0.15            | 0.258    | 3.67                              | 0.005                       |
| 2018.06.19 PAD    | 0.0668       | 0.16            | 0.189    | 3.71                              | 0.005                       |
| 2018.09.04 After autoHST | 0.0572   | 0.14            | 0.175    | 3.89                              | 0.005                       |

1Mobilization
BD: Bortezomib plus dexamethasone; CTX: Cyclophosphamide; PAD: Bortezomib plus doxorubicin and dexamethasone; autoHST: autologous stem cell transplantation.

Discussion
C3GN is mainly caused by abnormal factors involved in the alternative pathway of complement system. Previous studies found that the light chain acted as a mini-autoantibody bind within the complement regulator region of factor H, resulting in the continuous activation of the alternative pathway of complement system which resulted in C3GN[7]. In our case, this patient’s C3 nephritic factor, complement factor H antibody, and complement factor H concentration were normal. Under the treatment, as in Fig. 2, there was a negative correlation between serum lamda free light chain and complement C3. This showed to a certain extent that the light chain was the key factor of the activation of the complement system.

Mark T. Drayson and Bilge Karatoy Erdem found that there was a strong correlation between higher levels of serum free light chains (greater than 800 mg/dl) and the severity of multiple myeloma renal impairment[8, 9]. There were varying degrees of renal injury in these 6 patients previously reported, but our patient who had a higher level of lamda serum free light chain didn't show a significant increase in serum creatinine and 24hUTP. There were two reasons for this situation: First of all, although our patient had a higher level of serum free light chain, the time from onset to diagnosis was too short to result in renal dysfunction. Secondly, after our patient received treatment, the serum free light chain rapidly fell below to the threshold resulting in renal dysfunction. Therefore, the condition for light chain to cause renal impairment of C3GN in multiple myeloma is that the light chain reaches a certain level and lasts for a long time. We need to further explore the threshold of light chain for renal impairment of C3GN.
The early diagnosis of C3GN by renal biopsy can shorten the duration of high-level light chains before the diagnosis. In addition, we can use early diagnosis of C3GN by renal biopsy to promote early treatment to further shorten the above-mentioned duration. C3GN may affect the survival time of the patients with multiple myeloma, so the early diagnosis of C3GN by renal biopsy in multiple myeloma is particularly important. Therefore, in patients with renal injury of multiple myeloma, if the patient's complement C3 is low, it is recommended to actively perform renal biopsy to determine the type of renal pathology. Since the level of light chain is obviously related to the severity of the disease, we recommend using a stronger treatment plan in the early stage to obtain a lower level of light chain.

Conclusions

In summary, the condition for light chain to cause renal impairment of C3GN in multiple myeloma is that the light chain reaches a certain level and lasts for a long time. Early diagnosis and early intensive treatment are extremely important for the prognosis of such patients.

Declarations

Acknowledgments

We thank his close relatives for allowing us to publish his case.

Authors’ contributions

JHX and XJY participated in the acquisition of clinical data and wrote the manuscript. MJW, MY, JPO, LHW and HHL carried out the histological examination and interpretation. XNC and SXJ revised the manuscript. All authors read and approved the final manuscript.

Funding Sources:

Beijing Municipal Science Technology Commission (No. Z191100006619026 and Z141107002514017). The funders have no role in the study except for financial support.

Availability of data and materials:

All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate:

Not applicable.

Consent for publication:

Written informed consent for publication was obtained from the participant.
Conflict of Interest Statement:

The authors declare that they have no conflict of interest.

References

1. Sethi S, Fervenza FC, Rajkumar SV. Spectrum of manifestations of monoclonal gammopathy-associated renal lesions. Curr Opin Nephrol Hypertens. 2016;25: 127-37.
2. Gale DP, Maxwell PH. C3 glomerulonephritis and CFHR5 nephropathy. Nephrology Dialysis Transplantation. 2013;28: 282-8.
3. Cooper DL, Munday WR, Moeckel GW. C3 glomerulonephritis and plasma cell dyscrasia: expanding the etiologic spectrum. Biology and Medicine. 2015;7: 1.
4. Bourke E, Campbell Jr WG, Piper M, Check IJ. Hypocomplementemic proliferative glomerulonephritis with C3 nephritic-factor-like activity in multiple myeloma. Nephron. 1989;52: 231-7.
5. Bridoux F, Desport E, Frémeaux-Bacchi V, Chong CF, Gombert J-M, Lacombe C, et al. Glomerulonephritis With Isolated C3 Deposits and Monoclonal Gammopathy: A Fortuitous Association? Clinical Journal of the American Society of Nephrology. 2011;6: 2165-74.
6. Yin G, Cheng Z, Zeng CH, Liu ZH. C3 glomerulonephritis in multiple myeloma: A case report and literature review. Medicine. 2016;95: e4843.
7. Jokiranta TS, Solomon A, Pangburn MK, Zipfel PF, Meri S. Nephritogenic I Light Chain Dimer: A Unique Human Miniautoantibody Against Complement Factor H1. Journal of Immunology. 1999;163: 4590-6.
8. Punit Y, Paul C, Mark C, Jennifer P, Hannah G, Sandar AY, et al. Serum free light chain levels and renal function at diagnosis in patients with multiple myeloma. Bmc Nephrology. 2018;19: 178-.
9. Erdem BK, Davran F, Yilmaz VT, Çetinkaya R, Akbas H. The association of serum-free light-chain levels with markers of renal function. Ren Fail. 2015;37: 1-4.

Figures
Figure 1

Patient's renal pathology report: A. showed granular C3 deposition mostly in the mesangial area on frozen section (×200); B. showed κ light chain was negative in the glomeruli and tubular epithelial cells on frozen section (×200); C. showed that the background staining for λ light chain was stronger than κ (yellow arrow) and there were massive λ reabsorption granules in the cytoplasma of tubular epithelial cells (red arrow) on frozen section (×200); D. showed moderate mesangial proliferation (black arrow) (×400, PASM+Masson); E. showed mesangial electron dense deposition (red arrow, ×8000); F. showed abnormal lysosomes in the cytoplasma of proximal tubular epithelial cells (red arrow, ×15000).
Figure 2

The timeline of kidney function, 24h UTP, C3, serum lambda light free chain and urine lambda light chain in relation to treatment. BD: Bortezomib plus dexamethasone; CTX: Cyclophosphamide; PAD: Bortezomib plus doxorubicin and dexamethasone; autoHST: autologous stem cell transplantation.