Case Report

Bortezomib-containing regiment in treating glomerulopathy with fibronectin deposits combined with monoclonal gammopathy of undetermined significance: a case report and literature review

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Background: Glomerulopathy with fibronectin deposits (GFND) is a newly recognized rare glomerular disease. As its onset can be stably inherited in affected families without sex differences and fibronectin 1 (FN1) mutations can be detected in 40% of patients' families, GFND is considered to be an autosomal dominant genetic disease. The main clinical manifestations are proteinuria, progressive renal failure, edema, hypertension, hematuria, and type 4 renal tubular acidosis. The diagnosis was confirmed by renal biopsy, and there was no specific treatment. Monoclonal gammopathy refers to the existence of monoclonal immunoglobulin (MIg) produced by monoclonal plasma cells in serum. When MIg damages the kidney by direct deposition or indirect mechanisms, it is defined as monoclonal gammopathy of renal significance (MGRS). The principle of treatment is to inhibit plasma cells from producing MIg.

Case Description: We report the efficacy of a case of GFND combined with monoclonal gammopathy of undetermined significance (MGUS) treated with a bortezomib-containing regimen. A 44-year-old female patient was admitted to the hospital for "edema of both lower extremities for 1 month and aggravation for 5 days". In May 2018, after exertion, the patient developed edema of both lower extremities, accompanied by foamy urine with no obvious deepening of urine color or decreased output, no gross hematuria, and gradual aggravation with fatigue.

Conclusions: After treatment, the edema of patient subsided, urinary protein decreased significantly, and serum albumin increased near to normal. It is achieving a very good therapeutic effect and long-term event-free survival. The treatment is safety and there are no obvious toxic side effects. It provides a new idea for the treatment of GFND.

Keywords: Glomerulopathy with fibronectin deposits (GFND); monoclonal gammopathy; bortezomib; case report

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Introduction

Both glomerulopathy with fibronectin deposits (GFND) and monoclonal gammopathy of renal significance (MGRS) can damage the kidney, which can be distinguished by renal pathological biopsy, immunohistochemistry, and gene sequencing. We report a patient that was ultimately diagnosed with GFND unrelated to monoclonal immunoglobulin (MIg) injury. The incidence of GFND is rare, and the treatment methods are limited. Patients treated with bortezomib, a proteasome inhibitor, have a good response and mild adverse reactions, which provides a new idea for the treatment of GFND. We present the following case in accordance with the CARE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-242/rc).

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or

national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

A 44-year-old female patient was admitted to the hospital for "edema of both lower extremities for 1 month and aggravation for 5 days". In May 2018, after exertion, the patient developed edema of both lower extremities, accompanied by foamy urine with no obvious deepening of urine color or decreased output, no gross hematuria, and gradual aggravation with fatigue. The patient went to the local hospital for a routine urine test: occult blood (3+) and protein (3+). On June 14, 2018, the patient was hospitalized in the nephrology department of our hospital. There were no special medical notes related to past, personal or family history. Admission physical examination: blood pressure 92/60 mmHg, mild anemia appearance, heart, lung and abdomen (–), severe edema of both lower extremities. The results of some laboratory tests after admission are shown in *Table 1*. Serum immunofixation electrophoresis: monoclonal IgA, κ light chain. Blood free light chain: free κ 557.5 mg/L, free λ 14.6 mg/L, free light chain κ/λ ratio 38.1849 (normal range, 0.26–1.65). Urine free light chain: free κ 595 mg/L, free λ 147 mg/L, free light chain κ/λ ratio 4.0476 (normal range, 0.461–4.00). B-ultrasound of both kidneys: slightly enhanced parenchymal echo of both kidneys. Bone marrow cell morphology: 3% of mature plasma cells. Bone marrow biopsy showed plasma cells. Flow cytometry showed that 1.22% of abnormal cells expressed CD38, CD138, CD117, CD27, and CD200, and some expressed cKappa. Bone marrow karyotype: 46,XX.

On June 22, 2018, the patient underwent renal biopsy. Light microscopy: 38 glomeruli, glomerular sclerosis in 2 glomeruli, a large number of Periodic Acid-Schiff (PAS)-positive substances deposits in the remaining glomerular mesangial area and inside the basement membrane, no obvious proliferation of mesangial and endothelial cells, significantly widened mesangial area, a large number of fuchsinophilic protein deposits, narrow and occluded capillary cavity, thickened basement membrane, no segmental mesangial insertion and double-track formation, no hemangioma-like expansion and "eyelash-like" structure, no spike-like structure, no proliferation of parietal epithelial cells, no crescent formed, granular degeneration of renal tubular epithelial cells, focal atrophy (atrophic area of approximately 10%), renal interstitial focal inflammatory

Table 1 Laboratory tests

Variables	Value
WBC	3.7×10^9/L
RBC	3.0×10^{12}/L
HB	90 g/L
PLT	102×10^9/L
Rct%	1.52%
Urinalysis PH	6
Urinalysis SG	1.015
Urinalysis protein (3+)	15.092 g
Urinalysis occult blood	(3+)
Urinalysis RBC	30/HPF
BJP	(–)
ALB	19.6 g/L
GLB	24.2 g/L
BUN	3.9 mmol/L
Creatinine	54.6 μmol/L
Uric acid	232 μmol/L
TC	5.14 mmol/L
Na^+	144.5 mmol/L
K^+	3.6 mmol/L
Cl^-	116 mmol/L
Ca^{2+}	1.79 mmol/L
β2-MG	3.1 mg/L
HCV Ab	(–)
HBsAg	(–)
SF	21.34 (normal range, 4.6–204) ng/mL
FA	4.2 (normal range, 7–45) nmol/L
VitB12	99 (normal range, 138–652) pmol/L
C3	0.74 (normal range, 0.79–1.52) g/L
C4	0.23 (normal range, 0.16–0.38) g/L
IgG	3.41 (normal range, 7.51–15.6) g/L
IgA	8.66 (normal range, 0.82–4.52) g/L
IgM	0.74 (normal range, 0.46–3.04) g/L
ANA	(–)
MPO-ANCA	(–)
PR3-ANCA	(–)
Cryoglobulin	(–)

WBC, white blood cell; RBC, red blood cell; HB, hemoglobin; PLT, platelet; Rct, reticulocyte; PH, hydrogen ion concentration; SG, specific gravity ; BJP, Bence Jones proteins; ALB, albumin; GLB, globulin; BUN, blood urea nitrogen; TC, total cholesterol; Na, natrium; K, kalium; Cl, chlorine; Ca, calcium; β2-MG, β2-microglobulin; HCV Ab, hepatitis C virus antibody; HBsAg, hepatitis B virus surface antigen; SF; serum ferritin; FA, folic acid; VitB12, vitamin b12; C3, complement 3; C4, complement 4; IgG, immunoglobulin G; IgA, immunoglobulin A; IgM, immunoglobulin M; ANA, antinuclear antibodies; MPO-ANCA, myeloperoxidase antineutrophil cytoplasmic antibody; PR3-ANCA, protease 3 antineutrophil cytoplasmic antibody.

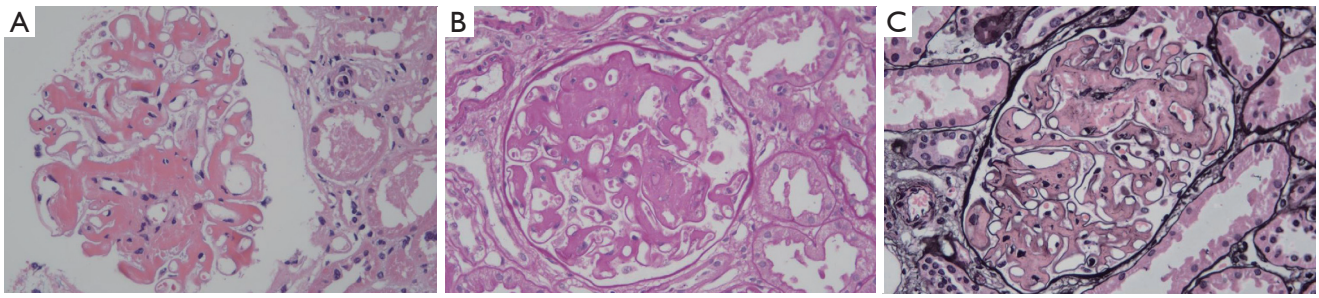

Figure 1 Renal pathological changes. (A) Significantly widened mesangial area (HE staining ×400); (B) a large number of PAS-positive substances deposits in the mesangial area (PAS staining ×400); (C) a large number of non-argyrophilic substances deposits in the mesangial area (PASM staining ×400). HE, hematoxylin and eosin; PAS, Periodic Acid-Schiff stain; PASM, periodic acid-silver methenamine.

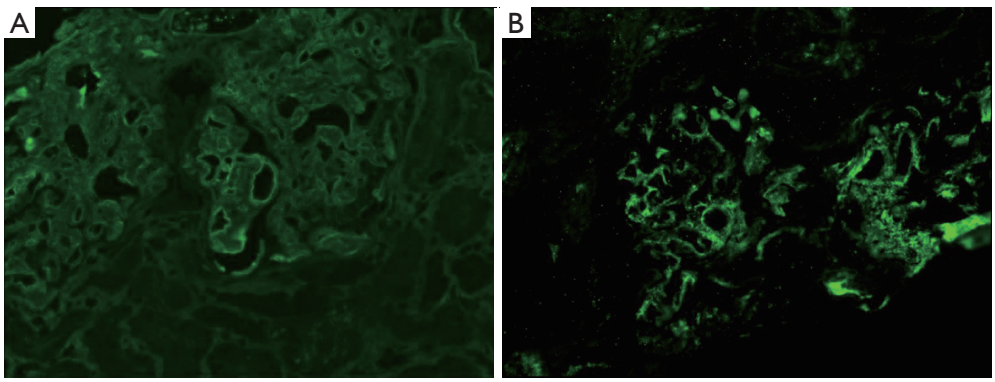

Figure 2 Immunofluorescence of the renal pathological changes. (A) κ (+), λ (+), distributed in the glomerular mesangial area and peripheral haptics (paraffin immunofluorescence × 400); (B) glomerular C3 positive (immunofluorescence ×100).

cell infiltration with fibrosis, thickened arteriolar wall, luminal stenosis, no red staining, no structure-like deposits, as shown in *Figure 1*, Congo red and oxidized Congo red staining negative. Immunofluorescence: IgG (2+), IgM (2+), IgA (3+), C3 (3+), C1q (2+), κ (+), λ (+), AA (–) (*Figure 2*). Electron microscopy: 1 glomerulus under the microscope, significantly vacuolated and degenerated capillary endothelial cells, red blood cells in individual lumen, no obvious endothelial cell proliferation, open capillary loops, no obvious thickening of the renal capsule wall layer, parietal cell vacuole and degeneration without significant proliferation, no obvious thickening of the basement membrane, thickness of approximately 250–350 nm, visceral epithelial cells swelling, vacuole and degeneration, segmental fusion of the foot process, mesangial cells and matrix proliferation in the mesangial area, a large number of clumps of electronic dense deposits in the mesangial area and inside the basement membrane, a small number of electronic dense deposits under the epithelium, fuzzy fiber-like structure by observation of electronic dense deposits at high magnification, renal tubular epithelial cells vacuole and degeneration, no special lesions in the renal interstitium, accumulation of red blood cells in individual capillary lumen of renal interstitial vessels, as shown in *Figure 3*.

According to light microscopy, immunofluorescence and comprehensive electron microscopy examinations, GFND was highly suspected. Therefore, immunohistochemistry was performed with the following: fibronectin (FN)-positive, as shown in *Figure 4*. Multigene sequencing of kidney-related genetic diseases detected heterozygous mutations in SCNN1G and PKD1. Based on the above medical history, laboratory and pathological examination results, the clinical diagnoses were: (I) GFND; (II) monoclonal gammopathy of undetermined significance (MGUS).

Treatment was divided into three stages. In the first stage, the CD regimen of chemotherapy (cyclophosphamide 450 mg, dexamethasone 20 mg/week ×4 weeks) was started on July 02, 2018, for 1 cycle, and the regimen

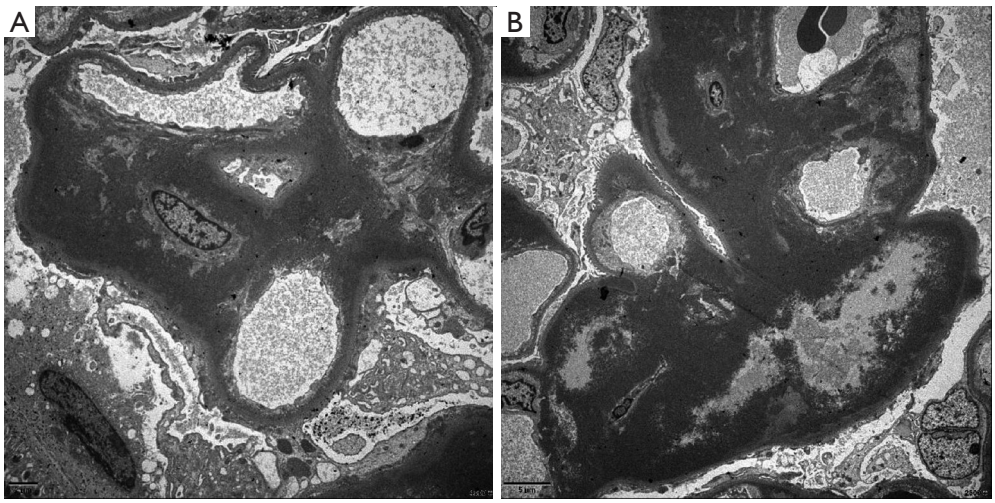

Figure 3 Electron microscopy of the renal pathological changes. (A) A large number of clumps of electronic dense deposits in the mesangial area and inside the basement membrane (electron microscope ×8,000); (B) a large number of clumps of electronic dense deposits in the mesangial area and inside the basement membrane (electron microscope ×3,000).

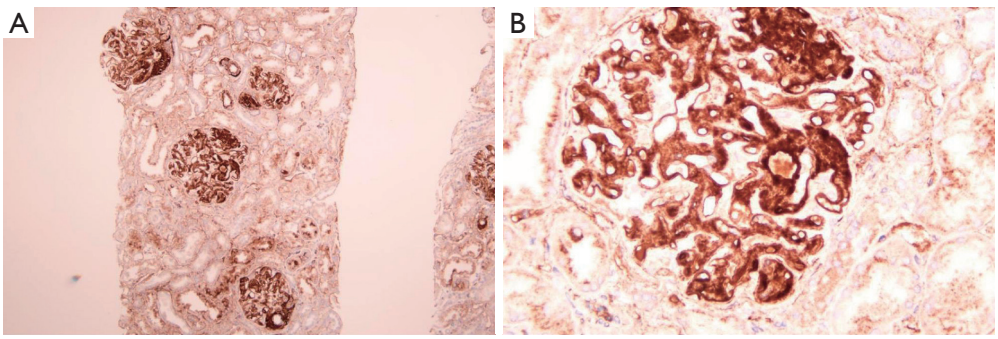

Figure 4 Immunohistochemistry of the renal pathological changes. (A) A large number of FN deposits in the mesangial area and under the endothelium (immunofluorescence ×100); (B) glomerular FN staining positive (immunofluorescence ×400). FN, fibronectin.

was repeated on August 8 and September 6, with regular review of biochemical examination and 24-hour urine protein quantification during the period (see *Figure 5*). The second stage, the BD regimen of chemotherapy (bortezomib 1.3 mg/m^2, dexamethasone 20 mg/week ×4 weeks) was started on October 12, 2018, for 4 cycles. The results of the review during the period are shown in *Figure 6*. In the third stage, the BD (bortezomib 1.3 mg/m^2, dexamethasone 20 mg/time/3 months) was used for maintenance therapy and regular review. The results are shown in *Figure* 7.

Results and follow-up: from July 2018 to September 2018, the patient underwent 3 cycles of chemotherapy with the CD regimen. The patient's edema did not improve, 24-hour urine protein fluctuated between 12–13 g, and serum albumin did not increase significantly. From October 2018, the BD regimen of chemotherapy was started for 4 cycles. The 24-hour urine protein gradually decreased to 4.008 g, serum albumin gradually increased to 33.5 g/L, and edema basically eased. Considering the many adverse reactions that might be induced by the long-term large-scale application of dexamethasone and the economic burden of using bortezomib, since June 2019, the patient was given BD maintenance treatment. During treatment with bortezomib, no adverse reactions, such as infection or neurotoxicity, occurred. At the time of the last follow-up on December 04, 2019, the patient's serum albumin was 41.2 g/L, and the 24-hour urine protein was 1.15 g.

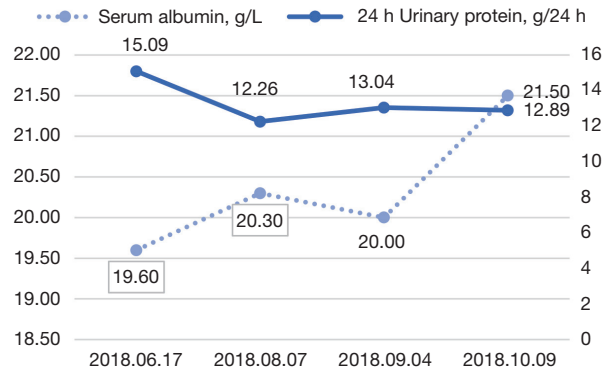

Figure 5 Changes in urinary protein and serum albumin during the first stage CD regimen. CD, dexamethasone with cyclophosphamide.

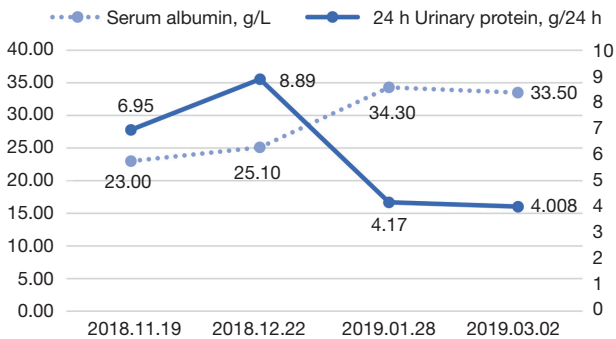

Figure 6 Changes in urinary protein and serum albumin during the second stage BD regimen. BD, dexamethasone with bortezomib.

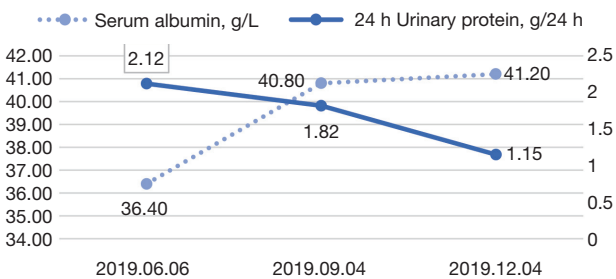

Figure 7 Changes in urinary protein and serum albumin during the third stage BD regimen of maintenance therapy. BD, dexamethasone with bortezomib.

Discussion

GFND was first reported by Tuttle *et al.* (1) as familial lobular glomerulopathy in 1987. In 1995, Strøm *et al.* (2) found a wide range of deposits under the glomerular vascular mesangium and endothelium, which had a strong immune response to FN and was named accordingly. The disease is mainly diagnosed by renal biopsy. To date, more than 90 cases of GFND have been reported worldwide. Most patients were male, and with the age of onset of 3–88 years.

GFND has no characteristic changes under light microscopy, mainly manifested as an increase in glomerular volume and a lobular shape. The total number of glomerular cells is generally normal, mainly with increased mesangial matrix, but without mesangial cell proliferation, possibly accompanied by widening of the glomerular basement membrane. These areas show deposits of PAS positive staining and Congo red negative staining. For some patients with insignificant fuchsinophilic deposition, periodic acid-silver methenamine (PASM)-Masson staining still shows mesangial argyrophil. Therefore, one study believes that whether the mesangial area is argyrophilic is related to the amount of FN deposition (3). As the disease progresses, there are nonspecific tubulointerstitial and vascular changes and increased fibrosis. Immunofluorescence examination confirms the presence of nonspecific immunoglobulin and C3 deposits, and immunochemical staining for FN shows strong positivity, which are also necessary conditions for the diagnosis of GFND. Electron microscopy manifestations were as follows: The subendothelial electronic dense deposits in the glomerular mesangial area of GFND patients are loose, uneven, granular, with a fiber-like structure 12–16 mm in diameter (4).

The patient in our case report started with edema, with a large amount of proteinuria and microscopic hematuria. Pathological biopsy of the kidney was consistent with GFND, immunochemical staining of FN was positive, and other immune-mediated glomerular diseases were excluded, thereby leading to the diagnosis of GFND. However, during the examination, the patient was found to have monoclonal gammopathy, and bone marrow flow cytometry also conformed to a monoclonal plasma cell phenotype but failed to meet the diagnostic criteria for multiple myeloma (MM). At this time, a differential diagnosis should be made with MGRS. MGRS refers to B cell clones that are temporarily not at risk of malignancy at this stage, kidney damage and clinical manifestations that are not directly related to the proliferation of B cell clones and may be related to their MIg deposition or other mechanisms involved with MIg; kidney damage caused by other factors should be excluded. See *Table 2* (5) for details. The

Table 2 Monoclonal gammopathy of renal significance-associated renal lesions (5)

Organized immunoglobulin deposits
Fibrillar deposits
Immunoglobulin-related amyloidosis
Fibrous glomerulonephritis
Microtubular deposits
Immunotactoid glomerulonephritis
Type I cryoglobulinemic glomerulonephritis
Nonorganized immunoglobulin deposits
Monoclonal: light chain deposition disease
Immunoglobulin: light and heavy chain deposition disease
Deposition disease: heavy chain deposition disease
Proliferative glomerulonephritis with monoclonal IgG deposits
C3 glomerulopathy with monoclonal gammopathy

IgG, immunoglobulin G; C3, complement 3.

polyclonal immunity and C3 deposits of glomerular light microscopy, electron microscopy and immunofluorescence showed that the patient's kidney damage was not related to MIg, thereby leading to a clear diagnosis of MGUS.

However, the pathogenesis of GFND is unclear. In 2008, Castelletti (6) identified the fibronectin 1 gene (FN1) at 2q32 as a gene responsible for the disease and sequenced FN1 to find heterozygous missense mutations such as W1925R, L1974R, and Y973C. In this study group, overall dominant mutations in FN1 accounted for 40% of GFND cases. However, the other 60% of familial GFND cases did not show mutations in the pathogenic gene FN1 (7). In addition, family members had different symptoms even if they had the same gene mutation. The case we reported did not have mutations of the *FN1* gene. FN is an adherent high-molecular-weight disaccharide protein that participates in cell adhesion, movement, morphological maintenance, conditioning, and wound healing. It is divided into two subtypes: insoluble and distributed in the extracellular matrix and soluble and derived from circulating blood (8). Research has shown that there is no difference in the content of FN in blood samples between GFND patients and healthy people, and FN deposition is not detected in other organs (such as lung, heart, brain, liver, and spleen) (9), only in glomeruli. It is speculated that the pathogenesis of GFND involves immune mechanisms. Another study suggests that the possible mechanism is a defect in FN metabolism and glomerular structure destruction caused by deposition of excess FN on the kidneys (10).

At present, there is no effective and specific treatment for GFND. Most researchers believe that GFND is not an immune disease; therefore, hormone and immunosuppressive therapies are not appropriate. Basic treatment includes blood pressure control and application of angiotensin converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs). Patients can undergo hemodialysis or peritoneal dialysis as they progress to the end-stage renal disease. Reviewing the literature, the vast majority of patients were given renin-angiotensin-aldosterone system (RAAS) application (11-15), but the effects were variable. There were significant reductions in urine protein to relieve clinical symptoms (11,12), while there were also cases that showed little effect (13,14) and even cases of recurrence after kidney transplantation (15). There were also some other attempted treatments with good effects (16). Jin *et al.* (17) reported that the urine protein of patients decreased significantly after treatment with tacrolimus. Stoppacciaro *et al.* (18) applied high-dose methylprednisolone and changed it to oral prednisone combined with cyclophosphamide, resulting in a significant decrease in urinary protein. Later, due to leukopenia, cyclosporine was substituted for cyclophosphamide, and the urine protein decreased significantly to 1.5 g/d. Yoshino *et al.* (19) and Mii *et al.* (20) applied prednisone in combination with the immunosuppressant mizoribine, resulting in the patients being completely or partially relieved.

MGUS is a type of plasma cell disease. Based on whether the serum M protein quantification is greater than 30 g/L, whether the bone marrow clonal plasma cells are greater than 10% and whether there are clinical symptoms, plasma cell disease is divided into MGUS, asymptomatic/smoldering myeloma (SMM) and MM. The current consensus is that there is a gradually evolving relationship between these three groups of diseases. Internationally, MM and MGUS are stratified by risk according to the quantification of M protein and the level of free light chain in hematuria. Therefore, the nodes of treatment vary with the risk of progression to MM.

In our case report, proteinuria was considered to be caused by GFND, and there was no relevant literature to show the correlation between GFND and MGUS. Therefore, there was no further treatment for MGUS. At admission, the patient had low basal blood pressure, so ACEI or ARB was not preferred. After 3 months of coadministration of the immunosuppressant dexamethasone

combined with cyclophosphamide, the patient's clinical symptoms and laboratory tests showed no significant improvement. To achieve a better therapeutic effect, we tried a combined treatment with bortezomib. As a selective and reversible proteasome inhibitor, bortezomib can inhibit the activation of nuclear factor-κB (NF-κB) and the IL-6 pathway in bone marrow stromal cells, a classic drug for treating plasma cell tumors. NF-κB is a DNA-binding protein with multiple transcriptional regulatory effects. It has a regulatory effect on the expression of immune and inflammation-related factors and inflammatory transmitters (21) and is activated by the phosphorylation regulation of various factors in the cell. In unstimulated cells, NF-κB and inhibitor of NF-κB (IκB) bind to form a complex that exists in the cytoplasm in an inactive state (22). When the cell is exposed to external stimuli, IκB kinase (IKK) is phosphorylated and activated (23). Activated IKK phosphorylates IκB, IκB is rapidly degraded, and the nuclear localization sequence of NF-κB is exposed, directing NF-κB from the cytoplasm into the nucleus, thereby promoting the transcription of related genes involved in physiological and pathological processes such as cell proliferation, inflammatory response, immune response, and neovascularization (24). The mechanism of bortezomib mainly includes the following: (I) selective binding to threonine at the active site of the proteasome to inhibit chymotrypsin and/or trypsin activity of the 20S subunit of the proteasome (25); (II) preventive degradation of IκB, making NF-κB in a complex state and reducing its activity; and (III) participation in T cell activation, blocking T lymphocyte proliferation, upregulating p53 gene expression and inducing apoptosis (26), downregulating CXCR3, inhibiting its activation and migration (27), and reducing the synthesis of cytokines such as TNF-α and IL-4 (28). Based on many pharmacological mechanisms, bortezomib has been widely used in a variety of lymphomas. There have also been many advances in the prevention and treatment of graft-versus-host disease (GVHD), such as a reduction in the incidence of acute graft-versus-host disease (aGVHD) and chronic graft-versus-host disease (aGVHD) (29,30). Studies have shown that bortezomib can also prevent fibrosis of the liver, skin and heart (31-33), treat pulmonary hypertension (34), and promote the apoptosis of non-small cell lung adenocarcinomas (35). Reviewing the literature on bortezomib in the treatment of kidney disease, Suo *et al.* (36) published a study on bortezomib to reduce the occurrence of interstitial fibrosis after kidney transplantation by inhibiting TNF-α-induced Smurf2 expression. Many cases at home and abroad have reported bortezomib with a good response and few adverse reactions in the treatment of membranous nephropathy, and on the mechanism may be related to multiple immune regulation, inhibition of plasma cell production of antibodies, and inhibition of inflammatory responses (37-39). Shuma once applied BD regimen containing bortezomib to treat a patient with dense deposit disease (DDD) secondary to MGUS in 2018, and the patient's edema symptoms and renal function were significantly improved. Histological elimination of DDD and serum complement activation were controlled after the second renal biopsy (40). The patient in our case was treated with the BCD regimen for 4 cycles, the clinical edema was completely relieved, and the serum albumin level was close to normal. The patient was satisfied with the treatment effect, stopped the treatment, and was regularly followed up. As GFND is a rare disease, most cases have been reported internationally at present, and there is no clear effective and specific treatment plan for this disease. Therefore, whether bortezomib can be widely used in GFND requires more case support. Renal failure due to the disease occurs approximately 10 to 15 years after diagnosis. Although early treatment is responsive, close follow-up is needed to prevent the occurrence of renal failure.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-242/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-242/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures

performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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