Bortezomib-induced glomerular microangiopathy complicated with monoclonal immunoglobulin deposition disease

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Abstract

A 75-year-old man admitted with IgG λ -type myeloma with creatinine level of 2.3 mg/dL. Serum lactate dehydrogenase level and platelet count were normal. Urinalysis demonstrated massive proteinuria dominated by albuminuria. Weekly bortezomib and dexamethasone therapy were started to treat myeloma but failed to be continued because of rapid deterioration of renal function and increase in proteinuria 1 week after the treatment. His renal function exacerbated to require hemodialysis for a month. There was no clinical evidence of tumor lysis syndrome or thrombocytopenia throughout the course of his acute kidney injury (AKI). After he became dialysis independent, a renal biopsy was performed to clarify myeloma-related renal involvement and the cause of AKI. As a result, IgG2- λ monoclonal immunoglobulin deposition disease (MIDD) and severe endothelial injury were revealed. There was no evidence of cast nephropathy. Bortezomib-induced glomerular microangiopathy (GMA) superimposed on MIDD. Bortezomib has a potential risk to cause drug-induced GMA without systemic thrombotic microangiopathy, in which vascular endothelial growth factor-nuclear factor- κ B pathway could be involved. This is the first case of biopsy-proven bortezomib-induced GMA. If proteinuria (mainly albuminuria) increases after using bortezomib, GMA should be suspected as an adverse effect of bortezomib even absent of clinical signs of systemic thrombotic microangiopathy.

Keywords Thrombotic microangiopathy (TMA) · Multiple myeloma · Bortezomib · Monoclonal immunoglobulin deposition disease (MIDD) · Glomerular microangiopathy · Acute kidney injury (AKI)

Introduction

Bortezomib is a first-generation proteasome inhibitor which is a key drug for the treatment of multiple myeloma (MM) with renal impairment (RI) [1]. However, proteasome inhibitors such as bortezomib have been reported to have a rare adverse effect of thrombotic microangiopathy (TMA) [2]. To our knowledge, there have been only two reports on renal TMA caused by bortezomib proven by renal biopsy; however, both cases demonstrated systemic TMA with fragmented red blood cells [3, 4].

Recently, endothelial injury to the glomeruli without typical systemic TMA caused by anti-vascular endothelial growth factor (VEGF) inhibitor such as bevacizumab has

been newly termed as anti-VEGF therapy-induced glomerular microangiopathy (GMA) [5, 6]. Proteasome inhibitors are known to affect VEGF pathway via reduction nuclear factor- κ B [7], suggesting that GMA could be induced by bortezomib treatment. Herein, we report a first case of biopsy-proven MM-related monoclonal immunoglobulin deposition disease (MIDD) complicated with bortezomib-induced GMA without systemic TMA.

Case report

A 75-year-old man with the elevated serum creatinine of 2.3 mg/dL and severe anemia with hemoglobin of 7.4 g/dL was admitted to our hospital. Initially, his total IgG level was 4963 mg/dL (IgG2; 98%) and IgG- λ monoclonal protein was detected. The serum κ chain was 16 mg/L and the λ chain was 236 mg/L; the ratio of the free light chain was abnormal at 0.06. Antinuclear antibodies were negative and complement fractions were normal. The platelet count

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was $407 \times 10^3/\mu\text{L}$ and the lactate dehydrogenase level was slightly high at 240 IU/L. Bone marrow examination demonstrated increased monoclonal CD138-positive plasma cells (80%). He was diagnosed as IgG- λ type MM with Revised International Staging System III without chromosomal abnormality. Urinalysis showed albumin-dominant proteinuria, indicating that his RI was not light chain cast nephropathy but glomerular disease such as amyloidosis or MIDD. To treat MM complicated with RI, weekly bortezomib ($1.3 \text{ mg}/\text{m}^2$) and dexamethasone (Dex; 20 mg) combination therapy was started. One week after the first dose of bortezomib, his creatinine was elevated to 4.7 mg/dL and 24-h urine protein increased from 1.0 to 2.0 g/day. Drug-induced acute kidney injury (AKI) was suspected and bortezomib/Dex treatment was discontinued. However, the creatinine level deteriorated rapidly to a maximum 11.8 mg/dL; he needed to start hemodialysis within two weeks. Throughout the course of AKI, there was no evidence of tumor lysis syndrome nor hemolysis. Platelet count and serum lactate dehydrogenase levels were maintained in the normal range. Neither progression of anemia with schistocytes nor abnormally high blood pressure was observed. Urinary β_2 -microglobulin was 4791 $\mu\text{g}/\text{L}$ (normal range, < 230) before chemotherapy, but there was no exacerbation after chemotherapy. After initiating dialysis, lenalidomide (5 mg/day) and Dex therapy was initiated as a second line of therapy, but due to severe systemic skin rash and fever, lenalidomide was discontinued after a week and only Dex was continued. One month after the episode of AKI, renal function was gradually ameliorated and he became dialysis independent, but 24-h urine protein (mainly albuminuria) remained high at 2.0–5.0 g/day. The biopsy was performed to unveil the pathogenesis of MM-related RI and subsequent AKI. A renal biopsy showed global sclerosis in 14 of 35 glomeruli and membranoproliferative glomerulonephritis-like changes which were characterized by mesangial proliferation with nodular lesions and glomerular basement membranes (GBMs) duplication with subendothelial spaces (Fig. 1a, b). One glomerulus with a small fibrous crescent showed subendothelial exudates and fragmentation of red blood cells (Fig. 1c). The arteries showed mild hyalinosis of the intima as arteriosclerosis, but there was no evidence of thrombosis in arterioles, small arteries (Fig. 1d). In the tubulointerstitium, moderate lymphocyte infiltration, tubular atrophy, and interstitial fibrosis were observed; however, tubulitis and tubular necrosis were not found. Amyloid deposits were not observed by direct fast scarlet staining. No evidence of light chain cast nephropathy was found by light and electron microscopy. The fluorescent immunostaining revealed positive IgG2 and λ light chain along the GBMs and tubular basement membranes (Fig. 1e–k), but other immunoglobulins or complements were negative. An

electron microscopy showed subendothelial electron dense deposits along the GBMs and tubular basement membranes which was compatible with MIDD (Fig. 2a, c). Meanwhile, marked edema in the subendothelial space as endothelial injury and extensive podocyte foot process effacement were observed (Fig. 2b). Platelet aggregates were noted in the subendothelial spaces and loss of endothelial cells was also found in some capillaries. These findings were consistent with IgG2- λ light and heavy chain deposition disease complicated by GMA.

According to the renal biopsy findings and clinical course, bortezomib was supposed to be a cause of AKI, thus we considered treatment without proteasome inhibitor to be preferable. Therefore, we had started dexamethasone monotherapy followed by carfilzomib and dexamethasone therapy (Fig. 3), but discontinued it after confirming the renal biopsy findings. He has been able to achieve a very good partial response with the elotuzumab, pomalidomide and Dex combination therapy. His renal function remained at serum creatinine level of 2.0–2.5 mg/dL after 1 year of the first treatment.

Discussion

MIDD is one of the complications of MM-related RI [8]. The pathological findings in glomeruli are nodular formation, mesangial proliferation and capillary wall thickening with depositions on basement membranes. These features were observed in the present case; however, widespread subendothelial space without immunoglobulin deposition was not compatible with MIDD. Progressive deterioration of renal function a week after the administration of bortezomib indicated that the proteasome inhibitor was involved in the glomerular TMA formation and subsequent AKI.

TMA is known to be a rare adverse effect of proteasome inhibitors such as bortezomib and carfilzomib [2]. Previous reports have shown bortezomib-induced systemic TMA characterized by thrombopenia, hemolytic anemia and renal injury. A renal biopsy, however, was performed in only two cases.^{3,4} These cases revealed renal thrombi in the glomeruli and arteries accompanied with hemolysis and thrombocytopenia, suggesting drug-induced systemic TMA. Although rare, monoclonal gammopathy including MM is known to cause systemic TMA but it usually develops at the initial presentation [9]. The present case had no clinical features supporting systemic TMA before and after the chemotherapy.

Endothelial injury without systemic TMA localized to the glomeruli has been reported in anti-VEGF inhibitor-related RI [5, 6] and in POEMS syndrome [10–12].

Fig. 1 Renal biopsy findings. **a** Membranoproliferative glomerulonephritis with nodular lesion (arrow) on periodic acid-Schiff staining (original magnification, $\times 400$). **b** Double contours of glomerular basement membranes (arrows) and subendothelial expansion with exudative lesion (double-headed arrow) on periodic acid methenamine silver stain (original magnification, $\times 400$). **c** Subendothelial exudates and fragmentation of red blood cells (arrows) on periodic

acid methenamine silver stain (original magnification, $\times 400$). **d** The hyalinosis of the small arteries and arterioles without thrombi on Elastica-Masson staining (original magnification, $\times 400$). **e–k** The findings of the fluorescent immunostaining (original magnification, $\times 400$). The IgG and λ chain are mildly linear positive on glomerular and tubular basement membranes. Only IgG2 is positive among IgG subclass staining

POEMS syndrome is a disease characterized by abnormally high serum VEGF [13]. In general, VEGF is produced by podocytes and contributes to maintain homeostasis between endothelial cells and podocytes in the glomerulus [14]. Lack of VEGF stability causes endothelial injury and podocytopathy, leading to advanced proteinuria and renal failure. Bortezomib has the potential to impair local VEGF homeostasis in the glomerulus via inhibition of nuclear factor- κ B pathway [7]. Recently, glomerular limited TMA is newly termed GMA by Pfister et al. [5] and Person et al. [6]. They reported that the GMA manifests double contours of GBMs and endothelial damage in the kidney but lacks findings suggesting systemic TMA, such as thrombopenia. Of note,

GMA is associated with nephrotic range proteinuria. The renal pathology and clinical features in our patient are compatible with GMA. Then, it has been suggested that the main pathogenesis of GMA is that the close crosstalk between endothelial cells and podocytes in the glomerulus is broken by VEGF inhibition, leading to increased permeability of endothelial cells [5]. TMA, which occurs in systemic vessels lacking the endothelial–epithelial cell relationship as in glomeruli, may be different from the pathogenesis of GMA, and therefore hemolysis as in systemic TMA may be less likely to be seen in GMA. However, since the same drugs are also known to cause systemic TMA, the precise mechanism is unknown.

Fig. 2 Electron microscopy findings (original magnification, $\times 5000$). **a** The subendothelial electron dense deposits (EDDs) along the glomerular basement membranes (arrows) and accumulation of plate-

lets into the subendothelial space. **b** Subendothelial edema (double-headed arrow). **c** The EDDs along the tubular basement membranes (arrows). *T* tubular, *I* interstitium

Theoretically, initial treatment of drug-induced nephropathy is withdrawal of the offending medication. The present case required dialysis due to bortezomib-induced GMA, but fortunately, the renal function was reversed by discontinuation of the drug. Because bortezomib is the preferred agent for the treatment of MM with RI [1], it is difficult to determine whether an exacerbation of renal dysfunction is an adverse effect of bortezomib or a deterioration of MM-related RI itself. Typically, proteinuria derived from light chain cast nephropathy is mainly non-albuminuria [15], suggesting that RI in the present case is not cast nephropathy. The present case showed proteinuria associated with MIDD before chemotherapy, but

the amount of proteinuria worsened further with deterioration in renal function after bortezomib administration. Therefore, it is important to focus on the urine protein before and after treatment, to speculate on the underlying cause of renal disease.

Bortezomib is one of the important agents for the treatment of MM with RI; however, it can cause renal failure as well. Both hematologists and nephrologists should be reminded that proteasome inhibitors have the potential to cause drug-induced GMA without systemic TMA. If AKI with increased proteinuria (mainly albuminuria) develops after bortezomib initiation, bortezomib-induced GMA should be listed as a potential cause.

Fig. 3 Clinical course. *Bd* bortezomib and dexamethasone, *Ld* lenalidomide and dexamethasone, *Dex* dexamethasone, *Kd* Carfilzomib and dexamethasone, *Pd* pomalidomide and dexamethasone, *EPD* elotuzumab, pomalidomide and dexamethasone, *HD* hemodialysis, *Cr* creatinine, *UP* urine protein

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Declarations

Conflict of interest The authors declare that they have no relevant financial interests.

Ethical approval This article does not contain any studies with human participants performed by any of the authors.

Informed consent Informed consent was obtained from the patient.

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