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# Carfilzomib Induced Microangiopathy due to Accumulation With Paxlovid



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## INTRODUCTION

Thrombotic microangiopathy (TMA) syndromes are characterized by the association of hemolytic microangiopathic anemia, thrombocytopenia, and organ injury due to arteriolar and capillary thrombosis. Establishing an etiological diagnosis of TMA is essential because it can help identify which therapies will be beneficial. In adults, etiologies of TMA include shiga toxin-related hemolytic uremic syndrome, *ADAMTS13* (genetic or acquired) deficiency (thrombotic thrombocytopenic purpura) and atypical hemolytic uremic syndrome secondary to complement alternative pathway dysregulation. TMA can also be the satellite of several conditions, such as malignant hypertension, malignancy, drug-induced systemic disease, infections, pregnancy, and transplantation. Among cases of drug-induced TMA, carfilzomib-induced TMA is an emerging problem.

We report the first case of carfilzomib-induced TMA due to an accumulation of the drug in the context of interaction with Paxlovid.

## CASE PRESENTATION

A 73-year-old man was admitted to the intensive care unit for acute kidney failure and cardiac dysfunction. His main medical history was multiple myeloma in remission treated with carfilzomib and dexamethasone. The patient was diagnosed with COVID-19 disease causing fever and a cough. Treatment with Paxlovid (nirmatrelvir/ritonavir) was initiated on the day carfilzomib was reinjected. Three days later, the patient developed anuria and dyspnea prompting intensive care unit admission. On clinical examination he had high blood pressure of 170/90 mm Hg and lower limb edema. No systemic sign was detected and no gastrointestinal disorder was observed.

The diagnosis of hemolytic microangiopathic anemia was established on the basis of the following results: hemoglobin 9.3 g/dl, lactate dehydrogenase 716 U/l (normal $<$ 246), haptoglobin $<$ 0.08 g/l, with schistocytes on peripheral blood smear, with a negative direct Coombs test. Other results of initial laboratory tests were as follows: platelets 14 G/l, serum creatinine level, was 607 µmol/l, (baseline estimated glomerular filtration rate was 85 ml/min per 1.73 $m^2$ Chronic Kidney Disease - Epidemiology Collaboration corresponding to a baseline serum creatinine of 78 µmol/l), glomerular selective proteinuria 7 g/g of creatinine (anteriority 0,15 g/g) without nephrotic syndrome, hematuria 77x$10^3$/m, kappa light chain 12 mg/l and lambda light chain 3 mg/l. SARS-Cov-2 nasopharyngeal polymerase chain reaction test was positive. Transthoracic echocardiography showed severe left ventricular dysfunction (30%) whereas the findings of a recently performed transthoracic echocardiography were normal. Renal ultrasonography revealed no obstructive etiology. Computed tomography scan ruled out pneumonia due to COVID-19 and showed cardiac overload. TMA was diagnosed with severe kidney acute injury, bicytopenia and myocardial injury.

Etiological analyses comprised negative results of stool cultures (polymerase chain reaction-based detection assay for shiga-toxin), of hepatitis and human immunodeficiency virus serologies, of antinuclear and antiphospholipid antibodies tests, and normal values of *ADAMTS13* activity (104%). The results of the plasma assessment of the alternative complement pathway were as follows: the complement factor proteins were

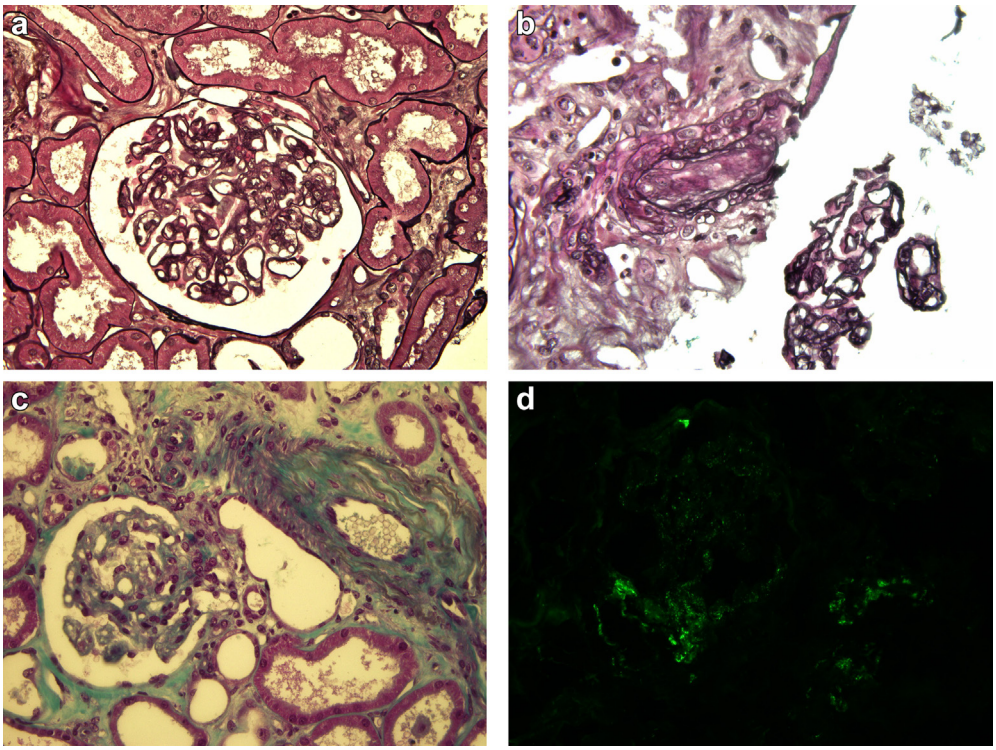


**Figure 1.** Kidney histology. (a) Light microscopy, Masson's trichrome staining, ×40. There was a diffuse augmentation of mesangial material and mesangial hypercellularity in all glomeruli, and a thickening of the glomerular basement membranes. Interstitial fibro-edema was estimated to cover 25% of the cortical surface. Acute tubular necrosis lesions were present with osmotic nephrosis (vacuolization of tubular cells) and exposure of certain tubular epithelia. (b) Light microscopy, silver staining, ×40. Thickening of the capillary wall with a duplication aspect of the glomerular basement membrane and endothelial cell swelling. (c) Light microscopy, silver staining, ×40. The vessels showed fibrinoid necrosis of the vascular wall of certain arterioles, thickening of certain arterial walls by mucoid endarteritis, arteriolar hyalinosis, and intravascular thrombi. (d) Immunofluorescence, C3 staining, × 60. Immunofluorescence evidenced mild glomerular capillary wall C3 deposits; IgA, IgM, IgG, kappa and lambda were negative.

within normal range values (total hemolytic complement 96%, C3 899 mg/l, C4 257 mg/l, factor H 99 %, factor I 83%), the expression of membrane cofactor protein was reduced (8,2) and the level of soluble terminal complement activation fragment was elevated (571 ng/ml). Anti-complement factor H (CFH) antibodies were negative. A full sequencing analyses for alternative pathway's genes are in progress.

A kidney biopsy was performed (Figure 1) and revealed the following: (i) glomerular injury with duplication aspect of the glomerular basal membrane, intraglomerular thrombi, and endothelial cell swelling (a and c); (ii) acute tubular injury (c); (iii) vascular injury with fibrinoid necrosis, mucoid endarteritis, and intravascular thrombi (b); and (iv) mild glomerular capillary wall C3 deposits (d).

Carfilzomib-induced TMA was diagnosed because it is a frequent complication of the treatment and because the addition of Paxlovid led to overdose. The treatment initiated was renal replacement therapy, and cessation of Paxlovid and carfilzomib, folinic acid and eculizumab.

The treatment achieved favorable outcome with renal replacement therapy being weaned 3 weeks after it was initiated. Three months after disease onset, eculizumab was administered and the following were observed: kidney function, proteinuria, and hypertension dramatically improved (creatinine 123 µmol/l–estimated glomerular filtration rate 50 ml/min Chronic Kidney Disease - Epidemiology Collaboration; proteinuria 0.2 g/g with blood pressure normalization), the hemogram returned to normal and there was no hemolysis stigma. Myeloma treatment remission was stopped for simple monitoring.

## DISCUSSION

Carfilzomib is an irreversible proteasome inhibitor currently used for the treatment of relapsed or refractory multiple myeloma. Proteasome inhibitors, especially carfilzomib, have been involved in the development of drug-induced TMA.[1] The incidence of this complication is unknown, but is unlikely to be more than 1%. Most cases of carfilzomib-induced TMA have been reported during the second or third cycle of therapy but the complication can occur at any stage. The onset of carfilzomib-induced TMA is sudden with a deterioration in general condition, anemia, mild thrombopenia, worsening of pre-existing hypertension, appearance or

worsening of pre-existing proteinuria, acute kidney injury, and rarely extrarenal manifestations.[2,3]

Proteasome inhibitor-induced TMA is due to a class effect, reported with bortezomib, carfilzomib, and ixazomib. The proposed pathogenesis of proteasome inhibitor-induced TMA includes immune-mediated and dose-dependent toxicity mechanisms.[4,5]

First, inhibition of the NFkB pathway causes a decrease in vascular endothelial growth factor in the podocyte that results in endothelial injury, which is the hallmark of TMA.[2] In addition, proteasome inhibitor can induce high levels of proinflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α which can promote the formation of autoantibodies directed at *ADAMTS13*.

Second, it has been recognized that a complement can play a central role in proteasome inhibitor-induced TMA. A few studies have reported activation of the alternative pathway of complement, which seems to occur by decreasing the expression of CFH in patients who are possibly genetically predisposed.[6] Portuguese *et al.*[4] described 3 patients with carfilzomib-induced TMA of whom 2 had heterozygous *CFHR3-CFHR1* deletions. Homozygous deletion in CFH-related protein genes is known to induce TMA, whereas heterozygous deletion is generally considered as a common benign variant.[6] However, the authors suggested that the administration of carfilzomib could "switch on" a benign variant (i.e., heterozygous *CFHR3-CFHR1* deletion) to a conditionally functional mutation leading to the development of TMA.[6]

Another study reported deposition of a membrane attack complex (C5b9) on endothelial cells in culture exposed to plasma from 3 out of 4 patients during the acute phase of carfilzomib-induced TMA.[7] In the same study, complement overactivation was suggested as a mechanism of potential endothelial damage.

A recent study recruited consecutive patients with carfilzomib-induced TMA and compared them with patients receiving carfilzomib treatment without TMA.[8] The authors analyzed genomic DNA from peripheral blood using next generation sequencing with a complement-related gene panel as follows: *ADAMTS13* activity and soluble C5b9. They showed that complement-related variants were more common in patients with carfilzomib-induced TMA than in non-TMA controls, regardless of patient and treatment characteristics. *ADAMTS13* activity was reduced and C5b-9 levels were elevated compatible with the phenotype of complement-related TMA.[8]

Previous reports have shown that immediate discontinuation of carfilzomib plus supportive care may be sufficient to improve the manifestations of the disease. There is limited evidence that eculizumab, a monoclonal antibody against the complement protein C5, could be beneficial in patients with carfilzomib-induced TMA.[3,6-8] The involvement of activation of the alternative pathway of the complement is an argument for the use of eculizumab in carfilzomib-induced TMA.

Moreover, SARS-Cov-2 infection could have been a factor promoting TMA because the virus can activate the endothelium and complement cascade.

To our knowledge, we are the first to describe carfilzomib-induced TMA caused by accumulation of the drug following interaction with Paxlovid (nirmatrelvir/ritonavir). Nirmatrelvir in association with ritonavir is an antiviral agent targeting the 3-chymotrypsin-like cysteine protease enzyme (3C-like protease or Mpro), which is a key enzyme of the viral cycle of the SARS-CoV-2 virus. This combination with a well-known pharmacokinetic enhancer leads to a high risk for drug-drug interactions.

Plasma concentration of carfilzomib declines rapidly and in a biphasic manner after intravenous administration.[9] The systemic half-life is short and the systemic clearance rate is higher than hepatic blood flow. Carfilzomib is largely cleared extrahepatically via peptidase cleavage and epoxide hydrolysis. Carfilzomib induces direct and time-dependent inhibition of *CYP3A* in human liver microsome preparations and exposure to carfilzomib results in reductions in *CYP3A* and 1A2 gene expression in cultured human hepatocytes.[9] The rapid systemic clearance and short half-life of carfilzomib limit clinically significant drug-drug interaction, but in the context of carfilzomib and Paxlovid coadministration we suggest that carfilzomib accumulation occurred leading to the promotion of side effects.

With the massive use of Paxlovid during the SARS-Cov-2 pandemic, particular attention should be given to patients undergoing proteasome inhibitor treatment.

## Teaching Points

- Proteasome inhibitors, especially carfilzomib, have been involved in the development of drug-induced TMA.
- The rapid systemic clearance and short half-life of carfilzomib limit clinically significant drug-drug interaction, but in the context of carfilzomib and Paxlovid coadministration, carfilzomib accumulation occurred leading to the promotion of side effects.
- With the massive use of Paxlovid during the SARS-Cov-2 pandemic, particular attention should be given to patients undergoing proteasome inhibitor treatment.

## DISCLOSURE

All the authors declared no competing interests.

## PATIENT CONSENT

The authors declare that they have obtained consent from the patient discussed in the report.

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