UC DAVIS HEALTH SYSTEM

# Therapeutic Plasma Exchange in Carfilzomib-Induced Thrombotic Microangiopathy


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**Background:**
A 60 year old man with IgA kappa plasmacytic myeloma status post multiple treatment regimens as well as auto- and allo-HCTs presented with thrombocytopenia, hemolytic anemia, schistocytosis (Figure 1) and renal failure. He had recently started treatment with carfilzomib, pomalidomide, and dexamethasone (CPD), having completed 32 doses of carfilzomib over 6 months. His presentation was attributed to a probable drug reaction to carfilzomib (now discontinued) using the Naranjo adverse drug reaction scale.

**Methods:**
Eight daily therapeutic plasma exchanges were performed and pertinent laboratory parameters were trended (Figure 2).

**Findings:**
At admission, urine protein was 9408 mg/24hr (reference range <150 mg/24hr), and complement and ADAMTS-13 levels were normal. The patient remained afebrile without neurologic alterations. Renal function improved and he was discharged.

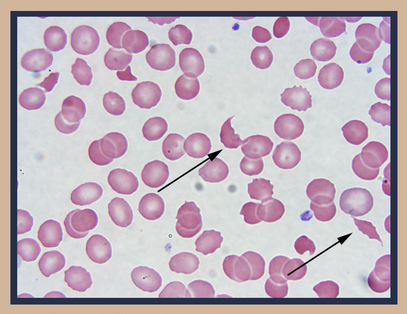

**Figure 1**: The peripheral smear shows multiple schistocytes in a background of microcytic anemia and thrombocytopenia. (1000x magnification)

**Conclusion:**
The FDA approved CPD in 2015 for the treatment of patients with relapsed myeloma who have received one to three prior lines of therapy.[1] An online FDA drug warning notes "cases of thrombotic microangiopathy, including thrombotic thrombocytopenic purpura/hemolytic uremic syndrome, have been reported."

Carfilzomib is a second generation proteasome inhibitor, binding irreversibly to the 20S core of the 26S proteasome.[2,3] While the action has some specificity for proteasomes of lymphoid origin (leading to neoplastic cell apoptosis), the disruption of intracellular signaling also results in a failure of ubiquination of IκB, which prevents nuclear localization of NF-κB.[2-4] This reduces VEGF production, which is thought to be a predisposing factor to thrombotic microangiopathy (TMA).[5,6] The mechanism of TMA has been proposed as either a result of immune mediation (usually within 21 days of the start of administration, or within 24 hours of re-exposure), or as a dose-related toxicity (as is likely in this case).[5]

The American Society for Apheresis guidelines do not include carfilzomib-induced thrombotic microangiopathy in its indications for therapeutic plasma exchange.[7] Animal and human studies suggest that carfilzomib is rapidly cleared from the plasma compartment, with a half-life ranging from 5-20 minutes.[4,6] Carfilzomib is broken down into several inactive metabolites, most of which are readily cleared by biliary and renal mechanisms within 4 hours.[2,4,6] Drug or metabolite accumulation has not been observed in patients with pre-existing renal failure.[3,8,9]

Several other case reports have been published on the possible connection of carfilzomib and TMA.[2,10,11] The success of TPE on the treatment of TMA has been an issue of disagreement among authors, with some suggesting a limited role and efficacy of TPE, and others suggesting supportive care and watchful waiting (in addition to cessation of therapy) are the best course. This case provides the strongest evidence in the available literature for a TPE-mediated recovery, with a marked improvement in all markers of TMA-related disease during the course of plasma exchange. (Other reported cases have not has as robust a recovery of platelets or decrease in schistocytes or serum creatinine during treatment with TPE.)

While TMA is an uncommon adverse event related to carfilzomib use,[12] emerging reports suggest that there may be a limited role for TPE use in treatment, provided patients show laboratory or clinical evidence of TMA recovery.

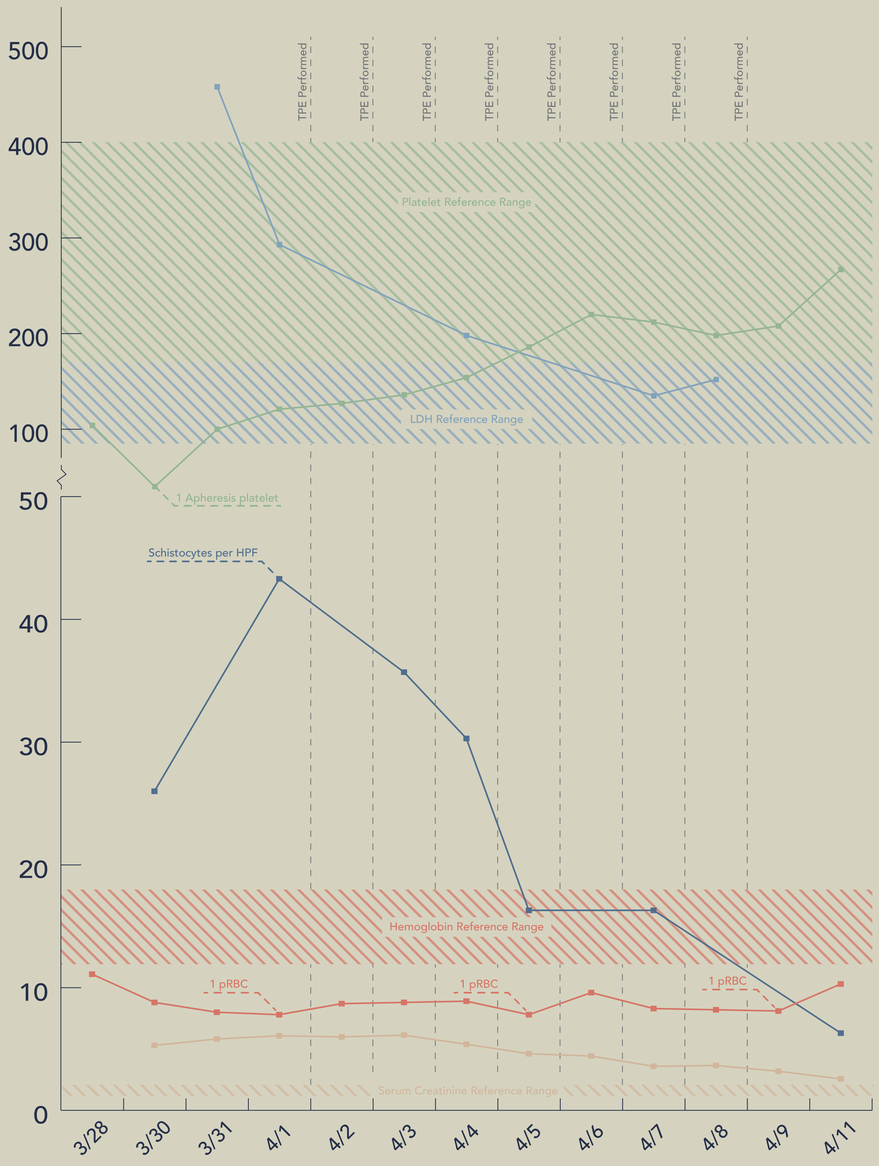


**Figure 2:** Summary of relevant laboratory values during the patient's hospitalization

## Citations


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