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The Reply

We thank Dr Murphy for his Letter to the Editor regarding our recent Diagnostic Dilemma article published in Issue 6 of this year's ***American Journal of Medicine***.[1]

To Dr Murphy's first point, we agree that fresh frozen plasma (FFP) alone would have been unlikely to reverse the coagulopathy that this patient experienced due to disseminated amyloidosis. By our estimations, a single unit of FFP contains approximately 200-250 IU of factor X, whereas a typical dose of prothrombin complex concentrate (PCC) could contain 1000-1500 units IU of factor X (and at a greater concentration, thus allowing for less volume overload in this patient who had renal dysfunction).[2] While PCC is available at our institution, high-purity factor X is not, and FFP is preferred in terms of availability and cost. We did not consider later use of PCC for the following reasons: by the time it became apparent that this patient had an unconventional coagulopathy that would not correct with FFP, we had already made arrangements for a less invasive procedure (a fat pad biopsy) that would confirm the suspected diagnosis of amyloid.

To Dr Murphy's second point, he is also correct that the treatment of systemic amyloidosis has markedly advanced in recent years. In fact, at the time that this patient was undergoing workup, the ANDROMEDA Trial—a pivotal phase 3 clinical trial investigating the addition of the human IgG-kappa anti-CD38 monoclonal antibody daratumumab to a standard therapy regimen of cyclophosphamide, bortezomib, and dexamethasone—was underway. Primary results were first reported in 2021 (three years after this patient initially presented), and showed a statistically significant response in the endpoints of complete hematologic response (primary endpoint, 53.3% in the daratumumab group versus 18.1% in the control group, $P<0.001$) and survival free from major organ deterioration or hematologic progression (hazard ratio 0.58, $P=0.02$, secondary endpoint).[3] Unfortunately, our patient would not have qualified even for the ANDROMEDA trial, which had as an exclusion criterion an estimated glomerular filtration rate (eGFR) of less than 20 ml per minute per 1.73 square-meter of body-surface area; our patient's eGFR was 22 at time of presentation, with further progressive decline over only a few days down to 16. However, with the results of ANDROMEDA now reported, off-label use of their regimen could have been considered for this patient.

In summary, Dr Murphy's correct points further underscore our case's teaching point regarding prompt consideration of disseminated systemic amyloidosis when confronted with a coagulopathy that proves refractory to transfusions. Should such a coagulopathy be recognized and amyloidosis suspected, a patient could be identified earlier in the amyloid course and thus prognosis (thanks to treatment advances, both those cited by Dr Murphy as well as others) would be more favorable.

Douglas M. Ornoff, MD, PhD[a]
Andrew Berry, MD[b]
Ajay Major, MD, MBA[c]
[a]*SCL Healthcare / Intermountain Healthcare, Denver, Colo*
[b]*Division of General Internal Medicine, Department of Medicine, University of Colorado School of Medicine, Aurora, Colo*
[c]*Division of Hematology, Department of Medicine, University of Colorado School of Medicine, Aurora, Colo*

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Requests for reprints should be addressed to: Doug Ornoff, MD, PhD, 835 East 18th Avenue, Denver, CO 80218.
E-mail address: doug.ornoff@cuanschutz.edu

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