Challenges of Caring for an Advanced Chronic Kidney Disease Patient with Severe Thrombocytopenia

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Introduction
The survival of patients on hemodialysis (HD) depends on the ability to gain repeated and reliable access to the circulation system.¹ There are currently three forms of vascular access, including the native arteriovenous fistula (AVF), arteriovenous graft (AVG), and tunneled and cuffed central venous catheter, that are accepted for use in the clinical setting.² Despite their advantages, such as a large surface area available for cannulation and a short lag-time from insertion to maturation, AVGs require more intervention to maintain patency and have a higher rate of infection than AVFs.³ On the other hand, the use of a central venous catheter as the long-term vascular access for chronic HD has been discouraged due to the risk of infection, the susceptibility to thrombosis, and inconsistent delivery of blood.² For these reasons, an autogenous AVF has been considered to be the optimal form of vascular access for HD in the field of nephrology.²⁻⁵ Nevertheless, the decision regarding the type of access used must still be individualized even in the ordinary clinical setting. In the present report, we describe the case of a female patient with advanced chronic kidney disease (CKD) associated with a hemostatic disorder. Despite the exhausted peripheral vasculature, she required recurrent platelet transfusions for severe thrombocytopenia due to aplastic anemia. The goal of care for this patient was to optimize the dialysis treatment without increasing the bleeding risk. Various concerns regarding the therapeutic conundrums encountered in the case are also discussed.

Case Report
A 57-year-old female with aplastic anemia was admitted to our hospital with pancytopenia. She had a white blood cell (WBC) count of 1.7 × 10⁹/µL, red blood cell (RBC) count of 266 × 10⁹/µL, hemoglobin (Hb) of 6.8 g/dL, and platelet count of 1.9 × 10⁴/µL. She had an unremarkable history except...
for rheumatoid arthritis diagnosed in 1993, for which she had been administered oral prednisolone at a dose of 2.5 mg/day for more than three years, with successful control of the disease activity. She was in the terminal stage (stage IV) in the classification of the progression of rheumatoid arthritis, and her functional status was class III based on the American College of Rheumatology criteria. Two months before admission, she was found to have thrombocytopenia and anemia with distinct signs of bleeding, including the presence of petechiae or purpura in the upper and lower extremities, combined with sporadic hemorrhage in the gingiva and conjunctivae, when her serum creatinine level was 4.0 mg/dL. She manifested a non-nephrotic range of proteinuria of 0.8 to 1.0 g of protein in a 24-hour urine specimen. Renal sonography revealed that both kidneys were reduced in size, with a renal length of approximately 8 cm, and the renal cortex echogenicity of each side was isoechoic to the liver, thus suggesting concomitant chronic renal damage. A bone marrow analysis showed hypocellular marrow with a percentage below 5%, without specific markers for other causes of pancytopenia, such as leukemia, lymphoma, or myelodysplastic syndrome (Fig. 1). A diagnosis of aplastic anemia was made, and other medications, including rabeprazole and allopurinol, were prescriptively stopped, although both of them had been initiated more than one year before the diagnosis. Supportive management, including multiple transfusions of packed RBCs and random-donor platelet concentrates, combined with subcutaneous administration of human recombinant erythropoietin, was then initiated, which maintained her Hb levels and platelet counts around 8 g/dL and 1 × 10^9/µL, respectively. However, she had been burdened with recurrent venipuncture for transfusion, and her peripheral venous access was almost exhausted when she became oliguric and developed fluid overload with an increased serum creatinine level of 6.4 mg/dL and a blood urea nitrogen level of 75 mg/dL, despite an attempt at forced furosemide diuresis. A further physical work-up by vascular surgeons ruled out the possibility of peripheral access. We therefore decided to place a tunneled and cuffed catheter for long-term HD treatment.

Random-donor platelet concentrate (200 mL including 200 × 10^9 platelets) was transfused for five days prior to catheter placement, resulting in a platelet count of 6.4 × 10^9/µL on the day of the procedure, when a prophylactic single intravenous dose of doripenem hydrate (0.25 g) was given. After confirming the patency of the right internal jugular vein (RIJV) by duplex Doppler ultrasound, a cuffed and tunneled central venous catheter (The Split-Cath® 14 French, MedComp, Harleysville, PA, USA) was placed there under local anesthesia in a standard radiological fashion, with the tip of the catheter kept at the level of the atrium as described previously (Fig. 2). The intervention was carried out by experienced nephrologists. No bleeding complications were observed after the catheter placement. Although the periodic HD treatment three times per week commenced on the following day and was uneventful, the patient remained dependent on RBC and platelet transfusions, which were administered during each HD session as needed. Two weeks after the catheter placement, the administration of granulocyte colony-stimulating factor (G-CSF) at a dose of 5 µg/kg three times per week was also initiated due to the gradually progressing neutropenia, which reached a nadir of 428/µL.

Despite these treatments, the patient’s hematological profile did not improve and reduced neutrophil count persisted around 600/µL, and the transfusion interval decreased.

Figure 1. A photomicrograph of the hypocellular bone marrow showing limited hematopoiesis and numerous fat cells.

Figure 2. A chest radiograph taken just after the placement of a cuffed and tunneled central venous catheter. The patient was placed in the supine position, and the patency of the right internal jugular vein (RIJV) was confirmed by duplex Doppler ultrasound. After the successful puncture of the RIJV, a catheter was placed, with the tip of the catheter kept at the level of the atrium.
She was thus scheduled to received immunosuppressive treatment for aplastic anemia with antithymocyte globulin (ATG) and cyclosporine A (CsA); however, protracted petechiae or purpura around several joints, such as the elbow and knee, combined with sporadic nasal bleeding and hemorrhage in the gingiva and conjunctivae as well as frequent febrile episodes, most of which were able to be rapidly controlled by empiric antibiotics, precluded the pursuit of such management. Nevertheless, severe leukopenia of 200 to 300/µL with a neutrophil count of 40 to 90/µL had developed after approximately four months after admission; this state persisted for approximately four weeks. Finally, the patient developed respiratory failure probably due to infectious pneumonia despite receiving periodic HD and aggressive antibiotic treatments combined with frequent RBC and platelet transfusions. She subsequently received palliative care through a shared effort, and went into shock and died 153 days after admission. The relatives of the patient declined a postmortem autopsy.

**Discussion**

Hemostatic disorders are a potentially life-threatening complication in advanced CKD patients and limit the use of surgery and invasive procedures. However, such a condition resulting from a uremic milieu may be corrected by the provision of an adequate HD program, mainly through the improvement of functional platelet abnormalities. 

Otherwise, HD may contribute to uremic bleeding diathesis through the use of systemic anticoagulation. It has been demonstrated that peritoneal dialysis (PD) is more effective for correcting platelet abnormalities than HD, although the precise reason for this has not been completely delineated. PD may thus be considered as safer for advanced CKD patients with hemostatic disorders, since it also minimizes the hemorrhagic risk of each peripheral vascular access for HD treatment. However, PD might not have been appropriate in the current case, as our patient required repetitive transfusions, implying that comparable venipuncture would have been needed even if the patient had been treated with PD, although a qualitative platelet disorder might also have been, at least in part, implicated in the patient's bleeding diathesis.

Several cases of aplastic anemia in subjects with advanced CKD have been described anecdotaly, however, none of these reports provided information regarding the vascular access conundrums related to the hemostatic disorders. Thus, the clinical significance of the current patient should be emphasized in terms of the impact of the hematological manifestations on the therapeutic management of the advanced CKD. We believe that the initiation of long-term renal replacement therapy with a tunneled and cuffed central venous catheter, rather than with peripheral vascular access, such as an AVG, which may be used even in subjects with exhausted peripheral vasculature, was an appropriate therapeutic option for the current patient. Indeed, such a procedure enabled us not only to continue the dialysis treatment, but also to perform repetitive transfusions without concerns about the assumptive risk of active and sustained bleeding due to severe thrombocytopenia from the access cannulation site. One may argue against the potential risk for vascular access bleeding resulting from low platelet counts. Nevertheless, we believe that it is necessary to take a proactive approach and not wait until fatal vascular access bleeding becomes apparent before the severe thrombocytopenia is treated. It should be kept in mind that we are always facing, as do most physicians at various times, different types of therapeutic dilemmas, as described herein.

There are numerous patients who require central venous catheterization as long-term access to allow for the safe delivery of therapeutic agents, transfusion of blood and blood products, or the performance of laboratory investigations. The catheter choice, however, depends on the indication and treating physician, and reflects the findings of various reviews of the morbidity and longevity, the hospital or surgical availability, as well as personal experience. Cuffed and tunneled central venous dialysis catheters, which are specifically designed for HD treatment and are reserved for temporary use or as a last resort for patients with an exhausted peripheral vasculature, serious cardiac diseases, a reduced life expectancy, and perhaps for those who are particularly sensitive to recurrent venipuncture, might also be used as a common vascular access for treatment and blood sampling in some subsets of HD patients with diseases such as hematomatologic disorders and malignancies. However, the only literature describing such a case was published by Wolfrum, in which the availability of a permanent dialysis catheter as not only dialysis access, but also as a parenteral route for various therapeutic agents, was described in a patient with hemorrhagic diathesis due to hemophilia. One may argue that this kind of shared access may already be too common to describe in the literature. Nevertheless, such a potential role of central venous dialysis catheters may not necessarily be recognized, and the paucity of information regarding concrete examples may also preclude their flexible application in the field of nephrology. In this regard, we believe that our experience with the current patient would help to evaluate the impact of the procedure among the overall population of patients with bleeding disorders who require periodic HD treatment and repetitive parenteral administration of various kinds of therapeutic agents.

The placement of central venous catheters would alternatively be a serious problem in the subjects with hemorrhagic diathesis due to thrombocytopenia. A significant relationship between the degree of thrombocytopenia and an increased risk of bleeding has been demonstrated, and platelet transfusion has clinical benefits in decreasing the hemorrhagic risk and intervention-related mortality in thrombocytopenic patients. The current recommendations regarding the platelet threshold during the peri procedural period for various invasive interventions, such as lumbar puncture, laparotomy, and the insertion of indwelling lines, has been \( 5 \times 10^9/\mu L \), which was also the target for the current patient.
the optimal platelet threshold under various clinical settings might be determined only when more experience with patients who have thrombocytopenia has been accumulated. Indeed, uneventful placement of central venous catheters is not exceptional among patients with reduced platelet counts below 5 × 10^9/L, regardless of their caliber.26,27

Aplastic anemia is characterized by a peripheral pancytopenia associated with the hypocellularity of bone marrow, without an excess of blast cells. Various agents and infections have been implicated in the development of the disease; however, it has not yet been elucidated as to why only some individuals are susceptible, while the majority of cases with aplastic anemia are categorized as idiopathic, since their primary etiology cannot be identified.30 The association of aplastic anemia with hepatitis and/or acute liver failure has been well described,30-32 while there have been few reports of aplastic anemia in patients with advanced CKD.15-17 Although the impact of CKD on the development of aplastic anemia remains to be delineated, a possible relationship between the response of bone marrow to recombinant erythropoietin as a therapeutic agent for protracted anemia, and the removal of uremic toxins by HD, has been described anecdotally.15 In the current patient, objective assessments, including the clinical course, laboratory examinations, and careful interviews about the use of therapeutic drugs and her occupational history, led us conclude that she should be categorized as having idioopathic aplastic anemia.

Although the mainstay of treatment for aplastic anemia consists of immunosuppression with ATG and CyA, prior to application of such treatment, it is necessary for the patient to be stabilized clinically in terms of controlling their bleeding and treating their infections.30 It is dangerous to administer these agents in the presence of infection due to their immunosuppressive nature. Aggressive platelet transfusion might be required to maintain a safe platelet count during the treatment, but they should not be given concomitantly with ATG administration because of its anti-platelet activity, which results in platelet consumption.30 There have been several reports of acute renal failure which developed after ATG treatment for aplastic anemia, although the precise pathogenesis regarding the nephrotoxicity of such management remains to be explained.33-35 Thorough experiences with ATG treatment combined with oral cyclosporine for aplastic anemia in patients with advanced CKD are lacking.37,38 At present, we have no idea of how the concurrent presence of CKD affects such immunomodulation, although one should not hesitate to use such a regimen, as proposed in a previous study.17 Nevertheless, the clinical manifestations in the current patient made it impossible to pursue immunosuppression, leading to the severe neutropenia which lead to her lethal condition. Obviouly, the establishment of an optimal management strategy for patients with a neutropenic status, which predisposes patients with aplastic anemia to various infections,37 is a matter requiring continuous and careful attention.

Author contributions
TA and CI drafted the manuscript. AK, MO, TS, RS made contributions to the acquisition of the clinical data. EK, DN provided a detailed review of the contents and structure of the manuscript, thus resulting in significant changes to the original document. All authors have read and approved the final manuscript.

DISCLOSURES AND ETHICS
As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

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