Case Report
Thrombocytopenia in the Setting of Hemodialysis Using Biocompatible Membranes

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1. Case

A 91-year-old African American man with a past medical history of chronic kidney disease presented with night sweats, myoclonic jerks, dysphagia, and loss of appetite all progressively worsening for approximately one year, in addition to a 40-pound weight loss over the past nine months. On admission, BUN and creatinine levels were 89 and 9.1, respectively. Hemodialysis was initiated on day four of hospital admission using the Fresenius Optiflux 200 dialyzer with a synthetic polymer (polysulfone) membrane. A nontunneled right internal jugular catheter was inserted for vascular access, and heparin was given per standard dialysis protocols. After two hemodialysis sessions over the course of 36 hours, the patient's platelet count decreased from 184,000 to 22,000. The hemoglobin and WBC remained at stable baseline levels of 10.4 g/dL and 4.13 × 10³/L, respectively, and continued in this range during the period of thrombocytopenia. Heparin-Induced Thrombocytopenia (HIT) was suspected; all heparin products and clopidogrel were discontinued and argatroban therapy was started. Despite this, the patient continued to demonstrate variably low platelet counts. A HIT panel, including PF4, PLT AB-Heparin dependent (SRA), and platelet antibody screen, was found to be completely negative and argatroban therapy was subsequently discontinued. With HIT no longer suspected, the patient was rechallenged with heparin during hemodialysis, with no change in the pattern of decreased platelet levels. On day thirteen of hospitalization, the dialyzer was switched to the Braun 18NR, also containing a synthetic polymer (alpha polysulfone) membrane; platelet levels continued to be variably depressed. Chronological correlation of platelet levels and hemodialysis sessions demonstrated a consistent decrease in platelet levels following each hemodialysis treatment (Figure 1) at which point it was suspected that thrombocytopenia was likely dialysis induced. The dialyzer was switched from the F18NR to the AM100 dialyzer with an alkyl ether polymer-grafted cellulose membrane. After initiating dialysis using the AM100, the patient's platelet levels began to recover without any regression. No episodes of postdialysis thrombocytopenia were recorded once the use of the AM100 was initiated. (See Table 1 for technical details of the 3 dialyzers used for this patient, and dates of use.)

2. Discussion
Platelets have been known to interact with dialysis membranes since the 1970's; dialysis membranes have been shown to cause platelet adhesion, aggregation, and activation [1–5].
Platelet activation has been demonstrated by elevated levels of platelet factor 4 [2, 3] as well as thromboxane [4], follow-
ing hemodialysis. Accordingly, thrombocytopenia is also a
well-known complication of hemodialysis treatment. Hakim
and Schafer suggested that thrombocytopenic episodes
occurring with hemodialysis were associated with comple-
ment activation, specifically C3a, in addition to activation
of platelets themselves [5]. Complement activation occurred
specifically in the setting of cuprophane membranes, and
thrombocytopenia was only observed in the presence of
complement activation [4]. Verbeelen et al. showed that
cellulose acetate dialyzer membranes can also cause transient
thrombocytopenia and platelet activation [6]. In contrast,
there were no changes in platelet levels and decreased com-
plement activation when dialysis was undertaken using non-
cellulose polymethylmethacrylate membranes [5]. Accord-
ing to Verbeelen et al., polyacrylonitrile, hemophan, polysulfone,
and cuprammonium membranes did not cause significant
decreases in platelet levels in hemodialysis patients [6]. Thus,
the use of biocompatible dialyzers has greatly reduced the
occurrence of hemodialysis-associated thrombocytopenia.
Recently, there have been three reported cases of throm-
bo cytopenia likely induced by exposure to a biocompatible
polysulfone dialyzer that resolved following the use of a
hydrophilic gel-coated polysulfone dialyzer [7] or a cellulose
triacetate dialyzer [8, 9]. In the case reported by Post in
2010 [7], the dialyzer in question was an Optiflux 160
(Fresenius Medical Care), which was subsequently switched
to a REXEED 255 dialyzer with a hydrophilic gel layer coating
the polysulfone membrane (Asahi Kasei Kuraray Medical).
That patient recovered platelet levels but did continue to
have recurrent episodes of thrombocytopenia associated
with hemodialysis. In the case reported by Posadas et
al. [8], hemodialysis-associated thrombocytopenia resolved
when the patient was switched from a Fresenius F180NR
Polysulfone dialyzer to a Baxter CT190G cellulose triacetate
dialyzer. Olafiranye et al. [9] describe a similar case where
thrombocytopenia resolved after switching from a Fresenius
F200NR polysulfone synthetic dialyzer to a Baxter cellulose
triacetate dialyzer.

Kiaii et al. [10] have recently reported a cohort of
20 patients who developed thrombocytopenia following
electron beam sterilization of polysulfone dialysis mem-
branes. The thrombocytopenia resolved when nonelectron
beam sterilization methods were used. The authors postu-
late that electron beam radiation might affect membrane
integrity, structure, or physical properties that could lead
to platelet activation, aggregation, or adsorption, causing
thrombocytopenia. In our patient’s case, electron beam
sterilization was used initially with the Optiflux 200 dialysis

| Name          | Manufacturer | Size                   | Membrane          | Sterilization      | Dates used               |
|---------------|--------------|------------------------|-------------------|--------------------|-------------------------|
| Optiflux 200  | Fresenius    | 2.0 square meter surface area | Polysulfone     | Electron beam      | 11/20, 11/21, 11/22, 11/24, 11/27 |
| Diacap 18NR   | B Braun      | 1.8 square meter surface area | Alpha polysulfone | Gamma irradiation  | 11/29                   |
| AM-BIO-100    | Asahi        | 2.0 square meter surface area | Alkyl ether polyeR-grafted cellulose | Gamma irradiation | 12/2, 12/4, 12/7        |
membrane, but the thrombocytopenia recurred when he was switched to a Braun 18NR dialyzer that was sterilized with gamma radiation. It therefore appears unlikely that electron beam membrane irradiation was the sole cause of thrombocytopenia in our patient.

The notable difference between the Fresenius membranes and the AM100 membrane used in this patient, all of which were polysulfone membranes, is the presence of a thin polyethylene glycol (alkyl ether) layer covering the polysulfone membrane in the AM100. According to Ashai, the manufacturer, the AM100 is made of modified cellulose (alkyl ether polymer-grafted cellulose) derived from cuprammonium rayon. The cuprammonium rayon is manufactured to have a thin layer of modified cellulose exposed to blood contract surfaces, making it more biocompatible as manifested by lower complement activation (C3a and C5a) compared to regular cellulose. Neither of the first two dialyzers used on our patient contained a polyethylene glycol layer. The presence of this layer in the AM100 membrane prevents direct interaction between polysulfone and platelets during hemodialysis, which may be responsible for prevention of platelet activation. The cellulose triacetate dialysis membranes mentioned above [8, 9] may also reduce platelet aggregation membranes by the virtue of their decreased activation of bound glycoprotein IIb/IIIa as compared with polysulfone membranes [11].

The exact mechanism of thrombocytopenia in our patient is unknown. Perhaps contact between a variant platelet surface protein and polysulfone resulted in platelet activation or agglutination and thrombocytopenia. Perhaps this patient was particularly susceptible to C3a activation following interaction with polysulfone, indirectly causing platelet activation and thrombocytopenia. It is uncommon for a 91-year-old to be initiated on dialysis, and age may have played a role in this patient. In older patients, there is a higher likelihood of point mutations in platelet precursors, which could theoretically produce platelets more susceptible to activation, resulting in thrombocytopenia.

This case of hemodialysis-associated thrombocytopenia in a new dialysis patient demonstrates that polysulfone dialysis membranes can variably affect platelet levels, despite previous evidence indicating that polysulfone membranes do not affect platelet counts [6]. Based on the Naranjo ADR Probability Scale [12] score of 9, it is highly probable that the observed episodes of thrombocytopenia were the result of hemodialysis using two different polysulfone dialysis membranes. Explanation of the Naranjo score is as the following.

(+1) There are previous conclusive reports on this reaction (see [7–9]).

(+2) The adverse event appeared after the suspected drug was administered.

(+1) The adverse reaction improved when the drug was discontinued.

(+2) The adverse reaction reappeared when the drug was readministered.

(+2) There were no clear alternate causes (other than the drug) that could have caused the adverse reaction.

HIT was ruled out, and no other drugs or local factors were implicated. Electron beam sterilization was not a likely cause since the patient also developed thrombocytopenia from a gamma-irradiated polysulfone dialysis membrane (the Braun Diacap 18NR).

(+1) The patient had a similar reaction to the same or similar drug. The patient developed similar degrees of thrombocytopenia with two different polysulfone dialysis membranes.

Total Score: (+9).

Hemodialysis-associated thrombocytopenia is an important, if rare, potential complication of hemodialysis that should be assessed via monitoring of platelet levels in both patients newly initiated on hemodialysis therapy as well as those with recent modifications in their hemodialysis regimens. This case demonstrates that there may be a small subset of patients for whom direct contact of platelets with polysulfone results in thrombocytopenia. This reaction may be preventable with use of a dialysis membrane that is treated with polyethylene glycol to eliminate a direct interaction between platelets and polysulfone. Cellulose triacetate dialyzers may also be a good option for these patients.

Explanation of Significance

This paper discusses thrombocytopenia associated with use of a biocompatible membrane in the setting of newly initiated hemodialysis in an elderly patient that resolved with use of a different biocompatible membrane containing a polyethylene glycol layer preventing direct interaction between platelets and polysulfone.

Disclosure

Authors have not published any similar work; data from this case is not under review or in press; none of these results have been previously presented or published. Information in this paper has not been presented as part of a presentation, abstract, or poster.

Conflict of Interests

Authors report no conflict of interests including consulting fees, paid expert testimony, employment, grants, honoraria, patents, royalties, stocks, or any other relationships or ethical considerations that may involve the subject matter of the paper and compromise its integrity.

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