

Dialysis Rounds

A Dialysis Case Presentation and Discussion

Series Editor: **Roger A. Rodby****Anaphylactic Shock at the Beginning of Hemodialysis**Khaleel Sayeed,* Charlene Murdakes,*
Andrej Spec,† and Casey Gashti**Section of Nephrology, Rush University
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†Department of Medicine, Rush University
Medical Center, Chicago, Illinois**ABSTRACT**

In patients who receive hemodialysis, most hypersensitivity reactions to components of the dialysis circuit are due to ethylene oxide or complement activating bio-incompatible membranes. We present a case of a 59 year-old female, with a 4-year history of uneventful hemodialysis using a cellulose based dialyzer membrane at her outpatient dialysis center, who developed repeated anaphylactic reactions associated with markers of an IgE mediated hypersensitivity reaction when a polysulfone based dia-

lyzer membrane was used while she was hospitalized. Only when the patient's dialyzer was changed back to her usual cellulose based membrane, did these reactions cease. On the basis of her clinical course and laboratory findings, we concluded that the patient's symptoms were due to exposure to polysulfone. This case reminds us that "biocompatible" membranes are not free from dialyzer reactions, and can be especially severe if the mechanism is an IgE mediated anaphylactic hypersensitivity reaction.

Tolerance to hemodialysis has improved considerably since the "early days," when patients were exposed to acetate based dialysate, transmembrane pressure based volume removal calculations, and bio-incompatible dialyzer membranes among other factors. The newer technologies and components that go into a hemodialysis treatment have made uneventful dialysis sessions the rule. The "first-use" syndrome is a complement-mediated reaction that has all but disappeared with the newer dialyzer membranes that are typically employed throughout the more developed countries. Thus, dialyzer reactions are uncommon and generally felt to be avoidable. A recent *Dialysis Rounds* reported anaphylaxis that occurred at the *end* of hemodialysis and was related to an IgE mediated hypersensitivity reaction to erythropoietin (1). This is a case report of anaphylaxis that occurred at the *beginning* of hemodialysis that was caused by an unusual IgE mediated hypersensitivity reaction to polysulfone, a membrane polymer that has been generally considered to be "biocompatible."

Case Report

A 58-year-old female with a history of end-stage renal disease secondary to hypertensive nephrosclerosis on chronic outpatient hemodialysis was admitted to Rush University Medical Center after developing chest pain and hypertension during an elective outpatient coronary angiography as part of a renal transplant workup. Her angiogram was consistent with significant multivessel coronary artery disease and she was scheduled for coronary artery bypass surgery. She had no prior history of asthma, atopy, or allergies to any known foods or medications. She was not receiving an angiotensin converting enzyme inhibitor (ACEi).

On her first day of hospitalization, she received hemodialysis using an electron beam sterilized polysulfone filter (Optiflux F160NRE; Fresenius Medical Care, Waltham, MA, USA). We follow a heparin-free hemodialysis protocol at our institution and thus the patient did not receive any heparin during this or any subsequent hemodialysis treatments. Immediately after initiation of the first dialysis session, she experienced dizziness, dyspnea, hypotension (blood pressure prior to HD was 148/63 and fell to 82/48 soon after initiation of treatment), and cyanosis. She was placed on supplemental oxygen with improvement in her oxygen saturation. The blood flow and ultrafiltration rates were both decreased, she received a saline bolus, and her blood pressure

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improved. Her other symptoms gradually resolved as well and she was able to complete the session. At the time, her symptoms were attributed to aggressive ultrafiltration for lack of any other explanation. The patient subsequently underwent a successful coronary artery bypass surgery. She continued to receive intermittent hemodialysis on a thrice-weekly schedule postoperatively. At the initiation of each subsequent dialysis session, she continued to experience the symptoms of hypotension, dyspnea, desaturation, and cyanosis. Once hypotension developed, ultrafiltration was stopped and saline was infused with an appropriate hemodynamic response. She was given supplemental oxygen from the beginning of the treatment. In addition, she was premedicated with diphenhydramine and the dialyzer was flushed with 2 l of saline prior to initiation of each session. Despite these interventions, she continued to experience these symptoms following initiation of dialysis. The symptoms slowly abated over 20 minutes and she was able to complete her full treatment; epinephrine was never used. Blood was drawn 30 minutes after initiation of dialysis and demonstrated a number of markers, suggesting an IgE mediated allergic hypersensitivity reaction (Table 1). The patient's peripheral eosinophil count rose throughout the admission, peaking at 42.7% (Fig. 1). Radioallergosorbent testing (RAST) against formaldehyde/formalin, latex, and ethylene oxide IgEs were all negative.

Her outpatient dialysis center was contacted to obtain more information about her treatments. The patient had been dialyzed for the previous 4 years with a gamma irradiated cellulose triacetate membrane (Baxter CT 110G; Baxter Healthcare Corporation, McGaw Park, IL, USA). Her outpatient dialysis unit supplied us with several of her usual cellulose triacetate filters that were used for the remainder of her dialysis treatments, which were completed without any further symptoms or complications.

Discussion

Hypersensitivity reactions are a rare but potentially serious complication of hemodialysis. In addition to the risks of exposure to iron, erythropoietin, heparin, latex, and formaldehyde (2–4), dialysis patients can develop hypersensitivity “dialyzer reactions” to the components of the extracorporeal cir-

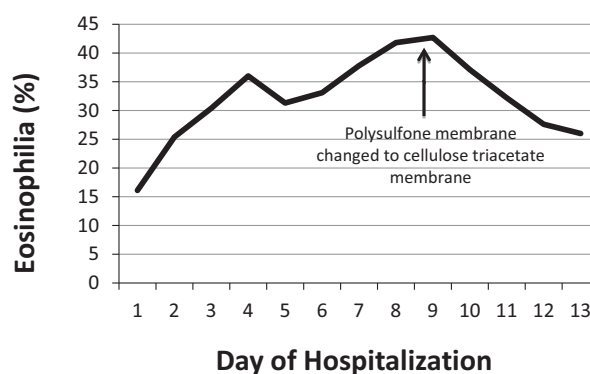


Fig. 1. Percent peripheral eosinophilia during hospital stay.

cuit. Based on the severity and timing of symptoms, dialyzer reactions have been categorized as either Type A or Type B. Type A reactions usually occur within a few minutes of starting a treatment. This condition is identified by an acute and severe onset of anaphylactic symptoms such as burning, urticaria, angioedema, dyspnea, and hypotension. Most Type A reactions are related to either an allergy to the ethylene oxide (EtO) sterilant present in some dialyzers or the specific use of ACEi in the setting of acrylonitrile-sodium methallyl sulfonate (AN-69) dialyzers (5). The AN-69 membrane is highly negatively charged, which can bind and alter Hageman factor, leading to a cascade of reactions that produce elevated levels of kinins (6). In the setting of an ACEi, bradykinin levels can increase 20- to 30-fold (ACEi prevent kinin breakdown) leading to anaphylactoid reactions. Dialyzers now tend to be gamma sterilized and thus allergic reactions to EtO are not commonly seen in the United States. An awareness of the reaction of AN-69 membranes in the setting of ACEi has also led to this being an uncommon occurrence. Thus, as a result of these two practice changes, Type A reactions are unusual in the modern era.

Type B reactions typically appear later in the treatment (15–30 minutes), and although they are more common than Type A reactions, they are usually self-limiting and produce milder symptoms such as chest and back discomfort, and nausea and vomiting (“anaphylactoid” as opposed to “anaphylactic”) (7). These Type B reactions are typically felt to be complement mediated, and are related to free hydroxyl groups on the membrane that activate the alternate complement pathway leading to neutrophil activation and pulmonary leukocyte sequestration (8). This reaction has been termed “first-use” because it does not occur in dialyzers that have undergone reuse as exposure to blood mitigates the reaction, which may explain why it is typically self-limiting and may not require discontinuation of the treatment. While this reaction was not uncommon in the early days of hemodialysis when cellulose based membranes were the rule, the risk of Type B reactions has decreased substantially with the use of more biocompatible membranes (e.g. polyacrylonitrile, polysulfone, and polymethylmethacrylate) as

TABLE 1. Hypersensitivity markers drawn 30 minutes post anaphylactic reaction

	Patient's value	Reference range
Eosinophil absolute count	9000/ μ l	<600/ μ l
Eosinophil percent	42.7%	0–6%
Tryptase	14 μ g/l	1.9–3.5 μ g/l
Total immunoglobulin E	815 IU/ml	0–125 IU/ml
C3	107 mg/dl	88–203 mg/dl
C4	35 mg/dl	13–49 mg/dl

they have been shown to activate complement to a much lesser degree (9).

Our patient had been receiving hemodialysis as an outpatient for 4 years without any complications. Only during an inpatient admission, did she develop repeated episodes of anaphylaxis within minutes of starting the hemodialysis treatment. Although this presentation resembled a Type A reaction, we were frankly at a loss to explain her symptoms. The dialyzer being used was gamma sterilized (no EtO exposure), the patient was not receiving an ACEi, and the dialyzer filter was made of a biocompatible polysulfone membrane. Heparin was not used during the treatments. Because of the lack of typical reasons for this type of reaction, we had trouble accepting that this was a dialyzer reaction and kept challenging her with the same treatment, putting her at substantial risk. Finally, because she tolerated her outpatient hemodialysis treatments without incident, we contacted the dialysis unit and determined that they dialyzed her with a cellulose triacetate membrane based dialyzer. We subsequently obtained several cellulose triacetate dialyzers from her outpatient HD unit and the adverse dialysis reactions completely resolved.

Polysulfone based dialysis membranes have been rarely reported to cause anaphylaxis (9,10). The patient reported by Arenas et al. had also been stable as an outpatient (using a cellulose diacetate filter) and similarly developed acute anaphylactic shock when a polysulfone based dialyzer was used during her treatment. Like our patient, her IgE level was significantly elevated, suggesting she also may have had an IgE mediated hypersensitivity allergic response. The similar clinical presentation for anaphylactic and anaphylactoid reactions can be differentiated with IgE levels since anaphylaxis is an IgE mediated event. After contacting and cross-linking an allergen, IgE signals the effector cell to release cellular mediators such as histamine, heparin, cytokines, and arachidonic acid derivatives (2). Anaphylactoid reactions are non-IgE mediated events resulting from direct antigen stimulation of effector cells releasing the same cellular mediators (11). Our patient had an elevated total IgE level of 815 IU/ml [normal 0–125 IU/mL], which supports the notion that her reaction was more likely a classic allergic reaction opposed to complement mediated “first-use” reaction.

Ethylene oxide gas, a potent alkylating agent used to sterilize heat sensitive material including dialysis tubing and filters, has been reported to cause anaphylaxis in dialysis patients (2,5). EtO forms conjugates with serum albumin among other endogenous proteins to form haptens that can elicit an immune response. Most reactions to EtO are also IgE mediated and the RAST can be used to detect immunoglobulin levels (12). Both the polysulfone and cellulose filters with which the patient was dialyzed lacked exposure to EtO. However, we were concerned that potential EtO exposure through the

dialysis tubing could still exist and thus we had RAST testing for EtO performed, which was negative. Moreover, although we changed the dialyzer, we did not change blood tubing and the reactions ceased, excluding the tubing as a possible precipitant. Although a RAST test was not performed for polysulfone, it has been negative in similar clinical scenarios suggesting lack of sensitivity for this test (10).

Our patient may have been predisposed to an IgE mediated hypersensitivity reaction given her baseline eosinophilia prior to exposure to polysulfone (16% eosinophils on admission). Eosinophilia, however, is not uncommon in patients on hemodialysis (observed in as high as 52% of ESRD patients (13)) and it is unclear if this has any impact on allergic risk. The exact mechanism for this is unknown, but is thought to involve an immune reaction to components of the dialysis apparatus. This explanation, however, may be too simple as similar findings have been described in patients receiving peritoneal dialysis and even in patients with CKD prior to receiving renal replacement therapy (14,15).

Management of anaphylaxis from dialyzer reactions include stopping the treatment *without* return of the blood to the patient, followed by the use of antihistamines, steroids, epinephrine, bronchodilators, and vasopressors depending on the severity of symptoms. Rinsing the filter prior to use with 2–3 l of saline has been reported to help prevent some symptoms, but this literature reports its use to prevent the complement mediated anaphylactoid Type B reactions. The real treatment for anaphylactic reactions is absolute avoidance of exposure to the antigen, and our patient should avoid exposure to polysulfone just as anyone allergic to peanuts should avoid any exposure to that antigen.

The present case reinforces the fact that biocompatibility is a relative term when it comes to exposing blood to a foreign material, and polysulfone, despite being considered a more biocompatible membrane, can still initiate a life-threatening acute IgE mediated reaction.

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