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SHORT COMMUNICATION

Anaphylactoid reaction during first hemofiltration with a PUREMA® polysulfone membrane

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ABSTRACT

Adverse reactions during hemodialysis are extremely common and include a wide range of clinical presentations from mild to life threatening. We present a case of a 34 year old woman in the Burn Intensive Care Unit, who developed acute kidney injury requiring renal replacement therapy. She was placed on continuous veno-venous hemofiltration with the NxStage® machine which uses a synthetic PUREMA® polyethersulfone filter sterilized by gamma radiation. Within two minutes of initiating hemofiltration, the patient complained of pruritus as well as dyspnea and became flushed and agitated. She subsequently developed hypotension ultimately resulting in cardiopulmonary arrest. Cardiopulmonary resuscitation was initiated and the patient was given epinephrine with return of spontaneous circulation. The following day, the patient was rechallenged with a PUREMA® filter, and had a similar reaction with flushing, dyspnea, pruritus and hypotension requiring treatment to be discontinued. The patient was transitioned to the Prismaflex® filter, another synthetic membrane, which she tolerated well and continued to utilize through the remainder of her hospital course without complication. Her clinical presentation was consistent with an anaphylactoid reaction, though a tryptase level was not obtained and a radioallergosorbent test performed with membrane material was negative. This case shows the difficulty of identifying the cause of hypersensitivity reactions involving synthetic membranes not sterilized by ethylene oxide, a commonly use sterilizing agent known to cause hypersensitivity reactions. This rare, but potentially fatal reaction has not previously been reported with a PUREMA® filter and this case should raise awareness of hypersensitivity reactions with this widely used method of renal replacement therapy.

KEY WORDS: *Hemodialysis, Hemofiltration, Hypersensitivity reaction, Acute kidney injury, Dialyzer reaction*

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INTRODUCTION

Adverse reactions during hemodialysis are extremely common and include a wide range of clinical presentations from mild to life-threatening. When an adverse reaction occurs during the initial introduction of dialysis, it is sometimes referred to as “first-use reaction”. These reactions are typically categorized as either type A, characterized by anaphylactic signs and symptoms; or type B, which is more nonspecific and generally less severe. Type A reactions, which usually present within the first few minutes of initiating dialysis, are often attributed to the initial exposure to the dialyzer membrane (1). It is difficult to determine the incidence without mandatory reporting by physicians or manufacturers, but estimates from voluntarily reported

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data in the early 1980s puts the incidence of type A reactions at 3 to 5 per 100,000 dialysis sessions (2).

Type A reactions present clinically with the hallmarks of anaphylaxis, including flushing, pruritus, bronchospasm, and hypotension. There are a variety of pathophysiologic mechanisms that account for these clinical manifestations, but most commonly it is thought to be an immunoglobulin E (IgE)-mediated process resulting in degranulation of mast cells and basophils with histamine release. Type A reactions are classically associated with ethylene oxide, an organic compound used in the sterilization of dialysis filter membranes. Hypersensitivity to ethylene oxide has been widely reported with severe clinical consequences, including fatalities (3). Patients exposed to any number of haptens develop IgE antibodies to ethylene oxide or one of its breakdown products, resulting in anaphylaxis at the initiation of dialysis (4).

A second mechanism resulting in an indistinguishable clinical presentation has been reported in patients whose hemodialysis was initiated with a polyacrylonitrile (PAN) membrane, particularly if they were being treated with an angiotensin converting enzyme (ACE) inhibitor (5, 6). This mechanism is mediated by bradykinin, the concentration of which has been shown to increase from exposure to PAN membranes. ACE inhibitors, though not necessary for a reaction to occur, impede kinin degradation which increases bradykinin levels resulting in vasodilatation and angioedema. This reaction is not IgE-mediated and is typically a diagnosis of exclusion in the appropriate clinical setting as there is no commercially available assay to quantify serum bradykinin levels.

Although these mechanisms are believed to account for a large majority of hypersensitivity reactions, several alternative hypotheses have been proposed because numerous case studies have been reported that cannot be attributed to either of these processes (3). This case report represents an anaphylactoid reaction during initiation of dialysis with a polysulfone membrane not sterilized by ethylene oxide.

CASE REPORT

A 34-year-old woman with no significant past medical history was brought to the Burn Intensive Care Unit after suffering 51% total body surface area (TBSA) mixed depth burns to the face, chest, back, bilateral upper and lower extremities secondary to a gasoline fire. On admission, the patient was hemodynamically stable and breathing comfortably but was prophylactically intubated to protect her airway from the onset of laryngeal edema. She was found to have an acute kidney injury (AKI) that was prerenal, and resolved with intravenous fluids. She had not previously been on any medications and had no known history of asthma, atopy, or allergies to any foods or medications.

The patient had a prolonged hospital course complicated by Gram-negative bacteremia and ventilator-associated pneumonia treated with tobramycin and vancomycin. Despite close monitoring, the patient became supratherapeutic on these nephrotoxic agents, likely in part to her already declining renal function. She also had one episode of hypotension that briefly required vasopressors; however, the patient was quickly weaned and remained hemodynamically stable. She maintained her renal function and her urine output throughout the first 3 weeks of her hospitalization. However on hospital day 24, her renal function and urine output began to decline. Despite aggressive resuscitation with both colloid and crystalloid fluids, her renal function and her urine output continued to diminish. The patient eventually developed AKIN stage III acute kidney injury requiring renal replacement therapy.

Per our institutional practice, the patient was placed on continuous veno-venous hemofiltration (CVVH) with the NxStage® machine (Lawrence, MA, USA), which uses a PUREMA® (Wuppertal, Germany) polyethersulfone filter. The circuit was primed for fifteen minutes with normal saline at flow rates of 200 mL per minute. Trisodium citrate was utilized for anticoagulation within the circuit and no new medications were administered to the patient while she was initiated on CVVH. Within 2 minutes of initiating hemofiltration, the patient complained of pruritus and dyspnea and became flushed and agitated. She subsequently developed hypotension, ultimately resulting in cardiopulmonary arrest. CVVH was immediately discontinued without returning blood to the patient. Cardiopulmonary resuscitation was initiated, and the patient was given epinephrine. Spontaneous circulation returned after 4 minutes and the patient remained hemodynamically stable. A tryptase level was not obtained. A complete blood count prior to initiating CVVH demonstrated a white blood cell (WBC) count of 9.4×10^3 (with 7.2% eosinophils) and a platelet count of 290,000. Post-procedure WBC count had increased to 14.4×10^3 (with 2.0% eosinophils) and platelet count of 280,000. Renal replacement therapy was ultimately reinitiated with a Prismaflex® (Lund, Sweden) polyethersulfone dialysis filter, which was similarly primed with normal saline,

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and utilized citrate anticoagulation. The patient tolerated CVVH with the Prismaflex® without any adverse reaction.
The following day, the patient was once again started on hemofiltration with a PUREMA® filter. Again, within the first 5 minutes, the patient developed flushing, dyspnea, pruritus, and hypotension, requiring the discontinuation of dialysis. She was not treated with epinephrine but was briefly placed on a norepinephrine drip until she became normotensive. She was again transitioned to the Prismaflex® filter, which was tolerated without complication. She continued to require CVVH for several weeks and was eventually transitioned to intermittent hemodialysis. The patient tolerated dialysis well through the remainder of her hospital course and was ultimately discharged to a long-term care facility. Skin prick testing was not obtainable given the extent of her burn injuries. At followup, a radioallergosorbent test (RAST) was performed against the filter membrane; however, the results were negative. The patient was seen in followup for several months and continued to do well.

TABLE I - DAUGIRDAS AND ING CRITERIA

Major Criteria	Minor Criteria
Onset within 20 min of starting dialysis	Reproducible during subsequent dialysis using same type and brand of dialyzer
Dyspnea	Urticaria
Burning throughout the body and or access site	Rhinorrhea, lacrimation
Angioedema	Abdominal cramping
	Itching

Definite case: 3 major criteria or 2 major criteria and 1 minor criterion. Probable case: 2 major criteria, 1 major criterion and 2 minor criteria, or 3 minor criteria.

DISCUSSION

Despite negative RAST testing for polyethersulfone, the clinical presentation would suggest an anaphylactiod reaction. A tryptase level, which is typically elevated for up to 6 hours after an anaphylactic reaction, was not obtained in this case (7). However, the initial reaction started immediately after renal replacement therapy was initiated and included intense pruritus and hypotension. As expected with a hypersensitivity reaction, the reaction resolved shortly after the administration of epinephrine in the course of resuscitative efforts (8). Other clinical entities that may have explained sudden hypotension and dyspnea such as acute myocardial infarction, pulmonary embolism, and arrhythmia were all eliminated from consideration through subsequent clinical evaluation. Additionally, the patient underwent an *in vivo* challenge the following day when renal replacement therapy was reinitiated with the PUREMA® filter, only to have a similar clinical presentation unfold. According to the criteria developed by Daugirdas and Ing (1) listed in Table I, the patient in this case had a type A reaction with two major criteria (acute onset in less than 20 minutes of starting dialysis and dyspnea) and two minor criteria (reproducible during the subsequent dialysis using the same type and brand of dialyzer and itching).
While hypersensitivity reactions to dialysis membranes have been commonly reported in the past, especially in cellulose membranes or in membranes sterilized with ethylene oxide, they are now much less common (9). This is in large part due to the development of synthetic membranes such as polysulfone and innovative sterilization methods. Both of the dialysis filters used were synthetic; and whereas the Prismaflex® filter is sterilized with ethylene oxide, the PUREMA® filter and lines are sterilized with gamma radiation.
Despite these innovations, there have been case reports detailing hypersensitivity reactions to polysulfone filters, including at least one case of a patient who had a reaction to one manufacturer's polysulfone membrane but tolerated another's (10, 11). Additionally, it is possible that the manufacturing process could result in variation of biocompatibility from one batch to another, with certain batches being more likely to cause dialyzer reactions. While our patient reacted to dialyzer membranes from the same batch, no other patients in our facility had reactions after exposure to that batch. This case suggests that there may be subtle differences in production between manufacturers causing differences in their biocompatibility with certain patients. Our patient was able to tolerate Prismaflex® but not the PUREMA®, despite their similar chemical compositions, and is the first reported case of a hypersensitivity reaction to the PUREMA® filter.
Our case shows the difficulty of identifying the cause of such hypersensitivity reactions involving synthetic membranes. While ethylene oxide is still used in the sterilization process of some filters, there may potentially be other leachable materials within non-ethylene oxide sterilized membranes causing mast cell activation or bradykinin release. Polysulfone membranes are capable of activating complement;

however, the effects of this activation are typically blunted by adsorption and are not thought to be clinically significant. There may be other factors that influence hypersensitivity reactions as well. Investigators have found genetic variability in patients that have had hypersensitivity reactions to AN-69 dialysis membranes while taking an ACE inhibitor (12). While our patient was not dialyzed with an AN-69, nor was she on an ACE inhibitor, it suggests that certain patients may have a predisposition to hypersensitivity reaction. Additionally, recent data has shown increased levels of numerous hydrocarbon and halocarbon compounds in patients following dialysis (13). These increased levels are thought to be either introduced from the dialysis membrane and tubing, or endogenously produced in response to exposure to the dialysis circuit. While the clinical significance of these exposures has yet to be determined, they could play a role in the pathogenesis of hypersensitivity reactions and are a target for further investigation.

This case shows the complex nature of hypersensitivity reactions and the difficulty in elucidating an underlying pathogensis. Our patient had a clinically significant adverse reaction with the PUREMA® filter through an unidentified mechanism that did not occur when she was dialyzed with a Prismaflex® filter. This case of hypersensitivity is the first to be reported with the PUREMA® filter and should raise awareness of this rare but potentially fatal reaction to this widely used method of renal replacement therapy.

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army, the Department of the Air Force or the Department of Defense.

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