

## CASE REPORT

# Anaphylactoid reaction during hemodiafiltration on AN69 membrane in a patient with atypical hemolytic uremic syndrome: A pediatric case report

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## Abstract

Reactions associated with hemodiafiltration can be life threatening if not recognized early in the course of dialysis. AN69 (acrylonitrile and sodium methallyl sulfonate copolymer) membrane-associated reactions during hemodialysis have been documented in adult patients receiving angiotensin converting enzyme inhibitors, which are thought to be triggered by the negative charge of the AN69 membrane. Here, we present a 5-month-old girl requiring continuous renal replacement therapy (CRRT) for acute kidney injury secondary to atypical hemolytic uremic syndrome who experienced acute cyanosis, angioedema, tachycardia, and impaired circulation during CRRT. After switching to a different type of hemofiltration membrane, her clinical findings improved and she was able to tolerate hemodialysis. We concluded that she had experienced an anaphylactoid reaction to the AN69 membrane. To our knowledge, this case is the first pediatric case report of AN69 membrane-associated anaphylactoid reaction.

## KEYWORDS

AN69 membrane, anaphylactoid reactions, hemodialysis

## INTRODUCTION

Hypersensitivity reactions (HSR) related to hemodialysis have been described in the last decades.<sup>1–5</sup> Polyacrylonitrile (AN69) membrane-associated reactions in hemodialysis patients receiving angiotensin converting enzyme inhibitors (ACEI) have been reported in adult patients.<sup>2–5</sup> Underlying reasons are suggested to be the induction of bradykinin release and reduced degradation of bradykinin in the presence of ACEI. In addition, back-filtration of bacterial endotoxin-contaminated dialysate has also been shown to cause HSR.<sup>4,6</sup> Successful management of these patients involves prompt recognition, treatment, and identification of responsible agent to avoid its use in the patient.<sup>7</sup>

Here, we report a pediatric patient who developed anaphylactoid reaction (AR) during hemodiafiltration with the AN69 membrane—despite not receiving ACEI. To our knowledge, there is no reported pediatric case in the literature.

## CASE REPORTS

A 5-month-old otherwise healthy female infant (10 kg) without any history of allergies was admitted to the PICU with somnolence and acute kidney injury secondary to atypical hemolytic uremic syndrome. She had had watery-bloody diarrhea with a frequency of 10 to 15 times per day which was preceded by loss of appetite lasting for 5 days. During a diarrhea episode, she suffered from a

generalized tonic-clonic seizure that lasted >15 min. She was treated on an emergency basis, and was then transferred to our PICU for further management.

Vitals on arrival were as follows: blood pressure 80/40 mmHg, heart rate 170/min, respiratory rate 62 breaths/min, body temperature 36°C, and SpO<sub>2</sub>



**FIGURE 1** Appearance of patient during anaphylactoid reaction [Color figure can be viewed at [wileyonlinelibrary.com](http://wileyonlinelibrary.com)]

100% with face mask. Physical examination showed encephalopathy with a Glasgow Coma Scale of 8 (E1M4V3), isochoric pupils with positive light reflex (+/+), tachypnea, subcostal/intercostal retractions with coarse breath sounds, tachycardia, abdominal distension, hepatomegaly, diffuse bilateral edema, and cold-pale extremities with poor peripheral perfusion (capillary refill time: 5 s).

Initial laboratory examination revealed abnormal results: Urea: 152 mg/dL, AST: 129 U/L, ALT: 92 U/L, LDH: 2844 U/L, creatinine 3.3 mg/dL, albumin 20 g/L, phosphorus 10.4 mg/dL, potassium 5.5 mEq/L, sodium 130 mEq/L, calcium: 7.1 mg/dL, CRP: 13 mg/dL (0–5 mg/dL), Hb: 5.2 g/dL, Htc: 20%, WBC:  $45.7 \times 10^3/\mu\text{L}$  (neutrophils:  $27.3 \times 10^3/\mu\text{L}$ ), PLT:  $32 \times 10^3/\mu\text{L}$ , RBC:  $2.6 \times 10^6/\mu\text{L}$ . She was determined to have Coombs'-negative hemolytic anemia along with elevated reticulocytes and decreased haptoglobin. She had positive results for fecal occult blood and rotavirus antigen. STEC PCR (*Escherichia coli*-157) test was negative and serum complement C3 was low (0.77, reference range: 0.9–1.8). Because she was anuric, no urine test for sediment could be obtained. Arterial blood gases showed severe metabolic acidosis (pH: 7.15; HCO<sub>3</sub>: 8 mEq/L; lactate: 4 mmol/L; PaCO<sub>2</sub>: 35 mmHg; base excess: −17 mmol/L). Chest X-ray showed bilateral effusion. Bedside-USG revealed pleural effusion and collection of fluid in the perihepatic area.

After stabilization and intubation of the patient, transfusion of erythrocyte suspension and early therapeutic plasma exchange (for 1 h) were performed. Continuous renal replacement therapy (CRRT) was initiated (with citrate/Calcium) due to volume overload, uremia, and severe metabolic acidosis. The M60 CRRT system (Prismaflex hemofilter set with AN69 dialyzer membrane, Baxter) was used to provide better surface area and blood volume. After 15 to 30 min of saline priming, the CRRT was started. Within 5 min of initiation, cutis marmorata, cyanosis, angioedema, tachycardia (185/min), and impaired peripheral circulation appeared (Figure 1). At this moment, blood flow was 60 mL/min, and dialysate flow rate was 300 mL/hour. First blood flow, then CRRT was stopped. She was treated with

**TABLE 1** Properties of dialyzer

| Dialyzer               | Reaction | Modality | Manufacturer      | Membrane type                                                | Blood line sterilization / membrane stabilization | Tubing material |
|------------------------|----------|----------|-------------------|--------------------------------------------------------------|---------------------------------------------------|-----------------|
| Prismaflex M60 Gambro  | YesX2    | CRRT     | Baxter Healthcare | AN69; acrylonitrile and sodium methallyl sulfonate copolymer | EtO/gamma ray                                     | PVC             |
| Prismaflex HF20 Gambro | No       | CRRT     | Baxter Healthcare | Polyarylethersulfone                                         | EtO/gamma ray                                     | PVC             |

Abbreviations: CRRT, continues renal replacement therapy; PVC, plasticized polyvinyl chloride.

subcutaneous adrenalin, methylprednisolone, ranitidine, and other supportive measures/precautions were taken. Her condition improved swiftly and signs of reaction resolved. The CRRT was restarted with a new M60 set, but the same clinical features reappeared within minutes; therefore, CRRT was again stopped. Because the same reaction had been observed twice, we suspected it might be related to the dialyzer membrane, and a clinical diagnosis of AN69-related AR was made. Her dialysis was continued with an HF20 set bearing a different type of membrane (Polyarylethersulfone, Prismaflex, Baxter) (Table 1). No incidents developed with the new set; she tolerated the CRRT session without any complications. She was extubated after resolution of volume overload and stabilization of hemodynamic characteristics and transferred to the nephrology ward for follow-up studies.

Informed written consent was obtained from the patient's parents for publication and the procedure was in accord with the Declaration of Helsinki.

## DISCUSSION

To our knowledge, this report is the first pediatric patient diagnosed with AN69-associated AR without concomitant use of ACEI. Patient developed cutis marmorata, cyanosis, angioedema, tachycardia, and disrupted peripheral circulation during CRRT, which is most consistent with dialysis-associated HSR. She was critically ill before dialysis but acutely worsened within minutes of initiation of CRRT. Her symptoms regressed when she was taken off the machine with the M60 set (AN69 membrane), but reappeared when a new set of the same type was applied. She had no reaction when she was treated with a set bearing a different membrane (Polyarylethersulfone), and perfectly tolerated subsequent CRRT applications.

Dialysis-associated reactions can be classified into Anaphylactic (IgE mediated) and ARs (non-IgE mediated).<sup>8</sup> Symptoms of both conditions can overlap; therefore, laboratory investigation (tryptase) is needed to confirm diagnosis. We could not measure tryptase concentrations; but because no preceding sensitization was documented, we suspect that the reaction was of the AR type.

Multiple factors are considered when evaluating dialyzer reactions, including type of dialyzer membrane, sterilizing agent, antiseptics, medications, the microbiological quality of dialysate, endotoxins/bacterial products, and heparin.<sup>1,9,10</sup> Ethylene oxide, used in gas sterilization of dialysis membranes, has been reported to cause AR.<sup>1,11</sup> In our case, both membranes were sterilized with ethylene oxide; therefore, AR was not due to this agent. The patient did not receive ACEI, and the swift improvement

of her condition excludes underlying sepsis. The dialysate used for the CRRT application was premixed manufacturer made bags and use of dialysate from the same lot was uneventful in other patients. As the patient tolerated Polyarylethersulfone membrane, we strongly believe that AR was related to AN69 membrane.

Numerous publications have focused on ARs in patients dialyzed with AN69 membranes, both with<sup>4,10,12,13</sup> and without concomitant ACEI intake.<sup>1,5,12,14</sup> The pathophysiology is largely thought to be associated with the generation of bradykinin, and considering the fact that ACEI prevent the degradation of bradykinin, it is likely the ACEI use potentiates its accumulation.<sup>7</sup> There are two hypotheses: the first hypothesis suggests that AR is due to contact between patient plasma and endotoxins.<sup>6,10</sup> The second is that AR is caused by the membrane itself.<sup>4</sup> Tielemans et al. reported that AR during hemodialysis was due to contact phase activation by the negatively charged AN69 membrane which increases bradykinin concentrations.<sup>4</sup> Surface-treated AN69 membranes are considered to be safer; however, coating may not cover all electronegative charges in the membrane.<sup>15</sup> In our patient, the mechanism of AR could be related to excessive bradykinin release; however, she was ACEI-free, so the severity of the reaction could be related to underlying presence of uncontrolled complement activation. Schaefer et al.<sup>13</sup> demonstrated that, in cases of AR with AN69 membrane, there was a 100-fold increase in the venous effluent of the AN69 dialyzer. In the current case, BK levels could not be measured.

The symptoms of HSR may be mild to moderate, depending on the degree of bradykinin synthesis and degradation. Our case was within the severe quarter of this spectrum. Symptoms are rapid-onset, beginning immediately after the blood is being returned to the patient from the dialyzer-device.<sup>7</sup> Such cases of AR are demonstrated to regress when the AN69 membrane is replaced by another membrane.<sup>1,10,12,13</sup>

Diagnosis of dialyzer reaction relies upon clinical history and exclusion of other causes. Hypersensitivity markers include eosinophil count, tryptase, total/allergen-specific IgE, C3, and C4; however, the duration of elevation of such markers can vary.<sup>11</sup> Serum tryptase can provide information with regard to the underlying mechanism of HSR, but lack of abnormal values does not rule out AR.<sup>7</sup>

Correct management requires prompt recognition and immediate termination of dialysis, without returning the blood to the patient. The next step includes symptom-based treatment, identification of the responsible agent and avoidance, followed by general and specific individualized procedures that are carried out with respect to the necessities of emergency treatment.<sup>7</sup>

In conclusion, dialysis-associated reactions are rare but potentially life-threatening complications. Our case shows that AR during dialysis with the AN69 membrane can develop in the absence of ACEI use. This report emphasizes the importance of rapid recognition and treatment of dialyzer reactions. Pathological mechanisms are accepted to rely on the bradykinin mechanism, but this explanation appears to be far from complete. In cases of suspected dialyzer reactions, dialysis should be stopped immediately and all components of the CRRT set should be investigated. We recommend the use of different dialysis membranes for subsequent treatments when facing clinical signs of AR.

### CONFLICT OF INTEREST

The authors declared that they have no relevant financial interests.

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