Hypersensitivity reactions to bicarbonate dialysate containing acetate: a case report with literature review

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Abstract

Although hemodialysis-hypersensitivity reactions have various causes, only a few cases of hypersensitivity to acetate dialysate accompanied by fever have been reported. We present the case of a 69-year-old hemodialysis patient who was admitted due to fever after dialysis. He had undergone online hemodiafiltration using acetate-free citrate-containing dialysate. After admission, we switched to acetate-containing bicarbonate dialysate. He was diagnosed with pneumonia and treated with ceftriaxone. However, fever that occurred post dialysis persisted, displaying a gradual elevation in CRP level and eosinophils (up to 9.7 mg/dL and 3774 cells/ μ L, respectively). After a series of negative workups for infection and dialysis membrane allergy, we suspected that acetate-containing bicarbonate dialysate to be the cause of the allergic reaction and switched to acetate-free bicarbonate dialysate. Consequently, eosinophil count decreased and the fever abated. The drug-induced lymphocyte stimulation test finding (for acetate dialysate) was positive, and he was diagnosed with acetate dialysate-induced hypersensitivity reactions. The condition was not detected earlier due to the complications associated with pneumonia.

Keywords Hypersensitivity reactions · Acetate dialysate · Allergy · Fever · Drug-induced lymphocyte stimulation test

Introduction

Hypersensitivity reactions in hemodialysis patients include reactions to ethylene oxide, formaldehyde, dialyzer membranes, erythropoiesis-stimulating agents, intravenous iron, and anticoagulants [1]. Clinical symptoms that are often seen in hypersensitivity reactions include asthma, rash, and hypotension and range in seriousness from mild to

life threatening [2]. There is an urgent need to develop an approach that can effectively manage these hypersensitivity reactions. However, because dialysis patients are exposed to various environments, identifying the cause of hypersensitivity reactions is sometimes difficult [1].

Fever after dialysis is a common finding and may be caused by infectious or non-infectious agents [3]. So, it is recommended to first exclude the possibility of an infection. Although acetate dialysate also causes anaphylactoid symptoms, only a few cases with fever have been reported. We present a case of acetate dialysate-induced hypersensitivity reactions manifesting as fever, which was resolved by the substitution of acetate-containing bicarbonate dialysate with acetate-free bicarbonate dialysate. This is the first case of hypersensitivity reaction to acetate dialysate presenting with fever and complicated with infection.

Case report

A 69-year-old man was admitted to our hospital with fever and shaking chills postdialysis. He was bitten in the left axilla by a tick 1 week before admission. He did not have

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any food allergies but had lacquer rash. There was no family history of allergic disease and had worked in the construction industry. He had undergone mitral valve replacement in 1995. This patient was diagnosed with renal dysfunction, and renal biopsy showed interstitial nephritis, which was likely due to hypersensitivity reactions against bucolome. Maintenance hemodialysis had been initiated 3 years ago and he was undergoing online hemodiafiltration (OL-HDF) using the acetate-free citrate-containing dialysate (Carbostar® P, AY Pharmaceuticals Co., Ltd, Tokyo, Japan) and polyethersulfone membrane for longer than 1 year. The patient was taking febuxostat, lanthanum carbonate hydrate, furosemide, esomeprazole magnesium hydrate, calcitriol, carvedilol, and warfarin potassium on prescription. After admission, we switched to acetate-containing bicarbonate dialysate (LympackTA3®, Nipro ES Pharma Co., Ltd Osaka, Japan). Dialysates and constituents used since the dialysis induction are shown in Fig. 1a.

On admission, his body temperature was 37.7 °C, blood pressure was 116/69 mmHg, heart rate was 96 bpm, and respiratory rate was 20 breaths per minute. He had no history of night sweats and weight loss, and both lungs made no crackling sounds. He had no symptoms such as cough and sputum but had a pink papule in the left axilla. Laboratory test findings on admission were as follows: white blood cells (WBC), 7200/μL; eosinophils, 274 cells/μL; hemoglobin, 10.3 g/dL; platelets, 101,000/μL; C-reactive protein

(CRP), 5.43 mg/dL; and immunoglobulin E (IgE), 223 U/mL (normal, < 170 U/mL). He tested negative for the presence of perinuclear anti-neutrophil cytoplasmic, cytoplasmic antineutrophil cytoplasmic, antinuclear antibodies, and serum β-d glucan, and T-SPOT.TB test finding was negative. Because chest X-ray and computed tomography (CT) scan revealed pneumonia, he was treated with ceftriaxone. The possibility of tick-borne infections such as Japanese spotted fever and scrub typhus could not be eliminated initially and we started minomycin administration. However, fever recurred postdialysis, with the re-elevation of the CRP level and eosinophils. The patient's clinical course is shown in Fig. 1b. Chest CT findings showed improvement in response to antibiotic treatment. Although we suspected infective endocarditis, the findings of several echocardiographies and blood culture examinations negated the possibility. Gallium-67 scintigraphy showed no abnormal findings. Despite diarrhea during hospitalization, the *Clostridium difficile* toxin A/B test finding was negative. We changed antibiotics and dialysis membranes (Fig. 1b), but fever after dialysis continued. Fever mainly occurred during dialysis sessions of 3.5 to 4 h each and after dialysis. CRP level and eosinophils gradually increased up to 9.7 mg/dL and 3774 cells/μL, respectively.

Finally, we have suspected acetate-containing bicarbonate dialysate might cause an allergic reaction and switched to acetate-free bicarbonate dialysate. Since then, he was

Fig. 1 **a** Dialysates and constituents used since the induction of dialysis. **b** The clinical course of the patient. Changes in the serum eosinophil and CRP levels. *HD* hemodialysis, *OL-HDF* online hemodiafiltration, *MINO* minomycin, *INH* isoniazid, *CTRX* ceftri-

axone, *TAZ/PIPC* tazobactam/piperacillin, *PS* polysulfone, *PMMA* poly(methylmethacrylate), *PES* polyether sulfone, *CTA* cellulose triacetate, *EVOH* ethylene vinyl alcohol copolymer, *BT* body temperature, *CRP* C-reactive protein

afebrile and eosinophils decreased (Fig. 1b). The result of the drug-induced lymphocyte stimulation test (DLST) against acetate-containing bicarbonate dialysate was positive (stimulation index: 220%, positive result: > 180%). We, therefore, diagnosed acetate-induced hypersensitivity reactions as a cause of recurrent fever after dialysis.

Discussion

The present case provides an important clinical suggestion. We should consider the allergic reaction to acetate as the cause of recurrent fever after dialysis when using acetate-containing bicarbonate dialysate. We found 11 case reports of hypersensitivity reactions related to acetate dialysate (summarized in Table 1) [4–14]. However, as seen in this case, fever is atypical, and has been reported only in two cases. Moreover, this is the first case complicated with infection. Because of the possibility of various infections, it is often difficult to establish the cause of fever. We consider this case to be novel and expect that the observations of this case can help better treat such hemodialysis patients.

Fever in hemodialysis patients can have various causes, including infections, malignancies, and autoimmune disorders [15]. The infection rate in hemodialysis patients is 5.7 times higher per 1000 dialysis days [16]. The patient in this case was initially treated for pneumonia; it was unclear if the pneumonia was bacterial in origin or related to

hypersensitivity. However, despite being responsive to pneumonia treatment, fever recurred postdialysis. The results of the workup for infections were all negative. Because we did not observe spreading of the rash, leukopenia, thrombocytopenia, and hepatic dysfunction, the possibility of tick-borne infection appeared less likely. Elevation of eosinophils and IgE levels and improvement of the number of eosinophils after changing the dialysate confirmed the diagnosis of hypersensitivity reaction related to acetate dialysate. However, the elevation of eosinophils and IgE levels depends on the case (Table 1). An increase in serum IL-6 has been reported as a cause of fever associated with acetate [18]. In this case, IL-6 serum level was elevated (153 pg/mL; normal: < 8 pg/mL), but this might have been due to pneumonia. In fact, he was previously treated with acetate dialysate (Fig. 1a) but was afebrile. The exact mechanism of acetate-induced allergy is still unclear. In addition, the CRP level had already decreased to nearly the normal range at 2 weeks before the dialysate switch. Therefore, the elevation of CRP level, in this case, might not be related to acetate hypersensitivity reactions.

DLST is evaluated for the auxiliary diagnosis of drug allergies [19]. The stimulation index is defined as the value of 3H-thymidine uptake with/without antigen [19]. However, considering the possibilities of false-positive and false-negative results, we should diagnose drug allergies basing on the clinical course in addition to the DLST results. The sensitivity and specificity of the DLST for the diagnosis of

Table 1 Literature review of hypersensitivity reactions related to acetate dialysate

No	Author	Age/sex	Primary KD	Dialysis vintage, months	Eosinophil	IgE	DLST	Infection	Clinical symptoms
1	Koinuma [4]	77 M	Diabetic nephropathy	The initiation of dialysis	Elevated	NA	(+)	(–)	Fever, rash, diarrhea, severe eosinophilia
2	Takagi [5]	62 M	Diabetic nephropathy	The initiation of dialysis	NA	NA	NA	(–)	Fever
3	Kato [6]	63 M	Diabetic nephropathy	21	Elevated	Elevated	(–)	(–)	Hypotension, severe eosinophilia
4	Caravaca [7]	35 F	Reflux nephropathy	60	Elevated	Elevated	NA	(–)	Asthma attack, severe eosinophilia
5	Inui [8]	NA, M	Unknown	1	NA	NA	(+)	(–)	Hypotension, rash
6	Takahashi [9]	36, NA	Unknown	108	NA	NA	NA	(–)	Asthma attack
7	Tanaka [10]	84, NA	Unknown	24	NA	Normal	(–)	NA	Dyspnea
8	Misaki [11]	35 M	Chronic nephritis	The initiation of dialysis	Normal	Elevated	NA	(–)	Dyspnea, rash
9	Ei [12]	30 M	NA	12	Elevated	Elevated	NA	(–)	Asthma attack
10	Papadakis [13]	23 F	NA	0.5	Elevated	Elevated	NA	(–)	NA
11	Yang [14]	46 F	NA	NA	Normal	Normal	NA	(–)	Skin itching, flushing, hypotension, dyspnea
12	Our case	69 M	Interstitial nephritis	36	Elevated	Elevated	(+)	pneumonia	Fever, moderate eosinophilia

KD kidney disease, IgE immunoglobulin E, DLST drug lymphocyte stimulation test, M male, F female, NA not available

allergy to acetate-containing bicarbonate dialysate have not been evaluated. The results of DLST and improvement with a substitute for acetate-free dialysate confirmed the diagnosis of the allergic reaction induced by acetate in the present case. However, because we used the whole dialysate, some minor elements contained in dialysate might have reacted in DLST.

Anaphylaxis and anaphylactoid reactions, such as asthma, hypotension, and shock, generally appeared immediately or 15–45 min after starting dialysis [2]. However, in this case, fever occurred 3–4 h after starting dialysis; we could not explain the reason for the delay. According to the Gell and Coombs classification [20], this case was unlikely to be type I hypersensitivity reaction because the reaction was noted a few hours after beginning dialysis. Considering the delayed-type, fever, eosinophilia, sudden onset by previously used dialysate, and DLST results, this case might be type III or type IV hypersensitivity reactions [20, 21]. However, immunological mechanisms underlying acetate hypersensitivity reactions are not fully understood.

Eosinophilia is defined as a peripheral blood eosinophil count exceeding 500 cells/ μ L [22]. Three levels of severity have been defined: mild (500–1500 cells/ μ L), moderate (1500–5000 cells/ μ L), and severe (> 5000 cells/ μ L). In the absence of organ involvement, eosinophilia need not be treated with drugs [22]. Since the severity of the condition in this case was moderate with no organ involvements, we did not treat it with corticosteroids. Eosinophilia was attenuated after substituting acetate-containing bicarbonate dialysate with the acetate-free one.

In conclusion, even though hemodialysis patients develop infections, it should be borne in mind that hypersensitivity reaction to acetate-containing dialysate might be a cause of fever that occurs postdialysis.

Compliance with ethical standards

Conflict of interest All authors declare no conflict of interest.

Human and animal rights This article contains no studies involving humans or animals.

Informed consent Informed consent was obtained from the patient whose case is reported in this study.

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