


Case Report

Repeated anaphylactic reaction after walking following an intraarticular injection of diclofenac etalhyaluronate sodium during a 3-day period

Youichi Yanagawa,¹  Kei Jitsuiki,¹ Yoshihiro Kushida,¹ and Itaru Morohashi²

¹Department of Acute Critical Care Medicine, Shizuoka Hospital, Juntendo University, Izunokuni City, Shizuoka, Japan, and ²Department of Orthopedics, Shizuoka Hospital, Juntendo University, Izunokuni City, Shizuoka, Japan

Background: There has been no English report of repeated anaphylactic reaction after exercise-induced anaphylaxis due to a single intraarticular injection of diclofenac etalhyaluronate sodium.

Case Presentation: A 60-year-old woman felt dyspnea, generalized itching, and urticaria following hypotension a few minutes after receiving an intraarticular injection of diclofenac etalhyaluronate sodium for the first time. She immediately received intramuscular adrenaline administration and her symptoms subsided. However, she received intermittent injections of adrenaline three times for repeated anaphylactic reactions after walking over a 3-day period, in addition to complication with Kounis syndrome. She was discharged on foot on day 9 without sequelae.

Conclusion: Physicians should have patients who receive intraarticular injection of diclofenac etalhyaluronate sodium walk for a short period and evaluate their status.

Key words: anaphylaxis, diclofenac etalhyaluronate sodium, intraarticular injection, Kounis syndrome

INTRODUCTION

EXERCISE-INDUCED ANAPHYLAXIS (EIA) denotes a range of disorders in which anaphylaxis occurs in relation to physical exercise. Typical symptoms include flushing, pruritus, urticaria, angioedema, respiratory symptoms, gastrointestinal symptoms, hypotension, and collapse during or after exercise.¹ Approximately 30% of cases of EIA are associated with cofactors.^{1,2} The most important cofactor is food ingestion, which is named food-dependent, EIA. Other cofactors identified to cause anaphylaxis from physical exercise are exposure to warm or cold temperature, the menstrual cycle, metal-containing dental amalgams, and drug intake.^{1,2} Exercise results in the transport of allergens, where mast cells have precise functional and metabolic characteristics, to the skin and skeletal muscle, where phenotypically different mast cells are present, and altered mediator release may occur. In addition, the known increase in plasma

osmolality caused by prolonged exercise is likely to increase the release of basophils as well as histamine production.^{1,2} However, the pathophysiological and immunological mechanisms of EIA are still largely unknown.¹ Management is centered upon avoidance of eliciting factors, and emergency plans are individualized, except for the mandatory prescription of an adrenaline auto-injector.

We herein report a case of repeated EIA for 4 days after the intraarticular injection of diclofenac etalhyaluronate sodium, which is a long-lasting analgesic with a disease-modifying effect for patients with osteoarthritis.³

CASE REPORT

A 60-year-old woman felt dyspnea, generalized itching, and urticaria following hypotension (blood pressure: 75/43 mmHg) within a few minutes after walking from the fluoroscope room to the observation room after receiving the first intraarticular injection of diclofenac etalhyaluronate sodium from an orthopedist. She had a history of asthma, atopic dermatitis, and osteoarthritis at the right hip joint, for which she had received uneventful intraarticular injection of purified sodium hyaluronate twice. The orthopedist immediately injected 0.3 mg of adrenaline intramuscularly, and an

Corresponding: Youichi Yanagawa, MD, PhD, Department of Acute Critical Care Medicine, Shizuoka Hospital, Juntendo University, 1129 Nagaoka, Izunokuni City, Shizuoka, Japan 410-2295. E-mail: yyanaga@juntendo.ac.jp
Received 7 Dec, 2021; accepted 12 Jan, 2022

intravenous drip infusion of 100 mg of hydrocortisone was added. After a few hours, her symptoms subsided, but she developed urticaria again after walking, so she received an additional infusion of 100 mg of hydrocortisone. After this event, she was managed on the bed. The orthopedist introduced her to the dermatologists at our hospital, and she was transported by a private automobile driven by her husband. When she visited the Department of Dermatology, her urticaria had deteriorated, and she felt dyspnea again. She was immediately transferred to the emergency room approximately 6 h after the initial anaphylaxis.

When an emergency physician checked her, she had clear consciousness, a blood pressure of 120/70 mmHg, a heart rate of 100 beats/min, a respiratory rate of 30 breaths/min, and an SpO₂ of 99% under 6 L/min of oxygen. A visual inspection revealed generalized itching and urticaria. Other physical findings were negative. She was administered 0.3 mg of adrenaline intramuscularly again and an intravenous drip infusion of 10 mg of chlorpheniramine and 20 mg of famotidine. Chest roentgen and electrocardiogram findings were negative. The results of a biochemical analysis on the same day are presented in Table 1. Her troponin T level was over the normal range, suggesting complication with Kounis syndrome. After improvement of her symptoms, she was admitted and on bed rest with a prescription of betamethasone and chlorpheniramine.

On day 2, she was asymptomatic, but her troponin T level had increased to 45 pg/mL, and precordial leads showed negative T wave (Fig. 1). She tried to walk to go to the toilet and moved to the echocardiogram room in a wheelchair. The echocardiogram findings were normal. After walking for 20 min without taking any food, she felt dyspnea, generalized itching, and urticaria again. She also received 0.3 mg of adrenaline intramuscularly and intravenous drip infusion of 10 mg of chlorpheniramine and 20 mg of famotidine. After the improvement of her symptoms, she underwent 3 mL of aspiration of yellowish, not cloudy synovial fluid at the right hip joint by needle puncture to remove diclofenac etalhyaluronate sodium (Fig. 2). She was then managed on bed rest.

On day 3, she was asymptomatic. Her troponin T level had decreased to 11 pg/mL (within normal range), and the negative T wave at the precordial leads was unchanged. She tried to walk but again felt mild dyspnea and moderate urticaria after 30 min. She was administered 0.3 mg of adrenaline intramuscularly and was managed on bed rest until day 5. On day 4, her electrocardiogram returned to normal. On day 5, she tried to walk again but felt mild urticaria after 30 min, which improved spontaneously. After this reaction, she showed no further allergic reaction after walking.

She underwent strength training to regain her walking ability and was discharged on foot on day 9.

Table 1. Laboratory data at the time of deterioration

| | |
|---------------------------------------|---|
| White blood cell | 15,000/ μ L |
| Hemoglobin | 15.4 g/dL |
| Platelet | 34.4 \times 10 ⁴ / μ L |
| Total protein | 6.9 g/dL |
| Albumin | 3.8 g/dL |
| Total bilirubin | 0.6 mg/dL |
| Aspartate aminotransferase | 48 IU/L |
| Alanine aminotransferase | 42 IU/L |
| Alkaline phosphatase | 80 IU/L |
| γ -Glutamyltransferase | 61 IU/L |
| Lactate dehydrogenase | 362 IU/L |
| Amylase | 39 IU/L |
| Blood urea nitrogen | 15.3 mg/dL |
| Creatinine | 0.72 mg/dL |
| Creatine kinase | 183 IU/L |
| Glucose | 192 mg/dL |
| HbA _{1c} | 6.7% |
| Sodium | 141 mEq/L |
| Potassium | 4.2 mEq/L |
| Chloride | 102 mEq/L |
| Calcium | 8.7 mg/dL |
| Phosphate | 4.5 mg/dL |
| C-reactive protein | 0.42 mg/dL |
| Prothrombin time | 11.6 (11.7) s |
| Activated partial thromboplastin time | 25.3 (27.4) s |
| Fibrinogen | 346 mg/dL |
| Fibrinogen degradation products | 20.6 μ g/mL |
| Troponin T | 16 (0–14 pg/mL) |

DISCUSSION

THIS IS THE first English case report of a patient who received intermittent injections of adrenaline three times due to repeated anaphylactic reaction after walking over 3 days due to a single intraarticular injection of diclofenac etalhyaluronate sodium. Previous reports have described anaphylactic reaction immediately after the intraarticular injection of drugs, most of which were steroids.^{4,5} We found no reports showing anaphylactic reaction induced by walking after the intraarticular injection of drugs. There may be criticism that this case was not typical EIA because typical EIA may be food dependent, the allergen generally spreads from the gut, and walking was not considered to be an exercise; however, the definition of EIA is simply anaphylaxis induced by physical exertion, regardless of its intensity.^{1,2} Accordingly, we classified the present case as EIA, even though the allergen spread from the joint and walking is a mild exercise.

Diclofenac etalhyaluronate sodium is reported to have a potent and long-lasting analgesic and disease-modifying

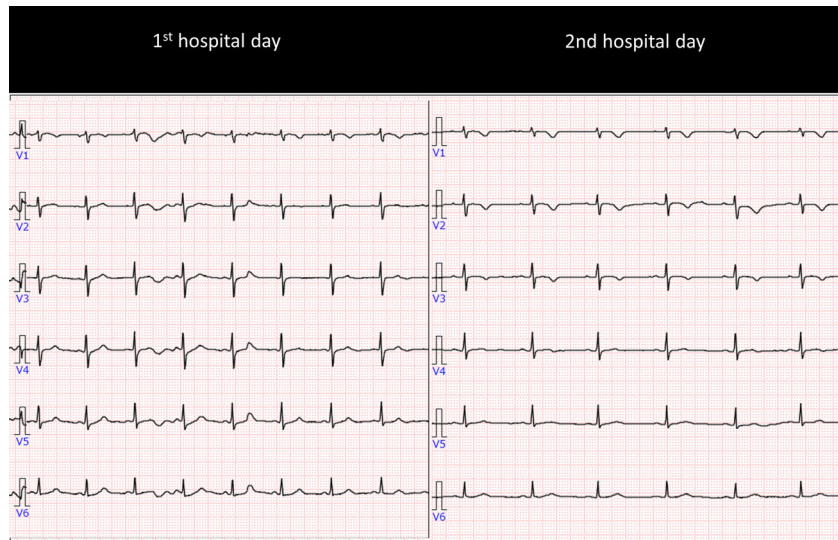


Fig. 1. Precordial leads in hospital day 1 (left) and 2 (right). On day 2, she was asymptomatic, but the troponin T level had increased to 45 pg/mL, and precordial leads showed negative T wave, suggesting complication with Kounis syndrome.

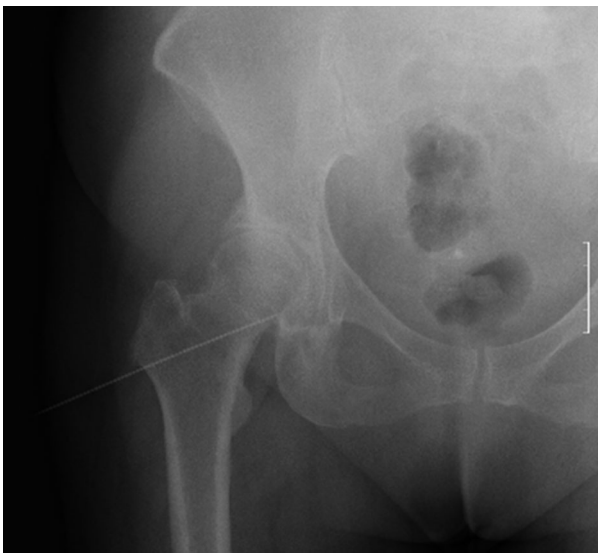


Fig. 2. Aspiration of synovial fluid by needle puncture. She underwent aspiration of synovial fluid at the right hip joint by needle puncture to remove diclofenac etalhyaluronate sodium.

effect for patients with osteoarthritis and was initially reported to be safe in comparison with control.^{3,6} However, the Ministry of Health, Labour and Welfare in Japan reported breaking news concerning the safety of diclofenac etalhyaluronate sodium on June 1, 2021 (<https://www.mhlw.go.jp/content/11125000/000787427.pdf>). Based on documents from March 2021, when diclofenac etalhyaluronate sodium began to be sold, to May 2021, there

were 10 cases (including 1 fatal case) of anaphylactic reaction among approximately 5,500 patients who were administered the intraarticular injection of diclofenac etalhyaluronate sodium. Among them were two cases that showed a delayed and repeated anaphylactic reaction treated by steroids, mainly without adrenaline. These cases might have also shown anaphylactic reaction after walking, but the events inducing anaphylactic reaction were not described. The one fatal case was that of a patient who went home the same day upon receiving the intraarticular injection of diclofenac etalhyaluronate sodium. The present case also showed a severe anaphylactic shock state immediately after injection and repeated delayed anaphylactic reactions, complicated with Kounis syndrome, all of which could be fatal.

Given the above, physicians should monitor patients not only immediately after injection but also after walking when administering the intraarticular injection of diclofenac etalhyaluronate sodium, as walking might scatter the allergen into the blood from the injected joints, resulting in a fatal anaphylactic reaction. Initially, the orthopedist thought that the anaphylactic reaction would improve soon without any medical intervention. However, the patient showed repeated anaphylactic reactions; thus, delayed aspiration of the intraarticular diclofenac etalhyaluronate sodium was performed. If the intraarticular diclofenac etalhyaluronate sodium had been removed soon after the first anaphylactic reaction, repeated anaphylactic reactions may have been avoided. In addition, physicians should evaluate electrocardiogram findings and the levels of cardiac enzyme to check for complication with fatal Kounis syndrome in patients

who show anaphylactic reaction after intraarticular injection of diclofenac etalhyaluronate sodium.⁷

CONCLUSION

TO OUR KNOWLEDGE, this is the first case report of a patient who received intermittent injections of adrenaline three times for repeated anaphylactic reaction after walking over 3 days due to a single intraarticular injection of diclofenac etalhyaluronate sodium. Physicians should have patients who receive intraarticular injection of diclofenac etalhyaluronate sodium walk for a short period and evaluate their status.

DISCLOSURE

Approval of the Research Protocol: This prospective study protocol was approved by the Review Board of Juntendo Shizuoka Hospital (approval number: 298).

Informed Consent: We obtained informed consent from the patient.

Registry and the Registration No. of the Study/Trial: N/A.

Animal Studies: N/A.

Conflict of Interest: We do not have conflict of interest to declare.

ACKNOWLEDGMENTS

THIS WORK WAS supported in part by a Grant-in-Aid for Special Research in Subsidies for ordinary expenses

of private schools from The Promotion and Mutual Aid Corporation for Private Schools of Japan (No grant number).

REFERENCES

- 1 Christensen MJ, Eller E, Kjaer HF, Broesby-Olsen S, Mortz CG, Bindslev-Jensen C. Exercise-induced anaphylaxis: causes, consequences, and management recommendations. *Expert Rev. Clin. Immunol.* 2019; 15: 265–73.
- 2 Pravettoni V, Incorvaia C. Diagnosis of exercise-induced anaphylaxis: current insights. *J. Asthma Allergy.* 2016; 9: 191–8.
- 3 Kisukeda T, Onaya J, Yoshioka K. Effect of diclofenac etalhyaluronate (SI-613) on the production of high molecular weight sodium hyaluronate in human synoviocytes. *BMC Musculoskelet. Disord.* 2019; 20: 201.
- 4 Sethi P, Treece J, Onweni C, Pai V. Antidote or Poison: A Case of Anaphylactic Shock After Intra-Articular Corticosteroid Injection. *Cureus.* 2017; 9: e1625.
- 5 Steiner UC, Gentinetta T, Hausmann O, Pichler WJ. IgE-mediated anaphylaxis to intraarticular glucocorticoid preparations. *AJR Am. J. Roentgenol.* 2009; 193: W156–7.
- 6 Nishida Y, Kano K, Nobuoka Y, Seo T. Efficacy and safety of diclofenac-hyaluronate conjugate (diclofenac etalhyaluronate) for knee osteoarthritis: a randomized phase 3 trial in Japan. *Arthritis Rheumatol.* 2021; 73: 1646–55.
- 7 Yanagawa Y, Kondo A, Ishikawa K *et al.* Kounis syndrome should be excluded when physicians treat patients with anaphylaxis. *Ann. Allergy Asthma Immunol.* 2017; 119: 392.