Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.1788-23
Intern Med 62: 3063-3067, 2023
http://internmed.jp

【 CASE REPORT 】

Nonepisodic Angioedema with Eosinophilia Following Receipt of the BNT162b2 mRNA COVID-19 Vaccine

Tamaki Koda, Bunki Natsumoto, Hirofumi Shoda and Keishi Fujio

Abstract:
Angioedema with eosinophilia (AE) is a rare disease of unknown etiology characterized by episodic (EAE) or nonepisodic AE (NEAE). Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA-based vaccines function as immunogens and intrinsic adjuvants and have been shown to be safe in large-scale trials. However, the long-term adverse reactions, especially those related to eosinophilic complications, have not been fully clarified. We herein report a case of self-limited but severe NEAE that developed in a young woman one week after receiving the second BNT162b2 mRNA vaccine. The symptoms that impaired her activities of daily living, such as edema, gradually resolved with supportive care over 10 weeks without corticosteroid treatment.

Key words: angioedema with eosinophilia, SARS-CoV-2, COVID-19, mRNA vaccine

(Intern Med 62: 3063-3067, 2023)
(DOI: 10.2169/internalmedicine.1788-23)

Introduction

Vaccines based on the messenger RNA (mRNA) of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been recommended and promoted worldwide during the coronavirus disease 2019 (COVID-19) pandemic. These mRNA vaccines have shown more than 90% efficacy in preventing COVID-19 (1, 2). Although acute adverse reactions to vaccines, such as a fever and pain, are common and well described, vaccines have been shown to be safe in large-scale trials (1, 2). Local or minor systemic acute reactions occur within a day or two after injection of the vaccine and usually resolve within a few days. However, several severe adverse events, including anaphylaxis, myocarditis, and thrombocytopenia, have also been reported (3). In addition, COVID-19 vaccines have sometimes induced autoimmune rheumatic disease (4) or worsening of the rheumatological signs/symptoms of affected patients (5). The long-term safety of these vaccines and the rare adverse reactions therefore remain to be fully clarified.

mRNA vaccine-induced T helper 2 (Th2)-type disorders are uncommon, but several cases of Th2-type disorders with eosinophilia, such as eosinophilic myocarditis (6, 7), asthma exacerbation (8), acute eosinophilic pneumonia (9-11) eosinophilic granulomatosis with polyangiitis (EGPA) (12), eosinophilic cellulitis (13, 14), eosinophilic panniculitis (15) and eosinophilic gastroenteritis (16), have been reported. Angioedema with eosinophilia (AE) is a rare disease characterized by episodic (EAE) or nonepisodic AE (NEAE). AE has been reported primarily in young women (17, 18).

We herein report a new case of self-limited but severe NEAE that developed in a young woman after she received the second BNT162b2 mRNA vaccine.

Case Report

A 26-year-old woman was referred to our department for edema and weight gain. The patient had been healthy until two months before admission, when she noticed urticaria and edema involving the dorsum of her left foot. A week before her signs/symptoms developed, she had received her second injection of the BNT162b2 mRNA COVID-19 vaccine. She was first examined at a clinic and administered antibiotics for suspected cellulitis. However, her edema gradually spread to involve her right lower extremity and both upper extremities. She developed problems walking and began to use a wheelchair. Seven days before her admission, she

Department of Allergy and Rheumatology, Graduate School of Medicine, The University of Tokyo, Japan
Received: February 23, 2023; Accepted: June 7, 2023; Advance Publication by J-STAGE: July 19, 2023
Correspondence to Dr. Bunki Natsumoto, natsumotobunki@gmail.com

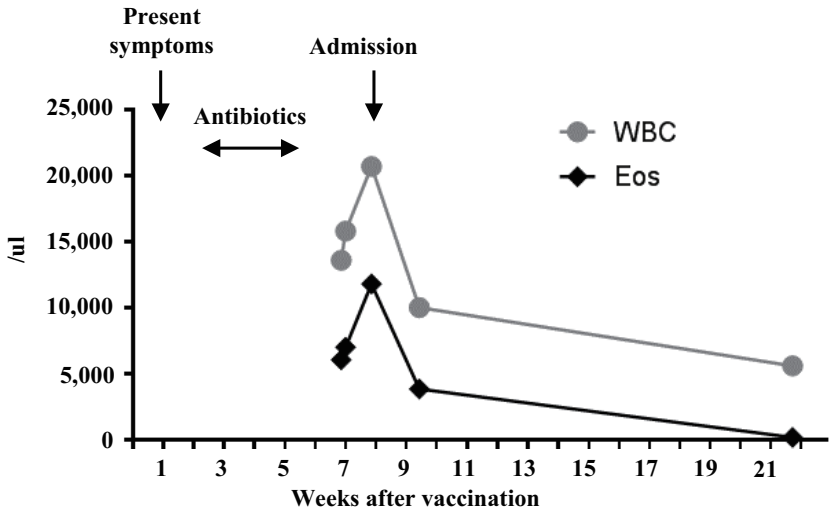

Figure 1. **Transition of WBC and eosinophil count after vaccination.**

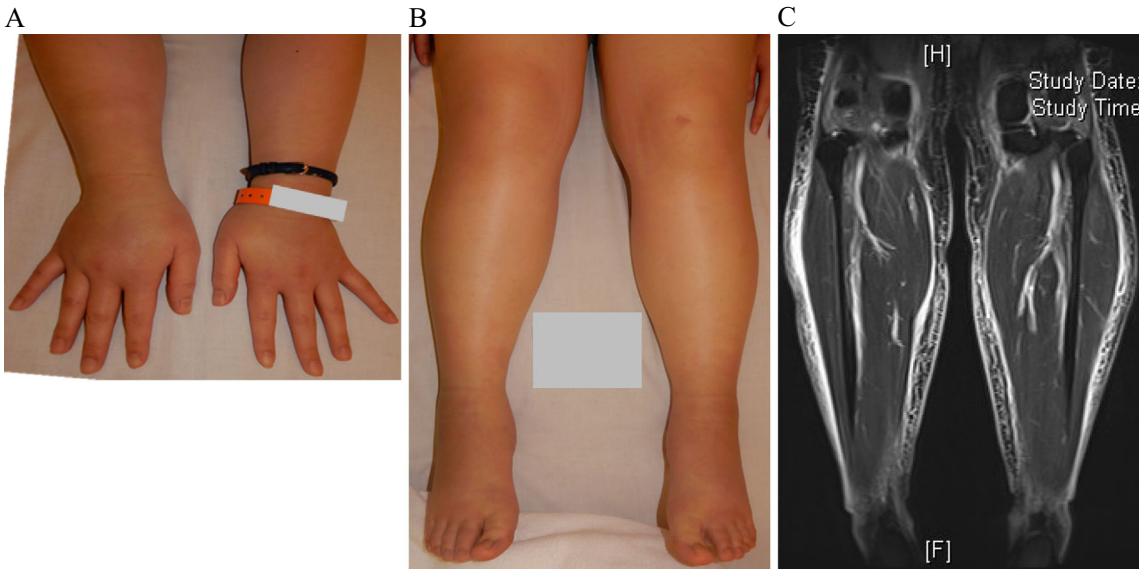

Figure 2. **Clinical image of the patient with angioedema with eosinophilia. (A, B) Symmetrical edema of her hands and legs. (C) MRI revealed prominent subcutaneous edema (short T inversion recovery).**

was seen at another clinic with prominent edema of the extremities (7 weeks after the second vaccination), a weight gain of 2 kg over a 2-month period, and increased eosinophil (Eos) and white blood cell (WBC) counts of 6,052/μL and 13,600/μL, respectively, in a peripheral blood specimen (Fig. 1).

On admission (eight weeks after the second vaccination), the physical examination revealed symmetrical fast pitting edema of her anterior tibia and symmetrical nonpitting edema of her hands (Fig. 2). She did not have a fever or complain of arthralgia or urticaria.

Laboratory tests showed a marked increase in the WBC (20,700/μL) and Eos counts (11,800/μL) (Fig. 1). She had slightly elevated levels of serum IgE at 480 (normal range 0-170) IU/mL, lactate dehydrogenase at 246 (124-222) U/mL and soluble interleukin-2 receptor at 1,000 (127-582) U/mL. Her levels of IgG, IgM, IgA, and C-reactive protein were within normal ranges, as were her erythrocyte sedimentation rate and complement 1-inactivator activity. There were no findings indicative of problems with the thyroid gland or organs, such as the heart, kidneys and liver.

A fecal smear test was negative for evidence of parasites. Tests for other infections with human immunodeficiency virus, human T-cell leukemia virus type-1, Epstein-Barr virus, hepatitis B virus and hepatitis C virus were negative, as were tests for tuberculosis and syphilis. Tests for the presence of autoantibodies, such as antineutrophil cytoplasmic antibodies, were negative. Hematological disorders, including chronic eosinophilic leukemia; abnormalities of Fip1-like-1/platelet-derived growth factor receptor-alpha, fibroblast growth factor receptor 1 and platelet-derived growth factor receptor-beta; and T-cell neoplasm/lymphoma, were

Table. NEAE Post Messenger RNA Vaccination and COVID19 Infection.

Age/Sex	Patient background	Vaccine/ COVID19 infection	Day to onset*	Maximum eosinophil (/μL)	Day to maximum eosinophil count†	Treatment	Prognosis
26/F (Our case)	None	BNT162b2	7	11,800	56	Supportive care (ex: Acetaminophen)	Improved in 70days
77/F (28)	Diabetes, dyslipidemia	BNT162b2	2	Not mentioned (3,750 during diagnosis)	Not mentioned	Systemic steroid	Improved
76/F (29)	Cephalosporin allergy	BNT162b2	3	Not mentioned (960 during diagnosis)	Not mentioned	Oral and topical antihistamine	Improved in approximately 42days
70/F (30)	Diabetes	mRNA-1273	5	18,125	22	Systemic steroid: From day 20 Reslizumab: From day 124	Controlled in 138days
29/F (31)	Allergic rhinitis, atopic dermatitis	COVID19 infection	13	7,536	30	Systemic steroid: From about day 30	Improved in approximately 40days

* Day to onset: Duration from vaccination or COVID19 to NEAE onset (days)

† Day to maximum eosinophil count: Duration from vaccination or COVID19 to maximum eosinophil count (days)

also excluded by genetic examinations.

Magnetic resonance imaging (MRI) revealed prominent subcutaneous edema (Fig. 2). There was no evidence of fasciitis or synovitis. A biopsy of the left upper extremity showed mild infiltration of inflammatory cells in the dermis. Based on these examinations and differential diagnoses, she was diagnosed with NEAE (followed for at least 11 months with no episodes of recurrence), and we suspected that the development of her NEAE had been triggered by BNT162b2 mRNA vaccination.

Fortunately, the edema and eosinophilia showed gradual improvement with supportive care, including maintaining a resting state and providing attentive nursing, along with symptomatic therapy using acetaminophen, without the need for corticosteroid administration. The patient's symptoms had completely disappeared by 10 weeks after vaccination, and the Eos count improved to the normal range after 22 weeks (Fig. 1).

Discussion

EAE was first described by Gleich et al. in 1984 (17). It is characterized by recurrent episodes of peripheral blood eosinophilia, elevated serum IgM levels, a fever, urticaria, weight gain, angioedema and absence of involvement of the internal organs. In 1998, Chikama et al. reported Japanese patients who had a single episode of AE in Japan, which they called NEAE (18). Most of the subsequent reports from Asia have been cases of NEAE that show the following characteristics: affected patients are young women, edema is localized to the hands and feet, arthralgia and eosinophilia are present, levels of immunoglobulin are normal, and internal organs are not involved (19).

Immunological studies suggest that activated T-cell-derived cytokines, mainly interleukin 5 (IL-5), are involved in the migration and activation of eosinophils in the skin (20). There are further reports suggesting that eosinophilia is a marker of severe COVID-19 (21, 22). It is possible that vaccines induce a similar immunological status in some patients. Indeed, as previously mentioned, mRNA vaccine-induced eosinophilic disease has been reported (8, 9, 12). However, COVID-19 mRNA vaccines basically induce T helper type 1 responses without elevated IL-5 levels (23). Mizukawa et al. reported that IL-5 levels were lower and TNF-α levels were higher in the acute phase of NEAE than in the acute phase of EAE (24). Okamoto et al. reported that TARC/CCL17 serum levels are elevated in NEAE and correlated with the disease activity and eosinophil count (25).

To date, two cases of NEAE following influenza vaccination have been reported (26, 27). Both cases involved Japanese women, 53 and 89 years old, who had a history of repeated influenza vaccinations. While further investigations are needed to determine the causal relationship between the influenza vaccine and NEAE, the potential involvement of antigens, such as chicken egg and gelatin, as well as the possibility of coincidental events have been discussed.

EAE was not reported after injections of the COVID-19 vaccines in the initial trials. However, subsequently, two elderly Japanese patients were reported to have developed NEAE following administration of BNT162b2 (28, 29) (Table). One of the patients was a 77-year-old woman with diabetes mellitus and dyslipidemia who was administered systemic steroids for the treatment of NEAE (28). The other patient was a 76-year-old woman with a history of drug rash caused by cephalosporin who was treated for NEAE with antihistamines, and the symptoms resolved in 6 weeks (29). Recently, a 70-year-old woman with diabetes developed NEAE after mRNA-1273 injection (30). She was treated with systemic steroids from day 20 of the onset and reslizumab from day 124, with her condition controlled by 138 days (Table). A 29-year-old woman with allergic rhinitis and

atopic dermatitis developed NEAE after COVID-19 infection (31). She was treated with systemic steroids from approximately day 30 and improved in approximately 40 days (Table).

Our patient was a 26-year-old woman with no underlying diseases, need for medication or allergic reaction to polyethylene glycol. The symptoms of NEAE were self-limited without corticosteroid treatment. Nakachi et al. reported that most AE patients showed a natural decrease in Eos count and achieved complete remission without corticosteroid treatment (19). Our patient's symptoms had completely disappeared by 10 weeks after vaccination, and the Eos count improved to the normal range by 22 weeks (Fig. 1). This course therefore suggests that a transient immunological process was triggered by vaccination, although NEAE is basically self-limited.

We experienced a young woman with NEAE after COVID-19 mRNA vaccination, and her disease course was self-limited. We find this case interesting from the perspective of immunological reactions after COVID-19 vaccination. Further studies are needed to elucidate the incidence, risk factors, clinical course and immunological responses after COVID-19 vaccination.

Author's disclosure of potential Conflicts of Interest (COI).
Bunki Natsumoto: Research funding, GlaxoSmithKline. Hirofumi Shoda: Fees, Pfizer, Bristol-Myers Squibb, Eli Lilly, Sanofi, AbbVie, GlaxoSmithKline, Gilead, Boehringer Ingelheim, Jansen, Novartis, Chugai, Takeda, Astellas, Eisai, Asahi Kasei and Daiichi-Sankyo; Research funding, Novartis. Keishi Fujio: Honoraria, Tanabe Mitsubishi, Bristol-Myers Squibb, Eli Lilly, Chugai, Jansen, Pfizer, Ono, Abbie, Ayumi, Astellas, Sanofi, Novartis, Daiichi Sankyo, Eisai, Asahi Kasei and AstraZeneca; Research funding, Tanabe Mitsubishi, Bristol-Myers Squibb, Eli Lilly, Chugai, Eisai, Tsumura and Asahi Kasei.

Tamaki Koda and Bunki Natsumoto contributed equally to this work.

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