



Letter to the Editor

Anaphylaxis associated with eosinophilic sialodochitis via periostin upregulation and mast cell activation

Dear Editor,

Eosinophilic sialodochitis (ES), first reported by Kussmaul in 1879, is characterized by swelling of the salivary glands and discharge of mucus plugs from the saliva tube.^{1,2} Approximately 60 cases have been reported to date.^{1–3}

Before the onset of ES, many patients have a long-term chronic eosinophilic disease, such as asthma, allergic rhinitis, or atopic dermatitis.^{1,2} Recently, it was reported that eosinophil extracellular trap cell death (EETosis) might play an important role in the formation of ES mucus plugs.³ Herein, we report a case of ES-associated episodic anaphylaxis through IgE-independent mechanisms.

A 64-year-old Japanese woman developed chronic allergic rhinitis. She had noticed a swelling in her submandibular region over the past 5 years, gradually increasing in incidence. She began to have generalized urticaria and swelling in the submandibular region while eating regardless of meal contents. She was under oral antihistamines for a year, as prescribed by her previous doctor. However, her symptoms did not improve. Subsequently, she experienced anaphylaxis twice. She was diagnosed with a food allergy by her previous doctor and referred to our hospital.

On admission, her laboratory test showed a white blood cell count of 5200 cells/ μ L (187 cells/ μ L eosinophils) and a serum IgE level of 191 IU/mL. Her serum antigen-specific IgE levels could not be detected by the simultaneous multiple antigen assay 39 (View Allergy39®, Thermo Fisher Scientific, Uppsala, Sweden) (39 allergens, including environmental, pollen, microbial, and food allergens, were tested). At 6 weeks after recovery from anaphylaxis, we performed a prick test with dietary content when both urticaria and anaphylaxis occurred, but all test results were negative. Food challenge tests did not induce any symptoms. Based on these results, we concluded that the patient was unlikely to have food allergies.

For the swelling in the mandible, ultrasonography was performed, and the findings showed dilatation of the salivary ducts. Moreover, a salivary gland biopsy was performed, and hematoxylin-eosin staining indicated fibrosis and prominent eosinophil infiltration around the conduit (Fig. 1A, B). A mucus plug formation was evident in the oral cavity after salivary gland drainage (Supplementary Fig. 1). Based on these results, the patient was diagnosed with ES.

A few days after the admission, the patient noticed swollen salivary glands, and soon after, urticaria appeared. Blood tests were performed, and elevated eosinophil counts (620 cells/ μ L: normal

range <300 cells/ μ L) and serum salivary gland-derived amylase levels (283 U/L, normal condition without urticaria 56 U/L, normal range 44–132 U/L) were observed. We also found a clear increase in plasma histamine levels (2.27 ng/mL, normal range 0.15–1.23 ng/mL) as measured with enzyme immunoassay (LSI Medience, Japan). Additionally, the tryptase level in the saliva, as measured with fluor enzyme-linked immunosorbent assay (LSI Medience), had increased significantly (50.7 ng/mL) compared with that under her normal conditions (2.5 ng/mL) (Fig. 1C). The histamine level in the saliva had also increased (133 ng/mL) compared with that under her normal conditions (32.4 ng/mL).

We hypothesized that mast cell-derived mediators, including histamine and tryptase in the salivary glands, might have leaked into the circulating blood following the swelling of salivary glands, leading to systemic urticaria. To confirm the presence of mast cells in the salivary gland tissue, we performed immunostaining for the c-kit (Fig. 2A). Compared with the normal tissue, no increase in mast cell number was observed. However, toluidine blue staining revealed a large amount of extracellular deposition of the dye around the conduit, indicating mast cell degranulation (Fig. 2B).

Periostin, an extracellular matrix protein, has recently been attracting attention as a biomarker of type 2 immunity.⁶ Immunostaining for periostin was performed, and we found periostin deposition around the salivary gland conduits, where fibrosis and eosinophilic inflammation were prominent (Fig. 2C). To study the eosinophil activation in the mucus plug, immunostaining for eosinophil-specific proteins, cytoplasmic protein galectin-10, and granular protein major basic protein (MBP) was also performed as previously described.⁷ A large number of eosinophils both in intact (galectin-10+ve, MBP+ve) and cytolytic (galectin-10-ve, MBP+ve) statuses were found inside the mucus plug (Fig. 2D). The citrullinated histone H3 was stained in conjunction with hematoxylin-eosin staining to detect eosinophil extracellular traps. Cytolytic eosinophils that release cell-free eosinophil granules and citrullinated histone H3 stained filamentous DNA were evident, indicating eosinophil EETosis (Fig. 2E). Additionally, aggregated intact eosinophils stained with extracellular citrullinated histone H3 were also observed (Fig. 2F). These results indicated that both intact and cytolytic eosinophils with extracellular traps were aggregated to form stable fibrous mucus plugs in the salivary ducts.

The expression of periostin is induced by interleukin (IL)-4/IL-13, which is upregulated by type 2 inflammation in allergic diseases, including chronic allergic rhinitis.⁵ Periostin has been reported to be induced by the disruption of epithelial cells and

Peer review under responsibility of Japanese Society of Allergy.

<https://doi.org/10.1016/j.alit.2022.10.008>

1323-8930/© 2022 Japanese Society of Allergy. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

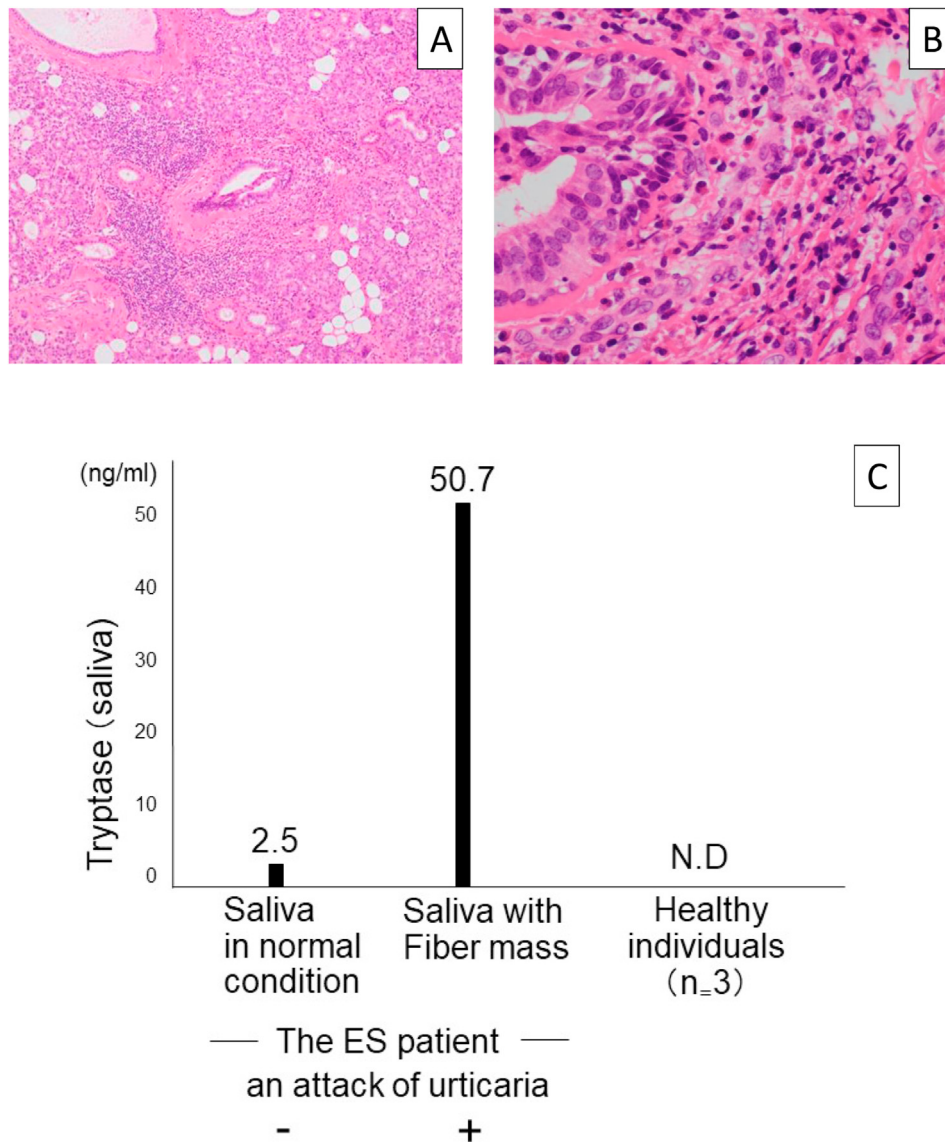


Fig. 1. Salivary tryptase levels in the fibrous sialadenitis (FS) patient and healthy control subjects. Hematoxylin-eosin staining of the salivary glands is shown at low (A) and high (B) magnifications. (C) Tryptase levels in saliva under normal conditions and with a fibrous mass during an attack of urticaria after salivary gland massage were measured in the FS patient and healthy controls.

endothelial cells via some physical stimuli.^{6,8} Periostin promotes the induction of eosinophil degranulation and oxidative burst through α M β 2 integrin.⁹ MBPs directly promote histamine release from mast cells through the IgE-independent mechanisms.⁴

Taken together, we speculated on the mechanism of ES as follows (Supplementary Fig. 2): (1) Type 2 cytokines IL-4 and IL-13 induce periostin, which deposits around the conduits of salivary glands with endothelial damage. (2) Increased eosinophil chemoattractants induce tissue eosinophilia, where they are further activated by local mediators, including periostin. (3) Luminal eosinophils were further activated to form aggregates and undergo EETosis to release extracellular traps, increase mucus plug formation, and obstruct the salivary gland. (4) With the increased intra-

ductal pressure load due to salivation associated with feeding behavior, salivary gland-derived amylase leaks into the interstitial tissues of the salivary glands and the circulating blood. Eosinophil-derived mediators, including MBP, stimulate mast cells around the conduit to release histamine and tryptase. They could move into the small capillaries to blood circulation, causing urticaria and anaphylaxis.

To the best of our knowledge, this is the first case of ES-associated anaphylaxis with a series of pathophysiological pieces of evidence. Prominent local type 2 immunity, upregulation of periostin, mast cell activation, and occurrence of EETosis might lead to systemic response caused by salivary duct obstruction. Further study is required to clarify our observation.

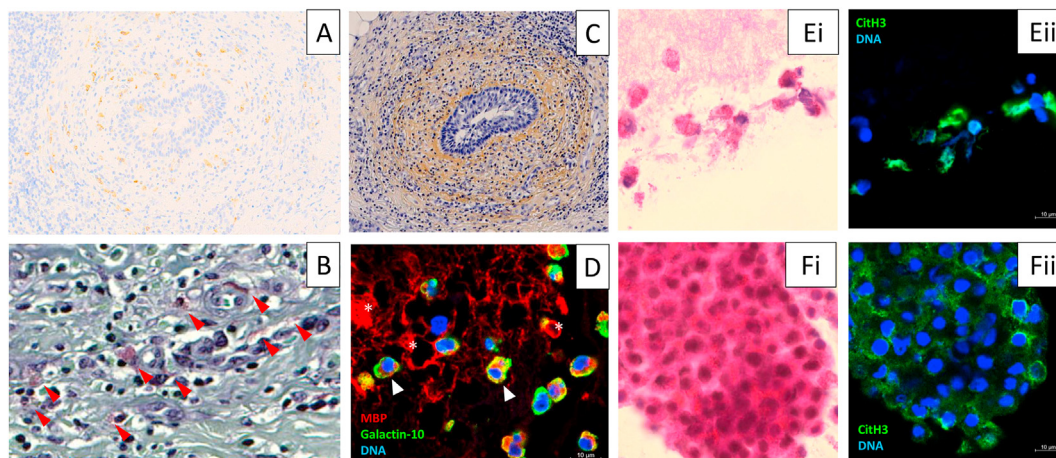


Fig. 2. Histological findings of the salivary glands and the fibrous mass in the saliva. To evaluate the density and degranulation of mast cells in the salivary glands (red arrow), immunohistochemical (c-kit) (A) and toluidine blue (B) staining were performed. (C) Immunohistochemical staining of the salivary glands indicates significant periostin deposition around the conduit. (D) Immunofluorescence staining for galactin-10 (green), MBP (red), and DNA (blue) in the salivary fibrous mass. Intact (arrowheads) and cytolytic eosinophils (asterisks) are indicated. Hematoxylin-eosin staining of the salivary fibrous mass indicated cytolytic eosinophils with cell-free granules (Ei) and aggregated eosinophils (Fi). (Eii and Fii) Immunofluorescence staining for citrullinated histone H3 (green), a marker for extracellular traps, and DNA (blue). Identical field with (Ei) and (Fi) are shown.

Acknowledgments

This study was conducted following the ethical principles of the Declaration of Helsinki and written informed consent to publish the findings was obtained from the patient. The authors are grateful to Noriko Tan for outstanding technical assistance and Satomi Misawa for outstanding assistance in drawing the figures.

This study was partly funded by Research Grants from the JSPS KAKENHI (20K08794, 20H03832, 21K07833, 21K08434, and 22K08595 to SU), Allergic Disease and Immunology from the Japan Agency for Medical Research and Development under grant number JP21ek0410055 (SU).

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2022.10.008>.

Conflict of interest

RTM has received grants as an investigator from Maruho, Mitsubishi Tanabe Pharma, and Teikoku Seiyaku. SU is an advisory board member of GlaxoSmithKline (GSK), received honoraria for lectures from AstraZeneca (AZ), GSK and Sanofi, and grant support from AZ, Novartis Pharma, VIB, and Maruho. NK has received honoraria as a speaker/consultant for Sanofi, Maruho, Abbvie, Eli Lilly Japan, and Leo Pharma, and has received grants as an investigator from Maruho, Eli Lilly Japan, Sun Pharma, Taiho Pharmaceutical, Torii Pharmaceutical, Boehringer Ingelheim Japan and Leo Pharma. The rest of the authors have no conflict of interest.

Ayano Maruyama ^{a,*}, Risa Tamagawa-Mineoka ^{a,1}, Shigeharu Ueki ^{b,1}, Koji Masuda ^a, Makoto Yasuda ^c, Eiichi Konishi ^d, Satoshi Nunomura ^e, Kenji Izuhara ^e, Misaki Arima ^b, Norito Katoh ^a

^a Department of Dermatology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

^b Department of General Internal Medicine and Clinical Laboratory Medicine, Akita University Graduate School of Medicine, Akita, Japan

^c Department of Otorhinolaryngology, Head & Neck Surgery, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

^d Department of Pathology, Graduate School of Medical Science, Kyoto Prefectural University of Medicine, Kyoto, Japan

^e Division of Medical Biochemistry, Department of Biomolecular Sciences, Saga Medical School, Saga, Japan

* Corresponding author.

E-mail address: maruchan@koto.kpu-m.ac.jp (A. Maruyama).

References

- Zhu WX, Chen Y, Liu DG, Yu GY. Eosinophilic sialodochitis: a type of chronic obstructive sialadenitis related to allergy. *Laryngoscope* 2021;**131**:E800–6.
- Baer AN, Okuhama A, Eisele DW, Tversky JR, Gniadek TJ. Eosinophilic sialodochitis: redefinition of 'allergic parotitis' and 'sialodochitis fibrinosa'. *Oral Dis* 2017;**23**:840–8.
- Kawamura Y, Ikeda R, Hori T, Sasaki T, Miyabe Y, Fukuchi M, et al. Sialodochitis fibrinosa: salivary duct obstruction by eosinophil extracellular traps? *Oral Dis* 2020;**26**:1459–63.
- O'Donnell MC, Ackerman S, Gleich G, Thomas L. Activation of basophil and mast cell histamine release by eosinophil granule major basic protein. *J Exp Med* 1983;**157**:1981–91.
- Izuhara K, Nunomura S, Nanri Y, Ogawa M, Ono J, Mitamura Y, et al. Periostin in inflammation and allergy. *Cell Mol Life Sci* 2017;**74**:4293–303.
- Pawankar R, Okuda M, Yssel H, Okumura K, Ra C. Nasal mast cells in perennial allergic rhinitis exhibit increased expression of the Fc epsilonRI, CD40L, IL-4, and IL-13, and can induce IgE synthesis in B cells. *J Clin Invest* 1997;**99**:1492–9.
- Fukuchi M, Miyabe Y, Furutani C, Saga T, Moritoki Y, Yamada T, et al. How to detect eosinophil ETosis (EETosis) and extracellular traps. *Allergol Int* 2021;**70**:19–29.
- Marbach-Breittrück E, Kalledat A, Heydeck D, Stehling S, Fluhr JW, Zuberbier T, et al. Atopic patients show increased interleukin 4 plasma levels but the degree of elevation is not sufficient to upregulate interleukin-4-sensitive genes. *Skin Pharmacol Physiol* 2019;**32**:192–200.
- Noguchi T, Nakagome K, Kobayashi T, Uchida Y, Soma T, Nakamoto H, et al. Periostin upregulates the effector functions of eosinophils. *J Allergy Clin Immunol* 2016;**138**:1449–52.

Received 29 September 2022

Received in revised form 29 September 2022

Accepted 16 October 2022

Available online 14 November 2022

¹ These authors contributed equally to this work.