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Case Report

Eosinophilic sialoadenitis in a patient with severe asthma: a case report

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ABSTRACT

Activated eosinophils can infiltrate various tissues and cause inflammatory tissue damage. Asthma is a typical type of eosinophilic inflammatory disease that occurs in the respiratory system. Eosinophilic sialodochitis and sialoadenitis of the salivary gland are rare diseases clinically characterized by painful swelling. In this report, we present a 68-year-old woman with asthma who presented to our hospital with mandibular swelling. Her asthma had been well controlled with an inhaled combination of a corticosteroid and a long-acting β2 agonist, although she reported a past history of frequent asthma attacks and hospitalization. Laboratory investigation on admission revealed blood eosinophilia (2,673/μL), high levels of total immunoglobulin E (390 U/mL) and immunoglobulin G4 (183 mg/dL). Bone marrow examination showed no evidence of eosinophilic neoplasia. Histological examination of her minor salivary glands disclosed an infiltration of mixed lymphocytes and eosinophils. Chromatolytic eosinophils with Charcot-Leyden crystals were also observed within the edematous dermis and fibrous tissues surrounding the minor salivary gland. The patient was diagnosed with eosinophilic sialoadenitis. Treatment with oral corticosteroids (0.5 mg/kg/day) was initiated. Thereafter, the mandibular swelling improved. This report describes a rare case of eosinophilic sialoadenitis in a patient with severe eosinophilic asthma, for which histopathological and immunefluorescence microscopic analyses were performed.

Keywords: Sialoadenitis; Asthma; Eosinophil; Degranulation; Charcot-Leyden crystal

INTRODUCTION

Eosinophils play an important role in the regulation of immune responses. Local activation of this type of cell causes inflammatory tissue damage by degranulation, production of reactive oxygen species, release of cytokine and lipid mediators, and extracellular trap formation [1, 2]. Thus, circulating, tissue-infiltrating, and tissue-resident eosinophils possess a broad range of effector functions in health and disease [3].

Salivary gland swelling occurs in various diseases, including immunoglobulin (Ig)G4-related diseases, Sjögren syndrome, and infectious salivary gland inflammation. Sialodochitis fibrinosa (Kussmaul disease), allergic parotitis, and Kimura disease are rare among diseases

Author Contributions

Conceptualization: Jun Miyata. Formal analysis: Jun Miyata, Susumu Matsukuma, Shigeharu Ueki. Investigation: Tomoya Sano, Jun Miyata, Azusa Sano, Yosuke Ono. Methodology: Jun Miyata, Susumu Matsukuma, Shigeharu Ueki. Project administration: Jun Miyata, Yuji Tanaka, Akihiko Kawana. Writing - original draft: Tomoya Sano, Jun Miyata. Writing - review & editing: Tomoya Sano, Jun Miyata, Susumu Matsukuma, Shigeharu Ueki.

characterized by salivary gland swelling and eosinophilic infiltration. Recently, a diagnosis of eosinophilic sialodochitis can be widely applied to patients with eosinophil-rich swelling of the salivary gland [4]. In this report, we present a case of eosinophilic sialoadenitis in a female patient with eosinophilic asthma and submandibular gland swelling.

CASE REPORT

A 68-year-old woman presented to our hospital with complaints of persistent sore throat and pain on swallowing for the past 1 month. She had no respiratory or gastrointestinal symptoms, such as dyspnea, sputum, cough, diarrhea, or nausea. Physical examinations showed edematous changes of eyelids and lower jaw, and sublingual swelling, but no leg edema. Her respiratory and cardiac sounds were normal.

The patient's diagnosis of asthma was confirmed at the age of 60 years. Her asthma was controlled by treatment with an inhaled combination of a corticosteroid and a long-acting β2 agonist, leukotriene antagonist, and low-dose theophylline. She was allergic to pollens of cedar, cypress, ragweed, house dust, and shrimp. Before this treatment was introduced, she frequently had experienced asthma attacks and hospitalization for receiving systemic corticosteroids. In addition, she was a never-smoker.

Her vital signs were within normal range: body temperature, 36.0°C; blood pressure, 122/67 mmHg; pulse rate, 75 bpm; SpO_2, 95%. The results of the laboratory investigations on admission are summarized in **Table 1**. These results demonstrated blood eosinophilia (27%, 2,673/μL) and high levels of IgE and IgG4. No autoantibodies, including anti-Sjögren-syndrome-related antigen A antibody, anti-Sjögren-syndrome-related antigen-B antibody, and myeloperoxidase-antineutrophil cytoplasmic antibody or antiparasitic antibody, were detected. Plasma concentrations of interleukin (IL)-5 and IL-4 were notably elevated (IL-5, 16.4 pg/mL; IL-4, 6.4 pg/mL).

Computed tomography (CT) of her head and neck revealed swelling of both submaxillary salivary glands (**Fig. 1A**). Chest CT showed only mild thickened peripheral airway wall with no distinct peripheral infiltrative shadows and/or ground glass-like opacities (**Fig. 1B, C**).

Bone marrow biopsy showed no immature or mature proliferation of eosinophils. Assessment for genetic mutations that cause clonal eosinophilia (FIP1L-PDGFRA, PDGFRB, and FGFR1) returned negative results.

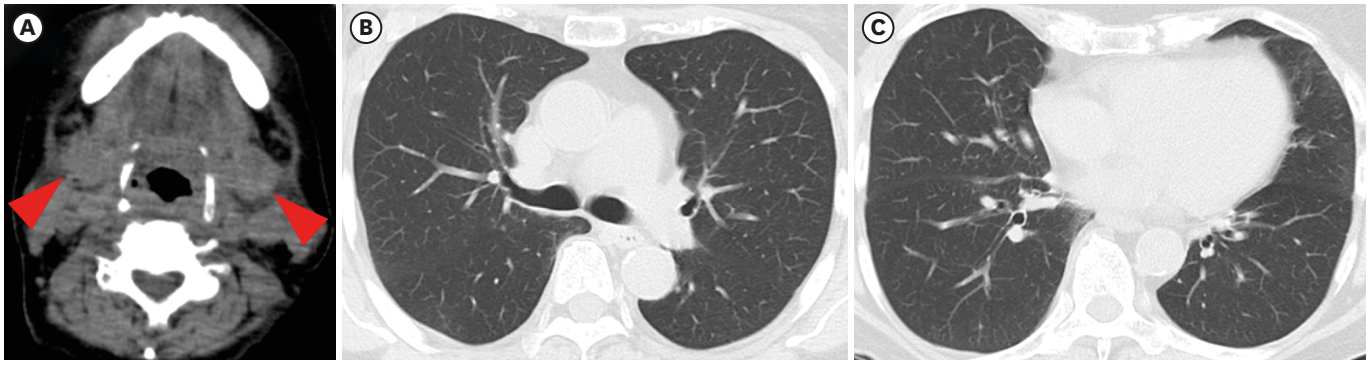

Fig. 1. Axial computed tomography (CT) images. (A) CT of the head and neck demonstrated swelling of the both submandibular glands (red arrowheads). (B, C) Chest CT showed mild thickening of the bronchial wall with no abnormal shadows on the lung parenchyma.

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Table 1. Results of the laboratory investigations in the present case

Parameter	Result
Hematological parameters	
White blood cells	9,900/mL
Neutrophil	55.20%
Lymphocyte	13.90%
Basophil	0%
Eosinophil	27%
Monocyte	4%
Red blood cells	507×10^4/mL
Hemoglobin	14.2 g/dL
Hematocrit	43.40%
Platelets	27.9×10^4/mL
Serological and biochemical parameters	
T-Bil	0.51 mg/dL
AST	18 IU/L
ALT	13 IU/L
LDH	318 IU/L
ALP	106 IU/L
Alb	4.4 g/dL
BUN	15 mg/dL
Cr	0.58 mg/dL
Na	143 mEq/L
K	4.2 mEq/L
Cl	108 mEq/L
Ca	9.2 mg/dL
P	2.9 mg/dL
CK	46 IU/L
Amylase	53 IU/L
Vit B_{12}	399 pg/mL
KL-6	180 U/mL
SP-A	55.5 ng/mL
SP-D	60.3 ng/mL
sIL-2R	1,050 U/mL
ACE	23.2 IU/L
TSH	0.68 μIU/mL
FT4	1 ng/dL
ACTH	14.8 pg/mL
Cortisol	12.7 μg/dL
HbA1c (NGSP)	6.20%
Immunological and infectious parameters	
CRP	0.7 mg/dL
IgG	793 mg/dL
IgA	185 mg/dL
IgM	73 mg/dL
IgE	390 IU/mL
IgG4	183 mg/dL
ANA	<40 times
Rheumatoid factor	49 IU/mL
Anti-SS-A/Ro antibody	(-)
Anti-SS-B/La antibody	(-)
MPO-ANCA	(-)
PR3-ANCA	(-)
HIV antibody	(-)
HTLV-1 antibody	(-)
T-SPOT. TB	(-)
Antiparasitic antibody	(-)

T-Bil, total bilirubin; AST, aspartate transaminase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; Alb, albumin; BUN, blood urea nitrogen; KL-6, Krebs von den Lungen-6; SP-A, surfactant protein-A; SP-D, surfactant protein-D; sIL-2R, soluble interleukin-2 receptor; ACE, angiotensin-converting enzyme; TSH, thyroid-stimulating hormone; FT4, free thyroxine 4; ACTH, adrenocorticotropic hormone; HbA1c (NGSP), hemoglobin A1c; CRP, ; ANA, antinuclear antibody; MPO-ANCA, myeloperoxidase-antineutrophil cytoplasmic antibody; PR3-ANCA, proteinase3-antineutrophil cytoplasmic antibody; HIV, human immunodeficiency virus; HTLV-1, human T-cell leukemia virus type 1; TB, tuberculosis.

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Mandibular biopsy specimens showed relatively prominent eosinophilic infiltration within the edematous dermis and fibrous tissues surrounding minor salivary gland (**Fig. 2A**). Lymphoplasmacytic infiltration containing eosinophils were also present in the minor salivary gland (**Fig. 2B**). No granulomas or immunohistochemically IgG4-positive plasma cells were found. Some eosinophils showed disintegration of their bilobular nuclei, i.e.,

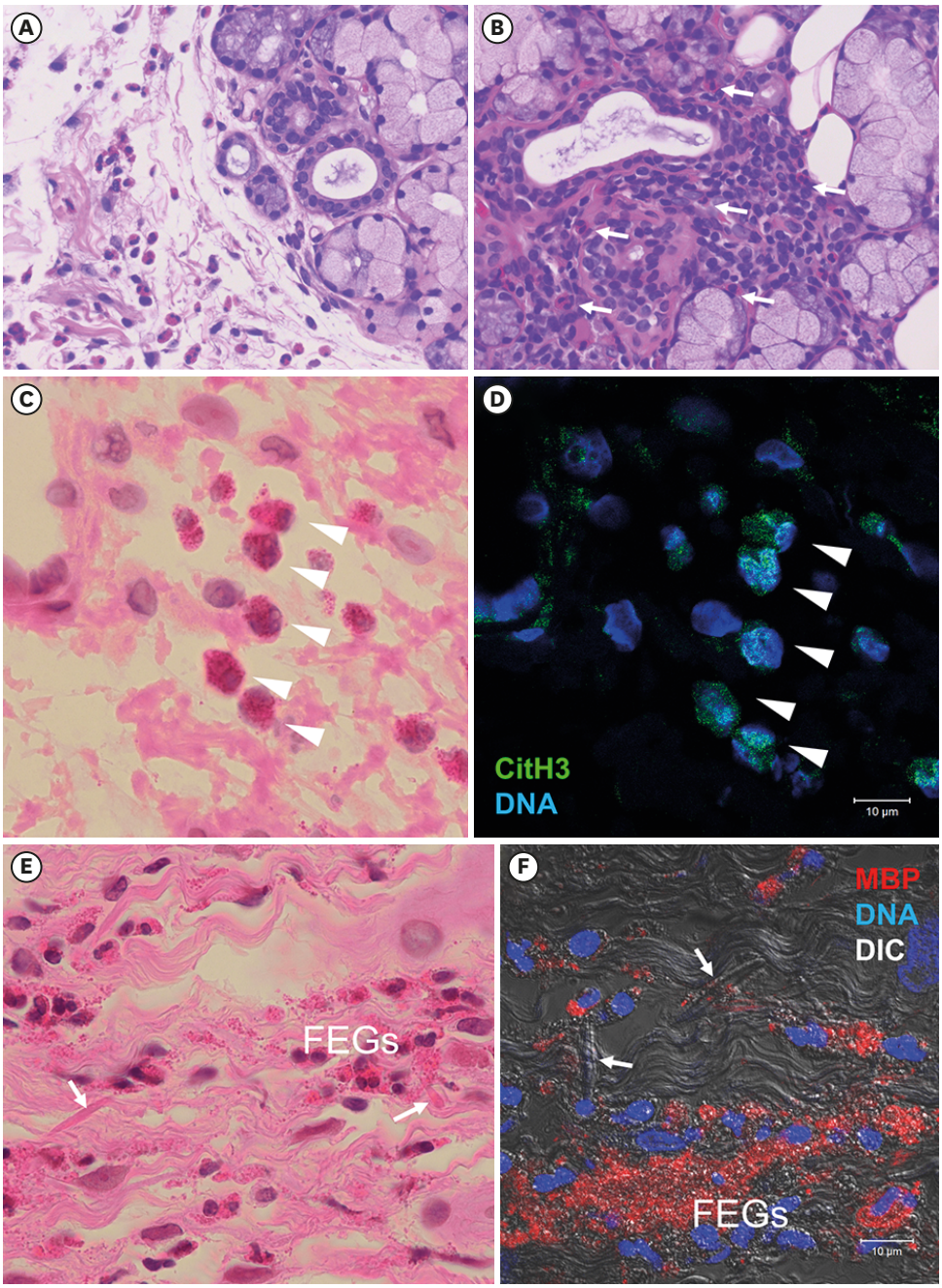

Fig. 2. Pathological findings. (A, B) Histological analysis of small salivary gland and the surrounding tissue showed infiltration of eosinophils and lymphocytes (hematoxylin and eosin staining, ×40). Eosinophils in the small salivary glands are noted in B (arrows). (C) The arrowheads indicate chromatolytic eosinophils within the edematous dermis and fibrous tissues. (D) The sections identical to C were stained with anti-citrullinated histone H3 (CitH3) antibody and Hoechst 33342 for DNA, which showed the CitH3-stained chromatolytic nuclei. Needle-like Charcot-Leyden crystals are noted in panel E (arrows, hematoxylin and eosin staining, ×100). (F) Intact free eosinophil granules (FEGs) were also noted in close proximity to Charcot-Leyden crystals. Immunohistochemical staining showed major basic protein (MBP)-positive cell-free extracellular granule deposition. Charcot-Leyden crystals were also noted in the differential interference contrast image (DIC) (arrows, ×100).

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chromatolysis within the edematous dermis and fibrous tissues (**Fig. 2C**, arrowheads). Immunohistochemical analysis indicated chromatolytic eosinophils stained with citrullinated histone H3 (CitH3), a known marker for extracellular traps (**Fig. 2D**) [2]. Charcot-Leyden crystals (CLCs), which are slender bipyramidal hexagonal crystals, were also observed in close proximity to the cell-free eosinophil granules (FEGs) (**Fig. 2E**). Immunostaining for major basic protein, a specific eosinophil granule protein, indicated a marked deposition of cell-FEGs and the presence of CLCs (**Fig. 2F**).

These findings suggested a diagnosis of eosinophilic sialoadenitis. Subsequently, treatment with oral corticosteroids (0.5 mg/kg/day) improved the patient's clinical manifestations including the swollen salivary glands and pharyngeal symptoms. No relapse was observed after gradual dose reduction. However, she experienced asthma attacks repeatedly after the oral corticosteroids were discontinued. Thereafter, she was treated with short-term oral administration of systemic corticosteroids (30 mg/day for 7 days).

DISCUSSION

Eosinophil sialodochitis is a rare disease and its diagnostic criteria include: (1) recurrent paroxysmal swelling of the major salivary glands, (2) presence of salivary duct mucus plugs that contain numerous eosinophils, (3) peripheral blood eosinophilia and elevated IgE level, (4) associated atopic diseases, (5) ductal dilatation and occasional focal narrowing of the major salivary gland ducts, (6) periductal eosinophil- and lymphocyte-rich inflammation and fibrosis with associated reactive ductal epithelial cells, and (7) failure to satisfy the diagnostic criteria for IgG4-related disease [4]. To make an eosinophil sialodochitis diagnosis, criteria (1) + (2) or (1) + (6) + (7) should be met. In the present case, criteria (1), (3), (6), and (7) were observed, supporting possible diagnosis of eosinophil sialodochitis. However, no ductal mucus plug or dilatation was observed in this case. Eosinophlia around the salivary gland ducts was not prominent. Thus, we assessed the present case as eosinophilic sialoadenitis.

Previous studies have revealed that eosinophil cytolytic degranulation does not represent a process of accidental necrosis or apoptosis; rather, eosinophils active select their death program, namely extracellular trap cell death (ETosis). Eosinophil ETosis (EETosis) is a nicotinamide adenine dinucleotide phosphate-oxidase-dependent pathway in most cases, culminating in plasma membrane disintegration, deposition of FEGs, nuclear chromatolysis, and development of CitH3-positive extracellular traps [2, 5-7]. Recent studies have also shown a close association between EETosis and natural formation of CLCs [2, 7]. In the present case, FEGs, CLCs, and CitH3-positive chromatolytic eosinophils were observed, suggesting an activated state of eosinophils in tissue (**Fig. 2C-F**) [8]. The liberated intracellular components lead to sterile inflammation [5-7, 9], suggesting a pathophysiological relationship between salivary gland swelling and EETosis.

The differential diagnosis of sialoadenitis includes Kimura disease, Sjögren syndrome, and IgG4-related disease. Kimura disease is a chronic inflammatory disease characterized by painless soft tissue masses with lymphoid follicles and eosinophilia, and lymphadenopathy in the head and neck region [10, 11]. Sjögren syndrome is an autoimmune disorder characterized by dry mouth and eyes with lymphocytic inflammation. In the present case, eosinophil was one of the cell types that infiltrated small salivary glands in an activated state. Also, clinical manifestations of Sjögren syndrome were unclear. Infiltration by IgG4-positive

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plasma cells was not observed as well. Therefore, a possible diagnosis of Kimura disease, Sjögren disease, and IgG4-related disease was ruled out.

The severity of eosinophilic sialodochitis and sialoadenitis could determine the treatment strategy. Antihistamines and oral corticosteroids have been widely used in previously reported cases [4, 12]. Disease recurrence often occurs when active treatment is not introduced or is discontinued [13]. In the present case, treatment with oral corticosteroids was successful and no recurrence was noted. However, the systemic eosinophilic inflammation was not completely controlled because frequent asthma attacks occurred. The details of a previous report and those of the present case indicate that type 2 cytokines, including IL-5 and IL-4, may play a crucial role in the pathogenesis of eosinophilic sialodochitis. High levels of IL-5 and/or IL-4 have been observed in the saliva and/or blood of patients with eosinophilic sialodochitis [14], suggesting that antibody drugs that target these cytokines may be effective in controlling disease activity or preventing recurrence of these diseases.

To our knowledge, this is a rare case report of eosinophilic sialoadenitis in a patient with severe eosinophilic asthma. Histological and immunefluorescence microscopic analyses were helpful in the understanding of the pathophysiology of this disease. Allergists and pulmonologists should be aware that patients with asthma who present with swelling of the salivary gland may have this rare eosinophilic inflammatory disease.

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