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【 CASE REPORT 】

Markedly Effective Steroid Treatment of Three Patients with Allergy-related Jackhammer Esophagus

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Abstract:
We experienced marked efficacy with steroid treatment of three patients with jackhammer esophagus (JHE). An esophageal biopsy revealed eosinophilic esophagitis (EoE) in two patients. One of the patients without EoE had eosinophilia and an increased serum immunoglobulin E level, and endoscopic ultrasonography revealed thickening of the esophageal muscularis propria. Esophageal manometry was used to diagnose all cases of JHE. Treatment consisted of steroid administration, which improved the symptoms and resolved the esophageal muscularis propria thickening in all patients. The esophageal manometry findings also normalized following treatment. Allergic diseases, including EoE, were assumed to have caused JHE.

Key words: eosinophilic esophagitis, gastroesophageal reflux disease, high-resolution manometry, Jackhammer esophagus, prednisolone

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Introduction

Jackhammer esophagus (JHE) is a rare type of esophageal dysmotility characterized by excessive peristaltic contractions in the esophagus (1). In the diagnostic criteria (2) developed in accordance with the Chicago classification version 3.0, in which high-resolution manometry (HRM) was used, when water is swallowed 10 times while in the supine position, JHE is diagnosed if the integrated relaxation pressure (IRP) is normal and hypercontractile peristalsis occurs [frequency: ≥20% of water swallows with a distal contractile integral (DCI) of >8,000 mmHg/s/cm] (2).

JHE occurs in cases of sudden-onset intense chest pain and dysphagia due to strong esophageal contractions. It is a type of non-cardiogenic chest pain (3). These symptoms are reportedly linked to strong contractions of the esophageal body that are related to a high lower esophageal sphincter pressure (LESP); however, no consensus has been reached regarding the pathological condition (4-6). Reports from Japan state that no significant infiltration of eosinophils into the esophageal epithelium was seen among patients exhibiting JHE, although some reports have noted that pathological conditions of eosinophilic esophageal myositis (EoEM) exist, wherein infiltration of the muscle layers by eosinophils is visible on a muscle layer biopsy (7-10).

Although the optimal treatment for JHE has not yet been established, cases of spontaneous remission have been reported (11). A calcium-channel blocker or nitrous acid agent is administered to relax the smooth muscles, and balloon dilatation and a muscle layer incision are performed (12). There are also cases in which a lengthy incision of the muscle layer from the middle to lower esophagus is required. In such cases, the incision of the muscle layer is reportedly performed under thoracoscopic assistance (13). In addition, peroral endoscopic myotomy (POEM), which was recently developed as a treatment for esophageal achalasia (14), is reportedly an effective treatment for JHE (15).

We herein report three cases of JHE suspected of being due to allergy-related diseases, including EoE, the onset of

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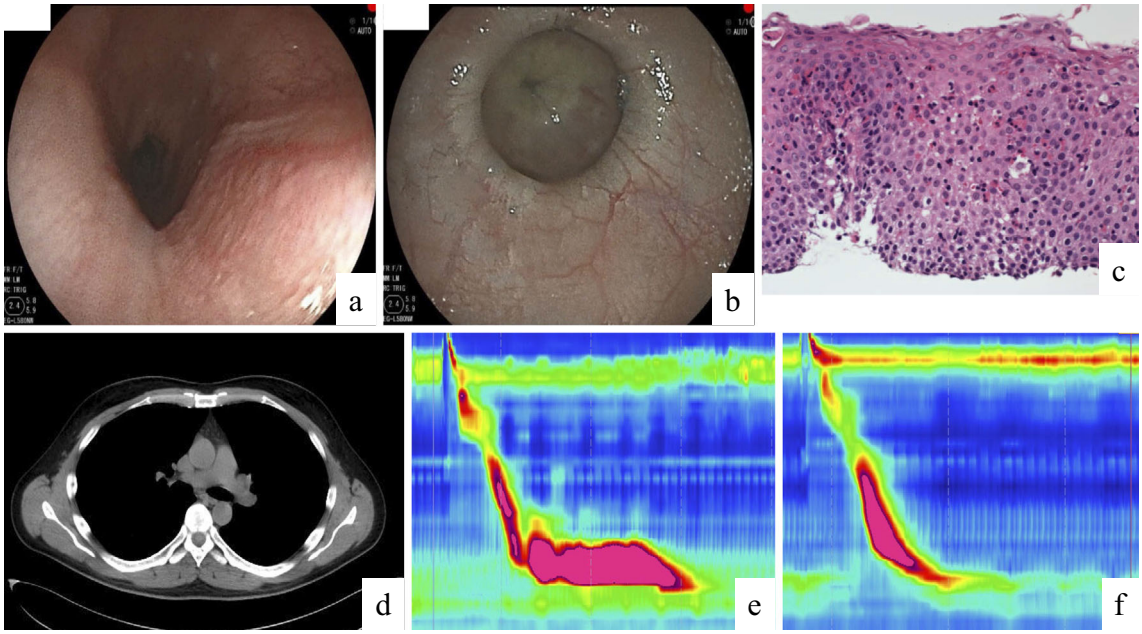

Figure 1. **Test findings in case 1. a and b: The upper gastrointestinal endoscopic findings prior to treatment. a: Longitudinal furrows and vitiligo, which are characteristic findings of eosinophilic esophagitis, are seen in the middle esophageal mucosa. b: An intense esophageal contraction is seen from the middle to lower esophagus. c: The histopathological findings from the esophageal biopsy at the time of upper gastrointestinal endoscopy prior to treatment are shown (400× magnification). Eosinophils at 28 cells/high-power field are visible in the esophageal epithelium. d: Chest computed tomography performed prior to treatment is shown. No thickening of the esophageal wall is evident. e: High-resolution manometry (HRM) findings prior to treatment are shown. A distal contractile integral (DCI) >8,000 mmHg/s/cm was noted at 60%. The maximum DCI was 21,538.2 mmHg/s/cm, while the mean DCI was 13,058.0 mmHg/s/cm. f: HRM findings after treatment are shown. A DCI >8,000 mmHg/s/cm was noted at 0%. The maximum DCI was 5,905.6 mmHg/s/cm, while the mean DCI was 2,385.2 mmHg/s/cm. HRM was performed using a ManoScan ESO Z (Medtronic, Shoreview, USA).**

which was characterized by gastroesophageal reflux disease (GERD) symptoms followed by the rapid onset of dysphagia, a choking sensation on food ingestion, and chest pain that improved with steroid treatment.

Case Reports

Case 1

A 37-year-old man with a 3-month history of heartburn was treated at a neighborhood clinic with a proton pump inhibiter (PPI) (esomeprazole 20 mg/day), following which he developed a gradually worsening choking sensation on ingesting food. Ten days after the start of the PPI treatment, the patient was examined at our hospital. Blood biochemistry tests showed increased eosinophils of 576/μL (8%) in the peripheral blood and a high immunoglobulin E (IgE) level of 315 IU/mL. The patient had no history of allergies.

Upper gastrointestinal endoscopy [esophagogastroduodenoscopy (EGD)] revealed longitudinal furrows and vitiligo in the mucosa of the middle esophagus, and the intense esophageal contractions were not affected by the air flow from EGD (Fig. 1a, b). Biopsy specimens were obtained from the middle and lower portions of the esophagus, as well as the stomach and the duodenum, with seven specimens from the esophagus presenting longitudinal furrows. On a histopathological test of an esophageal biopsy specimen, eosinophil infiltration of 28 cells/high-power field (HPF) in the esophageal epithelium was seen (Fig. 1c). However, no significant eosinophil infiltration was noted in the stomach and duodenum. Chest computed tomography (CT) revealed no thickening of the esophageal wall (Fig. 1d). Since EGD revealed intense esophageal contractions and a choking sensation on food ingestion, esophageal dysmotility was suggested; we therefore performed esophageal manometry by HRM (ManoScan ESO Z, Medtronic, Shoreview, USA), which revealed a DCI >8,000 mmHg/s/cm for 6 of 10 water swallows (Fig. 1e). Given this result, JHE was diagnosed based on the Chicago classification version 3.0 diagnostic criteria of esophageal dysmotility (2).

As treatment for EoE, PPI and an inhaled steroid [budesonide 1,600 μg daily (800 μg twice daily)] were administered orally. Within 3 weeks of the treatment initiation, the food choking sensation was alleviated, and the dose of the orally administered steroid (budesonide; inhaled steroid) was decreased to 200 μg daily. At seven weeks after the

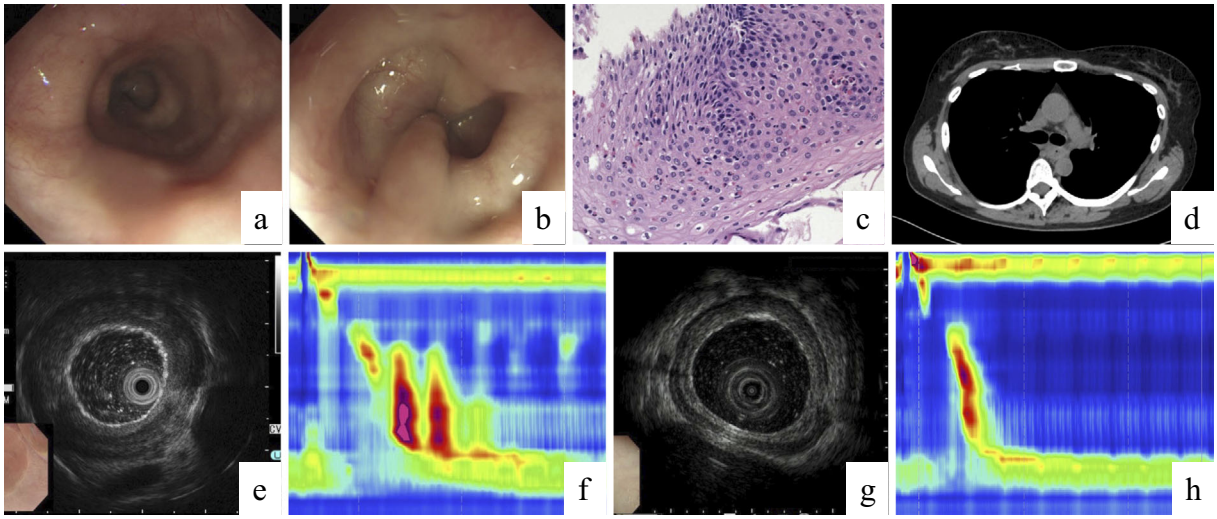

Figure 2. **Test findings in case 2. a. and b: The upper gastrointestinal endoscopic findings prior to treatment. a: Edematous mucosa, mucosa with a poor vascular pattern, and scattered vitiligo, which are characteristic findings of eosinophilic esophagitis are seen in the middle esophageal mucosa. b: An intense esophageal contraction is seen from the middle to lower esophagus. c: The histopathological findings from the esophageal biopsy at the time of upper gastrointestinal endoscopy prior to treatment are shown (400× magnification). Eosinophils at 25 cells/high-power field are seen in the esophageal epithelium. d: Chest computed tomography performed prior to treatment is shown. Uniform circumferential thickening of the esophageal wall from the middle intrathoracic to abdominal esophagus is visible. e: The endoscopic ultrasonography (EUS) findings prior to treatment are shown. Uniform thickening of the esophageal muscularis propria from the middle esophagus to the gastroesophageal junction is visible. f: High-resolution manometry (HRM) findings prior to treatment are shown. A distal contractile integral (DCI) >8,000 mmHg/s/cm was noted at 30%. The maximum DCI was 10,168.2 mmHg/s/cm, while the mean DCI was 8,632.5 mmHg/s/cm. g: The EUS findings after treatment. The thickening of the esophageal muscularis propria had disappeared. h: HRM findings after treatment are shown. A DCI >8,000 mmHg/s/cm was noted at 0%. The maximum DCI was 4,084.7 mmHg/s/cm, while the mean DCI was 2,037.8 mmHg/s/cm.**

dose reduction, the steroid drug treatment was discontinued altogether, while the PPI treatment was continued. Blood tests performed at that time showed an eosinophil count of 168/μL (3%) and an IgE level of 86 IU/mL, which was a marked improvement. At one month after the steroid drug had been discontinued, the food choking sensation and GERD symptoms disappeared. EGD revealed that the longitudinal furrows of the esophageal mucosa and vitiligo had disappeared along with the intense esophageal contractions. A histopathology test of an esophageal biopsy specimen showed no infiltration of eosinophils in the esophageal epithelium. HRM showed normalized esophageal peristalsis (Fig. 1f). It has now been 39 months since the patient last experienced symptoms, with no recurrence despite no further treatment.

Case 2

A 53-year-old woman with a 3-week history of heartburn was treated at a neighborhood clinic with a PPI (esomeprazole 20 mg/day). However, her symptoms did not improve, and a food choking sensation and chest pain later appeared. These symptoms gradually worsened, and the patient was examined at our hospital at 20 days after starting the oral PPI treatment. The patient had a history of beef allergy.

Blood biochemistry test showed an eosinophil count of 2,424.4/μL (31.9%) and IgE level of 153 IU/mL. EGD revealed vitiligo and swelling in the mucosa of the middle esophagus as well as disappearance of the vascular pattern. The intense esophageal contractions were not affected by air flow from EGD (Fig. 2a, b). Biopsy specimens were obtained from the mucosal vitiligo portions of the middle and lower sections of the esophagus, as well as from the stomach and duodenum, with seven specimens from the esophagus. A histopathological test of an esophageal biopsy sample revealed eosinophil infiltration of 25 cells/HPF in the esophageal epithelium (Fig. 2c). However, no significant eosinophil infiltration was noted in the stomach and duodenum. Chest CT revealed uniform circumferential thickening of the esophageal wall (Fig. 2d). Endoscopic ultrasonography (EUS) revealed uniform thickening of the esophageal muscularis propria (Fig. 2e). As the EGD findings and symptoms suggested esophageal dysmotility, we performed esophageal manometry by HRM, which revealed a DCI > 8,000 mmHg/s/cm for 3 out of 10 water swallows (Fig. 2f). Given these findings, JHE was diagnosed.

An oral PPI and oral steroid [budesonide; inhaled steroid

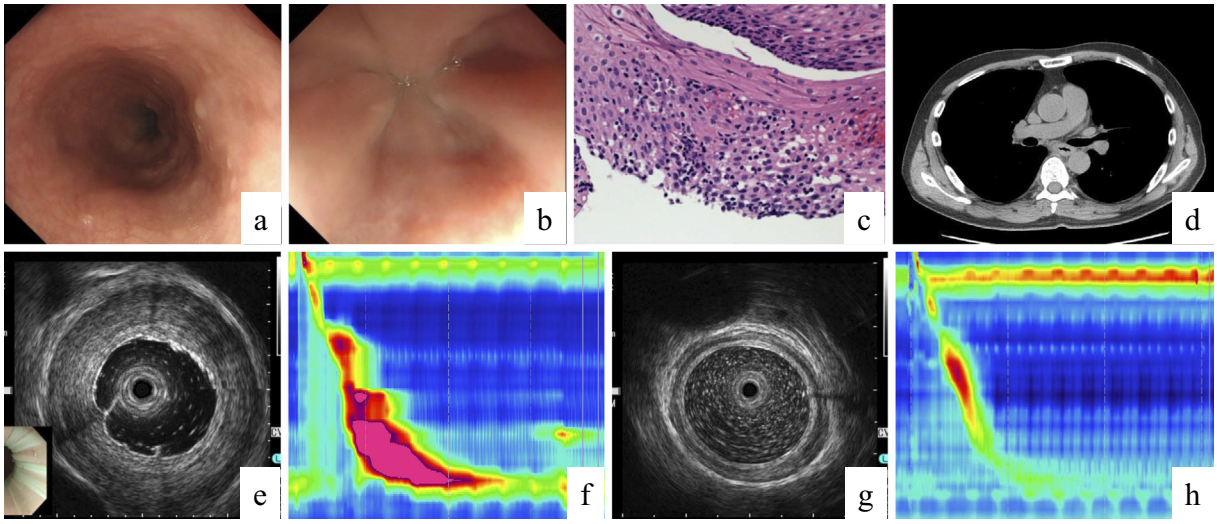

Figure 3. **Test findings of case 3. a. and b: Upper gastrointestinal endoscopic findings prior to treatment. a: Edematous mucosa and mucosa with a poor vascular pattern are visible. However, characteristic findings of eosinophilic esophagitis are not seen. b: An intense esophageal contraction is seen from the middle to lower esophagus. c: The histopathological findings from the esophageal biopsy at the time of the upper gastrointestinal endoscopy prior to treatment are presented (400× magnification). No eosinophil infiltration in the esophageal epithelium is visible. d: Chest computed tomography performed prior to treatment is shown. Uniform circumferential thickening of the esophageal wall from the middle intrathoracic esophagus to the lower esophagus is visible. e: Endoscopic ultrasonography (EUS) findings prior to treatment are shown. Uniform thickening of the esophageal muscularis propria from the middle esophagus to the gastroesophageal junction is visible. f: High-resolution manometry (HRM) findings prior to treatment are shown. A distal contractile integral (DCI) >8,000 mmHg/s/cm was noted at 70%. The maximum DCI was 13,556.0 mmHg/s/cm, while the mean DCI was 10,085.0 mmHg/s/cm. g: EUS findings after treatment are shown. Thickening of the esophageal muscularis propria disappeared. h: HRM findings after treatment are shown. A DCI >8,000 mmHg/s/cm was noted at 70%. The maximum DCI was 1,327.4 mmHg/s/cm, while the mean DCI was 765.1 mmHg/s/cm.**

drug, 1,600 μg daily (800 μg twice daily)] were started. By four weeks after treatment inception, the chest pain had disappeared, and the food choking sensation had decreased. The orally administered steroid dose was gradually decreased; at 12 weeks after the start of treatment, the steroid was discontinued. One month after steroid discontinuation, the choking sensation during meals and symptoms of heartburn had completely disappeared. Blood test results revealed a normalized eosinophil count [198/μL (0.3%)]. EGD at one month after the steroid discontinuation revealed that the vitiligo and swelling of the esophageal mucosa had disappeared; the vascular pattern was also visible. Furthermore, intense esophageal contraction was no longer seen. A histopathology test of an esophageal biopsy specimen showed no infiltration of eosinophils into the esophageal epithelium. EUS showed that the thickening of the esophageal muscularis propria had improved (Fig. 2g). HRM showed that the esophageal peristalsis had normalized (Fig. 2h). It has been 24 months since the steroid treatment was discontinued, and with continued oral PPI treatment and the administration of a leukotriene receptor antagonist (LTRA; pranlukast hydrate 225 mg/day) and an antihistamine (fexofenadine hydrochloride 120 mg/day), the patient has experienced no symptoms of recurrence.

Case 3

A 48-year-old man with a 1-month history of heartburn was treated at a neighborhood clinic with a PPI (rabeprazole 10 mg/day). Thereafter, food choking sensation and chest pain developed and worsened. Oral ingestion became difficult, and the patient was examined at our hospital 12 days after the PPI treatment was initiated. He had a history of food allergy to nuts, shrimp, and kiwi.

Blood biochemistry tests showed an eosinophil count of 696.9/μL (10.1%) and a high IgE level of 650 IU/mL. EGD revealed edematous mucosa in the middle esophagus, and the vascular pattern had disappeared. Furthermore, intense esophageal contractions that were not affected EGD air flow were seen (Fig. 3a, b). Biopsy specimens were randomly obtained from the upper, middle, and lower portions of the esophagus, as well as from the stomach and duodenum, with seven specimens from the esophagus. A histopathological test of an esophageal biopsy sample revealed neutrophil and inflammatory cell infiltration of the esophageal epithelium, although no eosinophil infiltration was seen (Fig. 3c). In addition, no eosinophil infiltration was noted in the stomach

and duodenum. Chest CT revealed uniform circumferential thickening of the esophageal wall (Fig. 3d). EUS revealed uniform circumferential thickening of the esophageal muscularis propria (Fig. 3e). Esophageal dysmotility was suggested; we therefore performed esophageal manometry by HRM, which revealed a DCI >8,000 mmHg/s/cm for 7 of 10 water swallows (Fig. 3f). JHE was therefore diagnosed, and based on the blood test findings and symptoms, JHE involving an allergy was inferred.

The PPI treatment was continued, and a steroid (prednisolone 50 mg/day) intravenous drip infusion was initiated. After seven days of treatment, the chest pain disappeared, and the choking sensation decreased. Therefore, the steroid dose was decreased by 10 mg/day each week; on day 49, the steroid treatment was discontinued. By the time the steroid treatment was discontinued, the food choking sensation and chest pain had disappeared, and blood biochemistry test results showed normal values of eosinophils at 38.4/μL (0.6%) and IgE at 112 IU/mL. When the steroid treatment was discontinued, EGD performed one month later showed improvements in the edematous mucosa and vascular pattern but no intense contraction of the esophagus. EUS revealed that the thickening of the esophageal muscularis propria had disappeared (Fig. 3g). HRM showed normalization of the esophageal peristaltic movement (Fig. 3h). It has been 23 months since the steroid treatment was discontinued; with continued treatment with an oral PPI, an LTRA (pranlukast hydrate 225 mg/day), and an antihistamine (fexofenadine hydrochloride 120 mg/day), the patient has experienced no symptoms of recurrence.

Discussion

All cases described here manifested with GERD symptoms. Within at least one month after the onset of GERD symptoms, a choking sensation on food ingestion, dysphagia, and chest pain appeared, and JHE was diagnosed based on HRM findings. Furthermore, in cases 1 and 2, in which EoE was diagnosed with JHE as the causal factor, longitudinal furrows and vitiligo (characteristic endoscopic findings of EoE) and luminal compression exhibiting esophageal dysmotility were seen (12). Although case 3 was attributed to EGD, luminal compression was not seen, and an esophageal biopsy revealed no invasion of eosinophils, which is a definitive diagnostic criterion of EoE.

Sato et al. (16) proposed EoEM as a subtype of EoE. EoEM is not seen in eosinophil invasion of the esophageal epithelium; instead, it is localized in the esophageal muscle layers. Furthermore, they reported that hypercontractile esophageal peristalsis disorder occurred in all four cases of EoEM and that the three HRM cases in which hypercontractile esophageal peristalsis disorder was seen were cases of JHE. However, invasive procedures, such as a peroral esophageal muscle biopsy (PoEM-b) or EUS-guided fine-needle aspiration, are required to confirm the EoEM diagnosis. Thus, the clinical findings for which EoEM must be considered are high levels of serum IgE and hypercontractile esophageal peristalsis with esophageal dysmotility, including JHE in HRM (10). In case 3, EGD revealed that the characteristic findings of EoE were absent. Furthermore, in an esophageal biopsy, eosinophil infiltration, which is a definitive diagnostic criterion of EoE, was not seen; however, the eosinophilia of the peripheral blood and high serum IgE levels that were seen prior to steroid treatment normalized after treatment. In addition, EUS revealed mild thickening of the esophageal muscularis propria, while HRM revealed normal findings of esophageal peristalsis. These signs of clinical progress suggest that the JHE in case 3 was likely EoEM.

Tanaka et al. (17) reported a case of JHE caused by EoE. A 73-year-old woman had a 6-month history of dysphagia and chest pain, and EUS revealed thickening of the submucosal layer of the esophagus. The oral administration of an inhaled steroid was the initial therapy that resulted in disappearance of the eosinophil invasion of the esophageal epithelium. However, POEM was performed due to the presence of JHE and remnant symptoms. Thereafter, the symptoms subsided, and the steroid dose was reduced. Since eosinophil invasion of the esophageal muscularis propria was found in the histopathological test sample collected by POEM-b, the presence of EoEM characterized by the invasion of eosinophils located in the esophageal muscle layer was considered. In case 2, eosinophil invasion into the esophageal epithelium disappeared after treatment with steroids. Furthermore, the submucosal thickening of the esophagus that was seen on EUS decreased, and the esophageal peristalsis in HRM normalized. Thus, the pathological condition was assumed to be the same as that reported by Tanaka et al. (17). In addition, Tang et al. (18) performed POEM for JHE triggered by EoEM and reported long-term symptom improvement. However, despite these present and previous findings, the ideal treatment of JHE triggered by EoEM remains to be established.

In the study by (19) of four cases of JHE, EoE was ruled out in all cases. However, EUS revealed thickening of the submucosal layer of the esophagus. A two-month follow-up observation was the treatment plan for all cases. Regarding treatment, one patient was resistant to medical treatment; POEM was therefore performed. In another patient, the symptoms improved on follow-up observation. Two patients' conditions improved with medical treatment. In addition, the thickening of the esophageal wall disappeared in some patients but persisted in others, even after treatment. Thus, they reported that the symptom improvement was not correlated with the esophageal wall thickening. Given this previous report and the findings in our case 3, conservative therapy that includes medical treatment for JHE must take precedence. All three of our cases of JHE were trigged by allergy-related diseases, including EoE, which occurred subsequent to the appearance of acute dysphagia, food choking sensation, and chest pain, all of which are symptoms of GERD. Although the details of the mechanism by which EoE and EoEM trigger JHE-EoE are unknown, in all three

of our cases, the JHE occurred in relation to some form of allergy that included EoE.

EoE is generally treated by PPIs, which is the first-choice treatment. Steroid treatment is administered to non-responders. Steroid drug options include local or systemic administration. The local administration is performed with an inhaled steroid that is used to treat asthma. In Western countries, fluticasone 880-1,760 μg/day or budesonide 1-4 mg/day is recommended (20, 21), and a larger dose is required than when inhaled. For cases 1 and 2 in which local treatment was performed, budesonide 1,600 μg/day was administered. For case 3, the steroid was administered systemically. For case 3, the diagnosis of EoE was not confirmed by the biopsy-obtained sample of the esophageal mucosa. However, the patient had symptoms caused by esophageal dysfunction that constituted diagnostic criteria for EoE. The potential side effects caused by the systemic administration of steroids, such as diabetes, were considered in case 3 before initiating the treatment. However, the patient had severe chest pain accompanied by epigastralgia, and oral intake was difficult. Therefore, the oral administration of an inhalant steroid was not possible, and the patient was instead administered a systemic steroid during hospitalization with careful monitoring for potential side effects. At the time of recurrence, after confirming the existence of a definitive causal allergen for EoE, the oral administration of an inhalant steroid is considered the first-line treatment when oral intake is possible. The patients in cases 2 and 3 had food allergies. However, there were no findings that suggested the food allergies were related to seasonal variations, stress, or infection.

For EoE patients with esophageal dysmotility, local or systemic steroid treatment is administered, and consequent improvement in esophageal dysmotility is seen in most patients (22). In addition, a prospective observation study (HIMEOS study) that investigated the effect of budesonide treatment on esophageal dysmotility diagnosed based on HRM was recently reported (23). In patients with esophageal dysmotility and increased intrabolus pressure, esophageal dysmotility reportedly improved after budesonide treatment; however, no marked change was seen in the various parameters of the Chicago classification. There have been no previous reports of the marked treatment efficacy of steroids seen in our three cases. Steroid administration was so particularly effective in these cases because the initial GERD symptoms showed resistance to PPI; therefore, endoscopy and HRM were performed in the early stage, and the diagnosis was JHE triggered by allergy-related esophagitis, which was followed with early steroid treatment. Regarding the dose of steroids in EoE treatment, there are no reports describing the definite dose; however, a dose close to the upper limit was administered. This is because the rapid worsening of symptoms suggested the presence of acute inflammation related to an allergy. An inhaled steroid drug was orally administered between meals to prevent the effect of food on the steroid drug. Furthermore, the patient was kept in the supine position for 30 minutes after the oral administration to enable long-term persistence of the steroid drug in the esophagus. There was no symptom recurrence in any of the patients for a mean 29±8.6 months after the end of treatment. In cases 2 and 3, PPI treatment was continued after the steroid treatment was completed.

EoE is considered to have a weak relationship with serum IgE; however, about 50% of patients with EoE are reported to have some form of allergic disease, such as asthma and atopic dermatitis, and increased total serum IgE levels. There are reports in the literature of increased total serum IgE levels in patients having EoE with hypertrophy of the esophageal muscular layer (24, 25). These high levels of serum IgE are reported to be reduced after steroid administration. Those cases were similar to our own cases, wherein the patients had no obvious allergic diseases but might have had unnoticed ones. Therefore, the serum IgE levels in our cases were increased, and after steroid treatment, they decreased.

LTRA and pranlukast hydrate treatments were continued according to the mild intermittent bronchial asthma treatment guideline (26). Regarding maintenance therapy for EoE patients, reports with adequate evidence are sparse; however, Straumann et al. (27) induced remission in EoE patients by orally administering budesonide for two weeks followed by a placebo and low-dose budesonide in a comparative study. They reported that symptom recurrence was significantly inhibited in the low-dose budesonide group, suggesting that oral budesonide treatment is an effective maintenance therapy.

In conclusion, we reported our experience with JHE that was assumed to have been caused by allergy-related diseases, including EoE, against which steroid treatment was effective. Although the onset mechanism of JHE is unknown, the early treatment strategy is medical with follow-up observation. A detailed examination with consideration of the possibility of allergic diseases of EoE is necessary.

The authors state that they have no Conflict of Interest (COI).

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