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Pemphigus Vulgaris with Marked Stenosis of the Esophageal Orifice from an Osteoporosis Drug: a Case Study with Long-term Follow-up

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ABSTRACT

Pemphigus vulgaris produces multiple and intractable erosions of the oral mucosa in the head and neck region. We describe a case of pemphigus vulgaris that showed erosions in the hypopharynx and stenosis of the esophageal orifice from an osteoporosis drug. A 73-year-old woman was admitted with oral intake difficulty and erosions in the hypopharynx. During the first admission, we could not make a definite diagnosis by biopsy or blood examination. The condition of the mucosa worsened subsequently; an esophagram showed marked stenosis of the esophageal orifice. As a possible factor exacerbating the stenosis, an osteoporosis drug was considered. The stenosis was improved by balloon expansion. One year after the first medical examination, we finally made a definite diagnosis of pemphigus vulgaris from the results of a blood examination in which anti-desmoglein 3 turned positive when the hypopharyngeal erosions and stenosis of the esophageal orifice became worse. Systemic treatment with a steroid was effective for the control of pemphigus vulgaris; restenosis of the esophageal orifice was recognized twice during a state of remission, and careful follow-up will be necessary in the future.

Key words: *Pemphigus Vulgaris, Stenosis of esophageal orifice, Osteoporosis drug*

Pemphigus vulgaris (PV) is an autoimmune disease that mainly presents with blisters on the skin or mucosal epithelium. In head and neck lesions, PV is known to form multifocal refractory erosions in the oral cavity. Cell-cell adhesion is inhibited by epidermal autoantibodies against cell surface and acantholytic bullar antigens.

Based on clinical, pathological, and serological findings, pemphigus is classified into three major types: PV, pemphigus foliaceus (PF), and others [1,2]. The PV antigen is desmoglein (Dsg) 3 and the PF antigen is Dsg1. These are used for diagnosis, pemphigus staging, and an evaluation of the condition by measuring antibody titers of the IgG type. PV can be further classified as mucosa-dominant or mucocutaneous PV.

The initial symptoms of PV are generally painful refractory erosions and ulcers, which in severe cases can cause an inability to ingest food. In approximately 50% of patients with PV, the lesions are not only located on the oral mucosa but also involve the skin with flaccid bullae and erosions[2].

We report the case of a patient with PV who presented at our hospital with a chief complaint of oral intake difficulty due to hypopharyngeal erosion and stenosis of the esophageal orifice. Making a definite diagnosis and treating this case proved challenging.

CASE REPORT

A 73-year-old woman became aware of a gradually worsening feeling of dysphagia and her weight decreased by 10 kg over 3 months; hence, she visited a nearby hospital. She underwent esophagogastroduodenoscopy (EGD), which detected a hemorrhagic lesion in the esophageal orifice. Enhanced computed tomography (CT) and magnetic resonance imaging (MRI) revealed mucosal thickening and enhancement in the hypopharynx and esophageal orifice; as a result, hypopharyngeal cancer was suspected. She was referred to our hospital for a comprehensive examination.

Her medical history included oral lichen planus, mild liver dysfunction, and osteoporosis.

The buccal mucosa showed mild erosion. A hypo-

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pharyngeal fiberscope revealed extensive mucosal erosions in both arytenoid cartilages, the piriform fossa, and posterior wall with a left-sided predominance in the hypopharynx. No elevated lesion was found, and the mobility of the vocal cords was normal (Fig. 1a).

Cervical enhanced CT and MRI revealed mucosal swelling in both arytenoid cartilages, the piriform fossa, and posterior wall with a left-sided predominance in the hypopharynx. No elevated lesion was found (Fig. 1b, 1c).

We performed a biopsy under general anesthesia and obtained tissues from the hypopharyngeal posterior wall and both sidewalls; however, the pathology results only revealed a fibrin lump and chronic inflammation. Skin lesions were not observed over the whole body, the Nikolsky phenomenon was negative, and increases in Dsg1 and 3 antibodies were also not found in the blood examination from the first admission.

We referred the patient to the departments of collagenosis, dermatology, blood internal medicine, and gastroenterological internal medicine to exclude the presence of various diseases that could result in intraoral erosions. However, we could not make a definite diagnosis.

The erosions in the oral cavity and hypopharynx remained. However, she was discharged from the hospital because she could eat enough food to maintain her weight.

She was followed up once a month in the outpatient department with intractable recurrent ulcers. However, her dysphagia gradually worsened. One year after the first admission, she was hospitalized again because of an inability to ingest food and marked stenosis, which was found in the esophageal orifice by esophagography. The thoracic and abdominal esophageal mucosae were intact (Fig. 2a, 2b).

We checked the medication she brought to the second admission, and found that sodium risedronate hydrate had been prescribed as a treatment for osteoporosis by her family physician. This medication is contraindicated in patients with esophageal stenosis; hence, we advised her to stop taking it immediately. For her nutrition, we intended to place a nasogastric tube in her stomach. However, we could not do so because of the stenosis of the esophageal orifice; therefore, we initiated intravenous hyperalimentation.

When we again performed a biopsy and observa-

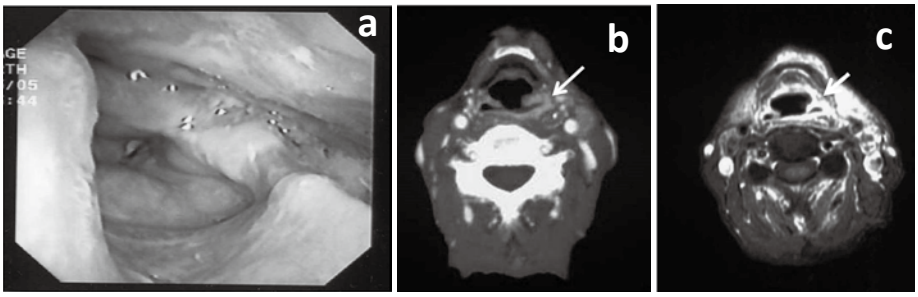

Fig.1: A hypopharyngeal fiberscope (a) reveals mucosal erosion in both arytenoids, the piriform fossa, and posterior wall with left-sided dominance in the hypopharynx. Enhanced CT (b) and MRI (c) reveal mucosal thickening and an enhancement effect (arrow) at the site.

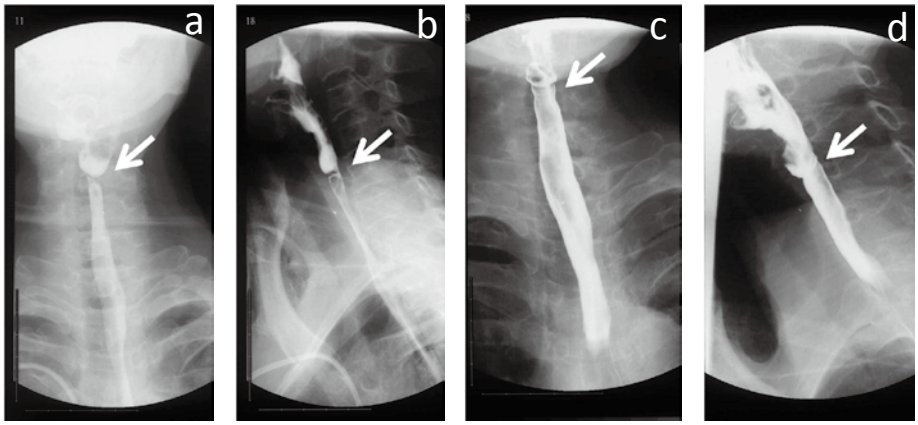

Fig.2: Esophagography before treatment (a: frontal position, b: left anterior oblique position) revealed marked stenosis (arrow) in the esophageal orifice. The stenosis was improved (arrow) after balloon expansion (c: frontal position, d: left anterior oblique position).

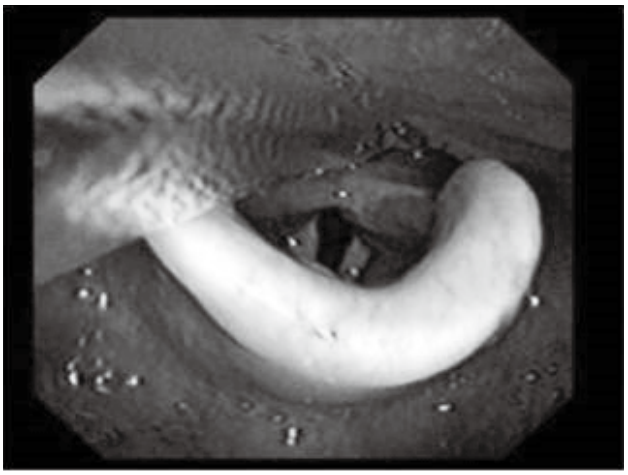

Fig.3: A view of the balloon expansion technique. We performed it twice over 5 minutes at 300kPa and the second expansion was easier than the first one.

tion under general anesthesia, erosions and a white coating were observed on all circumferences and the hypopharyngeal space had narrowed. At the narrowest region, the diameter of the esophageal orifice was only 4 mm wide and observation of the esophagus was not possible.

We obtained tissue from multiple sites including the posterior wall, sidewall, and some narrow segments in the hypopharynx and esophageal orifice. However, pathological analysis revealed that the quantity of the biopsy specimen was limited, malignancy was not found in any of the epithelia, immunostaining was negative for both anti-Dsg 1 and 3 antibodies, and increases in anti-Dsg1 and anti-Dsg3 antibody titers were not observed in the blood examination.

Consequently, we determined that the intractable recurrent ulcers were exacerbated by the osteoporosis drug and that treatment was necessary for benign hypopharynx/esophageal stenosis; thus, we performed balloon expansion. Since extensive expansion was thought to increase the risk of hypopharyngeal and esophageal orifice rupture in the patient, we performed a graded expansion according to a plan for 5 min at 300 kPa (Fig. 3).

The second balloon expansion was performed 2 weeks after the initial expansion. Her symptoms improved dramatically postoperatively, and the release of stenosis was confirmed by esophagography 1 week after the second expansion (Fig. 2c, 2d). On the day after the second expansion, she was able to eat and was discharged from the hospital.

When erosions in the oral cavity and hypopharynx rapidly worsened 8 months after the second discharge, we again performed a blood examination, and immunostaining was positive for the anti-Dsg3 antibody, while those for anti-Dsg1 antibody remained negative. Hence, we diagnosed her with mucosa-dominant PV. Systemic treatment with prednisolone from 10 mg/day was started in dermatology immediately, and the erosions improved significantly (Fig. 4a).

The stenosis of the esophageal orifice worsened with an exacerbation of PV and dysphagia appeared 9 months and 4 years after the start of steroid therapy. She was re-hospitalized on both instances. We performed balloon expansions immediately and the stenosis improved. With her condition in remission, enhancement of the hypopharyngeal mucosa on CT was only seen a little in the left piriform fossa (Fig. 4b).

Stenosis has not recurred in 6 years and her clinical course is favorable.

DISCUSSION

Autoimmune blistering disease is known to result in an esophageal mucosal disorder by a mechanism similar to that of a disorder of the skin, but esophageal stenosis is not usually found in mucosa-dominant PV and we could not find case reports in which esophageal stenosis was caused by PV. However, esophageal stenosis is found in pemphigoid and there are some case reports of pemphigoid that resulted in esophageal stenosis[5,6]. It is assumed that the difference between the two is where the site of

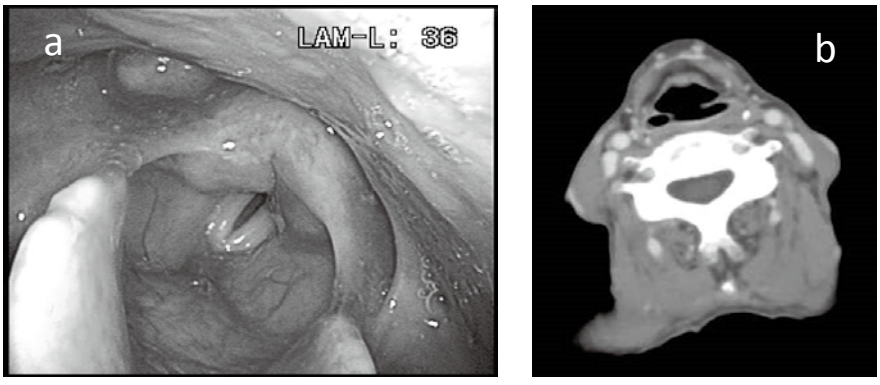

Fig.4: The hypopharyngeal fiberscope (a) only reveals slight scarring of the hypopharyngeal mucosa and enhanced CT (b) reveals slight mucosal thickening after steroid treatment.

the target antigen is localized.

Since PV is a disorder of a shallow layer of the mucous membrane, it only presents with esophageal erosions. However, as pemphigoid is a disorder in a deeper layer of the mucous membrane than PV[9], it presents as a serious disorder with symptoms such as exfoliation of all layers of the mucous membrane and esophageal stenosis caused by scarring.

A bisphosphonate preparation is widely used as a therapeutic drug for osteoporosis and upper gastrointestinal tract disorders such as esophagitis, esophageal perforation, esophageal stenosis, esophageal ulcer, etc., have been reported as serious side effects thus far[10]. These side effects result from the direct membrane-irritating effects of the preparation, sustained contact, and gastric reflux of the melted drug[8]. Hence, patients are required to consume this medication between meals with enough water (approximately 180 ml) and remain in a seated position for at least 30 min after use[4].

In the present case, PV caused the esophageal erosion; the osteoporosis drug came into direct contact with the area of the esophageal erosion, and inflammation occurred in a deep layer of the mucous membrane. Thus, we assume that esophageal stenosis as in pemphigoid occurred in this patient.

We could not make a definite diagnosis of PV at first by biopsy or blood examination because we considered that there are some cases in which anti-Dsg3 antibody cannot be detected meaningfully by staining the biopsy specimen, and an increase in anti-Dsg3 antibody is not found in the blood examination when disease progression is weak.

Kamiya et al reported that they could detect the anti-Dsg3 antibody by using serum condensed more than 10 times against PV in patients who could not be diagnosed using indirect immunofluorescence or enzyme-linked immunosorbent assay[7]. We assume this method would have been efficient for diagnosing this patient with PV.

In pemphigus treatment, a steroid is recommended by the Committee for Guidelines for the Management of Pemphigus Disease[2]. In this case, the mucosal lesion showed dramatic improvement after steroid administration; however, esophageal stenosis recurred during an exacerbation of PV. Since the antibody titers correlate with the activity of pemphigus[3], adjusting steroid doses by measuring antibody titers is required for adequate control.

When we use osteoporosis drugs in patients with PV, it is necessary to confirm the absence of esophageal and hypopharyngeal mucosal disorders.

Moreover, we performed the balloon expansion technique for the esophageal stenosis. Postoperatively, the patient was able to ingest food orally, and the expansion technique was thought to be effective for esophageal stenosis correlated with PV.

When her PV was in a state of remission, restenosis was found only twice in 10 years. We will perform a balloon expansion again if restenosis is found in the future with an exacerbation of PV.

Conflict of interest

The authors have no conflicts of interest.

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