

## Case Series

# Esophageal Intramural Pseudodiverticulosis: A Histopathological and Immunohistochemical Study of 2 Cases

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## Keywords

Esophagus · False diverticulum · Immunohistochemistry · Intramural pseudodiverticulosis · Squamous metaplasia

## Abstract

Esophageal intramural pseudodiverticulosis (EIPD) is a rare disorder characterized by an abnormal, cyst-like dilatation of the excretory ducts of esophageal submucosal glands. We aimed to elucidate the histopathological features and immunohistochemical properties of the epithelial lining of the cyst-like lesions in EIPD. We performed a histopathological and immunohistochemical study of 2 cases (one autopsy and one surgical) of EIPD. The ductal walls consisted of inner ductal cells, which were cytokeratin (CK) 7-positive and CK5/6-negative, and outer basal cells, which were CK7-negative and CK5/6-positive. The ductal epithelium frequently showed squamous metaplasia and rarely simulated a false diverticulum. Immunohistochemistry for CK7 was useful for distinction between the conditions because the surface epithelium was negative for CK7. We also confirmed that myoepithelial cells in the acinar portion of submucosal glands were well-preserved in EIPD, the finding that explained the periodic opening and closing movements of orifices of cyst-like lesions in this disorder. The immunohistochemical properties of the epithelial lining of cyst-like lesions in EIPD were essentially similar to those of the normal ducts of submucosal glands.

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## Introduction

Esophageal intramural pseudodiverticulosis (EIPD) is a rare disorder characterized by the formation of multiple, small, flask-shaped outpouchings within the esophageal wall [1, 2]. Although the pouches have been demonstrated to consist of dilated excretory ducts of submucosal glands [3–6], the etiopathogenesis of EIPD remains unknown.

Since EIPD infrequently produces overt clinical symptoms (mostly dysphagia) and most patients are medically treated, the number of pathological studies performed on EIPD is small [3–6], and, to our knowledge, no immunohistochemical studies have been performed on esophageal glands in this disorder. Here, we present the results of a histopathological and immunohistochemical study of 2 cases of EIPD. We demonstrated that the walls of dilated excretory ducts in EIPD consisted of inner ductal cells showing immunoreactivity for cytokeratin (CK) 7 but not for CK5/6 and outer basal cells, which showed reverse patterns of immunoreactivity (CK7-negative and CK5/6-positive). The lining epithelium of the dilated ducts frequently showed squamous metaplasia with basal cell hyperplasia. Although this change rarely produced features that were difficult to distinguish from a false diverticulum [7], the metaplastic cells (except the outer basal cells) retained CK7-immunoreactivity and clearly contrasted with the CK7-negative surface epithelium, which formed the wall of the false diverticulum.

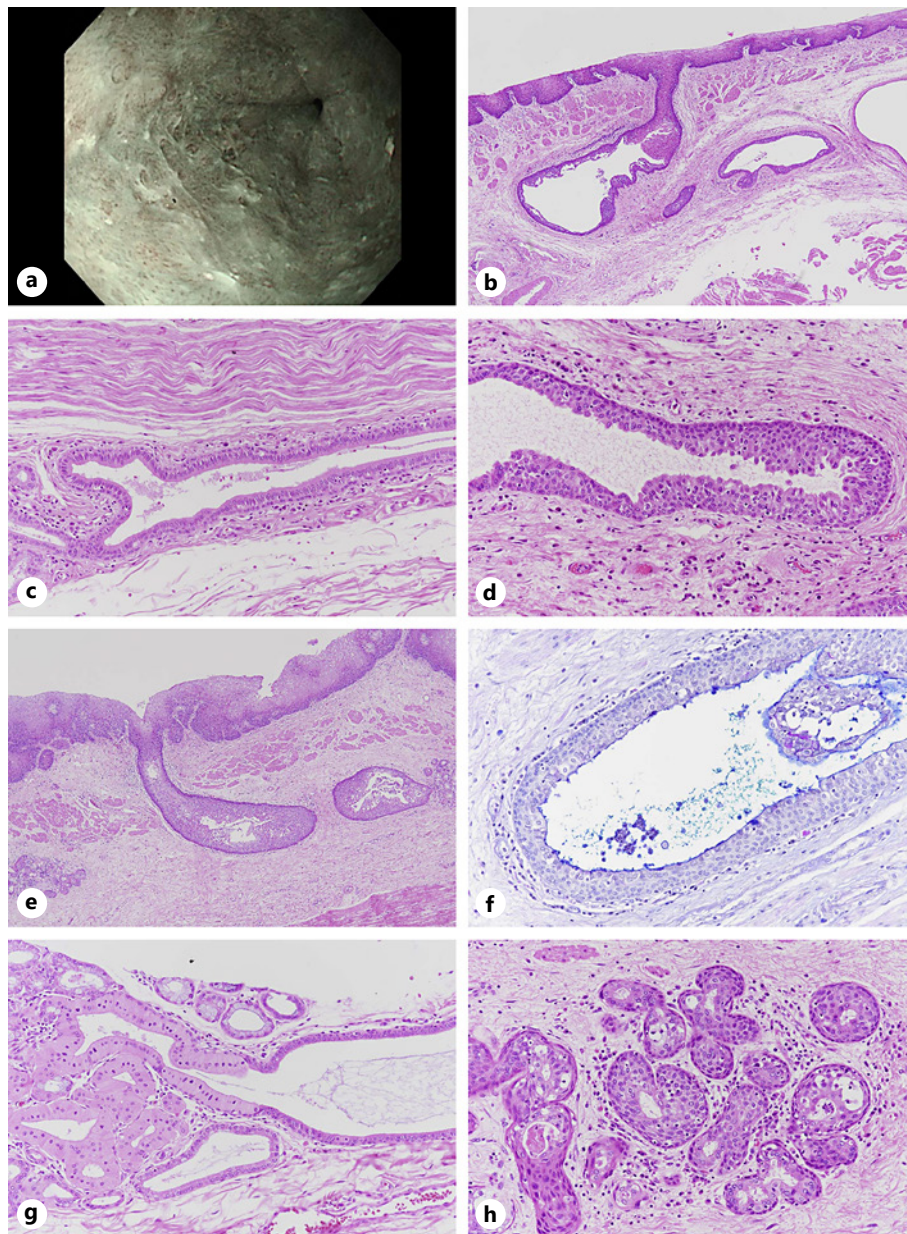
## Case Report

### Case 1

The patient was a 60-year-old man who had worked in a port in Japan and died of fulminant hepatic failure following infection by *Leptospira interrogans* (Weil's disease) after a clinical course of 2 months. The clinical and main pathological findings of this case were previously reported [8]. EIPD was an incidental finding detected at autopsy, and whether the patient had any symptoms that could be ascribed to EIPD was unknown. Endoscopic examination of the esophagus had not been done ante-mortem. A small number of pinhole lesions compatible with the orifices of EIPD were scattered on the mucosa throughout the whole length of the esophagus at autopsy.

### Case 2

The patient was a 68-year-old male cook with a past history of noninvasive urothelial carcinoma of the urinary bladder that had been treated by transurethral resection 5 years previously. He was a heavy smoker (15 cigarettes per day for about 50 years) and had a history of excessive alcohol intake (50 mL of whiskey every day for several years). He consulted our hospital complaining of difficulty swallowing and body weight loss, and an endoscopic examination revealed an advanced cancer, measuring 37 by 33 mm, in the mid-thoracic esophagus. In addition, the esophageal mucosa showed a mottled appearance as a whole, and several small holes were scattered. The small holes were more clearly visualized by narrow band imaging than by white light imaging because the holes (orifices of EIPD) and the surrounding mucosa were clearly depicted on narrow band imaging due to their brown color on the background mucosa showing a pale moss-green color (Fig. 1a). After preoperative chemoradiation therapy, a subtotal esophagectomy was performed. This was a recent case, and so the postoperative follow-up period was short.



**Fig. 1.** **a** NBI of the esophagus in Case 2. Many small holes representing the orifices of EIPD were observed on the mucosal surface. **b** Many large, cyst-like lesions were formed in the esophageal submucosa. The lining epithelium of some cyst-like lesions was contiguous with the surface epithelium (Case 2, HE stain,  $\times 100$ ). **c** The walls of cyst-like lesions were lined by biphasic epithelial layers: the inner ductal cell layers and outer basal cell layers (Case 1, HE stain,  $\times 200$ ). **d** The lining cells frequently showed squamous metaplasia. Mild inflammatory changes were found in the stroma (Case 2, HE stain,  $\times 200$ ). **e** Cyst-like lesions in EIPD rarely simulated a false diverticulum (Case 2, HE stain,  $\times 100$ ). **f** The luminal surface of the cyst-like lesions was linearly stained blue-purple by PAS-AB stain (Case 2, PAS-AB stain,  $\times 200$ ). **g** Some intralobular terminal ducts of submucosal glands were ectatic and continuous with the cyst-like lesions. Some acinar and ductal cells showed an oncocytic change (Case 1, HE stain,  $\times 200$ ). **h** The acini of submucosal glands were occasionally replaced by metaplastic squamous epithelium, resembling necrotizing sialometaplasia (Case 2, HE stain,  $\times 200$ ). NBI, narrow band imaging; PAS-AB, periodic acid-Schiff and Alcian Blue.

## Materials and Methods

The esophagi of the patients were examined by histopathological and immunohistochemical methods after formalin fixation and longitudinal (Case 1) or coronal (Case 2) sectioning. Twelve (Case 1) and twenty-seven (Case 2) paraffin blocks of the esophagus, respectively, were examined. The immunohistochemical study was performed employing monoclonal antibodies against the following substances: CK5/6 (clone D5/16B4, Dako, Glostrup, Denmark, 1:200), CK7 (clone OV-TL12/30, Dako, 1:800), CK19 (clone A53-B/A2.26, Roche Diagnostics, Tokyo, Japan, prediluted), CK20 (clone Ks20.8, Dako, 1:600), p63 (clone 7-Ju1, Leica Biosystems, Wetzlar, Germany, 1:100), and  $\alpha$ -smooth muscle actin ( $\alpha$ -SMA) (clone 1A4, Dako, 1:1,000). Immunostains were performed using an automated immunostainer, Leica Bond-Max (Leica Biosystems). The (non-dilated) ducts and acini of the normal esophageal glands found in the examined sections served as an internal control. The esophagus of an autopsy case (69-year-old man) without any esophageal lesions was also similarly examined.

## Pathological Findings

### *Histopathological Findings*

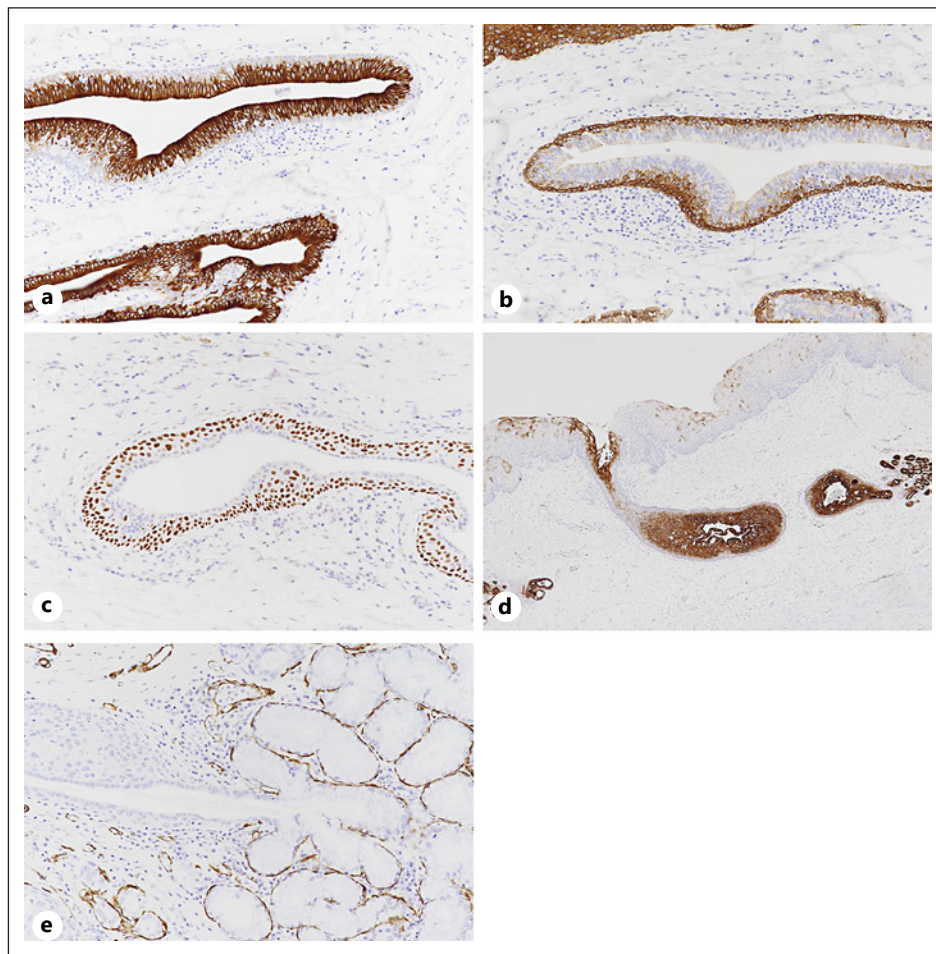
Both cases showed essentially similar findings, although a few minor differences were noted. Multiple, cyst-like lesions of irregular shapes and variable sizes were predominantly distributed in the submucosa (Fig. 1b). The minority of them were located in the lamina propria mucosae. In Case 1, they were relatively large, with the largest one being 7 mm in maximal dimension, and occasionally contained palely basophilic mucous material and degenerating epithelial cells. The cyst-like lesions in Case 2 were smaller and of a more uniform size and shape than those in Case 1.

The walls of the cyst-like lesions were lined by the inner layer of ductal epithelial cells of cuboidal shape and the outer layer of basal cells (Fig. 1c). The lining epithelium frequently showed squamous metaplasia associated with basal cell hyperplasia (Fig. 1d), and in Case 2, this finding rarely led to features that were difficult to distinguish from those of a false diverticulum (Fig. 1e). In Case 2, within and around the walls, and also in the lumina of these cyst-like lesions, prominent neutrophil infiltration was occasionally observed. A few ductal cells showed mucous metaplasia or an oncocyctic change. Mucous cells were stained blue-purple or magenta by periodic acid-Schiff and Alcian Blue staining, and the luminal surface of the dilated ducts was stained blue-purple in a linear fashion (Fig. 1f). In Case 1, inflammatory cell infiltration was scarce, but the submucosal glands showed mild inter- and intralobular fibrosis, and acinic cells often showed an oncocyctic change. Some intralobular terminal ducts were ectatic and continuous with the cyst-like lesions (Fig. 1g).

In Case 2, the esophageal cancer was moderately differentiated squamous cell carcinoma, whose invasion reached the adventitia, but no special topographic relationship was observed between the cancer and the EIPD lesions. Acute and chronic inflammatory cell infiltration and fibrosis in the submucosa were more pronounced than in Case 1, and the acini of submucosal glands were occasionally replaced by solid growth of metaplastic squamous epithelium, creating a feature resembling necrotizing sialometaplasia of minor salivary glands [9] (Fig. 1h). These changes were considered to be related to EIPD, but the possibility of effects of chemoradiation therapy could not be excluded.

### *Immunohistochemical Findings*

The biphasic structure of the epithelial lining of cyst-like lesions in EIPD was more clearly demonstrated by immunohistochemistry for CK7, CK5/6, and p63. Whereas the inner ductal



**Fig. 2.** **a** Whereas the inner ductal cells lining cyst-like lesions were immunoreactive for CK7, the outer basal cells were not (Case 1, Immunostain for CK7,  $\times 200$ ). **b** On the contrary, the inner ductal cells were not immunoreactive for CK5/6, while the outer basal cells were positive (Case 1, Immunostain for CK5/6,  $\times 200$ ). **c** The hyperplastic basal cells showed nuclear immunoreactivity for p63 (Case 2, Immunostain for p63,  $\times 200$ ). **d** The same area as shown in Figure 1e. Whereas the surface epithelium was largely negative for CK7, the epithelium that appeared to have been invaginated was immunoreactive for CK7, indicating that this portion was ductal epithelium showing squamous metaplasia (Case 2, Immunostain for CK7,  $\times 100$ ). **e** The acini of the submucosal glands were surrounded by a layer of myoepithelial cells, while the dilated ducts were not (Case 2, Immunostain for  $\alpha$ -SMA,  $\times 200$ ).

cells were strongly immunoreactive for CK7 (Fig. 2a) and negative for CK5/6 (Fig. 2b), the outer basal cells showed the reverse pattern, being CK7-negative and CK5/6-positive. The basal cells, including hyperplastic ones, showed nuclear immunoreactivity for p63 (Fig. 2c). These immunohistochemical findings were similar to those of the normal submucosal glands of the esophagus. The surface squamous epithelium was diffusely positive for CK5/6 but negative or at most only faintly and focally positive for CK7 (Fig. 2d). No epithelial cells were immunoreactive for CK20.

In the cyst-like lesions whose lining epithelium showed squamous metaplasia, most metaplastic squamous cells retained immunoreactivity to CK7. In rare cyst-like lesions that histopathologically simulated a false diverticulum, the epithelium showed strong reactivity for CK7, confirming the epithelium to be of excretory duct origin and not invaginated surface

epithelium (Fig. 2d). The immunoreactivity for CK19 was largely similar to that for CK7, with the exception of the immunoreactivity of basal and parabasal cells of the surface epithelium.

Myoepithelial cells immunoreactive for  $\alpha$ -SMA surrounded the acini of submucosal glands, but no myoepithelial cells were found in the walls of the cyst-like lesions of EIPD (Fig. 2e). A few cyst-like lesions were surrounded by thin layers of  $\alpha$ -SMA-positive myofibroblasts of the stroma.

## Discussion

Lesions in EIPD consist of abnormal, cyst-like dilatations of the excretory ducts of submucosal glands [3–6]. We do not consider that the term “pseudodiverticulosis” is, as Lupovitch and Tippins pointed out [3], an appropriate one because it does not reflect the true nature of the disorder and, moreover, is liable to be confounded by a false diverticulum (invagination or prolapse of surface epithelium) [7]. We previously reported that the orifices of “pseudodiverticula” in EIPD periodically repeated opening and closing movements, excreting mucous material onto the mucosal surface, and stated that EIPD is not a static condition but a continuously moving pathological process [10]. We did not consider that the opening and closing movements of the orifices of EIPD were passive movements caused by the pressure changes due to the respiratory movements of the thorax because their movements synchronized neither with each other nor with the respiratory movements of the thoracic cavity. We hypothesized that the movements were driven by contractions of myoepithelial cells surrounding the acini of submucosal glands [10–12]. As clarified in the present study, myoepithelial cells were well preserved in the acini of glands, which were continuous with the cyst-like lesions of EIPD, but they were not found in the walls of cyst-like lesions themselves. As previously shown by Harada et al. [13], the extralobular excretory ducts do not have a myoepithelial cell layer and are invested by layers of basal cells, which do not have contractile ability.

Previous articles reported that the walls of cyst-like lesions of EIPD were lined by simple or stratified cuboidal epithelium of excretory ducts [3–7], but their immunohistochemical properties have not been studied. In the present study, we clarified some immunohistochemical characteristics of epithelial cells lining cyst-like lesions in EIPD. They were basically similar to those of the excretory ducts of normal esophageal glands, and no specific histopathological or immunohistochemical alterations that could suggest the pathogenesis of this disorder were observed. Squamous metaplasia of ductal walls is probably a secondary change caused by dilatation of the ducts and an inflammatory reaction against it.

With regard to the etiopathogenesis of EIPD, most investigators suggested that chronic inflammation involving the mucosa and submucosa caused stenosis or occlusion of the orifices of the ducts of the esophageal glands and resulted in cyst-like dilatation of the ducts [5–7]. However, in EIPD, the orifices of ducts are actually larger than those in the normal state, discernible only by dissecting microscopy [12], and, as mentioned above, they repeat opening and closing movements [10]. Furthermore, in many radiological studies, the “pseudodiverticula” (i.e., dilated ducts) were clearly depicted by filling them with contrast medium [1, 4, 7, 10]. These findings suggest that the orifices of dilated ducts in EIPD are not occluded or narrowed, or, at least, the occlusion of orifices is not a primary event in the pathogenesis, although we do not deny the possibility that inflammatory changes may secondarily cause obstruction of some orifices. Some investigators proposed congenital or acquired proliferation of submucosal glands (adenosis) [3] as the cause of EIPD, and elevated intramural pressure or disordered esophageal motility, including abnormal peristalsis, was also suspected to be an etiological factor [1]. A small number of pediatric cases of EIPD have been

reported [14], and the possibility remains that some congenital, functional weakness of the ductal wall causes ductal dilatation.

Since we could not find any specific histopathological or immunohistochemical differences between the walls of dilated ducts in EIPD and those of the normal ducts of submucosal glands, we suggest that the pathogenesis of EIPD is more likely to be related to functional abnormalities involving movements of the esophageal wall or ducts of submucosal glands rather than structural alterations of ductal walls. It is also possible that some abnormalities of the autonomic nervous system that regulate the secretory movements of glands play a role in the pathogenesis.

As seen in Case 2, the epithelium lining cyst-like lesions in EIPD readily undergoes squamous metaplasia [15] and rarely produces features that closely simulate a false diverticulum [7]. Ota et al. [7] studied a case of EIPD and found that, among 88 cyst-like lesions they examined, only 20 were true “pseudodiverticula” and the rest were false diverticula. In contrast to their study, in our cases, the lesions that were difficult to distinguish from false diverticula were very few, and even in these lesions, the application of immunostain for CK7 easily differentiated between the two pathological conditions. In every cyst-like lesion that simulated a false diverticulum, the lining epithelium was immunoreactive for CK7, indicating that it belongs to excretory ducts but not to surface epithelium. In the study by Ota et al. [7], the distinction between the two lesions solely depended on histopathological appearances, without applying an immunohistochemical method, and the possibility was not ruled out that some of the false diverticula in their case were actually lesions of EIPD. Immunohistochemistry for CK7 was useful for the distinction between EIPD and a false diverticulum [15]. We consider that a false diverticulum is rare in the esophagus, except in the epiphrenic region [12].

In conclusion, by studying the 2 cases, we found that cyst-like lesions in EIPD were lined by ductal epithelium frequently showing squamous metaplasia with basal cell hyperplasia. Histopathological and immunohistochemical findings of the ductal walls basically did not differ from those of the ducts of normal submucosal glands. Dilated ducts with squamous metaplasia in EIPD rarely simulated a false diverticulum, but immunohistochemistry for CK7 was useful for distinction between the conditions. We also showed that myoepithelial cells in the acinar portion of submucosal glands were well-preserved in EIPD, the finding that explained the periodic movements of orifices of cyst-like lesions in this disorder.

### Statement of Ethics

This study protocol was reviewed, and the need for approval was waived by the Ethical Review Board of Hikone Municipal Hospital. Written informed consent to use both clinical data, pathologic material, and any accompanying images was obtained from the patient in Case 2, and the same in Case 1, it was obtained from his next of kin, in accordance with the 1964 tenets of the Declaration of Helsinki and its later amendments.

### Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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## Author Contributions

Masayuki Shintaku drafted the manuscript and figures. Makoto Ohta supervised the work and gave critical advices on the contents of the article. Akito Noguchi provided the clinical information and the figure of endoscopy. Masako Shintaku checked the clinical data and also gave critical advices on the contents of the article. All the authors read and approved the final manuscript.

## Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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