CASE REPORT

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Endoscopic submucosal dissection for early esophageal cancer associated with achalasia

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Esophageal achalasia is often associated with esophageal cancer. However, in many cases, esophageal cancer tends to be found in an advanced stage, with a poor prognosis. However, early-stage cancer was detected recently due to the advances in endoscopic instruments. In those cases, it is important to facilitate successful treatment by endoscopic submucosal dissection. We analyzed a total of six cases of esophageal cancer with achalasia in four patients treated with endoscopic submucosal dissection. Three features common to all six cases had a bearing on how endoscopic submucosal dissection was performed. First, esophageal dilatation and diminished peristalsis facilitated the performance of successful endoscopic submucosal dissection. Second, the esophageal wall was thickened, primarily with muscular tissue. Third, the submucosal layer contained abundant blood vessels that made it difficult to minimize bleeding during dissection. Those findings suggest that endoscopic submucosal dissection for early esophageal cancer associated with achalasia is a safe and potentially curative procedure. It is important, therefore, to detect esophageal cancer early.

Key words: Achalasia, esophageal cancer, endoscopic submucosal dissection

Akalazya ile ilişkili erken özofagus kanseri için endoskopik submukozal diseksiyon

Özofagus akalazisi, sıklıkla özofagus kanseri ile ilişkilidir. Ancak, birçok hastada özofagus kanseri ileri evrede bulunma eğilimi göstermekte ve prognozu kötü olmaktadır. Öte yandan son yıllarda endoskopik aletlerin gelişmesiyle kanser erken evrede yakalanabilir olmuştur. Bu hastalarda, başarılı tedaviyi kolaylaştırmak için endoskopik submukozal diseksiyon önemlidir. Özofagus kanseri ve akalazyası olan 6 hastanın 4 tanesi endoskopik submukozal diseksiyon ile tedavi edildi ve analize alındı. Her altı vaka için 3 ortak nokta endoskopik submukozal diseksiyonun nasıl yapıldığı olmuştur. Birincisi özofagus dilatasyonu ve azalmış peristalsis başarılı endoskopik submukozal diseksiyon performansını artırmıştır. İkincisi, özofagus duvarı, primer olarak da kas tabakası kalınlaşmıştı. Üçüncüsü, submukozal tabakada diseksiyon sırasında kanamayı en aza indirmeyi zorlaştıran birçok kan damarı olmasıdır. Bu bulgulara göre, akalazya ile birlikte olan erken özefagus kanseri için endoskopik submukozal diseksiyon güvenilir ve potansiyel olarak küratif bir prosedürdür. Bu nedenle özofagus kanserini erken yakalamak önemlidir.

Anahtar kelimeler: Akalazya, özofagus kanseri, endoskopik submukozal diseksiyon

INTRODUCTION

Achalasia is an idiopathic primary esophageal motor disorder characterized by insufficient relaxation of the lower esophageal sphincter and the absence of esophageal peristalsis (1). The main symptoms of achalasia are dysphagia and regurgitation of undigested food. Some achalasia patients also experience weight loss, coughing when lying in a horizontal position, and chest pain that may be perceived as heartburn. Food and liquid, including saliva, are retained in the esophagus and may be inhaled into the lungs. Achalasia is often associated with esophageal cancer - it is thought

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that the chronic inflammatory irritation caused by retained food and saliva might induce carcinogenesis of the esophageal squamous epithelium. The rate of carcinogenesis is particularly high in sigmoid-type achalasia, where intestinal contents are stagnant. The chronic irritation is thought to increase cell turnover and cause epithelial cell dysplasia (2-6). In addition, a p53 protein mutation study of the esophageal mucosa in patients with achalasia suggests that the entire esophagus may be in a precancerous state (7).

Several reports have described the relationship between achalasia and esophageal cancer, beginning with that by Fagge et al. (8) in 1872. However, in many cases, esophageal cancer tends to be found in an advanced stage because the symptoms of esophageal cancer are similar to those of achalasia. Moreover, the food residue in the esophagus makes it difficult to observe the entire esophagus by endoscopy. A few reports have described cases of early esophageal cancer associated with achalasia that could be resected by endoscopic mucosal resection (EMR) (3,9–11). Here, in order to facilitate successful treatment by endoscopic submucosal dissection (ESD), we analyzed the specific features of esophageal achalasia in association with esophageal cancer as seen during ESD. This article reports the features found to be common to six cases of esophageal cancer associated with achalasia in four patients who were treated successfully with ESD.

CASE REPORTS

The main characteristics of each case are summarized in Table 1.

Case 1

A 58-year-old female with an approximately 11-year history of esophageal achalasia presented to our hospital in May 2005 with a chief complaint of persistent dysphagia. The esophageal achalasia was initially diagnosed at another medical center in 1995 based on an upper gastrointestinal (GI) series. Esophagography had revealed marked dilatation of the esophagus, to about 2 cm in diameter, proximal to the gastroesophageal junction, which was diagnosed as achalasia of the esophagus. Endoscopic balloon dilatation was performed six times from May 1995 to May 2000. In May 2009, routine follow-up upper GI endoscopy revealed a shallow depressed lesion (0-IIc) in the proximal esophagus (Figures 1, 2).

Endoscopic submucosal dissection (ESD) was performed in June 2009 (Figure 3) according to the following procedure. After application of iodine to determine the extent of the lesion, spots were mar-

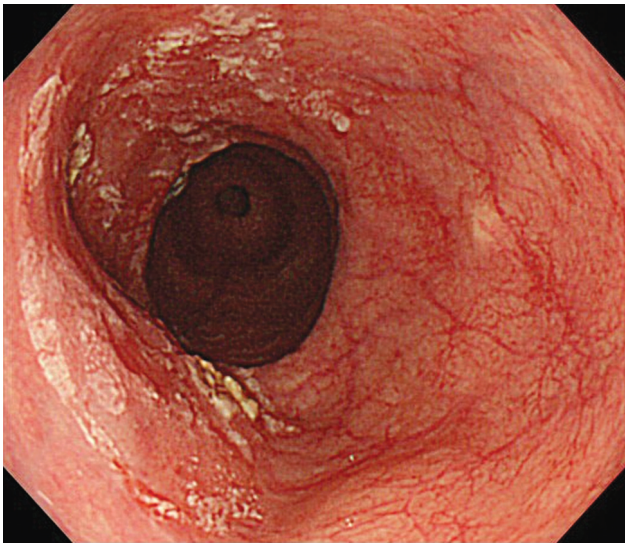

Figure 1. Preoperative endoscopic view of early esophageal cancer associated with achalasia in Case 1. Upper GI endoscopy shows a shallow depressed lesion (0-IIc) in the upper esophagus located 24–28 cm from the incisors. The depression could not be seen when the esophagus was expanded with air, so the depth of the tumor was thought to be M1.

Table 1. Characteristics of six cases in four patients of squamous cell carcinoma of the esophagus associated with achalasia and treated by endoscopic submucosal dissection (ESD)

Patient Age and sex	Site	Duration of ESD Min	Type	Depth	Size (mm)
①58 y/o F	Ut	170	0-IIc, ly0, vo	EP	41x57
②53 y/o M	Ut	90	0-IIc, ly0, v0	EP	27x20
③65 y/o F	Ut	147	0-IIc, ly0, v2	SM2	21x13
④71 y/o M	Lt	105	0-IIc, ly0, v0	LPM	28x15
73 y/o M	Mt	35	0-IIb,ly0, v0	EP	15x12
75 y/o M	Ut	35	0-IIc, ly0, v0	EP	10x10

Ut: Upper thoracic. Lt: Lower thoracic. Mt: Middle thoracic. EP: Epithelium. SM: Submucosa. LPM: Lamina propria mucosa.

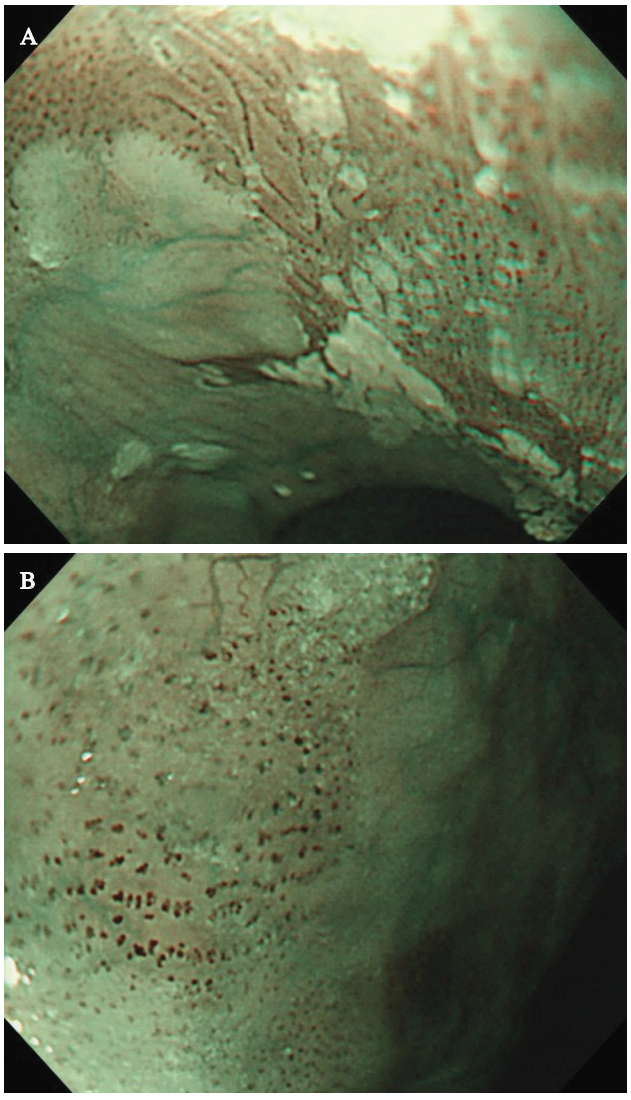

Figure 2. Magnified endoscopy in Case 1: **(A).** Magnified endoscopy with narrow band imaging reveals a large number of intra-epithelial papillary capillary loops (IPCLs) in the lesion and dilation of each IPCL. **(B).** A white coat of fibrin was attached to more than half of the lesion, preventing precise detection of the microvascular pattern.

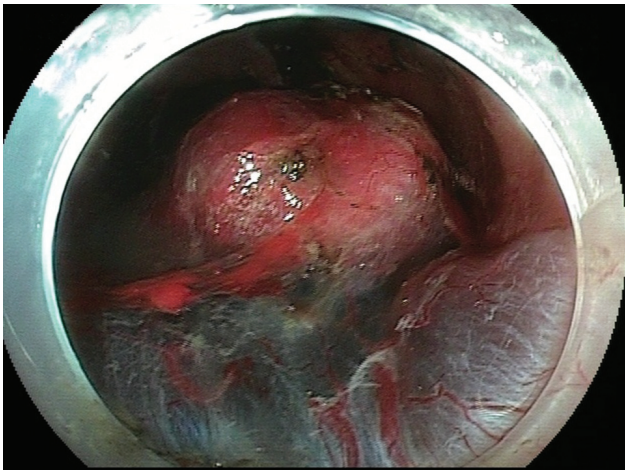

Figure 3. Endoscopic images before and after resection of the lesion in Case 1: The esophageal lesion was expanded by infusion of a mixture of glycerol, epinephrine, and indigocarmine. Submucosal blood vessels, some of which are dilated, are abundant. The same area after resection shows the multiple submucosal blood vessels cauterized (these appear black).

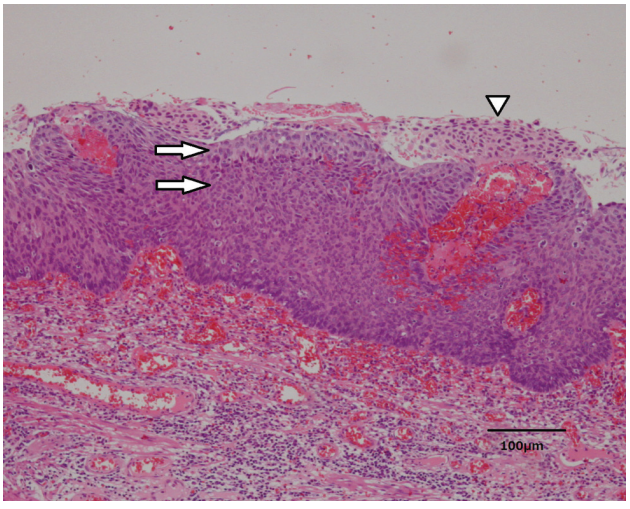

Figure 4. Microscopic findings of achalasia-associated squamous cell carcinoma in Case 1. Two areas (arrows) show layers of epithelium disordered by atypical cells and surrounding regions with relatively retained differentiation. Esophageal mucosa is thickened in areas (arrowhead). (H&E: x100)

ked outside the margin of the lesion with a Flex knife. First, a solution was locally injected into the site distal to the lesion. The solution was a mixture of glyceol® and small amounts of epinephrine and Indigo Carmine. This was injected into the submucosa until an adequate bulge appeared. Along the marking, an incision was made with a Flex knife. Esophageal dilatation and diminished peristalsis made it easier to successfully perform ESD, but the many microscopic vessels in the submucosal layer bled extensively during dissection, making the procedure more difficult than usual. The lesion in the bulge was excised (Figure 4), and pathological findings revealed partial thickening of the mucosa and squamous cell carcinoma (0-IIc, 41 x 57 mm, depth T1a-EP(M1), ly0, v0, pHM0, pVN0).

Case 2

A 53-year-old male presented to our hospital in 1992 with a chief complaint of dysphagia. Esophagography demonstrated marked dilatation of the esophagus, to about 3 cm in diameter, proximal to

the gastroesophageal junction. In September 2009, an upper GI endoscopy performed as part of the routine follow-up showed a shallow depressed lesion (0-IIc), 25 mm in size, in the upper esophagus. Similarly to Case 1, esophageal dilatation and diminished peristalsis facilitated successful ESD, but the procedure was made difficult by bleeding from several microvessels in the submucosal layer. The pathological examination revealed squamous cell carcinoma (0-IIc, 27 x 20 mm, depth M1, ly0, v0, pHM0, pVM0).

Case 3

A 65-year-old female who had suffered from esophageal achalasia since 1978 presented to our clinic in 1995 with a chief complaint of dysphagia. Endoscopic balloon dilatation was performed in 1989. In 1995, esophagography demonstrated marked dilatation of the esophagus, to about 7 cm in diameter, proximal to the gastroesophageal junction. In 2007, routine follow-up upper GI endoscopy showed a shallow depressed lesion (0-IIc) in the upper esophagus. As with the other cases, ESD was made difficult by bleeding from abundant microvessels in the submucosal layer. The pathological examination revealed squamous cell carcinoma (0-IIc, 21 x 13 mm, depth T1b(SM2), ly0, v2, pHM0, pVM0). After ESD, based on the tumor depth and vascular permeation, surgery was performed because of potential lymph node metastasis. There was no residual lesion in the resected esophagus, so ESD was regarded as a curative resection. The pathological examination showed esophageal wall thickening, mainly due to hypertrophy of the circular muscle. Since the operation, the patient has had recurrence.

Case 4

A 71-year-old male presented to our clinic in 2005 with a chief complaint of unintentional weight loss. He had a history of esophageal achalasia diagnosed in 1995 and suffered from emesis beginning in 1995. Upon presentation, esophagography revealed marked dilatation of the esophagus, to 5 cm in diameter, proximal to the gastroesophageal junction. The achalasia was classified as sigmoid type, Grade II. A Heller-Dor operation was performed in June 2005. In February 2007, routine follow-up upper GI endoscopy showed a shallow depressed lesion (0-IIc), 30 mm in size, in the proximal esophagus. ESD was performed, with excessive bleeding occurring from submucosal vessels. The pathological diagnosis was squamous cell carcinoma (0-IIc, 28 x 15mm, depth T1a(M2), ly0, v0, pHM0, pVM0). In November 2007, follow-up upper GI endoscopy revealed a new shallow, depressed, 15-mm lesion (0-IIb) in the upper esophagus. This lesion appeared to have no relation to the previous site. The pathological diagnosis after ESD was squamous cell carcinoma (0-IIb, 15 x 12 mm, depth Tis (EP), ly0, v0, pHM0, pVM0). In July 2009, another follow-up upper GI endoscopy showed a shallow depressed lesion (0-IIc), 20 mm in size, in the upper esophagus. The pathological diagnosis was squamous cell carcinoma of the esophagus (0-IIc, 18 x 7 mm, depth M1, ly0, v0, pHM0, pVM0). A third ESD was performed for this patient, and similar bleeding recurred.

Endoscopic ultrasound (EUS) was performed in all cases and showed esophageal wall thickening. In Case 3, the wall thickening was actually proven by pathological findings.

Common to these six cases were esophageal dilatation and diminished peristalsis, esophageal wall thickening mainly composed of the circular muscle, and abundant blood vessels in the submucosal layer that presented a challenge for hemostasis during dissection.

DISCUSSION

Achalasia of the esophagus is a noncancerous disease caused by dyskinesia of the lower esophagus and gastric cardia, and is regarded as a risk factor for squamous cell carcinoma. The literature contains many case reports on the relationship between achalasia and esophageal cancer. Wychulis et al. (12) reported that patients with achalasia have 7 to 8 times the risk of developing esophageal cancer than individuals without achalasia (9,12). Unfortunately, the number of patients with achalasia and the incidence of developing cancer in our hospital were unclear, because patients with achalasia referred to respective sections, e.g. Gastroenterology, Gastrointestinal Surgery, or a branch department of gastroenterology. However, the incidence of developing cancer in patients with achalasia has been reported as 3–8%. In many cases, the esophageal cancer is found at an advanced stage, because its symptoms are similar to those of achalasia (13-19), and food residue in the esophagus makes it difficult to observe the esophagus on endoscopy (13). However, earlier diagnosis has become more likely with advances in endoscopic equipment, which allow, for example, narrow band imaging, and by having patients discontinue ea-

ting the day before the procedure. In our experience, after achalasia has been diagnosed, early esophageal cancer associated with the disorder can usually be discovered with regular, periodic upper GI endoscopy.

The depth of invasion was investigated by white light endoscopy and EUS in all enrolled patients. During EUS, a GIF-Q230 and a 30 MHz miniature probe (Olympus Optical, Tokyo, Japan) were used. A soft balloon was attached at the tip of the scope and filled with de-aerated water during observation. Backward and forward movements of the probe in the soft balloon were performed to obtain the best imaging.

In the six cases of esophageal carcinoma associated with achalasia in the four patients described herein, the three features common to all six cases had a bearing on how the ESD was performed. The first feature stems from the very definition of achalasia as a primary esophageal motor disorder characterized by insufficient relaxation of the lower esophageal sphincter and the absence of esophageal peristalsis (1); the dilatation and absence of peristalsis allowed us to expand our field of vision and perform ESD more safely. The second common feature is that achalasia is associated with esophageal wall thickening, mainly due to hypertrophy of the circular muscle. As a result of this thickening, the risk of esophageal perforation during ESD for esophageal cancer is considered lower in patients that also have achalasia than in those who do not. The third feature present in all six cases was the abundance of blood vessels in the submucosal layer, which caused profuse bleeding during dissection. This hypervascularity is thought to be due to the chronic inflammation in the dilated esophagus. To prevent bleeding during dissection, physicians should be cognizant of the many blood vessels in the submucosal layer in cases of esophageal cancer associated with achalasia. In terms of the technique used, solution should be injected at a much higher volume than usual, and this preventive hemostasis enables the submucosal layer to be dissected safely because it affords a good working view of the blood vessels at the operative site. Attaching the hood to be longer at the tip of the endoscope and decreasing the volume of Indigo Carmine are also useful techniques in this respect.

In summary, we report herein the successful treatment by ESD of esophageal cancer associated with achalasia. We performed ESD in six cases (four patients), all of which showed dilatation of the esophagus (which facilitated the procedure), a thickened esophageal muscular layer, and proliferation of submucosal blood vessels that bled extensively during dissection. The findings suggest that ESD for early esophageal cancer associated with esophageal achalasia is a safe and potentially curative procedure. It is important, therefore, to detect esophageal cancer early in patients showing esophageal achalasia by performing upper GI endoscopy periodically.

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