Introduction

Achalasia of esophagus is an idiopathic primary esophageal motor disorder characterized by insufficient relaxation of the lower esophageal sphincter and the absence of esophageal peristalsis. Decreased and/or diminished myenteric ganglia have been reported in the lower esophagus. Achalasia is known as a risk factor of esophageal squamous cell carcinoma. Fagge first reported the relationship between achalasia and esophageal carcinoma in 1872. Since this initial observation, the increased risk of developing esophageal carcinoma has been postulated in the patients with long-standing achalasia. The incidence of carcinoma in achalasia patients has been reported to range from 1.7 to 20%. Chronic inflammatory by retained food may induce carcinogenesis of the esophageal squamous epithelium. In this report, a case of two lesions of early esophageal carcinomas treated by endoscopic submucosal dissection (ESD) developing after the operation for achalasia is described.

Case Report

A 46-year-old man was suffering from dysphagia from 1998. The patient had been treated by pneumatic dilatation for symptomatic achalasia conservatively. The patient was operated by Tokai University method, Heller’s long esophagomyectomy, Hill’s posterior cardioectomy, fundoplication and selective proximal vagotomy using a laparotomy in August 2009. One year and three months after the operation, two lesions of early carcinomas of type 0-IIb and 0-IIc, each 1cm in size, were detected in the middle thoracic esophagus, and treated by endoscopic submucosal dissection. Pathological examination of the each lesion revealed proliferation of squamous cell carcinoma in situ (T1a-EP). The entire esophageal mucosa around the carcinoma demonstrated hyperplastic changes of stratified squamous epithelium and foci of intraepithelial neoplasia. In the patient of achalasia, food stasis in esophagus is thought to induce chronic hyperplastic squamous esophagitis, converting eventually to malignant transformation. Achalasia is known as a risk factor of esophageal squamous cell carcinoma. Careful long-term follow-up for patients of achalasia by endoscopic screening is recommended, even if after treatment by pneumatic dilatation or operation for achalasia.

Key Words: Achalasia of esophagus, esophageal carcinoma, carcinogenesis, endoscopic submucosal dissection
Tokai University method\(^{13}\) with Heller’s long esophagomyectomy, Hill’s posterior cardiopeaxy, fundoplication (4/5 of circumference) and selective proximal vagotomy using a laparotomy was performed on August 5, 2009. The postoperative course was uneventful and the patient was discharged two weeks later. He has been getting well without complaint of dysphagia after the operation.

Endoscopic examination was performed after the operation, and esophagitis was well controlled without marked hyperplastic change. One year and three months after the operation, early carcinomas of type 0-IIb and 0-IIc, each 1 cm in size, were detected at 29 cm and 32 cm from incisor in the middle thoracic esophagus by endoscopic examination with iodine staining. Narrow Band Imaging (NBI) and magnified findings showed brownish area composed of irregular vessels (Fig. 2A, B, C, D, E, F). Computed tomography and echogram showed no evidence of metastasis. ESD was performed on April 20, 2011 (Fig. 3). Pathological examination of the resected specimen revealed proliferation of squamous cell carcinoma, closely associated with dysplastic foci. The invasion of carcinoma cells of the each lesion was limited to the squamous epithelium (T1a-EP: M1) (Fig. 4A, B)\(^{14}\). The entire esophageal mucosa around the carcinoma demonstrated hyperplastic changes of stratified squamous epithelium accompanying foci of intraepithelial neoplasia (Fig. 4C, D). No lymphatic or blood vessel invasion was found. He was discharged five days after ESD without complication.

**Discussion**

Achalasia of the esophagus is regarded as an increased risk of squamous cell carcinoma due to persistent mucosal irritation by alimentary retention. According to the Japanese classification, the types of dilatation is divided into three groups as follows: (a) spindle type, (b) flask type, (c) sigmoid type and the grades of dilatation is similarly divided into three groups as follows: (a) Grade I: d (maximum diameter in lower esophagus) < 3.5 cm, (b) Grade II: 3.5 \(\leq\) d < 6.0 cm, (c) Grade III: 6.0 cm \(\leq\) d\(^{12}\). Most patients with achalasia undergo conservative endoscopic therapy and/or esophagomyectomy by surgery. The incidence of carcinoma is reported as 1.7 to 20% among achalasia patients\(^5,6-11\), while that of ordinary esophageal carcinoma is approximately 0.3%\(^{70}\). In the previous studies, the mean interval from onset of dysphagia in achalasia patients to diagnosis of esophageal carcinoma demonstrated hyperplastic changes of stratified squamous epithelium accompanying foci of intraepithelial neoplasia (Fig. 4C, D). No lymphatic or blood vessel invasion was found. He was discharged five days after ESD without complication.
Fig. 2 An early esophageal carcinoma of type 0-IIb developed at 29 cm from incisor after the operation for achalasia. A: conventional endoscopic view, B: chromoendoscopic view with iodine staining, C: NBI magnified view. Another early esophageal carcinoma of type 0-IIc developed at 32 cm from incisor. D: conventional endoscopic view, E: chromoendoscopic view with iodine staining. F: NBI magnified view.

Fig. 3 Macroscopic view of the resected specimen by ESD with iodine staining.
was 17-21.5 years\(^2,3,11\). Most of the patients with achalasia had been performed pneumatic dilatation and/or esophagomyectomy for their symptom. In the myectomy cases, the carcinoma was diagnosed after a mean period of 17 years of post-operative follow-up\(^11\). The symptoms of carcinoma are usually hidden by the severe dysphagia of achalasia. Radiographically, most of the patients lose peristalsis, and distal esophageal stricture, retention of barium and food material in the esophagus is observed. Endoscopically, esophageal food stasis and chronic hyperplastic esophagitis are often observed. Thus, the carcinomas associated with achalasia are mostly found and often diagnosed in the advanced stages\(^11\). In patients with achalasia, the carcinoma was rarely found in its early stage, and the incidence of early carcinoma was reported only 9.1%\(^16\). Therefore, endoscopic surveillance using iodine staining and NBI has been recommended to detect the cancer in early stage\(^2,11\). Since persistent chronic hyperplastic esophagitis of achalasia is thought as a premalignant condition\(^4,5,8,11\), Heller’s esophagomyectomy or dilatable bouginage of esophagus are recommended in early stage of the disease. However, surgery in the late stage does not seem to be effective for achalasia-mediated carcinogenesis.

Histological examination of the resected esophageal specimens demonstrated marked hyperplastic changes of stratified squamous epithelium and multiple foci of dysplastic changes in the previous studies. The squamous cell carcinoma of differentiated type with low-grade atypia was closely associated with foci of intraepithelial neoplasia\(^11\). We speculate that food stasis induces chronic hyperplastic esophagitis, leading eventually to malignant transformation of esophageal epithelial cells, in accordance with dysplasia-carcinoma sequence\(^6,8,11\). The previous immunohistochemical investigations regarding p53 accumulation of esophageal squamous

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**Fig. 4** Microscopic findings of achalasia-associated squamous cell carcinoma (two lesions). The carcinoma showed a mucosal carcinoma, closely associated with dysplastic foci and hyperplastic mucosa. A: carcinoma in situ of type 0-IIb (x10, H & E), B: carcinoma in situ of type 0-IIc (x10, H & E), C: intraepithelial neoplasia (x20, H & E), D: hyperplasia (x10, H & E).
cell carcinoma show frequent over-expression of p53 in both achalasia-associated carcinoma and dysplasia. Immunohistochemical studies of p21 and p16 expression suggest that the cell cycle might be increased in achalasia-associated carcinoma because of persistent inflammation. Under these conditions of accelerated cell cycle, the achalasia-associated carcinoma may develop according to the dysplasia-carcinoma sequence.

In conclusion, we report a case of early esophageal carcinomas associated with postoperative achalasia treated by ESD. Long-term follow-up for patients of achalasia by endoscopic screening is recommended, even if after treatment by pneumatic dilatation or surgical operation.

References