

CASE REPORT

Achalasia Combined with Esophageal Cancer Treated by Concurrent Chemoradiation Therapy

Jun Chul Park*, Yong Chan Lee*, Sang Kyum Kim[†], Yu Jin Kim*, Sung Kwan Shin*, Sang Kil Lee*, Hoguen Kim[†], and Choong Bai Kim[†]

Departments of *Internal Medicine, Institute of Gastroenterology, [†]Pathology and [‡]Surgery, Yonsei University College of Medicine, Seoul, Korea

Achalasia is a rare neurological deficit of the esophagus that produces an impaired relaxation of the lower esophageal sphincter and decreased motility of the esophageal body. Achalasia is generally accepted to be a pre-malignant disorder, since, particularly in the mega-esophagus, chronic irritation by foods and bacterial overgrowth may contribute to the development of dysplasia and carcinoma. We present a case of a 51-year-old man with achalasia combined with esophageal cancer who has had dysphagia symptoms for more than 20 years. Since there was a clinically high possibility of supraclavicular lymph node metastasis, concurrent chemoradiation therapy was scheduled. After the third cycle of chemoradiation therapy, trans-thoracic esophageolympadenectomy was performed. Histopathological examination of the main esophagus specimen revealed no residual carcinoma. And the entire regional lymph node areas were free of carcinoma except for one azygos metastatic lymph node. In summary, achalasia is a predisposing factor for esophageal squamous cell carcinoma. Although surveillance endoscopy in achalasia patients is still controversial, periodic screening for cancer development in long-standing achalasia patients might be advisable. (*Gut and Liver* 2009;3:329-333)

Key Words: Esophageal achalasia; Esophageal neoplasms

INTRODUCTION

Achalasia is a disease of unknown cause in which aper-

istalsis in the distal esophagus and a failure of relaxation of the lower esophageal sphincter (LES) occurs. Since the etiology is unclear, treatment focuses on relieving symptoms. Nonetheless, despite treatment, food stasis often persists, causing development of chronic inflammation, dysplasia and possibly esophageal cancer.

The correlation between achalasia and esophageal cancer was first noted by Fagge in 1872.¹ Since this initial report, achalasia has frequently been described as a predisposing factor for esophageal cancer.^{2,3} When esophageal cancer develops in patients with underlying achalasia, diagnosis tends to be in the more advanced stages of cancer, compared to cases with no achalasia, because both physicians and patients often regard symptoms such as dysphagia and chest discomfort as attributable to the achalasia, rather than to other causes. Therefore, additional approaches that would lead to earlier diagnosis might be pursued less aggressively.

Here we report a case of achalasia combined with esophageal cancer treated by concurrent chemoradiation therapy.

CASE REPORT

A 51-year-old man was admitted to our hospital because of mild dysphagia. He was diagnosed as esophageal motor disorder at a local clinic when he was teenager. The symptoms, which occurred for for both solids and liquids simultaneously, had begun more than 20 years ago. And whenever swallowing solid or liquid diet, he al-

Correspondence to: Yong Chan Lee

Department of Internal Medicine, Yonsei University College of Medicine, 134, Shinchon-dong, Seodaemun-gu, Seoul 120-752, Korea

Tel: +82-2-2228-1960, Fax: +82-2-393-6884, E-mail: leeyc@yuhs.ac

Received on May 18, 2009. Accepted on August 3, 2009.

DOI: 10.5009/gnl.2009.3.4.329

ways felt the food was retained in the esophagus in a moment and passing through after a few seconds. However, there was no epigastric pain or chest pain. Sometimes vomiting and regurgitation developed after meal. Above symptoms had continued for several decades without significant change of their patterns and severities. Since his initial diagnosis at a local clinic, he did not go to hospital thereafter till this visit to our institute.

Physical examination revealed a small, round, palpable mass at the right supraclavicular fossa and routine blood tests were unremarkable. The patient underwent upper gastroendoscopy, showing a fungating, exophytic mass lesion with an irregular and friable surface involving 90% of the luminal circumference at 42 cm from the upper incisors, just above the gastroesophageal (GE) junction (Fig. 1A, B). The scope could be passed through the GE junction into the stomach body with mild resistance. Multiple biopsies were taken from the fungating mass, which allowed identification of squamous cell carcinoma upon histopathological examination. An esophagogram also showed a fungating mass of approximately 9 cm at the distal esophagus, and a dilated thoracic esophagus with bird-beak sign (Fig. 1C). Based on these results, esophageal squamous cell carcinoma with achalasia was considered and esophageal manometric study and positron emission

tomography-computed tomography (PET-CT) were undertaken. The result of manometry was compatible with achalasia, specifically simultaneous contraction (mean pressure 14.48 mm Hg) and incomplete lower esophageal sphincter relaxation. PET-CT showed a large, hypermetabolic mass lesion at distal esophagus which was compatible with esophageal cancer (Fig. 2A). Hypermetabolism at the right hilar lymph node area and the right supraclavicular lymph node were observed. Although the aspiration biopsy at the right supraclavicular lymph node was negative for malignancy, there was a clinically high possibility of lymph node metastasis. For this reason, concurrent chemoradiation therapy was suggested instead of esophagectomy. By this time, the patient's dysphagia symptoms had worsened, so dilation of the lower gastroesophageal junction was performed using a 30 mm achalasia balloon dilator (6 psi for 5 seconds, Boston Scientific Microvasive[®], Natick, MA, USA). Dysphagia symptoms greatly improved after dilation. Thereafter, concurrent chemoradiation therapy of 800 mg/m²/d fluorouracil was administered by continuous infusion on day 1 to 3, and cisplatin 80 mg/m² intravenously on day 2. Radiotherapy was delivered in five daily fractions per week of 1.8 Gy over 5.5 weeks, for a total of 50.4 Gy. Radiation fields also included the right supra-

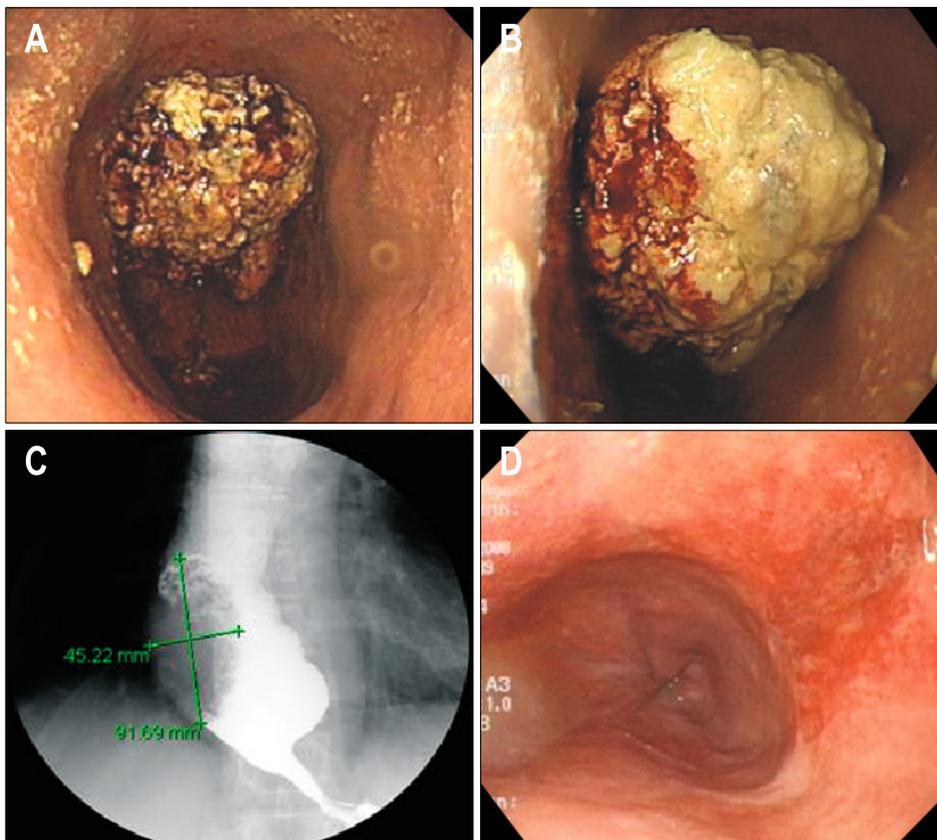


Fig. 1. (A, B) Endoscopic view of fungating mass lesion with dilated lower esophagus. (C) Fungating mass at distal esophagus and dilated distal esophagus with bird-beak sign. (D) Follow-up endoscopy showing disappearance of the previous cancer mass after the third cycle of concurrent chemoradiation therapy.

clavicular lymph node area. After the third cycle of chemotherapy with radiation, followup PET-CT was undertaken. The right hilar lymph node showed no definite ^{18}F -fluorodeoxyglucose (FDG) uptake. The main esophageal mass with the right supraclavicular lymph node demonstrated decreased size and mild FDG uptake, compared to the previous analysis (Fig. 2B). The follow-up gastroendoscopy also showed disappearance of the distal esophageal mass, with mild erythematous mucosal change at the previous cancer site (Fig. 1D). The patient had no serious complications during the third cycle of concurrent chemoradiation therapy. He was informed about his disease status and trans-thoracic esophageolymphadenectomy was performed (Fig. 3A). Histopathological examination of the main esophagus specimen revealed no residual carcinoma and negative resection margin. Chronic inflammatory cell infiltration with stromal edema, telangiectasia and fibroblast proliferation was observed from secondary changes of radiation therapy (Fig. 3B). The entire paraesophageal, subcarinal and regional lymph node areas were free of carcinoma except for one azygos metastatic lymph node. Myenteric inflammation with lymphocytic infiltration within the myenteric plexus was observed, and in particular, ganglion cells were absent (Fig. 3C).

The patient was discharged on the 29th postoperative day with no serious complications. Further postoperative

chemotherapy was scheduled.

DISCUSSION

Although achalasia is a common functional disorder of the esophageal body and lower esophageal sphincter (LES), it is still a relatively rare disease. Epidemiological data have demonstrated an annual incidence in the range of 0.5 cases per 100,000 people, with a prevalence of about 8 cases per 100,000 people per year.⁴

The risk of esophageal malignancy for patients with long-standing achalasia is between 14- and 140-fold over the rest of the population.^{3,5} A recent large cohort study showed male achalasia patients have substantially greater risk for both squamous cell carcinoma and adenocarcinoma of the esophagus.⁶ Several autopsy studies have reported an esophageal carcinoma prevalence of 20-29% in achalasia patients,⁷ and evaluation of esophagectomy specimens from patients with end-stage achalasia has demonstrated squamous hyperplasia.⁸ Most likely, in the late phase of achalasia, chronic irritation by food and bacterial overgrowth causes epithelial proliferation of the mucosa that may progress from squamous hyperplasia to dysplasia and carcinoma, similar to that seen in sporadic esophageal squamous cell carcinoma.⁹

Apart from esophageal food stasis, the possibility of ia-

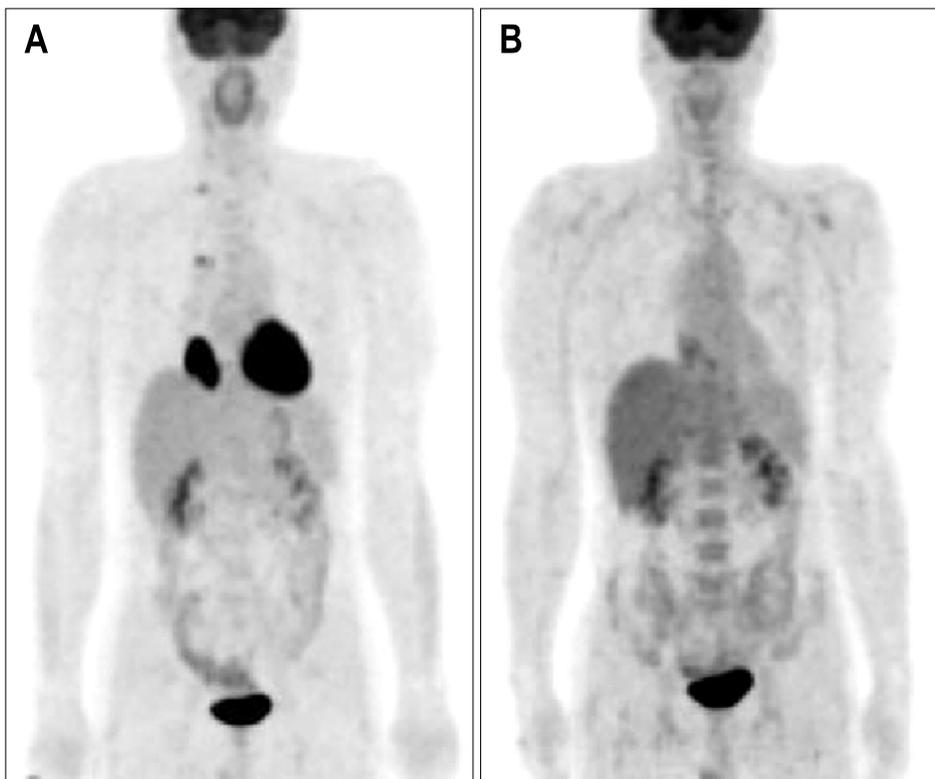


Fig. 2. (A) Intense ^{18}F -fluorodeoxyglucose (FDG) uptake is seen in the primary distal esophagus lesion with right hilar lymph node area and in the right supraclavicular lymph node. (B) The right hilar lymph node shows no definite FDG uptake. The main esophageal mass with right supraclavicular lymph node shows a decrease in size and mild FDG uptake compared to previous imaging.

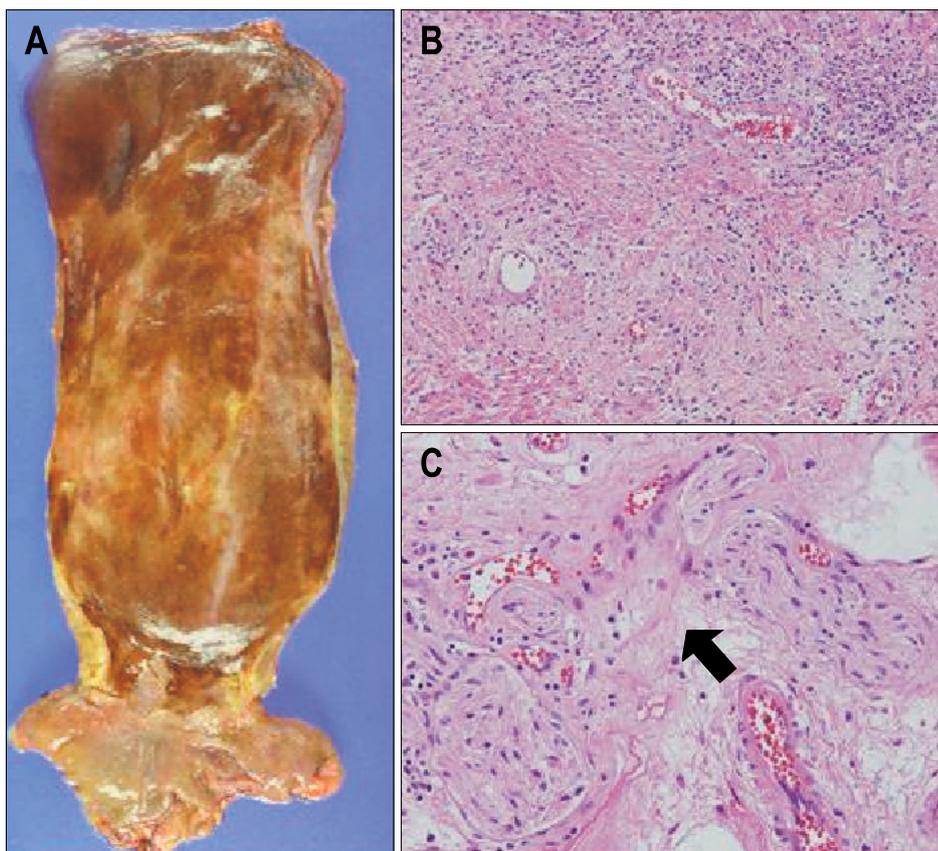


Fig. 3. (A) Gross specimen of the surgically removed esophagus after concurrent chemoradiation therapy. (B) Microscopic findings of achalasia-associated squamous cell carcinoma after concurrent chemoradiation therapy. Chronic inflammatory cell infiltration with stromal edema, telangiectasia and fibroblast proliferation is shown. (C) Myenteric inflammation with lymphocytes infiltration observed in the myenteric plexus (arrow). Ganglion cells are absent.

trogenic reflux after myotomy or pneumatic dilatation has been also suggested as cause of adenocarcinoma.¹⁰ In a Dutch study of 331 achalasia patients treated with pneumatic dilation, 28 (8.5%) developed endoscopical evidence of Barrett's metaplasia with intestinal metaplasia, seen in histological samples.¹¹ Other study also reported adenocarcinoma in Barrett's metaplasia in achalasia.² Barrett's esophagitis is probably the result of LES tone-lowering therapy, which may induce significant sphincter insufficiency, which, in theory, may lead to worsened gastroesophageal reflux.

In patients with underlying achalasia, esophageal cancers are generally diagnosed in advanced stages because the two diseases have similar symptoms, so rigorous diagnostic evaluation of symptoms might be undertaken less frequently. Patients also have a large amount of retained food in the mega-esophagus, making visualization difficult. Therefore, reports of operability have been infrequent and 80% of patients are inoperable at initial diagnosis.^{3,5} Nonetheless, whether surveillance endoscopy should be generally recommended for all patients with esophageal achalasia is still controversial because of the long interval between initial symptoms of achalasia and the development of carcinoma. A previous study on 1,062

achalasia patients reported that the mean age at entry was 57.2 years and the mean age at cancer diagnosis was 71 years.¹² Other studies also showed an interval between the first symptoms of achalasia and the diagnosis of esophageal cancer of at least 15 years.^{3,5} Based on these observations, a recommendation of regular surveillance endoscopy might be beneficial in long-standing achalasia patients. The benefits of surveillance endoscopy in these patients are seen in a higher prevalence of early esophageal cancer stages.³

The treatment of choice for early esophageal cancer is curative resection. Surgery for advanced esophageal carcinoma has been disappointing, however, because of low resectability and a high risk of distant metastasis, which is seen in about half of the patients at the time of initial diagnosis.¹³ Surgery has limited therapeutic effect, and therefore effective multimodality treatment is required to obtain better survival in advanced stage esophageal carcinoma cases.

Radiation and chemotherapy may synergistically enhance anti-tumor effects against esophageal cancer, so concurrent chemoradiotherapy (CRT) is an attractive strategy for radiosensitization and control of micrometastatic disease.¹⁴ Recent studies have shown that radiotherapy

with chemotherapy is superior to radiotherapy alone, based on the results of a number of randomized trials.¹⁵⁻¹⁷ A landmark study by the Radiation Therapy Oncology Group (RTOG) compared radiation alone versus chemoradiation treatment (RTOG 85-01).¹⁶ At 5 years of follow-up, the overall survival rates were 26% for patients who received combined modality treatment and 0% for those who received radiotherapy alone.

Cytotoxic agents, for example 5-Fluorouracil (5-FU) and cisplatin, have been used as radiosensitizers in many tumors, and a synergistic effect has been shown between the two drugs.^{15,17} Based on these results, continuous 5-FU and cisplatin can be used in concurrent chemoradiotherapy. In phase II studies on advanced or recurrent esophageal squamous cell carcinoma, this combination induced a response rate of about 33-35%, leading to a median overall survival of 6-8 months, although complete response was rare.^{18,19} This case presented here also represents an excellent response to preoperative, concurrent chemoradiation therapy. A large main esophageal mass disappeared with no remaining malignant cells. We also observed loss of ganglion cells in the myenteric plexuses, surrounded by lymphocytes representing achalasia (Fig. 3C). This inflammatory degeneration preferentially involves the nitric oxide-producing, inhibitory neurons that induce the relaxation of esophageal smooth muscle. Thus, the cholinergic neurons that contribute to LES tone by causing smooth muscle contraction are spared.²⁰

Our case represents achalasia with squamous esophageal carcinoma and mild dysphagia, which the patient experienced for more than 20 years. The long duration of dysphagia symptoms interfered with early diagnosis of esophageal cancer, and long-term food stasis might have been a factor in the precancerous state. Although surveillance endoscopy in achalasia patients is still controversial, periodic screening for cancer development might be advisable in long-standing achalasia patients.

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