

## Collision Carcinoma of the Residual Cervical Esophagus 27 Years after Esophageal Cancer Surgery

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**Abstract.** A case of collision carcinoma (squamous cell carcinoma and Barrett's adenocarcinoma) in the residual cervical esophagus of a 68-year-old woman at 27 years after subtotal esophagectomy for thoracic esophageal carcinoma is reported. The patient initially noticed cervical dysphagia in 2002, but did not seek treatment. In April 2004, the patient was referred to our department by a local physician with the diagnosis of carcinoma of the cervical esophagus. In September 2004, the patient underwent resection of the cervical esophagus and partial resection of the gastric tube combined with cervical lymph node dissection under a diagnosis of double cancer (i.e., metachronous cervical esophageal carcinoma and carcinoma of the gastric tube). Esophagogastric continuity was restored by transplantation of a free jejunal graft with vascular anastomosis. Pathological examination showed squamous cell carcinoma on the esophageal side of the esophagogastric anastomosis and columnar epithelium with a tongue-shaped extension across the anastomotic line that included Barrett's epithelium, as well as adenocarcinoma, on the gastric tube side. The squamous cell carcinoma and adenocarcinoma were contiguous, but there was a distinct border between them and no morphological transition. Immunohistochemical staining showed positivity for p53 in the squamous carcinoma cells, while it was negative in the adenocarcinoma cells. In contrast, HER2 (c-erb-2) was strongly positive in the adenocarcinoma cells, but negative in the squamous carcinoma. Based on these findings, it was concluded that two separate carcinomas had arisen at different sites and grown independently until they collided and merged to form a collision carcinoma.

As the prognosis of esophageal cancer has improved (1-2), there has recently been an increase of double cancer or metachronous multiple cancer in other organs among patients who have undergone surgery for esophageal cancer. Metachronous carcinoma of the residual esophagus has been reported to occur in 0.3 - 3.3% of patients who underwent resection of esophageal cancer, so this condition is relatively uncommon (3-4). A patient with collision carcinoma (consisting of squamous cell carcinoma and Barrett's adenocarcinoma) in the residual cervical esophagus at 27 years after initial surgery for thoracic esophageal cancer was encountered. This interesting case is reported here.

### Case report

The patient, a 68-year-old woman who presented with difficulty in swallowing, had undergone subtotal esophagectomy with retrosternal reconstruction for thoracic esophageal cancer at another hospital in 1977. Cervical swelling and dysphagia was noticed in 2002, but did not seek any treatment at the time. In April 2004, the patient visited a local doctor due to aggravation of these symptoms, and was referred to our department with the diagnosis of cervical esophageal cancer and admitted.

On admission, she was 152 cm tall and weighed 43 kg. She was moderately well nourished. The conjunctivae showed neither pallor nor icterus. There was a protruding mass on the left side of the neck (Figure 1), but physical examination revealed no abnormalities in the chest or abdomen. Laboratory findings included the following: CRP, 0.16 mg/dL; WBC, 6500/ $\mu$ L; Hb, 10.6 g/dL; TP, 6.3 g/dL; Alb, 3.2 g/dL; GOT, 21 IU/L; GPT, 12 IU/L; TB, 0.8 mg/dL; BUN, 9.9 mg/dL; and Cre, 0.53 mg/dL. Only mild anemia was indicated. With respect to tumor markers, CEA was 0.5 ng/mL (normal) and SCC was 4.5 ng/mL (increased).

The chest X-ray showed no abnormalities. Esophagograms demonstrated severe dilation of the cervical esophagus along

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Figure 1. A large oval mass protrudes from the left side of the neck.

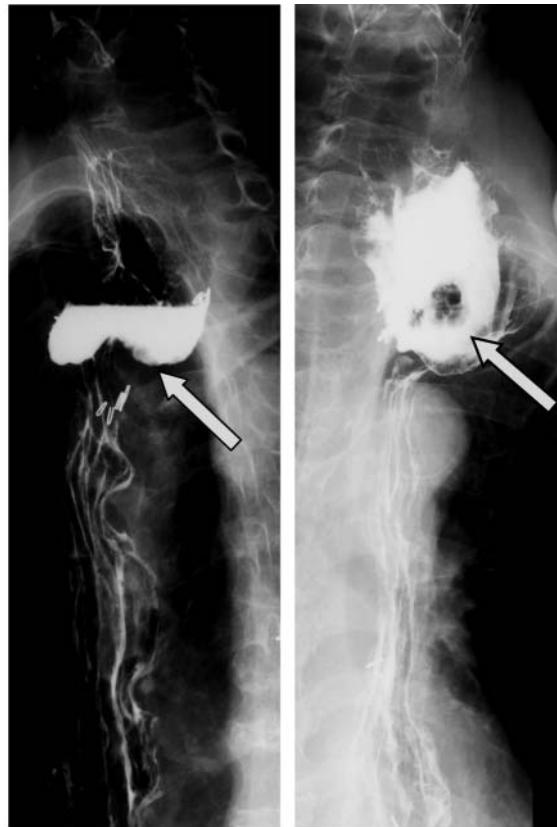


Figure 2. Esophagogram demonstrating massive enlargement of the cervical esophagus and anastomotic stenosis (left arrow), as well as a protruding lesion (right arrow).

with stenosis at the site of anastomosis. In addition, a protruding lesion was seen on the posterior wall of the cervical esophagus (Figure 2). Endoscopy demonstrated a 0-I lesion (diagnosed as squamous cell carcinoma by biopsy) extending from the posterior wall to the right lateral wall of the esophagus on the oral side of the esophagogastric anastomosis (Figure 3a). On the gastric tube side, a 0-IIa lesion (diagnosed as adenocarcinoma by biopsy) was detected on the posterior wall (Figure 3b). Thoracoabdominal CT scans showed severe dilation of the cervical esophagus, hypertrophy of the posterior wall and a protruding lesion. There was no detectable enlargement of lymph nodes in the mediastinum or abdominal cavity. No metastases were noted in other organs such as the lungs or liver.

Based on the findings described above, we made a diagnosis of double cancer, consisting of metachronous carcinoma (T1b, M0, N0, Stage I) of the residual cervical esophagus and adenocarcinoma (T1, M0, N0, Stage IA) of the gastric tube. In September 2004, cervical esophagectomy and partial resection of the gastric tube combined with cervical lymph node dissection was performed. Continuity

between the residual esophagus and remnant gastric tube was then restored by transplantation of a free jejunal graft with vascular anastomosis (Figure 4). Macroscopic examination of the surgical specimen revealed two protruding lesions, with one being 0-I + 0-IIa and the other being 0-IIa, on the esophageal and gastric tube sides of the anastomosis, respectively (Figure 5).

A diagram of these lesions based on the histological findings shows that there were two different neoplasms (Figure 6). The tumor on the esophageal side of the anastomosis was a squamous cell carcinoma (sm2), while the tumor on the gastric tube side was an adenocarcinoma (m3) arising from Barrett's epithelium, which formed a tongue-shaped extension of columnar epithelium from the gastric tube into the esophagus across the anastomotic line. The squamous cell carcinoma and adenocarcinoma were continuous, but there was a clear border between them and no findings suggestive of morphological transition. Neither tumor involved the blood vessels (Figure 7).

In order to confirm that the squamous cell carcinoma and adenocarcinoma were independent tumors, sections were

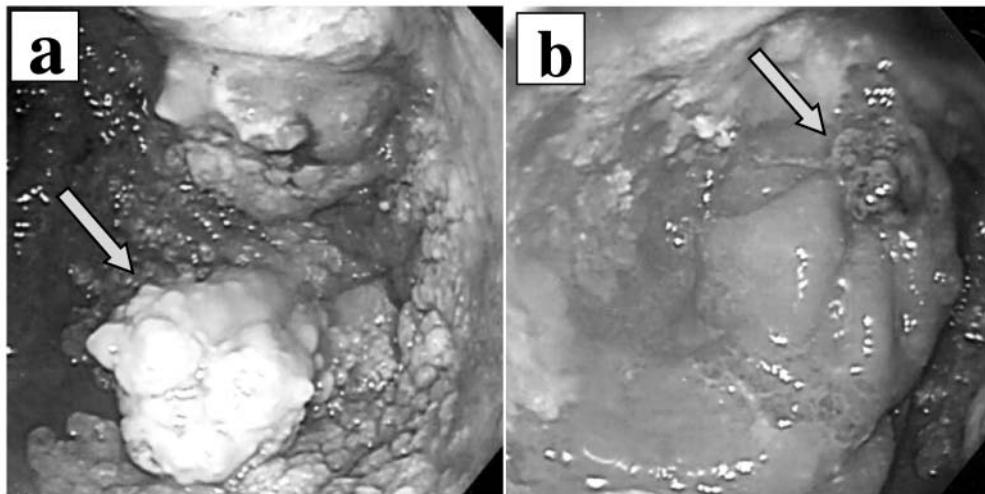


Figure 3. Endoscopic examination showed (a) a 0-I type lesion (arrow, squamous cell carcinoma) that extended from the right lateral wall to the posterior wall on the esophageal side of the anastomosis, and (b) a 0-IIa type lesion (arrow, adenocarcinoma) on the posterior wall distal to the anastomotic line.

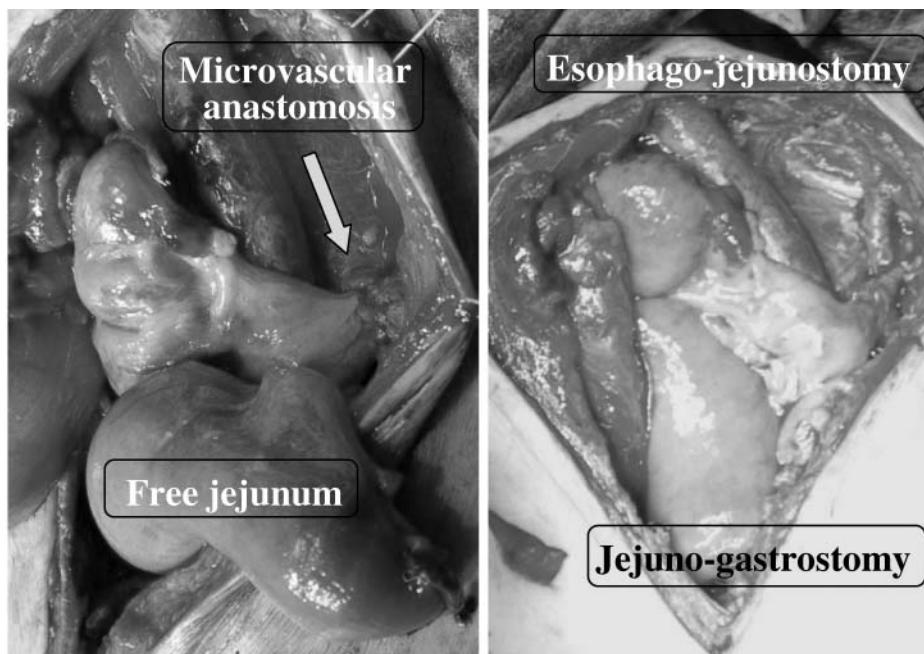


Figure 4. After resection of the cervical esophagus and part of the gastric tube, gastroesophageal continuity was restored by transplantation of a free jejunal graft with vascular anastomosis (arrow).

stained immunohistochemically for p53 and HER2 (c-erb-2). It was found that the squamous carcinoma cells positive stained for p53 (Figure 8a), whereas the adenocarcinoma cells were negative. In contrast, HER2 (c-erb-2) was strongly positive on the cell membranes of the adenocarcinoma cells (Figure 8b), whereas the squamous carcinoma cells were negative. From these findings, a diagnosis of collision

carcinoma was made. It was considered that these two tumors had developed and grown independently until they collided and merged near the anastomotic line.

The patient's postoperative course was satisfactory; she began to eat a soft diet and a solid diet from 2 and 3 weeks after surgery, respectively. Neither anastomotic leakage nor stenosis occurred. The patient was discharged on postoperative



**Figure 5.** The resected specimen features a protruding lesion composed of 0-I + 0-IIa (arrow) and 0-IIa (arrow) tumors on the esophageal and gastric tube sides of the anastomotic line, respectively.

day 40 and there has been no recurrence or difficulty in swallowing for 18 months since the operation (Figure 9). The patient is undergoing regular follow-up as an outpatient.

The above-mentioned clinicopathological features of the tumors of the esophagus and gastric tube were described in accordance with the Japanese General Rules for Esophageal Cancer Study (5) and the General Rules for Gastric Cancer Study (6).

## Discussion

Esophageal collision tumors in all previously reported cases were primary tumors located at the cardiosophageal junction. Many of these tumors were a combination of adenocarcinoma and sarcoma, or adenocarcinoma and lymphoma (7, 8), while adenocarcinoma plus squamous cell carcinoma have only been reported in 12 cases (9-13). The collision carcinoma of the present patient was a metachronous tumor of the cervical esophagogastric anastomosis arising after surgical resection of thoracic esophageal carcinoma. A similar case could not be found in the literature, suggesting that this is an extremely rare collision carcinoma.

Méyer (14) has regarded collision carcinoma as one of the subtypes of multiple neoplasms; in 1919 he defined it as a single mass composed of two or more independent tumors

that have arisen at a single site, grown into contact with each other and then merged. The diagnostic criteria for collision carcinoma according to Spagnolo and Heenan (8) include the following three features: (i) two topographically separate sites of origin for the different tumor components; (ii) at least some separation of the two tumors, despite intimate mixing at points of juxtaposition, so that a dual origin can still be recognized; (iii) at the sites of collision, in addition to intimate mixing of the two components, some transitional patterns may be acceptable, such as a mucoepidermoid appearance in the case of collision between squamous carcinoma and adenocarcinoma.

However, Dodge (15) had a different view from Spagnolo and Heenan (8) and only defined tumors without any histological transition between the two components as true collision carcinoma. In our patient, the two components were distinct without any histologically demonstrable morphological transition at the site of collision. This lesion satisfied the more strict criteria and, thus, can be considered a true collision carcinoma.

Immunohistochemical staining is a technique that has previously been used to demonstrate that two parts of a collision carcinoma are independent (16). In our patient, p53 staining was positive in the squamous cell carcinoma, whereas HER2 staining was positive in the adenocarcinoma. In other

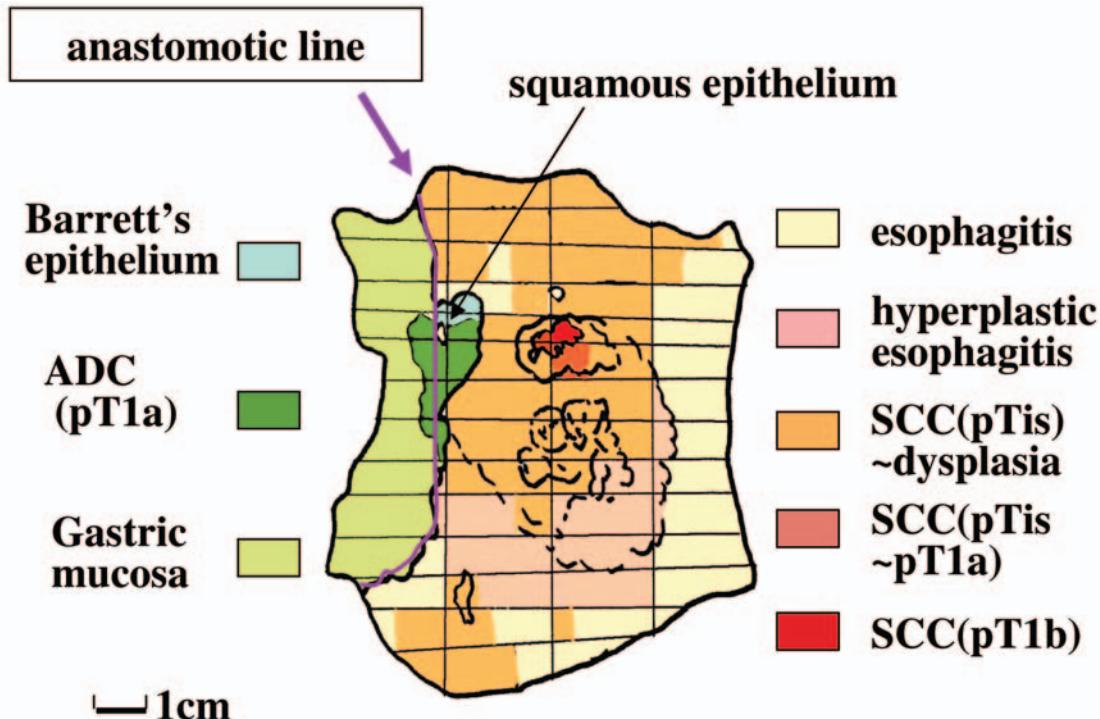


Figure 6. Diagram of the collision carcinoma based on the histological findings. Squamous cell carcinoma (SCC; sm2) is seen on the esophageal side of the anastomotic line. On the gastric tube side, adenocarcinoma (ADC; m3) arises from Barrett's epithelium, which forms a tongue-shaped extension of columnar epithelium across the anastomotic line to the esophageal side.

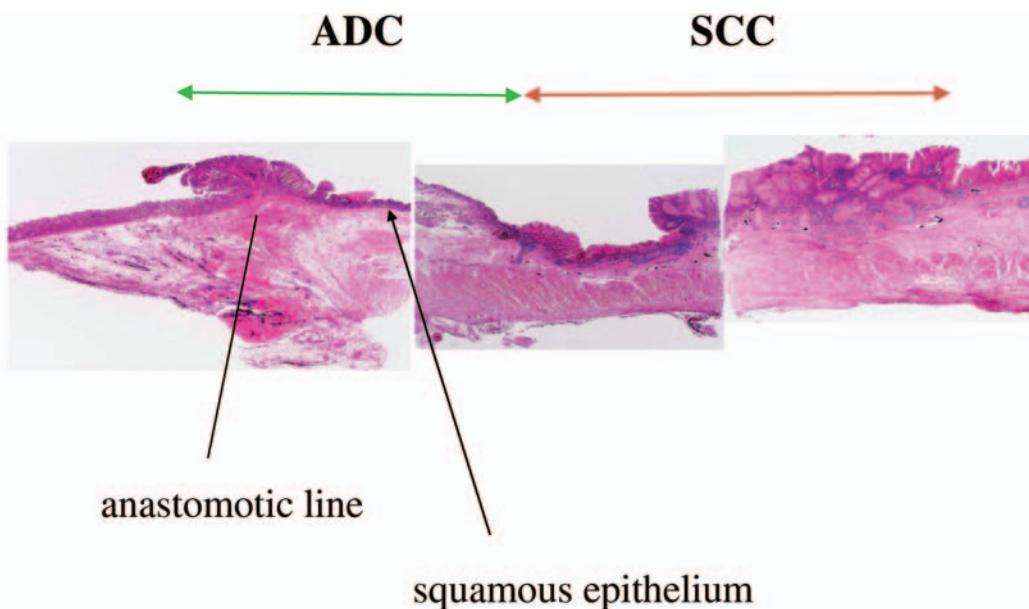


Figure 7. Squamous cell carcinoma (SCC) and adenocarcinoma (ADC) are contiguous with an obvious border between them. There is no morphological transition. Neither tumor involves the vascular system.

words, these two components had a different origin and were independent at the molecular biology level. Consequently, the expression of cancer-related genes by these tumors also supported our diagnosis of collision carcinoma.

Esophageal adenocarcinoma has been reported to arise from a background of Barrett's epithelium. Reflux esophagitis is considered to be related to the development of Barrett's epithelium at the esophagogastric junction (17-

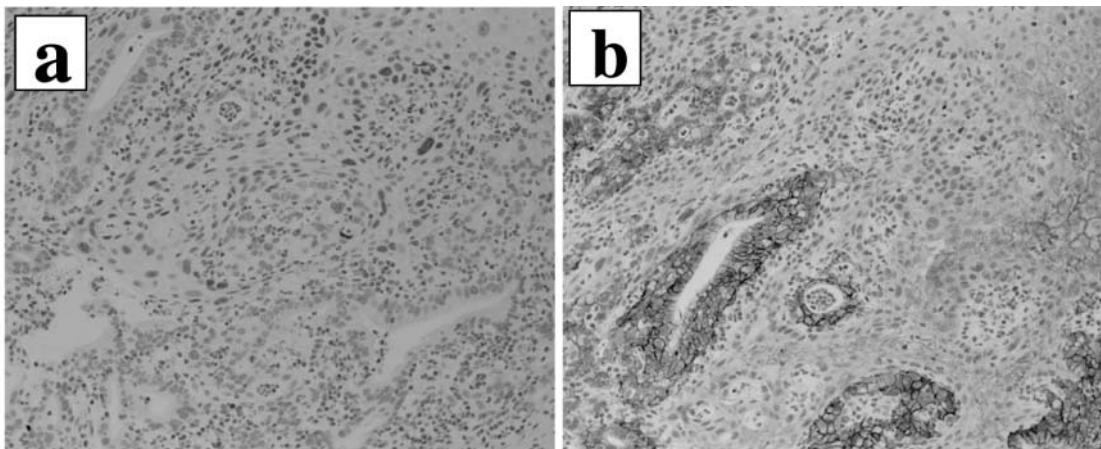


Figure 8. Immunohistochemical staining shows (a) that the squamous carcinoma cells are positive for p53, whereas the membranes of the adenocarcinoma cells are positive for HER2 (b).

19). According to Ide *et al.*, who have reviewed 181 patients after surgery for esophageal carcinoma, 18% had reflux esophagitis, reflux esophagitis ulcers, or Barrett's epithelium in the residual esophagus (4). In the present patient, Barrett's epithelium was recognized around the adenocarcinoma on the esophageal side of the anastomosis. Gastroesophageal reflux persisting for more than 20 years presumably caused Barrett's epithelium to arise in the residual esophagus. Further chronic inflammatory stimulation (by gastric juice or other factors) of this Barrett's epithelium, as well as the esophageal epithelium, may then have led to carcinogenesis.

As a rule, collision carcinomas like the tumor in this case should be surgically resected, if possible. The present lesion was easy to resect, but reconstruction posed problems. Anastomosis of the remnant gastric tube (which should have been freed in advance) to the short esophageal segment left after cervical esophagectomy was initially thought to be the procedure of choice. Because a retrosternal approach had been chosen for reconstruction after esophagectomy 27 years earlier, however, the gastric tube could not be freed easily without longitudinal division of the sternum. Taking the high risk of failure of the sutures and possible inhalation of food due to the high-level anastomosis into consideration, gastroesophageal continuity was instead restored by insertion of a free jejunal graft with microsurgical vascular anastomosis (20, 21). The patient's postoperative course was not complicated by anastomotic leakage, stenosis at the anastomosis, or difficulty in swallowing. Since free jejunal transfer was effective in this case, although reconstruction after cervical esophagectomy seems likely to be difficult, this procedure is a reasonable choice.



Figure 9. There has been no evidence of recurrence and no dysphagia for 18 months after surgery (arrow).

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