

## Case Report: A Young Woman with Advanced Esophageal Cancer Showing Pathological Complete Response to Neoadjuvant Chemotherapy (CDDP, 5-FU and ADM)

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**Abstract.** A 32-year-old woman was admitted to our hospital with dysphagia. An upper gastrointestinal series revealed Borrmann type 2 esophageal cancer in the lower thoracic esophagus. Because direct invasion of the thoracic aorta was suspected, FAP therapy (CDDP, 5-FU and ADM) was given as neoadjuvant chemotherapy. After completion of two courses, her dysphagia resolved and the tumor shrank by over 90%, so radical surgery was performed. No lesions were found when the resected specimen was examined macroscopically. The only histological change was hyperplasia of collagen fibers in the submucosa, lamina propria and adventitia of the esophagus. No cancer cells and no metastases to the lymph nodes were observed. Because the tumor had completely disappeared, the histological effect of chemotherapy was classified as grade 3, i.e., pathological complete response (PCR). The response to FAP therapy was excellent and no serious adverse events occurred. Therefore, this is one of the treatments that should be actively applied in patients who have advanced esophageal cancer with suspected lymph node metastasis and invasion of other organs.

Multimodal therapy that combines adjuvant chemotherapy and radiotherapy is necessary to improve the results of treatment for esophageal cancer (1). Since 1994, we have used cisplatin(CDDP)/5-fluorouracil(5-FU) therapy as neoadjuvant chemotherapy for advanced esophageal cancer in patients for whom radical surgery is difficult. In recent years, FAP therapy, i.e. CDDP, 5-FU and adriamycin (ADM), has been employed to improve the response rate.

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We recently experienced a case of advanced esophageal cancer in a young woman in whom the tumor disappeared completely after FAP therapy, i.e., a pathological complete response (PCR) was obtained. This case is reported here with some discussion of the literature.

### Case Report

The patient was a 32-year-old woman with dysphagia as the chief complaint. She had no history of smoking or alcohol consumption and nothing remarkable in her family history. From around July 2002, she noticed mild dysphagia. The dysphagia became more severe from January 2003 and she visited a local clinic where esophageal cancer was diagnosed by endoscopy. She was then referred to our department. She was 160 cm tall, weighed 54 kg and her nutritional status was moderate. Physical examinations on admission did not show any abnormalities.

All laboratory studies, including liver function tests, were normal. When tumor markers were examined, carcinoembryonic antigen (CEA) was within the normal range (0.5 ng/mL) and squamous cell carcinoma-related antigen (SCC) was slightly elevated (1.8 ng/mL). On plain chest X-ray films, no abnormalities were found in the lung fields, bone, soft tissues and cardiac shadow. Esophagography revealed an elevated lesion with a long diameter of 6 cm and a shallow indentation in the center that covered about two-thirds of the circumference of the esophagus (Figure 1a). On endoscopy, a lesion with a shallow ulcer in the center and a ridge around it was detected at 34 cm to 40 cm from the incisors (Figure 2a). From these findings, Borrmann type 2 advanced esophageal cancer was diagnosed. Histological examination of the endoscopic biopsy specimen demonstrated moderately-differentiated squamous cell carcinoma (Figure 3). CT of the thoracoabdominal region showed circumferential hypertrophy of the wall of the lower esophagus. Direct invasion of the tumor (T4) into the thoracic aorta was suspected due to extensive contact (Figure 4a). No

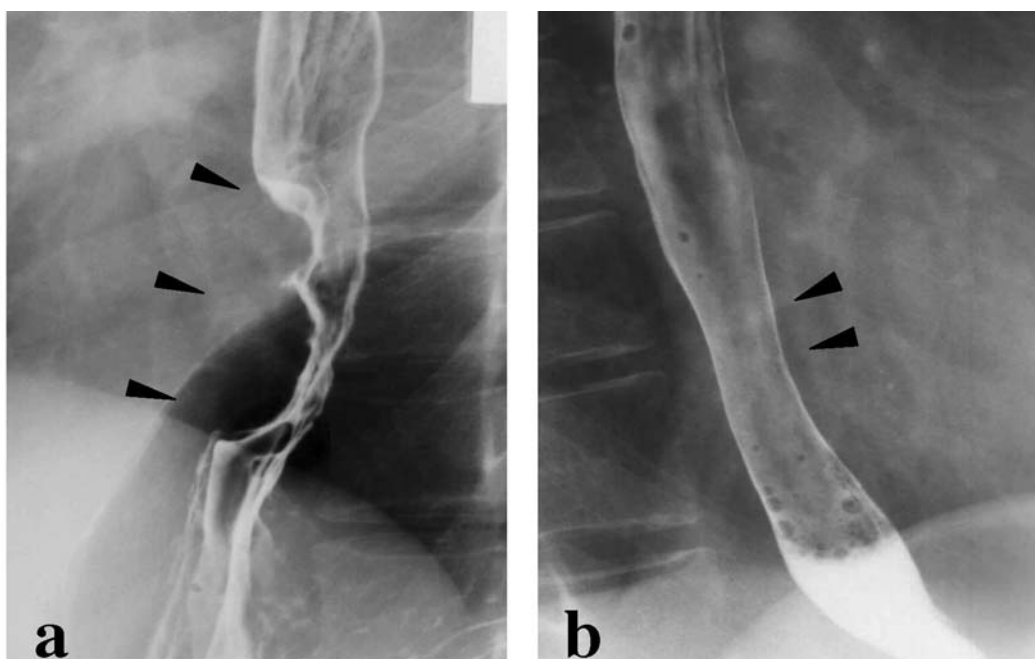


Figure 1. Esophagography. a. An elevated lesion with a shallow indentation in the center of the lower thoracic esophagus is seen before chemotherapy (arrowhead). b. After chemotherapy, the tumor has been reduced in size by more than 90% (arrowhead).

obvious enlargement of the mediastinal or peritoneal lymph nodes was seen and no distal metastases were found in the lungs or liver. From the above findings, T4, N(-), P0, M(-), stage III esophageal cancer was diagnosed.

Because direct invasion of the aorta was suspected, FAP therapy was given as neoadjuvant chemotherapy. The regimen consisted of a 24-hour intravenous infusion of 5-FU (750 mg/day) on days 1-5, a 2-hour intravenous infusion of CDDP (20 mg/day) also on days 1-5, and an intravenous injection of ADM (30 mg) only on day 1. This regimen was followed by a 2-week washout period. Each course lasted for 3 weeks and two courses were performed. On completion of the two courses, her dysphagia resolved. Adverse events included gastrointestinal symptoms such as anorexia and grade 2 leucopenia. On repeat esophagography after chemotherapy, the tumor was seen to have decreased by more than 90% in size (Figure 1b). Endoscopy showed that the ridge around the tumor had become flat and the ulcer was covered with regenerated epithelium (Figure 2b). On chest CT, hypertrophy of the esophageal wall showed marked improvement (Figure 4b). Accordingly, the tumor was considered to be resectable at this time with chemotherapy achieving partial response (PR) or better, so surgery was performed. In April 2003, she underwent mini-thoracotomy and 3-field dissection of lymph nodes in the neck, chest, and abdomen based on the method of Ide *et al.* (2) for esophageal cancer. This achieved a better cosmetic outcome since the patient was a young woman. Macroscopic examination of the resected specimens showed disappearance of the tumor ridge and the ulcer covered with regenerated

epithelium, and no residual lesion could be found (Figure 5). Histopathologically, there was hyperplasia of collagen fibers in the submucosa, lamina propria and adventitia of the esophagus, but no cancer cells or metastases were found (Figure 6 a, b). The tumor had disappeared completely and the histological effect of chemotherapy was rated as grade 3 (*i.e.*, PCR). The patient's postoperative course was good and she was discharged after one additional course of adjuvant chemotherapy using the same regimen. At 10 months postoperatively, recurrence has not occurred.

The clinicopathological features of esophageal cancer, the response to chemotherapy and the histological effect were assessed according to the General Rules for Esophageal Cancer Studies (3), while adverse events were classified by National Cancer Institute Common Toxicity Criteria (NCI-CTC).

## Discussion

In Japan, more than 90% of esophageal cancer patients have squamous cell carcinoma and many of them are elderly men aged 60 years or older. In fact, esophageal cancer arising in young women in their early thirties, as in the present case, only accounts for 0.1 to 0.3% (4) and thus is quite rare.

The etiology of esophageal cancer is still uncertain, but epidemiological studies have suggested that environmental factors such as smoking, alcohol consumption and long-term exposure to chemicals play a role. In addition, anomalies of genes such as p53 have been found in esophageal cancer, especially in the tumors of younger patients (5).

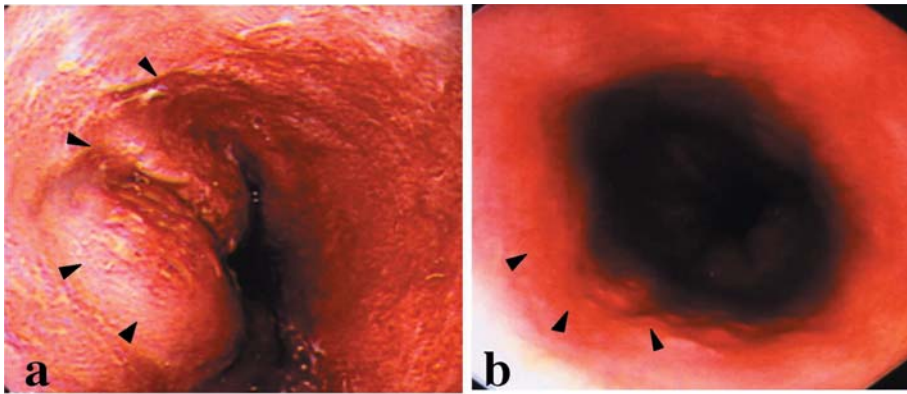


Figure 2. Esophagoscopy. a. A lesion with a shallow ulcer in the center and a surrounding ridge is observed before chemotherapy (arrowhead). b. After chemotherapy, the ridge has been flattened and the ulcer is covered with regenerated epithelium (arrowhead).

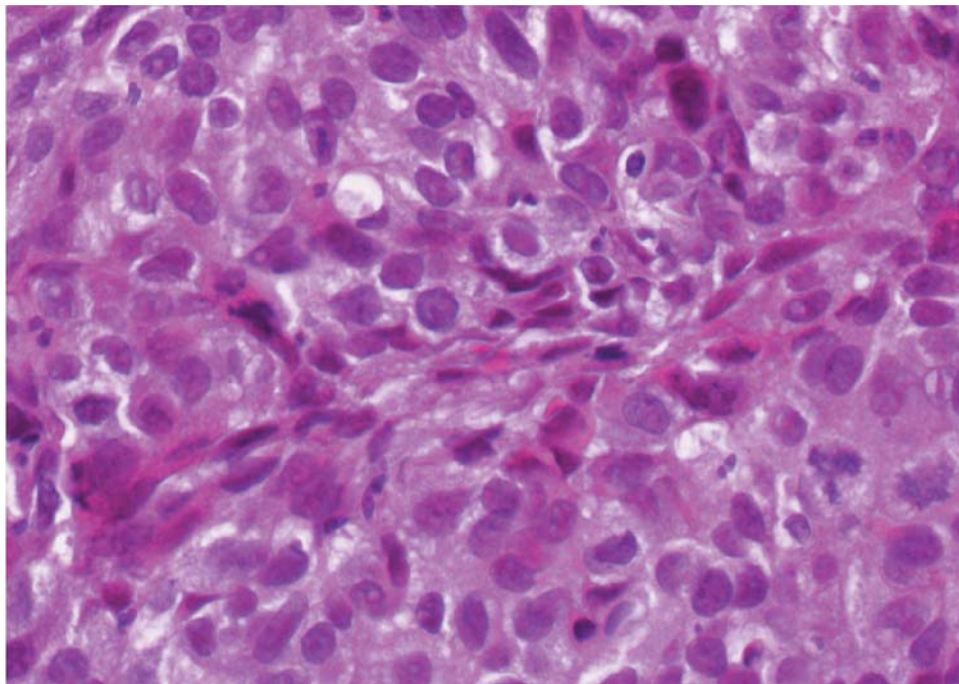


Figure 3. Microscopy of the endoscopic biopsy specimen before chemotherapy. The histological diagnosis was moderately-differentiated squamous cell carcinoma (H-E).

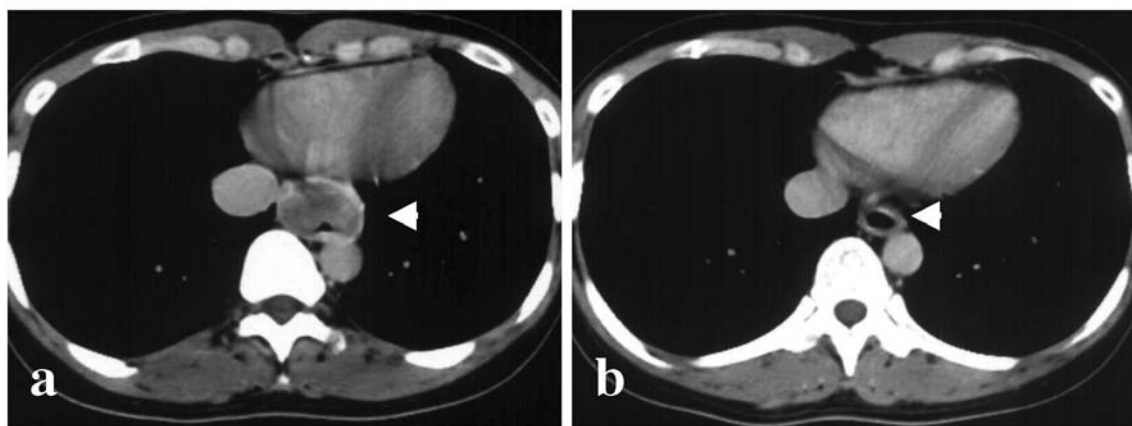


Figure 4. CT scanning. a. In the lower esophagus, almost circumferential hypertrophy of the wall is observed. Direct invasion of the thoracic aorta was suspected because of extensive contact with the tumor (arrow). b. Hypertrophy of the esophageal wall has improved markedly (arrow).



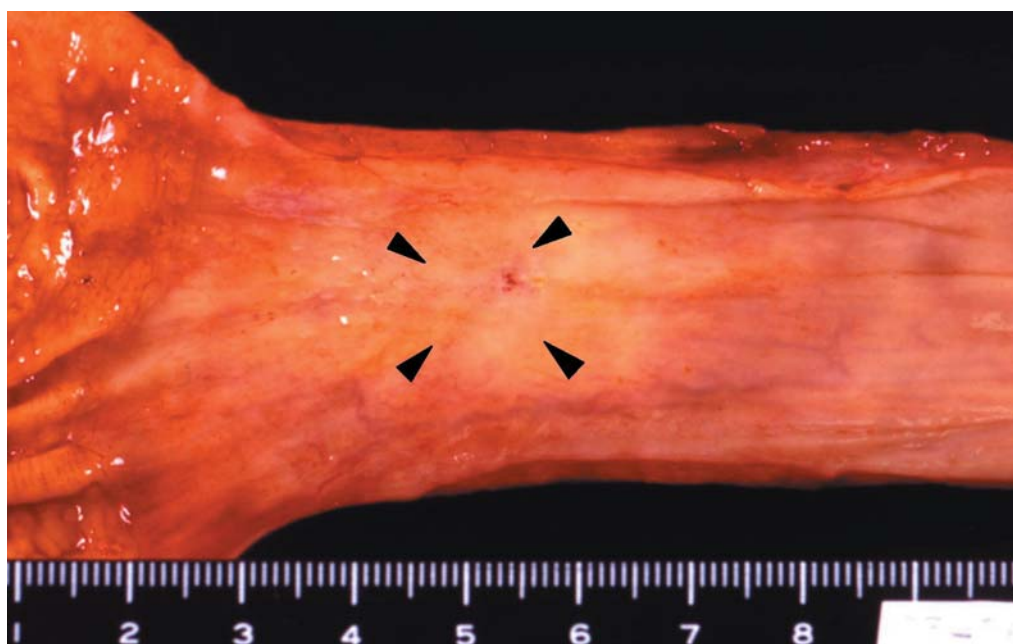


Figure 5. Macroscopic findings of the resected specimen. The ulcer is covered with regenerated epithelium and no tumor lesion is observed (arrowhead).

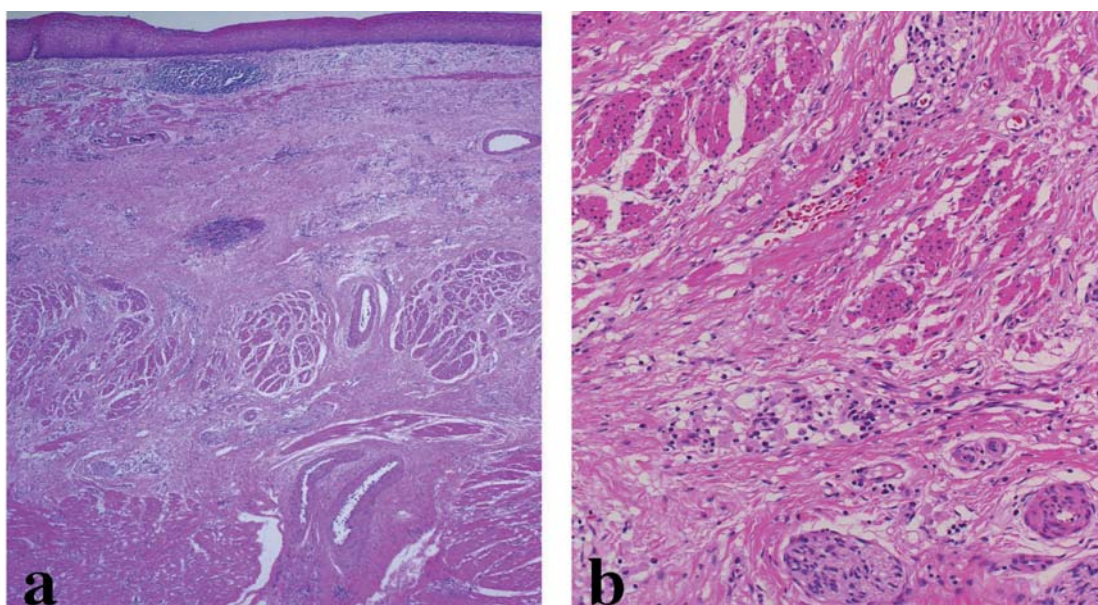


Figure 6. Histological findings of the resected specimen. a. There is hyperplasia of fibrous tissue in the submucosal layer, lamina propria and adventitia (H-Ex4) b. No cancer cells can be seen(H-Ex40).

The objective of neoadjuvant chemotherapy is to reduce the size of the primary lesion and control lymph node metastasis and micrometastasis to achieve down-staging so that a better result can be expected when surgical resection is performed (1). Another advantage of such treatment is that the effects of anticancer agents can be assessed both by imaging and by histopathological examination of the resected specimen. Disadvantages include the occurrence of tolerance and an

increased incidence of postoperative complications due to myelosuppression. When therapy is ineffective, progression of the primary tumor may be accelerated. The present patient was suspected of having invasion of the thoracic aorta (T4) based on preoperative imaging data and radical resection was considered difficult. Therefore, FAP therapy was given as neoadjuvant chemotherapy. Because the response was very good, down-staging was achieved and radical resection became possible.

Anticancer agents that show efficacy against esophageal squamous cell carcinoma include bleomycin (BLM), mitomycin C (MMC), CDDP, vindesine (VDS), methotrexate (MTX), 5-FU and paclitaxel (TXL) (6). However, CR is rarely achieved with monotherapy (7) and combination therapy is employed in most cases. The main combined regimens are BLM/CDDP/VDS and CDDP/5-FU, but the latter is most widely used at present. We have performed neoadjuvant chemotherapy using CDDP/5-FU since 1994 to treat advanced esophageal cancer with invasion of other organs and/or extensive lymph node metastasis on preoperative imaging for which radical resection is difficult, and the response rate was 40% (8). FAP therapy (ADM added to CDDP/5-FU) was introduced from 1998 to improve the response rate.

In 1983, Gisselbrecht *et al.* (9) reported a response rate of 33% to FAP therapy in patients with advanced esophageal cancer, but reports in Japan only appear from the 1990s. Yasuda *et al.* (10) applied this therapy to treat locally advanced esophageal cancer and reported a very high response rate of 70%, while CR has also been reported with FAP therapy (11). In the present patient, 90% tumor shrinkage was observed on imaging after two courses of this treatment and postoperative histopathological examination showed that the tumor had disappeared completely (*i.e.*, PCR was achieved). These results support the usefulness of this regimen as neoadjuvant chemotherapy.

The effect of neoadjuvant chemotherapy or various types of surgical treatment on the prognosis has been studied to determine whether extension of survival can be achieved. Kok *et al.* (12), Clark (13) and other investigators obtained a significantly better prognosis in patients responding to neoadjuvant chemotherapy than in non-responders and patients treated with surgery alone (14-16). Therefore, a good prognosis can be expected if down-staging is achieved, as happened in the present case.

Based on the above results, use of FAP therapy as neoadjuvant chemotherapy achieves a high response rate with few serious adverse events (17). Therefore, it should be performed in patients with advanced esophageal cancer who have suspected lymph node metastasis and/or invasion of other organs.

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