Occult Lung Cancer Incidentally Found during Surgery for Esophageal and Gastric Cancer: A Case Report

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Abstract. *A 70-year-old male was admitted to our hospital because of advanced esophageal squamous cell carcinoma and early gastric adenocarcinoma. A esophagectomy and partial gastrectomy with three-field lymph node dissection (neck, mediastinum and abdomen) was performed. Both tumors had lymph node metastases. In addition, three mediastinal lymph nodes (two subcarinal lymph nodes and a middle thoracic paraesophageal lymph node) were involved with adenocarcinoma. To elucidate whether they were metastases from the gastric cancer, an immunohistochemical analysis was performed. The cancer cells in these lymph nodes were positive for cytokeratin (CK) 7 and negative for CK 20, thus suggesting metastasis from a nondigestive organ. Interestingly, they were positive for thyroid transcription factor 1 (TTF-1), indicating metastasis from a lung cancer. Since the preoperative computed tomographic scan showed no evidence of lung cancer, a diagnosis of metastases from an occult lung cancer was finally recorded. Ten months after surgery, the patient was alive without a recurrence or the appearance of a lung cancer.*

A metastatic cancer from an unknown primary site is known as an occult cancer. It is reported that the frequency of metastatic cancer from an unknown primary site is approximately 0.5% to 5% (1-4). We recently encountered a case of occult lung cancer incidentally found during surgery for advanced esophageal cancer and early gastric cancer with lymph node metastases.

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Case Report

The patient was a 70-year old male who had suffered from dysphagia for one month. He was admitted to our hospital in October 2006. He had smoked for fifty years and drunk alcohol for forty years. He was on medication for arteriosclerosis obliterans, but had no history of cancer. His hematological data on admission were as follows: white blood cell $8600\times10^2/\mu L$, hemoglobin 15.0 g/dL, C reactive protein (CRP) 0.28 mg/dL, total protein 6.9 g/dL, albumin 4.4 g/dL, glutamic oxaloacetic transaminase (GOT) 15 IU/L, glutamic pyruvic transaminase (GPT) 10 IU/L, total bilirubin 0.8 mg/dL, blood urea nitrogen (BUN) 9.9 mg/dL and creatinine 0.64 mg/dL, and tumor markers were as follows: carcinoembryonic antigen (CEA) 2.4 ng/μL, squamous cell carcinoma related antigen (SCC) 1.3 ng/μL, cytokeratin 19 fragment (CYFRA 21-1) 1.3 ng/μL. All the laboratory data, including the tumor markers, were within the normal limit. On chest X-ray, no abnormality was found in the lung fields, bones, soft tissues and cardiac shadows.

Esophagography showed an irregular elevated lesion measuring 5 cm in longitudinal diameter with a shallow indentation on the top at the lower thoracic esophagus (Figure 1).

Endoscopy revealed a type 2 tumor located on the right posterior wall of the lower thoracic esophagus, 34-38 cm from the incisors (Figure 2a). Simultaneously, the endoscopy revealed a slightly depressed lesion which was not stained with iodine located at the middle thoracic esophagus, at around 25-30 cm from the incisors (Figure 2b). The pathological studies of the biopsy specimens of both lesions proved them to be squamous cell carcinoma. Furthermore, endoscopy revealed an irregular ulcerative lesion at the lesser curvature of the antrum (Figure 2c). Its pathological analysis revealed adenocarcinoma.

The chest computed tomography (CT) scan showed an irregular wall thickening at the lower esophagus and enlarged

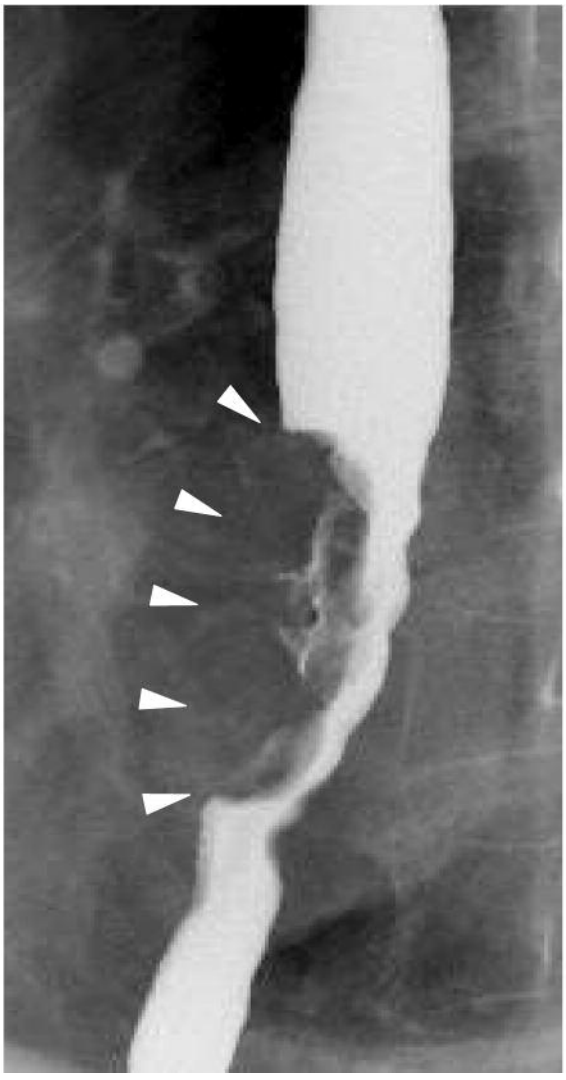

Figure 1. *Esophagography showing an elevated lesion with a shallow indentation on the top on the posterior wall of the lower thoracic esophagus (arrow head).*

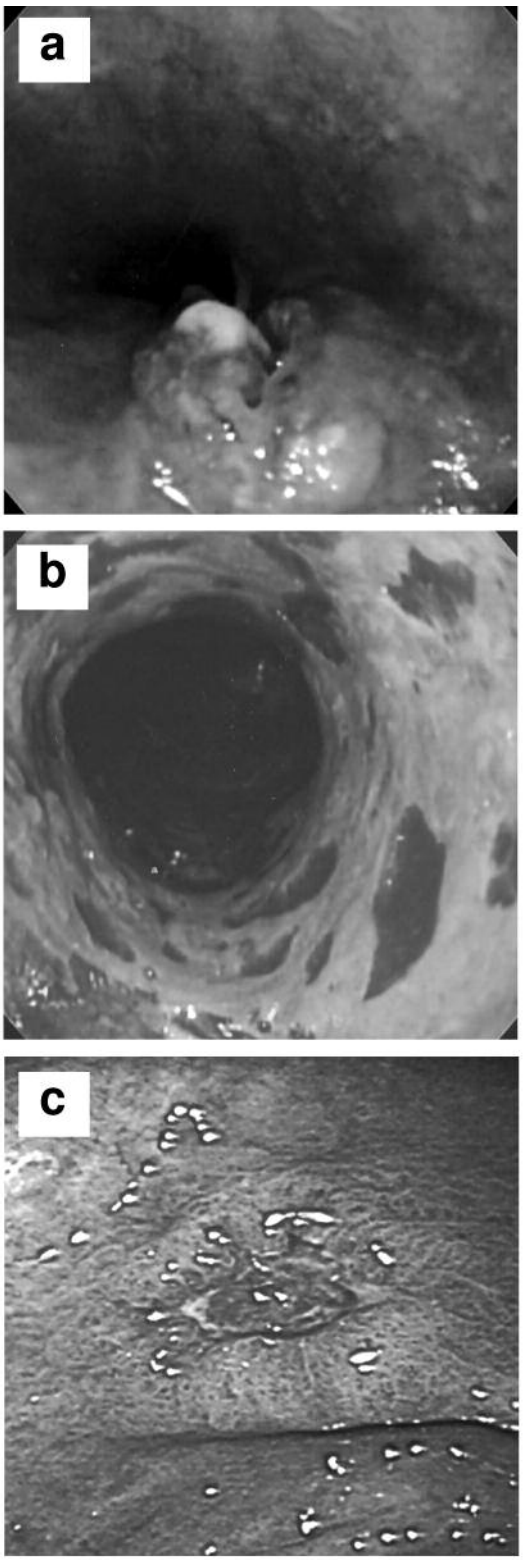

Figure 2. *Endoscopic findings: a. A type 2 esophageal tumor on the posterior wall of the lower thoracic esophagus, 34-38 cm from the incisors. b. A slightly depressed lesion which was not stained with iodine in the middle thoracic esophagus. c. An irregular ulcerative tumor at the lesser curvature of the antrum.*

lymph nodes at the right recurrent nerve and the subcarina (Figure 3a,b,c). There were no primary or metastatic tumors in the lung fields (Figure 3d). The neck and abdominal CT scans showed no metastatic sites.

Preoperatively, advanced esophageal cancer (T3, N1, M0, Stage III), early esophageal cancer (T1, N0, M0 Stage I), and early gastric cancer (T1, N0, M0, Stage IA) were diagnosed. An esophagectomy and partial gastrectomy with three-field lymph node dissection (neck, mediastinum, and abdomen) was performed. The surgical reconstruction was performed using a gastric tube. A gastric tube with a vascular pedicle of the right gastroepiploic artery was interposed between the cervical esophagus and the jejunum through the pre-sternal route.

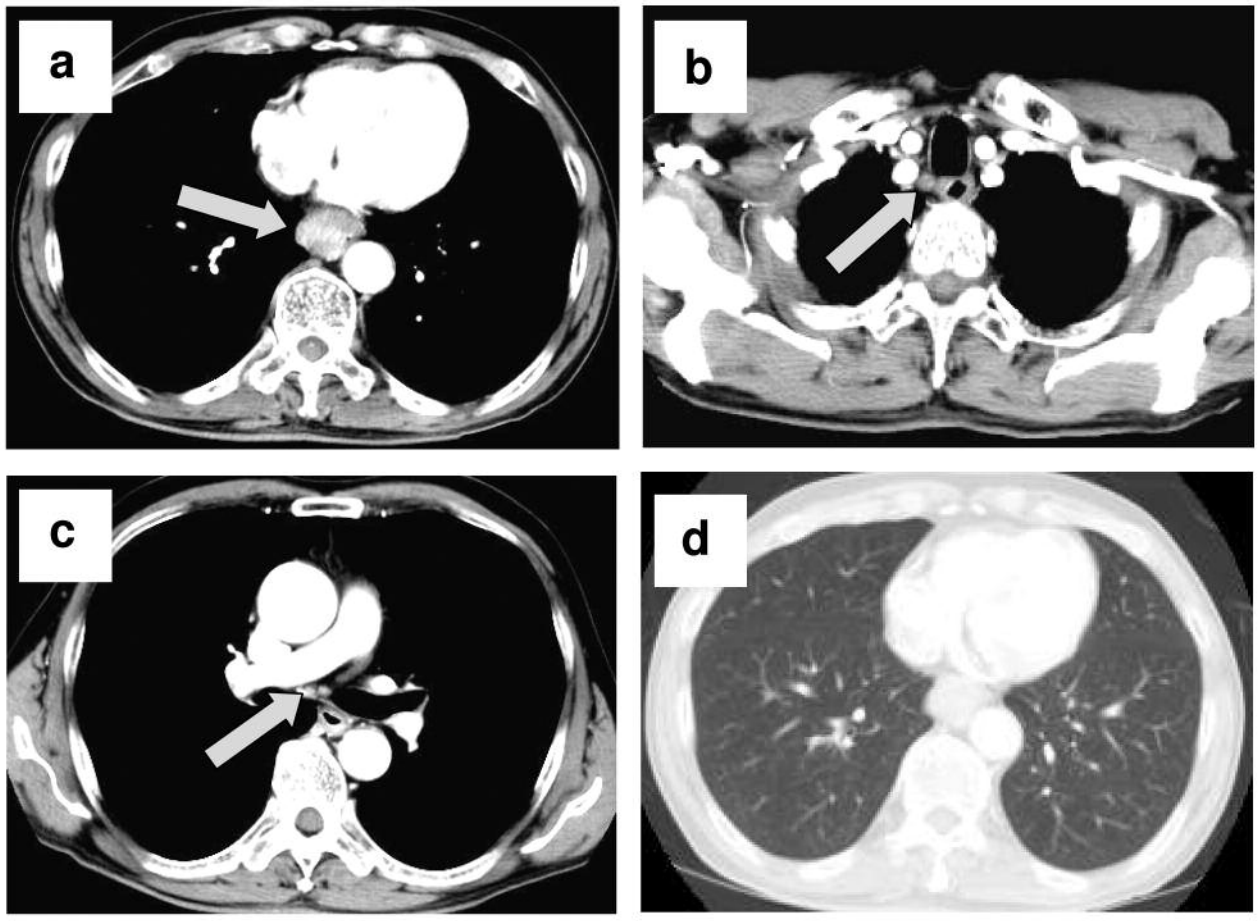

Figure 3. *Chest computed tomography (CT): a.b.c. The chest CT showing irregular wall thickening in the lower esophagus (arrow, a) and enlarged lymph nodes at the right recurrent nerve (arrow, b) and the subcarina (arrow, c). d. No primary or metastatic tumor evident in the lung fields.*

Macroscopicaly, the resected specimen showed a 46 mm × 30 mm type 2 tumor in the lower esophagus (Figure 4a), a 22 mm × 19 mm slightly depressed lesion in the middle thoracic esophagus (Figure 4b), and an irregular ulcerative lesion on the lesser curvature of the antrum (Figure 4c).

The microscopic examination of the type 2 tumor of the lower esophagus revealed a well differentiated squamous cell carcinoma (Figure 5a, b), and its depth was T3 (tumor invaded the adventitia), and that of the depressed lesion of the middle esophagus revealed a carcinoma *in situ*. Two lymph nodes (a right recurrent nerve lymph node and a lymph node along the lesser curvature) were involved with squamous cell carcinoma (Figure 5c, d). The pathological stages of the esophageal carcinomas were Stage III and Stage 0. The microscopic examination of the gastric cancer at the antrum revealed a poorly differentiated adenocarcinoma and massive invasion into the submucosal layer (Figure 6a, b). Two lymph nodes along the left gastric artery were involved with adenocarcinoma (Figure 6c). Each of the metastatic cancer cells in the lymph nodes along the left gastric artery had a hyperchromatic nucleus and clear cytoplasm (termed signet-ring cell). These cells closely resembled the cancer cells in the primary gastric cancer of the antrum. It appeared that they were metastases of the gastric cancer. Consequently, the pathological stage of the gastric cancer was Stage IB. However, three mediastinal lymph nodes (two subcarinal lymph nodes and a middle thoracic paraesophageal lymph node) were also involved with adenocarcinoma, and consisted of papillary structures (Figure 6d). These cells also had basophilic cytoplasm. These findings were quite different from those of the primary gastric cancer.

To elucidate whether the mediastinal lymph nodes involved with adenocarcinoma were metastases of the gastric cancer, immunohistochemical analysis was conducted. The cancer cells in the primary gastric cancer were negative for cytokeratin (CK) 7 and partially positive for CK 20 (Figure 7a, b). The cancer cells in the mediastinal

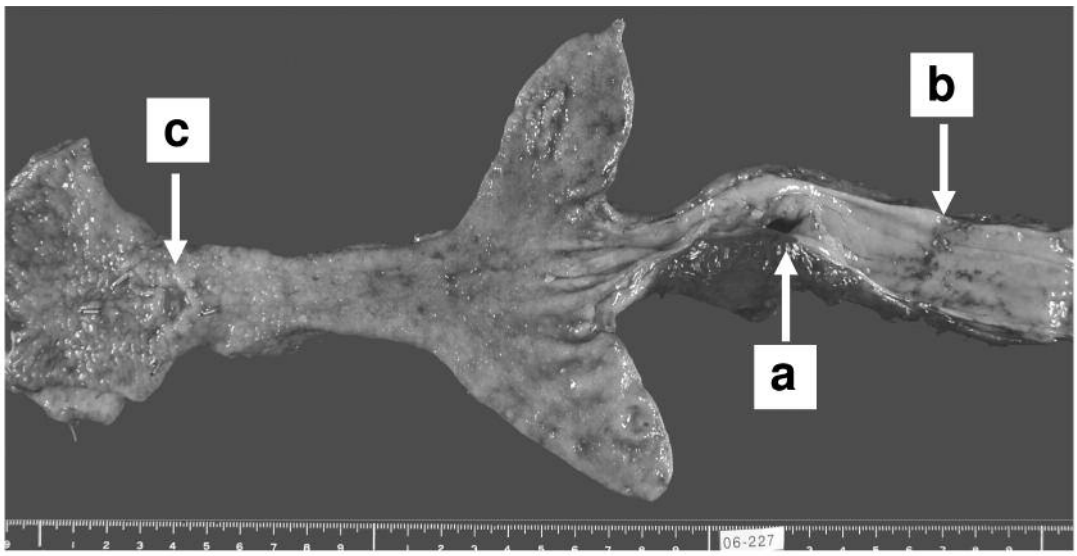

Figure 4. *Macroscopic findings: a. A 46 mm x 33 mm type 2 tumor in the lower esophagus (arrow). b. A 22 mm x 19 mm slightly depressed lesion in the middle esophagus (arrow). c. An irregular ulcerative lesion on the lesser curvature of the antrum (arrow).*

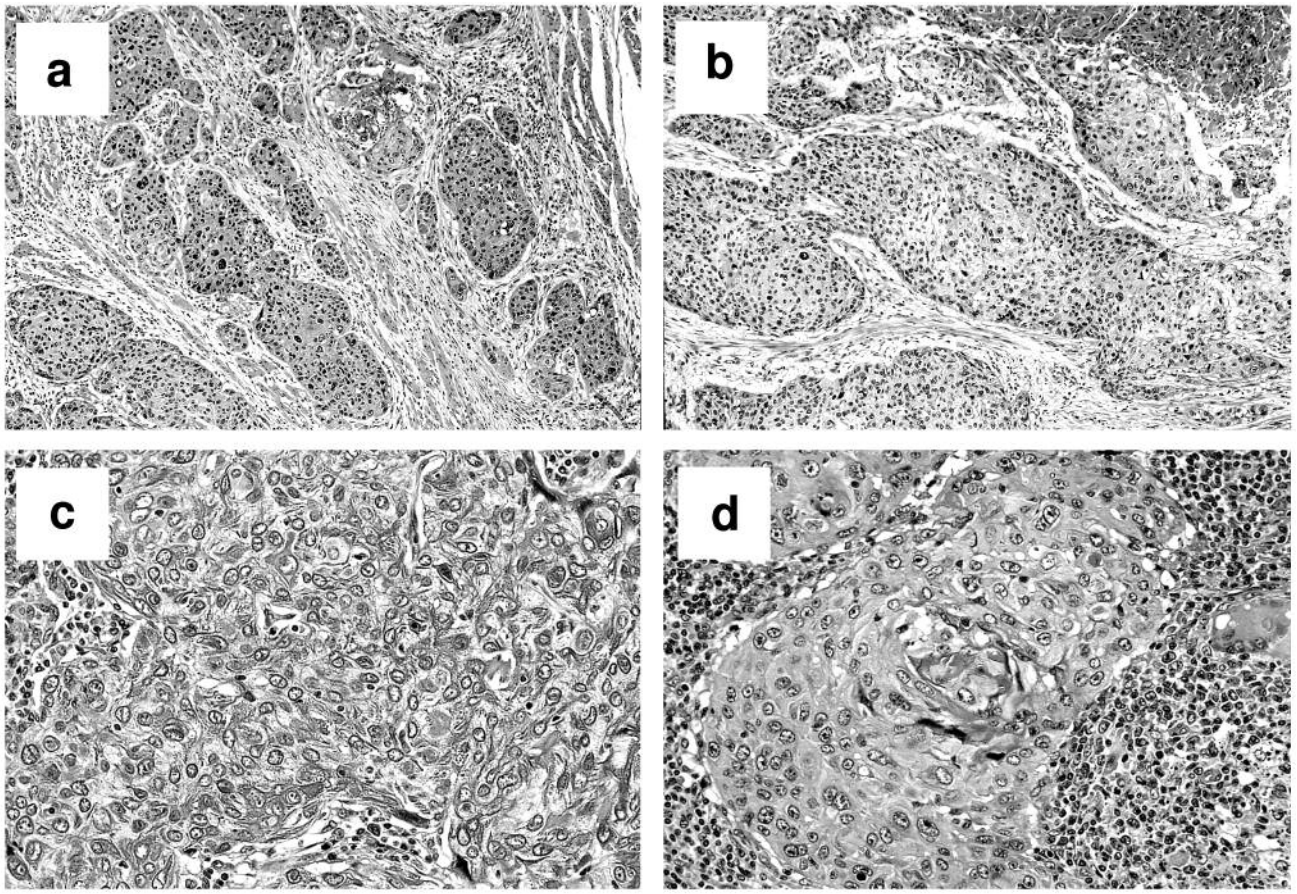

Figure 5. *Microscopic findings: a.b. Esophageal type 2 tumor showing a well differentiated squamous cell carcinoma with a proliferation of collagenous fiber in the stroma. (HE, x100, a), (×200, b). Metastases of squamous cell carcinoma c. in a right recurrent nerve lymph node (×200) and d. in a lymph node along the lesser curvature (×200).*

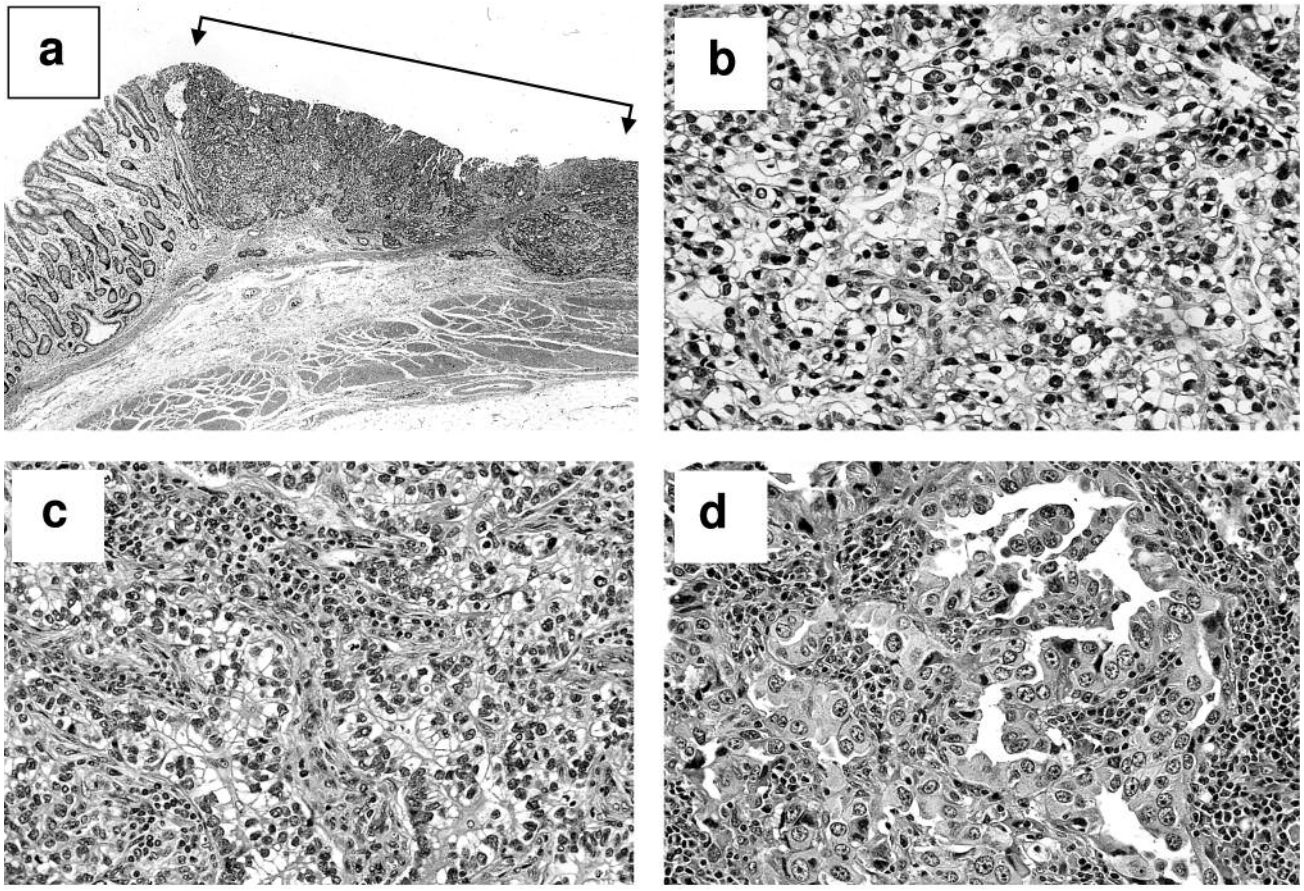

Figure 6. *Microscopic findings of gastric cancer in the antrum: a. Massive invasion of the gastric cancer cells into the submucosal layer, indicated by arrows (×40). b. The pathological findings show a poorly differentiated adenocarcinoma (×200). c. A lymph node along the left gastric artery showing a metastatic poorly differentiated adenocarcinoma (×200). d. The subcarinal lymph nodes involved with adenocarcinoma consisted of a papillary structure, and the character of these cells differed from that of the primary gastric cancer (×200).*

lymph nodes involved by adenocarcinoma were positive for CK 7 and negative for CK 20 (Figure 8a, b). These results showed that the mediastinal lymph nodes did not appear to be metastases from the digestive tract. Interestingly, almost all the cancer cells in the mediastinal lymph nodes were positive for thyroid transcription factor 1 (TTF-1) (Figure 8c). However, the primary gastric cancer was negative for TTF-1 (Figure 7c). There was no metastasis among the neck lymph nodes dissected during the operation. It was considered that the adenocarcinoma cells in the mediastinal lymph nodes originated from a lung adenocarcinoma. However, the preoperative chest X-ray and chest CT scan showed no suspicious lesions in the lung fields. Consequently, the mediastinal lymph nodes were diagnosed finally as metastases of an occult lung cancer. The patient's postoperative course was uneventful. One month after surgery, 5-fluorouracil (5-FU), cisplatin and adriamycin were administered as adjuvant chemotherapy. He was discharged on postoperative day 42. After discharge, S-1 and docetaxel were administered as the second line chemotherapy. Ten months after surgery, the patient was alive and faring well without recurrence of the esophageal cancer. No tumor was found in his lung fields during careful follow-up evaluations.

Discussion

In occult cancer, the common metastatic lesions are lung, lymph node, bone or liver (2, 4, 5). In regard to lymph nodes, the most common metastatic site is a cervical lymph node (2, 4, 5). Metastasis in the mediastinal lymph nodes is rare. Holmes and Fouts reported that there were only nine cases of metastases in a mediastinal lymph node among 686 cases of occult cancer (4). Our case differed from the previously reported cases in the existence of other primary malignancies at the same time. In most cases reported previously, there were no primary carcinomas except for the lymph node metastases (6-9). In our case, the metastatic mediastinal

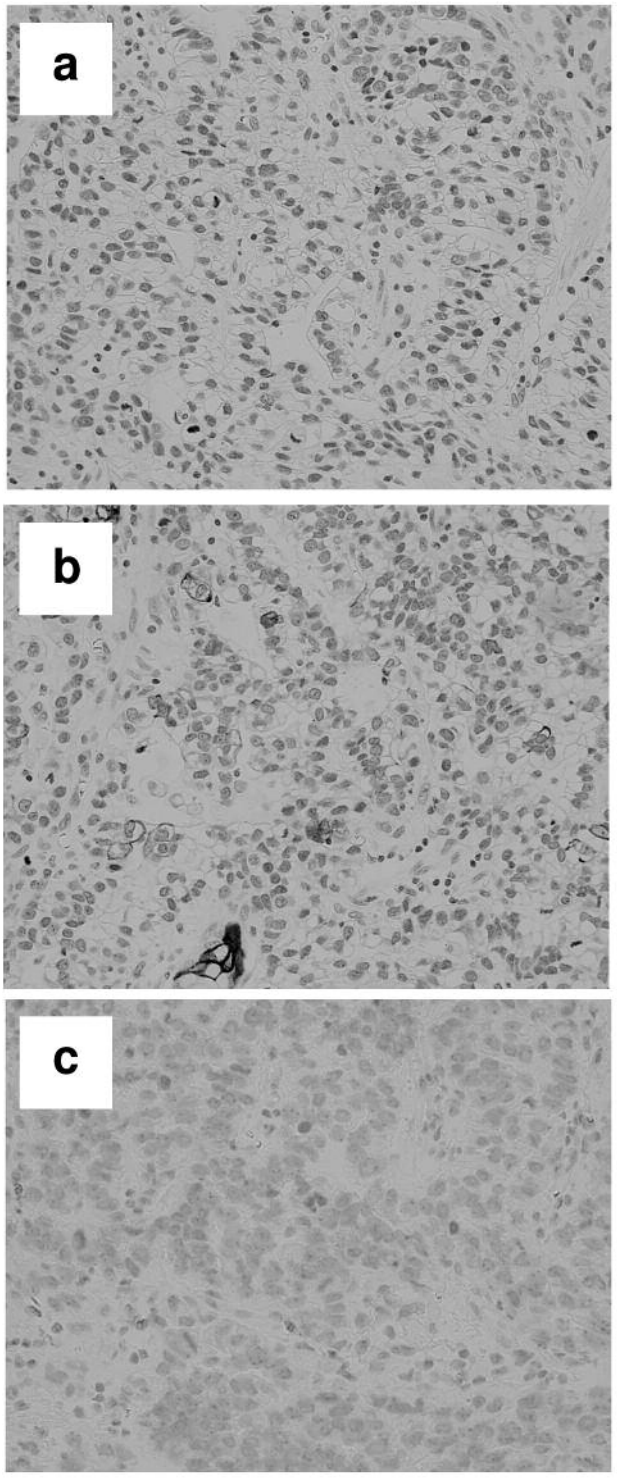

Figure 7. *Immunohistochemical staining of the primary gastric cancer: Primary gastric cancer cells a. negative f or CK 7 (×200), b. partially positive for CK 20 (×200) and c. negative for TTF-1 (×200).*

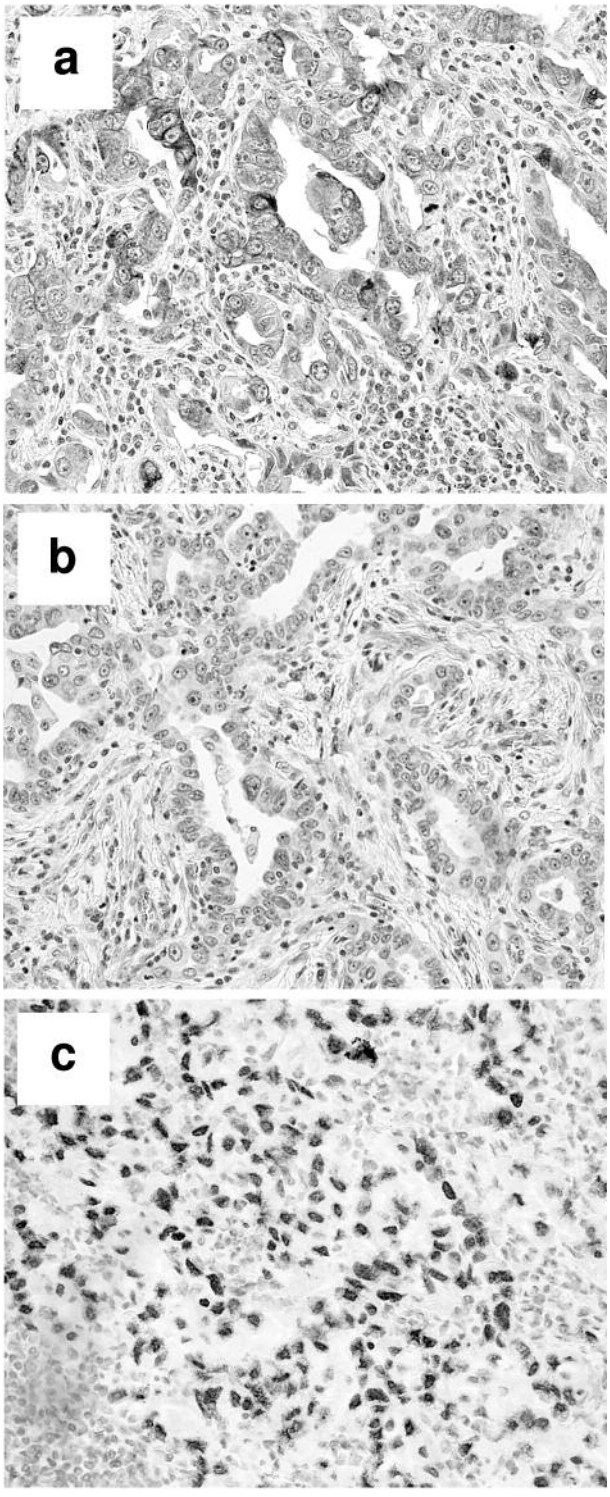

Figure 8. *Immunohistochemical staining of the subcarinal lymph nodes: Adenocarcinoma cells in the subcarinal lymph nodes a. positive for CK 7 (×200), b. negative for CK 20 (×200) and c. strongly positive for TTF-1 (×200).*

lymph nodes contained metastases of squamous cell carcinoma and adenocarcinoma at the same time. However, the character of the adenocarcinoma cells in the mediastinal lymph nodes differed from that of the primary gastric cancer and abdominal metastatic lymph nodes. The mediastinal lymph node is not a regional lymph node of the stomach.

Immunohistochemical analysis is helpful in identifying the primary site of an occult cancer (6, 7). CK 7, a 54-kDa basic CK protein, is typically located in the epithelia of the lung, breast, endometrium, urothelium, thyroid, stomach and pancreatobiliary tract (6, 10, 11). CK 20, a 46-kDa basic protein, is predominantly located in the epithelia of the gastrointestinal and pancreatobiliary tract (6, 10, 11). TTF-1 is a member of the NKX-2 (homeobox protein NK-2) gene family containing nuclear transcription factor. TTF-1 is located selectively in thyroid follicular and parafollicular C cells, type II pneumocytes and the non-ciliated bronchiolar epithelium (Clara cell) of the lung (6, 10, 11). TTF-1 is a sensitive and specific marker to confirm a cancer of pulmonary and thyroid origin. In our case, the primary gastric cancer cells were negative for CK 7, partially positive for CK 20 and negative for TTF-1. On the other hand, the adenocarcinoma cells in the mediastinal lymph nodes were positive for CK 7, negative for CK 20 and almost all the cells were positive for TTF-1. These results showed that the mediastinal lymph nodes involved with adenocarcinoma were metastases from a lung adenocarcinoma or a thyroid cancer. The preoperative neck CT scan and the ultrasound examination revealed no abnormality in the thyroid gland. There was no metastasis in the neck lymph nodes dissected during the operation. Consequently, we finally diagnosed these lymph nodes as metastases of an occult lung cancer. Immunohistochemical staining of thyroglobulin might be helpful to distinguish a thyroid origin from a pulmonary origin.

Riquet *et al*. have reported that no malignant cell was found in 6 patients who underwent thoracotomy and lung resection for occult lung cancer (7). In our case, chemotherapy was administered and, if a primary lung cancer appears during follow-up, lung resection will be considered. There are several reports that positron emission tomography using fluorodeoxyglucose (FDG-PET) is useful for detecting an unknown primary site (12,13). Even if no primary tumor appears with CT scan during follow-up, FDG-PET or magnetic resonance imaging (MRI) may be useful for detecting these tumors.

References

1 Muir C: Cancer of unknown primary site. Cancer *75(Suppl 1)*: 353-358, 1995.

2 Didolkar MS, Fanous N, Elias EG and Moore RH: Metastatic carcinoma from occult primary tumors. Ann Surg *186*: 625-630, 1977.

3 Altman E and Cadman E: An analysis of 1539 patients with cancer of unknown primary site. Cancer *57*: 120-124, 1986.

4 Holmes FF and Fouts TL: Metastatic cancer of unknown primary site. Cancer 26: 816-820,1970.

5 Greager JA, Wood D and Das Gupta TK: Metastatic cancer from an undetermined primary site. J Sug Oncol *23*: 73-76, 1983.

6 Yoshino N, Yamauchi S, Hino M, Ohaki Y, Koizumi K and Shimizu K: Metastatic thoracic lymph node carcinoma of unknown origin on which we performed two kind of immunohistochemical examinations. Ann Thorac Cardiovasc Surg *12*: 283-286, 2006.

7 Riquet M, Badoual C, Barthes FP, Dujon A and Danel C: Metastatic thoracic lymph node carcinoma with unknown primary site. Ann Thorac Surg *75*: 244-249, 2003.

8 Kaneko K. Yamada T, Haniuda M, Miyazawa M, Hanaoka T, Kondo R, Makiuchi A and Amano J: Metastatic squamous cell carcinoma of hilar lymph node with unknown primary site. Nihon Kokyuki Gakkai Zasshi *38*: 39-44, 2000.

9 Sakuraba M, Mae M, Oonuki T and Nitta S: Mediastinal and hilar lymph node of cancer unknown origin: 3 case report. Nihon Kokyuki Gakkai Zasshi *37*: 72-77, 1999.

10 Cai YC, Banner B, Glickman J and Odze RD: Cytokeratin 7 and 20 and thyroid transcription factor 1 can help distinguish pulmonary from gastrointestinal carcinoid and pancreatic endocrine tumors. Hum Pathol *32*: 1087-1093, 2001.

11 Jerome MV, Matieres J, Groussard O, Garcia O, Berjaud J and Dahan M: Expression of TTF-1 and cytokeratins in pulmonary and secondary epithelial lung tumors: correlation with histological type amd grade. Histopathology *45*: 125-134, 2004.

12 Alberini JL, Belhocine T, Hustinx R, Daenen F and Rigo P: Whole-body positron emission tomography using fluorodeoxy-glucose in patients with metastases of unknown primary tumors (CUP syndrome). Nucl Med Commun *24*: 1081-1086, 2003.

13 Aassar OS, Fischbein NJ and Caputo GR: Metastatic head and neck cancer: role and usefulness of FDG PET in locating occult primary Tumors. Radiology *210*: 177-181, 1999.

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