

Discovery of the Primary Site of Esophageal Squamous Cell Carcinoma Based on Axillary Lymph Nodes Metastasis Detected with Fluorodeoxyglucose Positron-emission Tomography: Report of a Case

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Abstract

A 60-year-old Japanese man with no chief complaints underwent 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET) during a medical check-up. FDG-PET revealed high tracer uptake in the left supraclavicular and axillary regions but no significant uptake in the esophageal region. However, upper gastrointestinal endoscopy revealed an ulcerative tumor in the middle third of the esophagus. Endoscopic biopsy revealed moderately differentiated squamous cell carcinoma. The patient underwent chemoradiotherapy. Follow-up FDG-PET and computed tomography after therapy revealed a complete response in the lymph nodes. The patient underwent subtotal esophagectomy with gastric tube reconstruction through the posterior mediastinum. However, metastasis to the axillary lymph nodes was detected 16 months after surgery, and lymph node dissection was performed. To our knowledge, this is the first reported case in which the primary site of esophageal squamous cell carcinoma was discovered on the basis of axillary lymph node metastasis detected with FDG-PET.

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Key words: axillary lymph node, esophageal squamous cell carcinoma, thoracoscopic esophagectomy

Introduction

Advanced squamous cell carcinoma (SCC) of the esophagus often metastasizes to regional lymph nodes but rarely metastasizes to axillary lymph nodes. Metastasis of esophageal cancer to axillary

lymph nodes is classified as distant metastasis by the Japanese Classification of Esophageal Cancer, 10th Edition¹. To date, metastasis of esophageal cancer to axillary lymph nodes has been reported in only 4 patients, all of whom underwent radical esophagectomy with lymphadenectomy². However, to our knowledge, discovery of the primary site on

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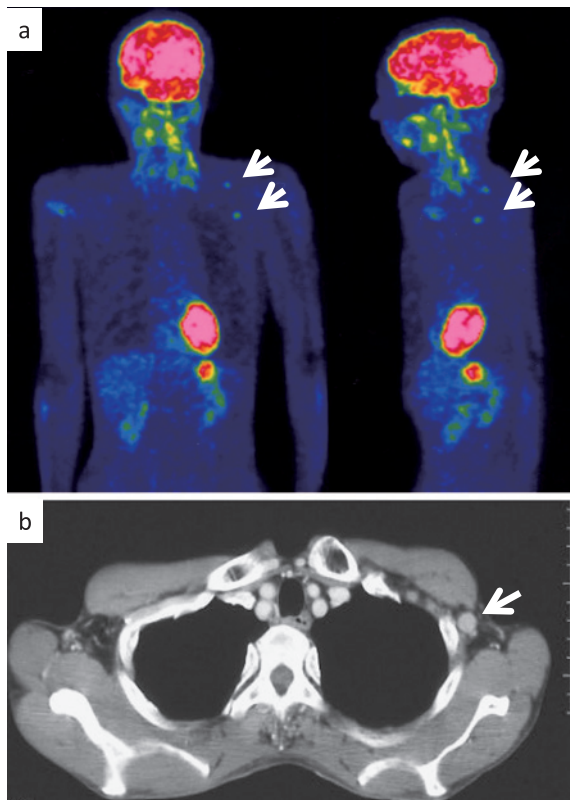


Fig. 1 Fluorodeoxyglucose positron-emission tomography showed high tracer accumulation in the supraclavicular and axillary regions (arrows) (a). Computed tomography showed a mass in the axillary region (arrow) (b)

the basis of a presentation of axillary lymph node metastasis has not been reported. We report a rare case of axillary lymph node metastasis from esophageal SCC that showed increased tracer uptake on 18F-fluorodeoxyglucose positron-emission tomography (FDG-PET) before treatment.

Case Report

A 60-year-old Japanese man with no complaints was referred to our hospital for a medical check-up. Results of laboratory tests were within the normal ranges. Tumor marker levels were as follows: carcinoembryonic antigen, 3.5 ng/mL (normal, 0–5 ng/mL); SCC antigen, 1.5 ng/mL (normal, 0–1.5 ng/mL); and p53 antibody, 11.7 U/mL (normal, 0–1.3 U/mL). A general FDG-PET examination showed high FDG uptake in the left supraclavicular and axillary regions, with standardized uptake values of 4.5 and 5.3, respectively (Fig. 1a). However, no significant

FDG uptake was shown in the esophageal region. Computed tomography showed a smooth and homogenous solitary tumor of the left axilla which had not invaded adjacent structures (Fig. 1b). Upper gastrointestinal endoscopy revealed an ulcerative and infiltrative mass in the lower thoracic esophagus (Fig. 2a). Endoscopic biopsy of this lesion, unstained with iodine, yielded a diagnosis of moderately differentiated SCC. Barium esophagography showed a mild stricture with irregular mucosa in the lower thoracic esophagus (Fig. 2b). The clinical tumor stage was IVa (T2N4M0) according to the Japanese Classification of Esophageal Cancer, 10th Edition².

The patient underwent neoadjuvant chemotherapy with fluorouracil at a dose of 400 mg/m² (days 1–5) and cisplatin at a dose of 40 mg/m² (day 1) and radiotherapy of the primary site and both sides of the neck and axilla (total dose, 30 Gy). Clinical evaluation after therapy showed a partial response of the primary esophageal tumor, and subsequent radiographic examination showed a complete response of the left supraclavicular and axillary lymph nodes. To treat the remaining esophageal tumor, we performed subtotal esophagectomy with 3-field lymph node dissection via a right thoracotomy. Reconstruction was performed with a gastric tube through the posterior mediastinal route.

Histologic examination of the resected specimens showed flat and superficial type SCC. However, this lesion was diagnosed as moderately differentiated SCC with extensive spread to the muscularis propria (pT2) (Fig. 3). Cancer cells were observed in 1 of 57 cervical lymph nodes (111 lymph nodes were dissected) (pT2N3ly1v0). The postoperative course was uneventful.

Sixteen months after surgery, follow-up computed tomography showed a recurrent mass in the left axillary region. The patient underwent radical dissection of the left axillary lymph nodes (Fig. 4a). The lymph nodes were hard, elastic masses 0.5 to 1.5 cm in diameter and showed no invasion of adjacent structures (Fig. 4b). Pathological examination demonstrated metastasis of moderately differentiated SCC from esophageal cancer in 3 of 12 dissected lymph nodes (Fig. 4c). The cancer

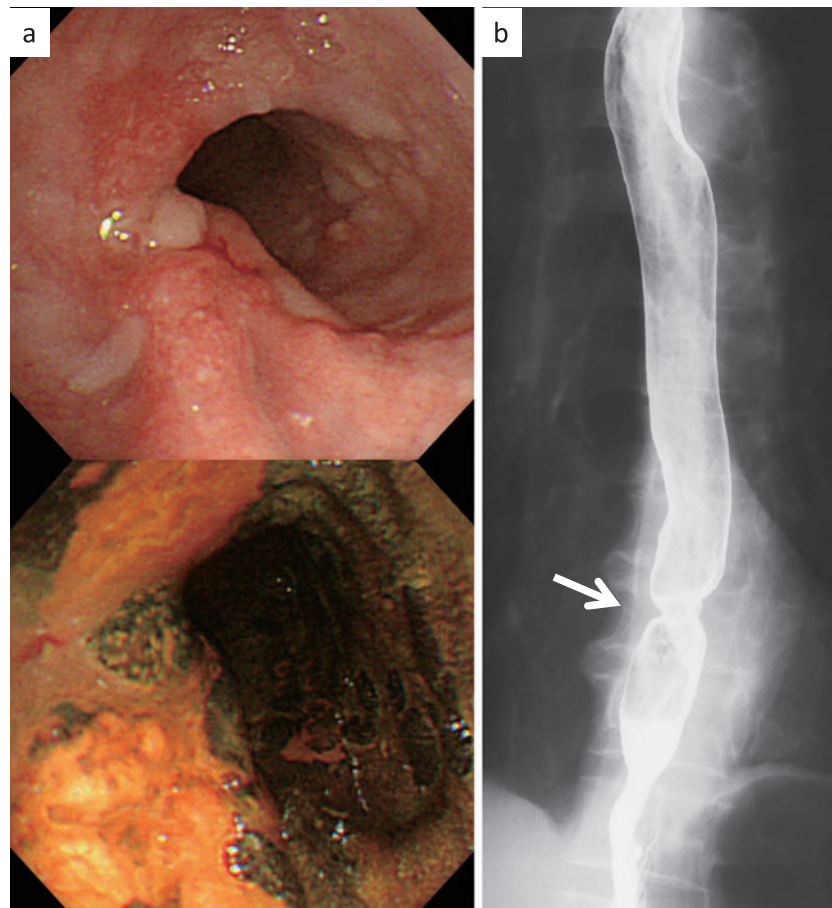


Fig. 2 Upper gastrointestinal endoscopy showed an ulcerative and infiltrative mass in the lower thoracic esophagus (a). Barium esophagography revealed a mild structural lesion with irregular mucosa in the lower thoracic esophagus (*arrow*) (b)

subsequently metastasized to multiple left subclavicular lymph nodes, and the patient died 49 months after the initial operation.

Discussion

Thoracic esophageal SCC frequently metastasizes to the cervical, mediastinal, and abdominal lymph nodes³. Even after esophagectomy with extended 3-field lymph-node dissection, disease recurs in approximately 50% of patients⁴. Metastasis to cervical lymph nodes is a common pattern of recurrence after radical surgery for esophageal cancer, whereas metastasis to axillary lymph nodes is rare and is considered to be distant metastasis. However, compared with recurrence in the mediastinal or abdominal lymph nodes, metastasis to axillary lymph nodes can be treated with surgical

resection, which is the treatment of choice. Few reports have described the prognosis and treatment of axillary lymph node metastasis. Komatsu et al.² have reported a median survival time of 30.5 months (range, 21–89 months) after initial treatment for advanced esophageal SCC, and recommended appropriate locoregional therapies, such as axillary lymphadenectomy and chemoradiotherapy, to prolong survival in patients with a solitary site of axillary lymph node metastasis.

The mechanisms of metastasis to the axillary lymph nodes are well documented in lung cancer^{5,6} but have rarely been described in esophageal cancer. Three routes of metastasis to the axillary lymph nodes have been proposed: newly developed lymphatic channels arising from pleural lesions of adhesive lung tumors, retrograde spread leading to the development of supraclavicular lymph nodes

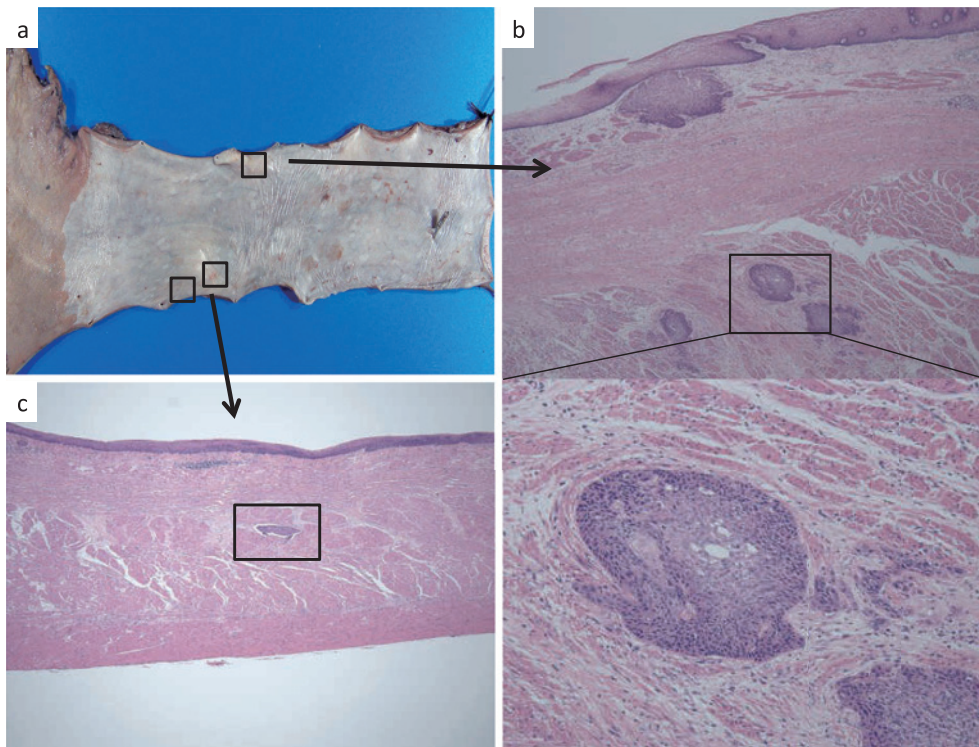


Fig. 3 The gross appearance of the resected specimen (a). Hematoxylin and eosin staining and the lesions surrounded in box frames showed the areas of carcinomatous components (b, c)

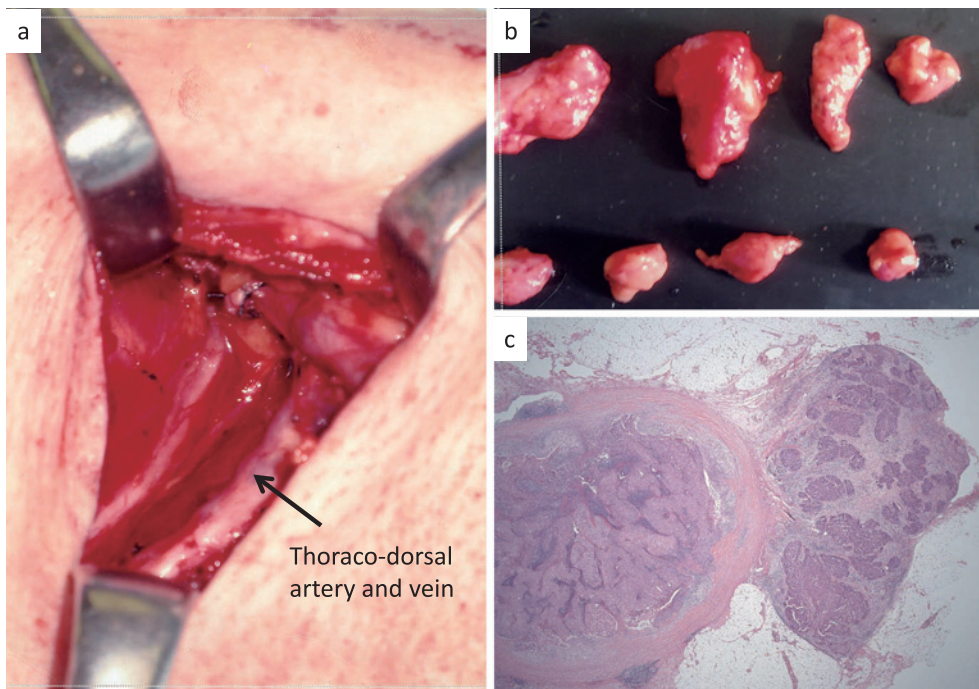


Fig. 4 Intraoperative view of the left axillary region (a). Gross appearance of the resected axillary lymph nodes (b). Photomicrograph shows infiltration of the lymph nodes by clusters of moderately differentiated squamous cell carcinoma (hematoxylin and eosin, $\times 100$) (c)

metastasis, and the development of axillary lymph-node metastasis from systemic disease. Komatsu et al.² have reported that 4 of 4 patients who presented with metastasis to the left axillary lymph nodes also had metastasis to the left supraclavicular lymph nodes. Our patient also had simultaneous metastases to the left axillary and supraclavicular lymph nodes. The connection between the supraclavicular and axillary lymph nodes has been investigated. Marcantonio et al.⁶ have reported retrograde flow of contrast material from the supraclavicular lymph nodes to the axillary lymph nodes in 4 of 200 (2%) consecutive lymphangiograms. These findings suggest that metastasis to the axillary lymph nodes in patients with esophageal cancer may be caused by retrograde flow due to lymphatic blockade by metastasis to the supraclavicular lymph nodes.

Metastasis to distant lymph nodes is generally a poor prognostic indicator reflecting potential systemic spread. In Japan, definitive chemoradiotherapy is the recommended treatment for metastasis to distant lymph nodes or localized advanced (T4) esophageal tumors or both⁷. In this context, definitive chemoradiotherapy has been the treatment of first choice for patients with non-T4 tumors and metastasis to distant lymph nodes, even when curative resection is possible. In the present patient, disease recurred in the axillary lymph nodes after neoadjuvant chemoradiotherapy and surgical resection with cervical lymphadenectomy. Salvage axillary lymphadenectomy was performed. We believe that in the present patient with axillary lymph node recurrence a good outcome could have been obtained with appropriate locoregional treatment. Our case may support the option of salvage lymphadenectomy for patients with axillary lymph node recurrence after initial treatment.

FDG-PET has recently been accepted as a metabolic imaging modality for staging and is now used to detect tumors, evaluate malignant potential, and monitor therapeutic response in patients with esophageal cancer^{8,9}. Increased vascularity, cellularity, and degeneration are thought to cause the higher FDG uptake, and high accumulation of FDG in esophageal cancer may result from the potential of cancer cells to transport glucose. In our

patient, increased FDG uptake was present only in the supraclavicular and axillary lymph nodes, and the standardized uptake values of the primary esophageal cancer were significantly lower than those of the metastatic lymph nodes. We speculate that the metastatic lymph nodes had a higher rate of tumor proliferation than did the primary cancer cells. A high rate of tumor proliferation is associated with aggressive biologic behavior. Yasuda et al.¹⁰ have reported that total numbers of cancer cells are significantly higher in PET-positive metastatic lymph nodes than in PET-negative lymph nodes. To our knowledge, the present case is the first reported case of axillary lymph-node metastasis from asymptomatic esophageal cancer detected with FDG-PET before treatment. Although asymptomatic esophageal cancer rarely metastasizes to axillary lymph nodes, clinicians should consider esophageal cancer as a differential diagnosis when axillary lymph nodes show FDG-PET positivity of unknown origin.

Conflict of Interest: The authors declare that they have no conflict of interest.

References

1. The Japan Esophageal Society: Japanese classification of esophageal cancer, tenth edition: part I. *Esophagus* 2009; 6: 1-25.
2. Komatsu S, Ueda Y, Ichikawa D, et al: Prognostic and clinical evaluation of axillary lymph node metastasis in esophageal cancer. *Jpn J Clin Oncol* 2007; 37: 314-318.
3. Sugimachi K, Inokuchi K, Kuwano H, Kai H, Okamura T, Okudaira Y: Patterns of recurrence after curative resection for carcinoma of the thoracic part of the esophagus. *Surg Gynecol Obstet* 1983; 157: 537-540.
4. Akiyama H, Tsurumaru M, Udagawa H, Kajiyama Y: Radical lymph node dissection for cancer of the thoracic esophagus. *Ann Surg* 1994; 220: 364-372; discussion 72-73.
5. Riquet M, Le Pimpec-Barthes F, Danel C: Axillary lymph node metastases from bronchogenic carcinoma. *Ann Thorac Surg* 1998; 66: 920-922.
6. Marcantonio DR, Libshitz HI: Axillary lymph node metastases of bronchogenic carcinoma. *Cancer* 1995; 76: 803-806.
7. Ohtsu A, Boku N, Muro K, et al: Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. *J Clin Oncol* 1999; 17: 2915-2921.
8. Kato H, Kuwano H, Nakajima M, et al: Comparison

- between positron emission tomography and computed tomography in the use of the assessment of esophageal carcinoma. *Cancer* 2002; 94: 921–928.
9. Kato H, Miyazaki T, Nakajima M, Fukuchi M, Manda R, Kuwano H: Value of positron emission tomography in the diagnosis of recurrent oesophageal carcinoma. *Br J Surg* 2004; 91: 1004–1009.
10. Yasuda T, Higuchi I, Yano M, et al: The impact of ¹⁸F-fluorodeoxyglucose positron emission tomography positive lymph nodes on postoperative recurrence and survival in resectable thoracic esophageal squamous cell carcinoma. *Ann Surg Oncol* 2012; 19: 652–660.

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