Case Report

Primary Esophageal Adenocarcinoma With Distant Metastasis to the Skeletal Muscle

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Hematogenous metastasis of esophageal adenocarcinoma to the skeletal muscle is uncommon. We report a rare case of esophageal adenocarcinoma with metastasis to the skeletal muscle. During pretherapeutic examination, a painful mass was detected in the left thigh of a 49-year-old man. Endoscopic biopsy identified poorly differentiated, advanced esophageal adenocarcinoma. Computed tomography (CT) revealed wall thickening in the distal esophagus. Two enlarged lymph nodes were detected—the middle thoracic paraesophageal lymph node in the mediastinum and the right cardiac lymph node. ¹⁸F-fluorodeoxyglucose (FDG) positron emission tomography demonstrated left thigh metastasis, which had not been detected by CT 3 weeks previously, with increased accumulation of FDG. Therefore, ultrasound-guided core-needle biopsy was performed. Histologic and immunohistochemical findings supported a diagnosis of poorly differentiated adenocarcinoma. The final diagnosis was primary esophageal adenocarcinoma with distant metastasis to the skeletal (left thigh) muscle. The rate of disease progression in this case emphasizes the malignant potential of esophageal adenocarcinoma. A few cases of skeletal metastasis from advanced esophageal adenocarcinoma have been previously reported. However, rapid metastasis to a distant skeletal muscle with no other hematogenous metastasis is quite rare. Early detection and rapid treatment are especially important in cases of esophageal adenocarcinoma.

Key words: Esophageal adenocarcinoma – Skeletal metastasis

Esophageal cancer is a common malignant neoplasm worldwide. Despite recent improvements in surgical techniques and adjuvant therapies, the prognosis for patients with advanced disease remains poor.^{1,2}

Diagnosis of esophageal carcinoma is often delayed because of its anatomic inaccessibility. Esophageal cancer is a well-known cause of distant metastases. It initially tends to spread locally, then metastasizes to the lymph nodes, and finally to the

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Fig. 1 Results of endoscopic examination. A slightly elevated lesion, occupying one third of the circumference of the lower third of the esophagus, measuring 30 cm to the esophagocardiac junction and 40 cm from the incisors. The Lugol solution staining technique was utilized.

distant organs.³ Metastases to the lungs, pleura, liver, stomach, kidney, adrenal glands, bones, and muscles have been reported in a few small series and clinical reports.³⁻⁸ However, skeletal muscle is a rare site of clinically apparent metastasis, despite its rich blood supply. The exact incidence of distant skeletal muscle metastasis from esophageal adeno-

carcinoma is unknown. Only 4 cases have been described previously in the literature.⁵⁻⁸

The incidence of and mortality due to esophageal adenocarcinoma have been increasing in the United States, several European countries, and Oceanus, whereas in Japan, no increase has been apparent. Obesity, gastroesophageal reflux, and tobacco smok-

Fig. 2 Results of CT. (a) Wall thickening in the distal esophagus. (b) Enlarged lymph nodes in the middle thoracic paraesophageal region (no. 108) were detected. A poorly margined tumor arising from the thoracic aorta is visible. (c) Enlarged right cardiac lymph node (no. 1).

Fig. 3 Results of FDG-PET/CT. (a) Increased FDG accumulation in the distal esophagus (SUVmax, 6.20) proximal to the tumor was detected. (b) Increased FDG accumulation in the right cardiac lymph node (SUVmax, 4.30) was detected according to the enlarged lymph nodes on the CT scan. (c) The PET scan identified a solitary focus of intense FDG accumulation in the left thigh (SUVmax, 23.39).

ing (to a lesser extent) are the principal factors associated with an increased risk of esophageal adenocarcinoma.⁹ Some data suggest that these factors may act synergistically when present together.^{10,11} A previous report demonstrated that infection with *Helicobacter pylori* markedly reduced the risk of esophageal adenocarcinoma and its precursor lesions.^{12,13}

We report a case of thigh muscle metastasis from primary esophageal adenocarcinoma.

Fig. 4 Results of CT of the left thigh. Only 3 weeks prior to FDG-PET, no left thigh metastasis was detected on the CT, although the upper thigh area was within the CT range.

Case Report

A 49-year-old man presented to the Gunma Cancer Center complaining of heartburn. Endoscopy of the upper gastrointestinal tract demonstrated a slightly elevated lesion (type 3) occupying one third of the circumference of the lower third of the esophagus and measuring 30 cm to the esophagocardiac junction and 40 cm from the incisors (Fig. 1). Transesophageal endosonography demonstrated submucosal invasion. No enlarged lymph nodes were detected in the mediastinum. Narrow-band imaging also showed a brownish area near the tumor. Histopathologic examination of the specimen obtained by endoscopic biopsy revealed poorly differentiated adenocarcinoma. Computed tomography (CT) of the thorax and abdomen showed wall thickening in the distal esophagus (Fig. 2a). Two enlarged lymph nodes were detected—the middle thoracic paraesophageal lymph node in the mediastinum (Fig. 2b) and the right cardiac lymph node (Fig. 2c). CT revealed no apparent distant metastasis at that time. Three weeks later, ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) detected increased levels of FDG accumulation in the distal esophagus [maximum standard uptake

Fig. 5 Results of ultrasonography. Ultrasonography identified an isoechoic mass with a marginal hypoechoic area in the left thigh.

value (SUVmax), 6.20] according to the tumor (Fig. 3a) and right cardiac lymph node (SUVmax, 4.30; Fig. 3b). In addition, FDG-PET/CT also revealed left thigh metastasis (SUVmax, 23.39; Fig. 3c). Although the upper thigh area was included within the CT range, no metastasis had been detected on the CT (Fig. 4). Thus, left thigh metastasis had developed over a very brief period. Left thigh pain had developed during the general examination.

Ultrasound-guided core-needle biopsy of the mass was performed (Fig. 5). Histologic and immunohistochemical findings supported a diagnosis of poorly differentiated adenocarcinoma. Immunohistochemical staining revealed the specimen to be positive for cytokeratin AE1/3, cytokeratin 20, and cytokeratin 7.

Further evaluation revealed no other possible sites of metastasis. Diagnostic imaging identified the tumor as a stage T1bN2M1 adenocarcinoma, in accordance with the guidelines of the Japanese Society for Esophageal Disease.¹⁴

Systemic chemotherapy with nedaplatin and 5-fluorouracil (5-FU) treatment was initiated. After 3 courses, thigh pain diminished, and a decreased size of the lesions was seen on FDG-PET/CT (Fig. 6). However, the primary lesion and lymph node metastases were unchanged. After 4 courses of treatment, FDG-PET/CT revealed an increased size of the lymph node and left thigh lesions. Docetaxel/cisplatin/5-FU (DCF) treatment was initiated as secondary chemotherapy. Unfortunately, the cancer metastasized to the liver, and the patient's general condition gradually deteriorated. Death occurred 6 months after the initial treatment.

Discussion

Although direct muscle invasion by carcinoma is well recognized, distant metastasis to skeletal

muscle is uncommon. Soft tissue mass caused by metastatic carcinoma is easily misdiagnosed as soft tissue sarcoma on physical examination and imaging studies.¹⁵ FDG-PET has been demonstrated to be more accurate than CT,¹⁶ especially in bodily regions that are not routinely evaluated by CT.⁴ Nevertheless, Wu *et al*⁵ reported the usefulness of combined FDG-PET/CT to detect skeletal muscle metastases from esophageal adenocarcinoma. In our patient, FDG-PET/CT was very useful in detection of left thigh metastasis. This case demonstrates the importance of comprehensive interpretation of and utilization of FDG-PET/CT for cancer staging, especially in cases with a possibility of widespread metastatic disease such as esophageal cancer. Needle biopsy is essential for a definitive diagnosis.

Intramuscular metastases usually develop in the muscles of or adjacent to the trunk, such as the in paravertebral, gluteal, and thigh muscles, in several carcinomas.^{18–21} These metastases often present as firm and tender masses exceeding 5 cm in diameter.^{18,19,22}

Skeletal muscle metastasis often presents as a painful mass in patients with known primary carcinoma.²³ Diagnosis of left thigh metastasis seems reasonable in this case. This case indicates that widespread metastatic carcinoma, such as esophageal adenocarcinoma, may extend to skeletal muscles, although the incidence of this metastasis is rare.

Metastasis to skeletal muscle from esophageal adenocarcinoma is extremely uncommon, although the skeletal muscle mass in the human body accounts for nearly 50% of the total body weight and has an abundant blood supply. The reasons for the rarity of intramuscular metastasis currently remain unclear. Some investigators have suggested that the rarity of this condition may be attributable to contractile activity, changes in pH, accumulation

Fig. 6 Results of FDG-PET during chemotherapy. FDG accumulation in the left thigh lesion was decreased after 3 cycles of chemotherapy (5-FU + nedaplatin).

of metabolites, intramuscular blood pressure, or local temperature.^{15,24,25} In any case, intramuscular metastasis is considered to be a sign of partial systemic hematogenous metastasis and is characteristic of the terminal stage of esophageal adenocarcinoma. The details in the case reported here are consistent with the findings of these studies.

External beam radiation, chemotherapy, or combination therapies have been considered as potential neoadjuvant or palliative treatments.⁷ Systemic chemotherapy using 5-FU and nedaplatin was administered for 4 cycles in this case. After completion of treatment, CT revealed disease progression. DCF was administered as a second-line

therapy. After only 1 cycle, chemotherapy with DCF was discontinued because of deterioration of liver functions. Death due to progressive esophageal adenocarcinoma with liver metastasis occurred only 6 months after appearance of the chief complaint. Therefore, the patient died because systemic chemotherapy was not of sufficient effectiveness for this aggressive esophageal adenocarcinoma. The metastasis of carcinoma to muscles is a late event in disease progression, and the overall prognosis for patients with esophageal carcinoma is poor. Palliative treatment with as little discomfort as possible is recommended.

This case is remarkable for the rapid progression of the metastasis of esophageal adenocarcinoma to the left thigh. FDG-PET was performed 3 weeks after the initial CT scan, revealing left thigh metastasis with a high accumulation of FDG. CT revealed no thigh metastasis.

El-Serag²⁵ suggested a 5-year survival rate in patients with esophageal adenocarcinoma of approximately 75% for those with carcinoma *in situ*, 30% for those with localized disease, and less than 5% for those with distant metastasis. Because the prognosis of esophageal adenocarcinoma with distant metastasis is very poor and the disease spreads aggressively, early detection and rapid treatment is especially important.

References

- Daly JM, Karnell LH, Menck HR. National Cancer Data Base report on esophageal carcinoma. *Cancer* 1996;**78**(8):1820–1828
- Wobst A, Audisio RA, Colleoni M, Geraghty JG. Oesophageal cancer treatment: studies, strategies and facts. *Ann Oncol* 1998;**9**(9):951–962
- Uygur S, Aral M, Kaya B, Ozmen S, Ozgun G, Latifoglu O. Giant temporalis muscle metastasis of esophageal carcinoma. *J Craniofac Surg* 2011;**22**(2):736–737
- Heffernan E, Fennelly D, Collins CD. Multiple metastases to skeletal muscle from carcinoma of the esophagus detected by FDG PET-CT imaging. *Clin Nucl Med* 2006;**31**(12):810–811
- Wu G, Bybel B, Brunken R, Lin H, Neumann D. PET detection of solitary distant skeletal muscle metastasis of esophageal adenocarcinoma. *Clin Nucl Med* 2005;**30**(5):335–337
- Rehman SU, Cope DW, Basile JN. Metastatic gastroesophageal adenocarcinoma to skeletal muscle: a unique event. *South Med J* 2002;**95**(9):1076–1078
- Norris WE, Perry JL, Moawad FJ, Horwhat JD. An unusual presentation of metastatic esophageal adenocarcinoma presenting as thigh pain. *J Gastrointest Liver Dis* 2009;**18**(3):371–374
- Heyer CM, Rduch GJ, Zgoura P, Stachetzki U, Voigt E, Nicolas V. Metastasis to skeletal muscle from esophageal adenocarcinoma. *Scand J Gastroenterol* 2005;**40**(8):1000–1004
- Olsen CM, Pandeya N, Green AC, Webb PM, Whiteman DC; Australian Cancer Study. Population attributable fractions of adenocarcinoma of the esophagus and gastroesophageal junction. *Am J Epidemiol* 2011;**174**(5):582–590
- Whiteman DC, Sadeghi S, Pandeya N, Smithers BM, Gotley DC, Bain CJ *et al*; Australian Cancer Study. Combined effects of obesity, acid reflux and smoking on the risk of adenocarcinomas of the oesophagus. *Gut* 2008;**57**(2):173–180
- Lagergren J, Ye W, Bergström R, Nyrén O. Utility of endoscopic screening for upper gastrointestinal adenocarcinoma. *JAMA* 2000;**284**(8):961–962
- Whiteman DC, Parmar P, Fahey P, Moore SP, Stark M, Zhao ZZ *et al*; Australian Cancer Study. Association of *Helicobacter pylori* infection with reduced risk for esophageal cancer is independent of environmental and genetic modifiers. *Gastroenterology* 2010;**139**(1):73–83; quiz e11–12
- Thrift AP, Pandeya N, Smith KJ, Green AC, Hayward NK, Webb PM *et al*. *Helicobacter pylori* infection and the risks of Barrett's oesophagus: a population-based case-control study. *Int J Cancer* 2012;**130**(10):2407–2416
- Japanese Society for Esophageal Disease. *Guidelines for the Clinical and Pathological Studies on Carcinoma of the Esophagus* [in Japanese]. 10th ed. Tokyo: Kanehara, 2008.
- Herring CL Jr, Harrelson JM, Scully SP. Metastatic carcinoma to skeletal muscle. A report of 15 patients. *Clin Orthop Relat Res* 1998;**355**:272–281
- Heeren PA, Jager PL, Bongaerts F, van Dullemen H, Sluiter W, Plukker JT. Detection of distant metastases in esophageal cancer with (18)F-FDG PET. *J Nucl Med* 2004;**45**(6):980–987
- Larson DA, Bottles K, Federle M, Fippin L, Luce J. Skeletal muscle metastases from pancreatic cancer. *Onkologie* 1988;**11**(6):282–285
- O'Keeffe D, Gholkar A. Metastatic adenocarcinoma of the paraspinal muscles. *Br J Radiol* 1988;**61**(729):849–851
- Porile JL, Olopade OI, Hoffman PC. Gastric adenocarcinoma presenting with soft tissue masses. *Am J Gastroenterol* 1990;**85**(1):76–77
- Torosian MH, Botet JF, Paglia M. Colon carcinoma metastatic to the thigh—an unusual site of metastasis. Report of a case. *Dis Colon Rectum* 1987;**30**(10):805–808
- Sridhar KS, Rao RK, Kunhardt B. Skeletal muscle metastases from lung cancer. *Cancer* 1987;**59**(8):1530–1534
- Tuoheti Y, Okada K, Osanai T, Nishida J, Ehara S, Hashimoto M *et al*. Skeletal muscle metastases of carcinoma: a clinicopathological study of 12 cases. *Jpn J Clin Oncol* 2004;**34**(4):210–214
- Nabi G, Gupta NP, Gandhi D. Skeletal muscle metastasis from transitional cell carcinoma of the urinary bladder: clinicoradiological features. *Clin Radiol* 2003;**58**(11):883–885
- Seely S. Possible reasons for the high resistance of muscle to cancer. *Med Hypotheses* 1980;**6**(2):133–137
- el-Serag HB. The epidemic of esophageal adenocarcinoma. *Gastroenterol Clin North Am* 2002;**31**(2):421–440, viii