Metastases of esophageal carcinoma to skeletal muscle: Single center experience

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INTRODUCTION

The prognosis of esophageal carcinoma is, in general, poor, with the mortality rate reaching 90% of the incidence rate. Both uncontrolled growth of the primary tumor or locoregional recurrence and distant metastases may be the ultimate cause of death in individual patient.

CASE REPORT

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Abstract

Metastases of esophageal carcinoma to the skeletal muscle are rare, but the incidence may be increasing because of better diagnosis resulting from widespread use of positron emission tomography/computed tomography (PET/CT). A cohort of 205 patients with esophageal carcinoma treated at our center who had PET/CT between 2006 and 2010 was retrospectively evaluated for the presence of skeletal muscle metastases. Four patients had skeletal muscle metastases of esophageal carcinoma, including two patients with squamous cell carcinoma. In another patient with squamous cell carcinoma of the esophagus and synchronous skeletal muscle metastases, muscle metastases were subsequently shown to be related to second primary pancreatic adenocarcinoma. In all cases, skeletal muscle metastases were the first manifestation of systemic disease. In three patients palliation was obtained with the combination of external beam radiation therapy, systemic chemotherapy or surgical resection. Skeletal muscle metastases are a rare complication of esophageal carcinoma.

Key words: Drug therapy; Esophageal neoplasms; Muscle; Skeletal; Positron-emission tomography; Radiotherapy

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Esophageal carcinoma commonly spreads to the liver, lung, adrenals, bone, pleura, peritoneum or pericardium. Less frequent sites of metastases include thyroid, pancreatic, spleen, ovary, kidney, heart, skin, gallbladder or small and large bowel. Metastatic involvement of skeletal muscle is rare.

Until recently, asymptomatic skeletal muscle metastases (SMM) were detected only fortuitously. The widespread use of positron emission tomography/computed tomography (PET/CT) resulted in the detection of asymptomatic metastases in different organs, including skeletal muscle. A number of case reports or case series on SMM in patients with different primary tumors, including esophageal carcinoma, have been published, but the natural history of SMM in patients with esophageal carcinoma remains largely unknown. We report five cases of patients with esophageal carcinoma and SMM observed in our center.

CASE REPORT

Records of 205 patients with esophageal carcinoma treated at our center who had PET/CT between 2006 and 2010 were searched to identify patients who had SMM diagnosed.

SMM were diagnosed in 5 patients (2%), all males. In one of these patients, SMM were subsequently shown to be related to a second primary tumor (Table 1). The details of these cases are outlined below.

Case 1

A 64-year-old male was diagnosed with adenocarcinoma of the distal esophagus in February 2004. The staging examination that included laparoscopy did not reveal distant metastases. The patient was treated with neoadjuvant chemoradiation. Transhiatal esophagectomy was performed on June 1, 2004. Histological examination of the resection specimen revealed pathologic complete response. The course of the follow-up was uneventful until October 2006 when the patient observed a resistance in the left thigh. Whole body $[^{18}F]$ fluorodeoxyglucose (FDG) PET/CT performed in December 2006 revealed high focal uptake in the left quadriceps femoris muscle and in the left inguinal and iliac lymph nodes (Figure 1), with no evidence of a second primary tumor. An excisional biopsy established the diagnosis of SMM of adenocarcinoma.

The metastatic involvement of skeletal muscle and lymph nodes was treated with external beam radiation (50 Gy) that was administered in February and March 2007 along with 2 cycles of systemic chemotherapy (cisplatin and 5-fluorouracil). Four cycles of systemic chemotherapy using the same schedule have been administered subsequently until September 2007. A control FDG PET/CT in October 2007 demonstrated persistent uptake of radioactivity in the thigh metastasis that decreased in size. Additional metastatic lesions were discovered in medial condylus of the left femur and the retroperitoneal lymph nodes. The patient was feeling well and was subsequently only followed. In May 2008 an edema of the left lower extremity manifested. Control FDG PET/CT in June 2008 demonstrated uptake in retroperitoneal, mediastinal and left supraclavicular lymph nodes, lungs and left tibia as well as persistent accumulation in the left thigh. Between July and October 2008, the patient was treated with 5 cycles of combination of cisplatin and 5-fluorouracil. After the completion of chemotherapy, only symptomatic therapy was administered. The patient died on May 18, 2009, 31 mo after the diagnosis of skeletal muscle metastasis. An autopsy was not performed.

Case 2

76-year-old male was diagnosed in June 2006 with squamous cell carcinoma of the middle esophagus. Staging FDG PET/CT did not reveal distant metastases or evidence of a second primary tumor. The patient was treated with neoadjuvant chemoradiation that consisted of external beam radiation (50 Gy in 25 fractions of 2 Gy with systemic cisplatin and 5-fluorouracil). The control FDG PET/CT in November 2006 revealed complete disappearance of FDG uptake in the primary, but a pathologic accumulation in the right gluteus minimus muscle (21 mm × 14 mm in size) was noted. Because of complete response, patient age and uncertainty about the systemic disease, esophagectomy was not performed, and the patient was further only followed. On control FDG PET/CT, no uptake in the primary tumor was observed, but the size of the lesion in gluteus minimus muscle increased to 66 mm × 44 mm × 34 mm and involved bone. In addition, similar lesion was noted in the left psoas muscle. A biopsy performed in April 2007 confirmed metastasis of squamous cell carcinoma. Between May and July 2007 external beam radiation was administered to both lesions (70 Gy in 35 fractions of 2 Gy) concomitantly with 2 cycles of systemic cisplatin and 5-fluorouracil. Control FDG PET/CT in September 2007 demonstrated metastatic spread to the lungs, pleura, adrenals and retroperitoneal lymph nodes. Only symptomatic therapy was administered after the diagnosis of progressive metastatic disease, and the patient died on March 4, 2008, 16 mo after detection of SMM. An autopsy was not performed.

Case 3

A 57-year-old male was diagnosed in September 2006 with squamous cell carcinoma of the middle third of the esophagus. Staging FDG PET/CT performed in October 2006 revealed an accumulation of radioactivity not only in the primary tumor, but also in the skeleton of the pelvis and in the right subscapularis muscle. No evidence of a second primary tumor was found. The biopsy of the lesions was considered technically difficult, and the diagnosis of metastatic esophageal carcinoma was made based on multiplicity and appearance of lesions. Between October and December 2006 the patient was treated with 3 cycles of systemic chemotherapy (cisplatin and 5-fluorouracil). Chemotherapy had to be interrupted in January 2007 because of pneumonia. A control FDG PET/CT...
in February 2007 revealed mild progression. Palliative external beam radiation therapy (45 Gy in 18 fractions of 2.5 Gy) of all three sites of disease was then performed, but the condition of the patient deteriorated, with the progression of dysphagia. The patient died on March 24, 2007, 5 mo after the diagnosis of SMM. An autopsy was not performed.

**Case 4**

42-year-old male presented with adenocarcinoma of distal esophagus and cardia in April 2010. Staging FDG PET/CT demonstrated high FDG uptake in the primary tumor and a 2 cm mass in the iliacus muscle, with no evidence of a second primary tumor. As staging laparoscopy performed in May 2010 did not reveal spread in the abdominal cavity, the patient was referred for concomitant chemoradiation (50 Gy in 25 fractions of 2 Gy) and 2 cycles of systemic chemotherapy (cisplatin and 5-fluorouracil). Control PET/CT in October 2010 demonstrated only moderate progression in the primary, but marked progression of SMM (4 cm). The patient underwent subsequently (in October 2010) esophagectomy and resection of the muscle mass. Histologic examination of the muscle metastasis demonstrated poorly differentiated adenocarcinoma similar to the esophageal primary. The patient was then followed. In April 2011, the patient presented again with dysphagic complaints. Stenosis of the anastomosis was detected, and biopsy confirmed recurrence of adenocarcinoma. During the surgery to perform a jejunostomy, peritoneal carcinomatosis was detected and a large abdominal metastasis was resected. After a brief course of investigational therapy in a clinical trial the disease progressed and the patient was treated symptomatically. The patient died on August 27, 2011, 16 mo after diagnosis of SMM. An autopsy was not performed.

**Case 5**

60-year-old male was diagnosed in January 2010 with squamous cell carcinoma of the distal esophagus. Staging FDG PET/CT performed in February 2010 demonstrated high uptake in the tumor of distal esophagus, in lymph nodes adjacent to lesser curvature of the stomach, in the liver, left adrenal, bone and multiple metastases in skeletal muscle, including gluteus maximus muscle. Because of the extent of metastatic disease, only symptomatic therapy was indicated and histological verification of metastases was not sought. An esophageal stent was introduced to palliate the stenosis. The procedure resulted in the relief of the symptoms of short duration, but in March 2010 the condition of the patient deteriorated, he was admitted for back pain and died on March 21, 2010. Autopsy demonstrated, besides squamous cell carcinoma of the distal esophagus, a second primary pancreatic adenocarcinoma. Autopsy also revealed metastases in mediastinal and abdominal lymph nodes, peritoneum, pleura, lung, liver, kidneys, adrenal, thyroid, left submandibular gland, skeletal muscle, subcutis and bone. The histology of all metastases was adenocarcinoma pointing to pancreatic primary.

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**Table 1  Patients with esophageal carcinoma and skeletal muscle metastases in the present series**

| Patient | Age at diagnosis (yr) | Histology | Stage at diagnosis | Timing | Primary therapy | Metastatic interval (mo) | Symptoms | Diagnosis | Location | Other metastases | Therapy for muscle metastases | Survival from the diagnosis of muscle metastasis (mo) |
|---------|----------------------|-----------|--------------------|--------|----------------|--------------------------|----------|-----------|----------|----------------|-------------------------------|-----------------------------------------------|
| 1       | 64                   | Adeno     | II                 | Metachronous    | CXRT  | 32                 | Mass     | PET/CT; biopsy | Quadriceps femoris | B; LN (subs) | CXRT                           | 31                                            |
| 2       | 76                   | SCC       | II                 | Metachronous    | CXRT  | 5                  | None     | PET/CT; biopsy | Gluteus minimus; psoas | L; P; A; LN (subs) | CXRT                           | 16                                            |
| 3       | 57                   | SCC       | IV                 | Synchronous     | None  | 0                  | None     | PET/CT; biopsy | Subscapularis | B | CRT; subs |                               | 5                                             |
| 4       | 42                   | Adeno     | IV                 | Synchronous     | CXRT  | 0                  | None     | PET/CT; biopsy | Iliacus | PR | XRT | S | 16                                           |
| 5       | 60                   | SCC; adeno (pancreas) | IV | Synchronous | None  | 0                  | None     | PET/CT; biopsy | Multiple | Multiple | None | 2                                             |

A: Adrenal; Adeno: Adenocarcinoma; B: Bone; CRT: Chemotherapy; CXRT: Chemoradiation; L: Lungs; P: Pleura; PR: Peritoneum; LN: Lymph nodes; S: Surgery; SCC: Squamous cell carcinoma; subs: Subsequently; XRT: Radiotherapy; PET/CT: Positron emission tomography/computed tomography.

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**Figure 1** [18F] fluorodeoxyglucose positron emission tomography/computed tomography showing a metastasis in the left quadriceps femoris muscle.
Table 2  Overview of the reports of esophageal carcinoma skeletal muscle metastases

| Ref.     | Sex | Age (yr) | Histology | Timing          | Symptoms                          | Diagnosis               | Location of muscle metastases | Other metastases | Therapy                  | Outcome     |
|----------|-----|----------|-----------|-----------------|-----------------------------------|-------------------------|------------------------------|-----------------|--------------------------|-------------|
| Heyer et al[20]  | M   | 54       | Adeno     | Synchronous     | Asymptomatic; fortuitously detected during CT; biopsy               | CT; MRI; biopsy     | Multiple                      | None            | CXRT (to the primary)    | ND          |
| Rehman et al[21] | M   | 71       | Adeno     | ND              | Pain; unable to walk                                                       | MRI; biopsy          | Thigh                         | ND              | XRT (metastases)         | Symptomatic relief 2 wk |
| Kozyreva et al[22] | M   | 72       | Adeno     | Synchronous     | Asymptomatic; fortuitously detected during PET/CT biopsy              | PET/CT; biopsy       | Deltoid                        | None            | C (oxaliplatin + 5FU/FA) | Progression of muscle metastases |
| Schultz et al[23] | ND  | ND       | SCC       | Synchronous     |                                                                  | CT; biopsy            | Gluteus minimus               | ND              | ND                       | ND          |
| Heffernan et al[24] | F   | 67       | Adeno     | 5 mo after surgery | Asymptomatic; fortuitously detected during PET/CT                    | PET/CT               | Multiple                      | Mediastinum       | ND                       | ND          |
| Wu et al[25]      | M   | 67       | Adeno     | Synchronous     | Asymptomatic; fortuitously detected during PET/CT biopsy              | PET/CT; biopsy       | Gluteus minimus               | None            | ND                       | ND          |
| Lekse et al[26]   | F   | 78       | Adeno     | 4 mo after diagnosis | PET/CT; Diplopia                                                      | CT; biopsy           | Inferior rectus ocular         | Lung            | Symptomatic              | ND          |
| Lekse et al[27]   | M   | 78       | Adeno     | 2 mo after diagnosis | Diplopia; loss of vision                                              | MRI                  | Lateral rectus ocular          | Lung; bone; liver | XRT; C (5FU + FA)      | ND          |

SFU: 5-fluorouracil; Adeno: Adenocarcinoma; C: Chemotherapy; CT: Computed tomography; CXRT: Chemoradiation; FA: Folinic acid; M: Male; F: Female; MRI: Magnetic resonance imaging; ND: Not described; PET: Positron emission tomography; XRT: Radiotherapy; SCC: Squamous cell carcinoma.

DISCUSSION

The 2% incidence of SMM in the present series may be affected by selection bias, as the primary diagnosis in one of the patients was performed before 2006. The information on esophageal carcinoma SMM is limited to individual case reports (Table 2), or to series of patients with SMM[26]. However, in most series of patients with SMM, no cases of patients with esophageal primary have been described[4,6-8]. SMM were also not reported in most autopsy series of esophageal carcinoma patients[2,3,9,10]. Cases of SMM have also been described in patients with gastric cancer[26]. To the best of our knowledge, only one case of squamous cell carcinoma of the esophagus metastatic to the skeletal muscle has been reported so far, with few details described[9]. Two of the patients reported here therefore represent the second description SMM of squamous cell carcinoma of the esophagus. The case of the patient with clinically undetected pancreatic adenocarcinoma demonstrates that histological verification may be needed not only to verify the neoplastic nature of the muscle lesion, but also to determine the primary as the frequency of second primary tumors is increasing. This case also indicates that a possible occult second primary tumor represents limitation in retrospective series of rare distant metastases. Histological verification confirming esophageal primary origin was possible in 3 out of 4 remaining cases. In all four cases SMMs were the first manifestation of metastatic disease. In patients with metachronous metastases, SMM involvement preceded the manifestation of metastatic spread to other organs by several months and survival times were relatively favorable in the context of metastatic esophageal carcinoma.

SMM detected with imaging studies were reported in 1%–2% of all patients with metastatic disease, with metastatic involvement limited to skeletal muscle reported in less than 10% of patients[21]. Similarly to the present series, most patients with SMM have metastasis only in one muscle[11]. Given the mass of skeletal muscle in the body, one would expect the metastases to this tissue to be more frequent. Experimental data suggest that muscle contractions result in mechanical destruction of tumor cells arrested in the microvasculature[22]. It has also been hypothesized that high lactate concentrations in the skeletal muscle microenvironment may decrease the responsiveness of muscle vessels to hypoxia, creating an environment unfavorable to angiogenesis[23].

PET/CT is currently being extensively utilized for pre-therapeutic staging of esophageal carcinoma because it was demonstrated that distant metastases missed by other imaging studies may be detected[14,15]. Individual cases of esophageal carcinoma SMM have been noted in cohorts of patients staged by PET/CT[16]. The increased incidence of esophageal carcinoma SMM may not only be the result of better diagnosis with PET/CT, but also of improved prognosis resulting from better control of the primary with the use of combined modality treatment. In fact, in one of the patients in the present series, the patient who had pathologic complete response after primary treatment two years earlier, the diagnosis could be made based on clinical presentation. It is therefore possible that with advances in the therapy of esophageal...
carcinoma we will witness a further continuous increase of the incidence of SMM.

Little is known about the outcome of metastases affecting specific sites and optimal management of these patients, with the only source of information being anecdotal reports like the present series. In contrast to metastases affecting other organs, e.g., bone, no organ-specific drugs like bisphosphonates are available for SMM. Moreover, the potential utilization of new radiotherapy techniques in SMM is, for obvious reasons, limited. Prolonged survival has been observed in individual patients managed by combination of external beam radiation, surgery or chemotherapy. Based on the experience in the present series and other cases reported in the literature, only general recommendations for the management of patients with SMM, including SMM of esophageal carcinoma, can be outlined. Important consideration is symptom control, and the therapeutic strategy has to be tailored according the muscle affected. Similarly to metastases of other location, the best control may be obtained with surgery which is, however, meaningful only in patients with isolated SMM. In addition, surgery may be necessary to establish the diagnosis of SMM. External beam radiation should be reserved for patients with inoperable or recurrent SMM, including patients with metastases in other sites, and best results may be obtained when combining radiation with platinum-based chemotherapy. No standard fractionation regimen or technique has been established in this rare indication. Outside of setting of chemoradiation regimens, the role of systemic chemotherapy in the management of SMM seems to be limited, but systemic chemotherapy may be an only option in patients with widespread metastases and good general condition. For patients in poor general condition, only symptomatic therapy (mostly corticosteroids and pain medication) is indicated.

In conclusion, while SMM represent a rare event in patients with esophageal carcinoma, the incidence may be increasing because of better diagnosis or improved control of the primary. SMM may represent the first manifestation of metastatic disease. An active therapeutic approach using surgery, external beam radiation and chemotherapy may result in survival that is substantially longer compared to other cases of metastatic esophageal carcinoma.

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