Orthopaedic Case of the Month

A 72-year-old Man With a Painful Flexion Contracture of the Left Thigh

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History and Physical Examination

A 72-year-old man presented with a 48-hour history of increasing left posterior thigh pain and a progressive left knee flexion contracture. Physical examination revealed that he recently had a left below knee amputation. The stump was healing well. He had a firm posterior thigh with a woody consistency extending from the popliteal fossa proximally to the midposterior left thigh. On attempted passive extension of the left knee, there was exquisite pain in the posterior thigh.

Four weeks before his current presentation for the left posterior thigh pain, he had been admitted to our institution with a 1-week history of worsening abdominal pain, nausea, and vomiting. The patient had general surgery and

gastroenterology consultations. Physical examination of his abdomen revealed a soft, nondistended abdomen with hyperactive bowel sounds. He had tenderness in the epigastrium, umbilical region, and right lower quadrant. There were no palpable masses or organomegaly. Imaging of the abdomen revealed a high-grade small bowel obstruction with a transition point seen in the right lower quadrant. The patient was treated with a small bowel follow-through and colonoscopy that led to an exploratory laparotomy with resection of a mass in the distal ileum. Pathologic examination of the small bowel mass showed a metastatic Stage IV carcinoma. Further immunohistochemical and tumor marker analyses suggested a primary neoplasm of gastric or esophageal origin. Staging with a CT of the chest, abdomen, and pelvis showed no other lesions of the viscera.

During the same hospital admission for his small bowel obstruction, orthopaedics was consulted for a chronic 4-cm × 2-cm wound of the left heel that had been present for 6 months. On evaluation, he also had chronic osteomyelitis of the left calcaneus and a left knee flexion contracture of 30° with mild tenderness to palpation about the knee. Radiographs of the left knee showed chronic degenerative changes. No additional or advanced imaging of his left knee or thigh was obtained at that time, as he had a relatively painless knee flexion contracture. His surgical history revealed that 2 years before his current presentation he had undergone a left Chopart amputation for dysvascular forefoot wounds. Although he did not have a diagnosis of diabetes, he had a history of peripheral vascular disease with neuropathy secondary to heavy tobacco use. As treatment for his chronic heel wound, the patient underwent a left below knee amputation 5 days after his exploratory laparotomy. Intraoperatively after the below knee amputation, he was treated with an intraarticular

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Fig. 1 An axial T1-weighted MR image of the semimembranosus shows a mass-like low signal peripherally of varying thickness (white arrow). In addition, the fat signal is more clumped and centrally located (black arrow). This pattern can be compared with the more typical muscle atrophy pattern seen in the rectus femoris (dashed oval), which has symmetric linear fatty streaking.

corticosteroid injection and the left knee was casted in extension. He wore the cast for 10 days. The patient's immediate postoperative course was unremarkable. Pathologic examination of the amputated left leg showed peripheral vascular disease and a chronic wound of the heel without evidence of neoplastic changes. The patient was discharged to a rehabilitation facility with further oncologic staging via a planned positron emission tomography (PET)/CT scan.

One month later, before the PET/CT scan was completed, he presented with his current complaint of increasing left posterior thigh pain and a progressive left knee flexion. On admission, his vital signs were stable and he was afebrile. His laboratory evaluation showed elevations of WBC of 18 K/uL, C-reactive protein of 55 mg/L, erythrocyte sedimentation rate of 38 mm/hour, and his creatine kinase was within normal limits. Radiographs of the left knee and femur showed degenerative changes of the knee but otherwise were unremarkable. MRI of the knee and thigh was performed (Figs. 1–3), and an orthopaedic oncologist was consulted.

Based on the history, physical examination, and imaging studies, what is the differential diagnosis?

Imaging interpretation

The T1 MR images showed an intrinsic bright fat signal (fatty atrophy) of all muscles. However, the posterior compartment muscles were abnormal in appearance in that they were enlarged and had a disorganized internal

Fig. 2 An axial T1-weighted pregadolinium MR image shows the symmetric low-level enhancement seen in the thigh muscle groups.

Fig. 3 An axial T1-weighted postgadolinium MR image shows the distorted muscle architecture.

architectural pattern. For example, a diffusely stippled fat signal in the quadriceps muscle group was replaced in the semimembranosus muscle with a band-like or lenticular low signal on the periphery and a central fatty signal. The semimembranosus had a mass-like low signal peripherally of varying thickness (Fig. 1, white arrow). In addition, the fat signal was more clumped and centrally located (Fig. 1, black arrow). This pattern can be compared with the more typical muscle atrophy pattern seen in the rectus femoris (Fig. 1, dashed oval), which showed symmetric linear fatty streaking. The symmetric low-level enhancement seen in the quadriceps muscle groups when comparing the before and after contrast images (Figs. 2 and 3) was similar in intensity to the other muscle groups, but further exemplified the distorted muscle architecture. The postcontrast

Fig. 4 A frozen section of the biopsy specimen shows a perimysial blood vessel with collections of poorly differentiated metastatic carcinoma in the lumen (Stain, hematoxylin and eosin; original magnification, $\times 40$).

Fig. 5 An ATPase 4.6 stained slide of the biopsy specimen shows muscle fibers with type grouping and denervation. The arrow points to the dark staining of Type I muscle fibers (Stain, ATPase; original magnification, $\times 20$).

images showed a heterogeneous low-level enhancement throughout the hamstring muscles, sparing the central fatty portion.

Differential Diagnosis

- Autoimmune myositis
- Infection
- Denervation of muscle (subacute phase)
- Rhabdomyolysis
- Metastatic carcinoma to muscle

A biopsy of the left biceps femoris muscle was performed and the histologic specimens were examined with

hematoxylin and eosin stain (Fig. 4) and an ATPase stain (Fig. 5). Based on the history, physical examination, imaging studies, and histology, what is the diagnosis and how should this lesion be treated?

Histology Interpretation

Frozen and formalin-fixed sections of skeletal muscle were stained with hematoxylin and eosin. Frozen sections also were stained with Gomori trichrome, oil red O, periodic acid Schiff (PAS), succinic dehydrogenase (SDH), ATPase (pH 9.4, 4.6, 4.2), nicotinamide adenine dinucleotide disodium salt (reduced), cytochrome C oxidase (COX), and acid phosphatase. The sections showed preservation of the fascicular architecture without perifascicular atrophy or increased connective tissue. On the frozen sections, a perimysial blood vessel had collections of apparent tumor cells in the lumen (Fig. 4). In the formalin-fixed tissue, there was diffuse infiltration by carcinoma cells in the endomysium. These cells showed extensive cytokeratin 7 and 20 and AE1/AE3 immunoreactivity. Nearly all neoplastic cells showed Ki-67 labeling. There was variation in muscle fiber sizes attributable to numerous atrophic, angular Type I and II fibers. ATPases revealed extensive Type I and Type II fiber grouping (Fig. 5). Gomori trichrome and SDH showed no ragged red or blue equivalents and there were no cytochrome COX-negative fibers. The PAS and oil red O revealed no evidence of excess storage product. Acid phosphatase activity was increased. In addition, comparing the muscle tumor cells with the small bowel tumor revealed that both tumors expressed cytokeratin 7, cytokeratin 20, and CK AE1/AE3.

Diagnosis

Poorly differentiated metastatic carcinoma infiltrating between muscle fibers.

Discussion

Metastatic carcinoma to skeletal muscle is rare. Surov et al. reported a series of 61 patients with skeletal muscle metastasis from a population of 5170 patients seen during a 7-year period [51]. Damron and Heiner described a series of 30 patients and identified an additional 91 cases from the literature [8]. Other, smaller series exist, including a series of 12 patients described by Tuoheti et al. [53], and 11 patients described by Yoshimura et al. [58]. The rarity of metastasis to skeletal muscle remains unexplained and is poorly understood. Skeletal muscle is well vascularized

and represents a substantial portion of the overall body mass relative to bone and other vulnerable tissues. The relative infrequency of metastatic carcinoma to skeletal muscle only further highlights the nonrandom process of metastasis. Because of the infrequency of this form of metastatic process, the diagnosis in question can be easily overlooked and ultimately delayed until after the therapeutic treatment window has closed. Our patient was, in the end, diagnosed with a poorly differentiated metastatic carcinoma infiltrating between muscle fibers of the posterior aspect of his left thigh, which initially imitated an inflammatory muscular process. Many of the cited reports [4, 6, 10, 11, 13, 14, 18–20, 22, 24, 25, 27, 29, 30, 33–35, 37–43, 46, 47, 49, 51–53, 55, 56, 59, 61] indicate that when carcinoma metastasizes to skeletal muscle, a mass often will be found, which may or may not be painful. However, the key difference in our patient is that there was no appreciable mass. His exquisite posterior thigh pain, physical examination, and radiographic imaging were more consistent with an acute form of myositis at the time of his presentation.

Myositis is a catchall term that refers to inflammation of the muscle and can be very painful. The causes of myositis are varied, and include autoimmune, infectious, denervation, idiopathic, or iatrogenic forms. Lipid-lowering medications, such as statins, are an example of how one can sustain a drug-induced, or rather, an iatrogenic form of myositis. However, because of the patient's overall poor medical condition, it was most likely that an autoimmune, denervative, or infectious cause of muscle inflammation was leading to his exquisite left posterior thigh pain. His elevated WBC, erythrocyte sedimentation rate, and C-reactive protein on presentation also indicated that an underlying infectious or inflammatory process most likely was occurring. His normal creatine kinase made it less likely that rhabdomyolysis was the cause of his pain. An MRI of the left thigh showed diffusely abnormal musculature with widespread muscle atrophy and low-level edema and enhancement throughout. The radiographic differential diagnosis also helped narrow the possible diagnoses to either a denervative form or an infectious form of myositis. It was recommended that the patient undergo a muscle biopsy to further understand the pathologic process occurring in his muscle. The diagnosis of metastatic carcinoma was not suspected until biopsy when a microscopically infiltrative metastatic carcinoma to muscle was identified in our patient with a recently diagnosed metastatic gastrointestinal carcinoma.

The most common types of skeletal muscle metastasis reported in the series by Surov et al. [51] are genital tumors (24.6%), gastrointestinal tumors (21.3%), urological tumors (16.4%), malignant melanoma (13.1%), bronchial carcinoma (8.2%), thyroid carcinoma (4.9%), and breast carcinoma (3.3%) [51]. Some authors have reported the

lung and gastrointestinal tract as the most common types [2–4, 6, 10, 12, 21, 22, 26, 30, 42, 43, 45–48, 50, 54, 56]. The variation in the incidence of skeletal muscle metastasis may be explained by the regional or institutional variation in the incidence of carcinomas in the populations under investigation. The literature contains many case reports of metastasis to skeletal muscle from rare sites such as colorectal carcinoma, carcinoid tumor, hepatocellular carcinoma, ovarian carcinoma, pancreatic carcinoma, and head and neck carcinomas, particularly of the tongue, larynx, and parotid gland [1, 5, 11, 18–20, 24, 25, 27, 28, 31, 33, 35–40, 49, 52, 57, 59, 60].

The histologic evaluation relies on immunohistochemical staining and ATPase photomicrography. Immunohistochemical analysis of the pathological specimen helps narrow the underlying tissue origin of the metastasis, as seen with both of the patient's tumors. Both tumors expressed cytokeratin 7, cytokeratin 20, and CK AE1/AE3, thus linking the metastatic muscle lesion to the small bowel tumor. ATPase staining of the muscle is also useful to assess the type of muscle fiber involved. The function of ATPase is to remove the terminal phosphate group from ATP. By varying the pH of the solution during the staining procedure, different muscle fiber types may be preferentially stained. When muscle groups occur and are well-developed, the question of denervation-reinnervation must be raised. In our histologic specimen, ATPase stain revealed extensive Type I and Type II fiber groupings (Fig. 5), with variation in muscle fiber sizes attributable to numerous amounts of atrophic changes.

Radiographically, the majority of metastatic carcinomas to skeletal muscle form intramuscular masses that can mimic primary neoplasms, such as lymphoma. The patient's MR images showed an intrinsic bright fat signal (fatty atrophy) of all muscles, and a disorganized internal architectural pattern, a pattern not typically observed with metastatic carcinoma to muscle. A similar pattern of muscle enlargement and loss of normal fatty marbling was described by Chun et al. [7], and can be seen with lymphoma, although there is typically asymmetric muscle enhancement in the affected muscles without a discrete mass. The possible appearances of metastatic carcinoma masses to muscle were discussed by Tuoheti et al. [53], in which some metastatic masses show isosignal intensity with poorly defined margins on T1-weighted imaging. In other metastatic masses, T2-weighted imaging may reveal the mass to have a well-defined margin and heterogeneity. Gadolinium-enhanced images also may show extensive peritumoral enhancement associated with central necrosis [53]. However, another interest in our patient is the central, lenticular, or band-like fatty atrophy seen on his MR images. We are not aware of any article in the literature describing this type of abnormal muscular appearance.

Increasingly, small asymptomatic masses are being found incidentally in the musculature as imaging technology continues to advance. Soft tissue masses found on routine imaging such as hematoma, myositis ossificans, and abscess, must be distinguished from metastatic carcinomas. Patients with discrete masses are referred to physicians who treat neoplastic disorders. However, the less common infiltrative pattern appears akin to myositis, and thus typically is evaluated as a primary or secondary muscle disorder [34]. As illustrated in our case, where the link between the patient's gastrointestinal carcinoma and progressive unilateral knee contracture was not initially appreciated, the diagnosis of skeletal muscle metastasis was delayed.

Treatment of metastatic carcinoma to muscle is not well defined in the medical literature. Asymptomatic, small muscle metastases are being identified by PET/CT imaging in patients with widely metastatic disease [13–17, 23, 29, 32, 44, 55, 61]. These patients are best treated with systemic therapy. Palliative radiation may have a role in symptomatic soft tissue metastasis, when other visceral or bone metastases are known to exist [9]. Wide surgical resection is most appropriate in isolated, soft tissue metastasis, when no other metastases are known to exist, particularly those occurring after a long disease-free period [41]. After the diagnosis of metastatic carcinoma to muscle, our patient was referred for palliative radiation therapy to the posterior thigh. However, his overall general health declined rapidly with a recurrent small bowel obstruction. The patient elected to proceed to palliative care and died soon thereafter. No postmortem examination was performed.

We present a rare case of metastatic carcinoma to muscle with a microscopically infiltrative pattern. A familiarity of variations of metastatic disease to muscle may facilitate early diagnosis and limit morbidity.

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