Thigh Mass in a 73-year-old Man

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History and Physical Examination

A 73-year-old man was referred with a chief complaint of a left posterior thigh mass. The mass had been present for 2 months. The patient reported mild pain that was intermittent, aching, and sharp and occurred only after prolonged sitting. He had no history of trauma, fever, chills, night sweats, weight loss, or night pain. His medical history included renal cell carcinoma treated with a right nephrectomy 21 years earlier, Type II diabetes of 15 years' duration, and a benign pancreatic mass. An MRI of the mass had recently been performed. The rest of the patient's history was unremarkable.

On physical examination of the left posterior thigh, a nontender soft tissue mass was palpated that was also firm, deep, and fixed with contraction of the hamstring muscles. There were no skin changes, erythema, or overlying

warmth. Active and passive range of motion of the hip and knee were full and painless. The neurologic examination of the left lower extremity was normal. Gait was normal. The remainder of the musculoskeletal examination was normal.

MRI scan (Fig. 1) of the lesion was performed without initial radiographs.

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

Imaging Interpretation

MRI without contrast of the left thigh showed a well-circumscribed mass 16 cm × 7.5 cm in its greatest diameter (Fig. 1A–C). The lesion was located in the biceps femoris muscle in the posterior aspect of the midthigh. The mass abutted the fascia of adjacent muscles on either side and the subcutaneous fat posteriorly. It was heterogeneous and had many large vessels, particularly on its surface (Fig. 1D). The lesion had a hypointense to isointense signal to muscle on T1-weighted images and a hyperintense signal on T2-weighted images.

Differential Diagnosis

Malignant fibrous histiocytoma
Liposarcoma
Leiomyosarcoma
Rhabdomyosarcoma
Hemangioma
Metastasis

A needle biopsy was performed in the operating room with a dozen core samples taken (Fig. 2).

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Fig. 1A–D (A) A T1-weighted axial MR image with fat saturation shows the intramuscular location of the lesion. (B) A T2-weighted axial MR image with fat saturation shows the high water content of the lesion. (C) A sagittal STIR MR image illustrates the large craniocaudal size of the lesion. (D) A T1-weighted sagittal MR image illustrates the blood vessels supplying the lesion.

Based on the history, physical findings, imaging studies, and histologic picture, what is the diagnosis and how should this lesion be treated?

Histology Interpretation

On gross examination, the specimen consisted of multiple cores of yellow-tan tissue measuring from 0.5 to 1.5 cm.

Histologic sections showed a malignant epithelial neoplasm consisting of fine papillae with chicken wire vascular channels comprising cells with prominent clear to eosinophilic cytoplasm (Fig. 2A–B). There was mild nuclear pleomorphism with occasional nucleoli.

Immunohistochemistry staining showed the cells strongly and diffusely positive for low-molecular-weight keratins, CAM 5.2 (Fig. 2C) and AE1/AE3; focally positive for CD10 and renal cell carcinoma antigen; and negative for

S-100 (expressed in a variety of tumors), cytokeratin-7 (CK-7, epithelial-like sarcoma marker), cytokeratin-20 (CK-20, epithelial-like sarcoma marker), HMB-45 (melanocytic marker also present in some benign lesions), Melan-A (adrenocortical neoplasm marker), thyroid transcription factor-1 (TTF-1), tyrosinase, smooth muscle actin, thyroglobulin, leukocyte common antigen, desmin, and hepatocyte-specific antigen.

Diagnosis

Metastatic renal cell carcinoma.

Discussion and Treatment

Less than 1% of all metastases from carcinomas are found in skeletal muscle [23]. Two musculoskeletal oncology centers identified 20 cases of skeletal muscle metastases from carcinoma over an 11-year period [39]. Another study found 12 cases from three oncology centers over a 10-year period [7]. The most common skeletal muscle carcinoma metastases are from the lung and gastrointestinal tract [7, 11]. Other primary tumors that rarely metastasize to skeletal muscle include soft tissue sarcoma, renal cell carcinoma, melanoma, and head and neck cancers [7, 11].

Age, location, and lack of pain in this patient were suspicious for soft tissue sarcoma. Location within skeletal muscle is consistent with rhabdomyosarcoma; however, the older age of the patient made this less likely. Soft tissue hemangiomas are more common, but this was less likely because they often cause pain. Skeletal muscle metastases commonly present with pain [7, 11]. Histology is necessary to differentiate between these rare lesions and an unusual presentation of metastasis. Identifying a primary tumor versus a metastasis is critical because of the great differences in their treatment and prognosis [11].

Renal cell carcinoma most commonly metastasizes to the lungs, lymph nodes, bone, and liver [12, 31]. Skeletal muscle metastasis rates of 0.6% and 1.1% were found in two large studies of renal cell carcinoma patients [4, 30]. Two other large studies of 1451 and 586 patients had no skeletal muscle metastases [31, 37].

Reviewing the literature, we found 27 cases of renal cell carcinoma skeletal muscle involvement. The most common sites were the thigh (30%), upper arm (18%), and shoulder (15%) (Fig. 3) [1, 2, 5, 6, 8–11, 13–19, 21, 25, 27, 28, 32, 34–36, 41–43]. Five cases had multiple skeletal muscle metastases (19%) [8, 13, 21, 27, 28]. Slight to mild pain was reported in eight cases (24%) [2, 5, 11, 16, 17, 19, 25, 42].

Fig. 2A–C (A) A low-power histology image shows the sheets of cells with eosinophilic to clear cytoplasm punctuated by a fine vascular network (arrow) (stain, hematoxylin and eosin; original magnification, $\times 20$). (B) A higher-power view demonstrates the cells with prominent cytoplasmic clearing known as clear cells (stain, hematoxylin and eosin; original magnification, $\times 40$). (C) Immunohistochemistry staining illustrates the strong and diffuse cytoplasmic staining for CAM 5.2 (original magnification, $\times 20$).

Fig. 3 A diagram illustrates the distribution of skeletal muscle metastasis of renal cell carcinoma (percentage, with the number of cases in parentheses) found in the literature [1, 2, 5, 6, 8–11, 13–19, 21, 25, 27, 28, 32, 34–36, 41–43]. Modified and reprinted with permission from Patrick Hermans. © Patrick Hermans.

Several theories have attempted to explain why metastases are rare in skeletal muscle in spite of its rich blood supply and large percentage of body mass. Production of lactic acid by skeletal muscle may result in resistance to angiogenesis thereby impeding tumor establishment [15, 33]. Frequent contractions of the muscle may prevent cancer seeding and metastatic growth through wide variation in blood flow [26]. High concentrations of free radicals and local temperature fluctuations may also hinder development of metastases in skeletal muscle [16]. Additionally, specific receptors influence metastatic potential in renal cell carcinoma [24, 40] and these receptors may be absent or scarce in muscle. One study [20] suggests skeletal muscle trauma during active disease may increase the risk of metastasis at that site.

The mass in this case is larger and presented later than previously described renal cell carcinoma muscle metastases. Reported sizes range from 1.5 to 10 cm (average, 5.4 cm) in largest diameter [1, 2, 5, 6, 8, 9, 13, 16, 18, 21, 25, 27, 32, 36, 41]. While 11% of renal cell carcinoma metastases occur more than 10 years after nephrectomy [22], skeletal muscle metastasis after long-term survival remains uncommon. The average time to muscle metastases after nephrectomy found in the literature was 9.1 years (range, 6 months to 19 years) [2, 6, 9, 10, 13–17, 19, 21, 25, 27, 32, 34–36, 41, 43]. It is important for orthopaedic surgeons to recognize that delayed skeletal muscle metastasis does occur so that early diagnosis and intervention is possible.

Muscle metastases from carcinoma are typically hypointense to slightly hyperintense relative to skeletal muscle on T1-weighted images and isointense to hyperintense on T2-weighted images [6, 8, 16, 21, 25, 27]. MRI with gadolinium enhancement is useful in evaluating the vascularity of the tumor, differentiating areas of necrosis [16, 39], and planning operative treatment [21]. MRI findings alone are insufficient to differentiate metastatic lesions from soft tissue sarcomas [7, 11]. Biopsy is needed to make a definitive diagnosis. Plain radiography has little use in differentiating metastases from soft tissue sarcoma [11].

Grossly, renal cell carcinoma metastases can have a grey-white, multinodular appearance. Focal necrosis and hemorrhage may be seen. The tumor may have a fibrous capsule [1, 8, 25]. Histologic sections demonstrate large cells that can be either columnar or cuboidal. The histologic pattern varies from papillary to glandular to undifferentiated, and the cells appear clear, with central hyperchromatic nuclei and prominent nucleoli [1, 11, 18, 27]. Spindlelike cells may be present and may be mistaken for sarcoma cells [1, 17].

Periodic acid-Schiff stain shows the high cytoplasmic glycogen content of renal cell carcinoma epithelial cells, and silver stain identifies their glandular nests. Immunohistochemical markers, such as low-molecular-weight cytokeratin (CAM 5.2), epithelial membrane antigen, CD10, and renal cell carcinoma marker, should be positive, greatly aiding in diagnosis [29, 38].

Treatment of renal cell carcinoma metastases to skeletal muscle depends on the overall clinical picture of the patient. Surgical excision may be attempted in the absence of widespread disease [1, 2, 6, 9, 15, 19, 25, 27, 35], although recurrence has been reported [15]. Disseminated disease to the lung, bone, and liver requires treatment with chemotherapy and/or radiation [5, 16, 17]. Renal cell carcinoma can spontaneously regress, suggesting a response from the immune system [3, 12]. Consequently, therapies were developed using immunoreactive cytokines including IL-2 and interferon- α , though results have been variable [8, 15, 21, 32, 34, 43].

We present a 73-year-old man with a left thigh mass and minimal symptoms 21 years after nephrectomy for renal cell carcinoma. A diagnosis of soft tissue sarcoma was suspected due to the large size and appearance of the lesion, but the final diagnosis was metastatic renal cell carcinoma. This case highlights the fact that a metastasis should be considered for a skeletal muscle mass in patients with a history of renal cell carcinoma even though they received adequate treatment and had a long disease-free interval.

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