Thigh Pain of 5 Years' Duration in a 48-year-old Man

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History and Physical Examination

A 48-year-old man presented to his primary physician with pain localized to the medial region of the left knee of 6 months' duration. The physical examination was normal. His medical history was unremarkable. He was treated empirically with nonsteroidal antiinflammatory medications and physiotherapy without relief. After 3 months of continuing pain, he was referred to an orthopaedic surgeon who ordered an MRI scan which was interpreted as normal. The patient was maintained on symptomatic treatment for several more months with no substantial improvement. The patient continued to endure the pain and utilise symptomatic treatment for the following couple of years. Three years after initial presentation, he obtained a second

orthopaedic opinion and had another MRI scan. The examination was again normal and the MRI interpreted as normal. The patient was maintained on symptomatic treatment with no improvement. Throughout he had no constitutional symptoms.

The patient presented to our clinic 5 years after his pain first developed. Physical examination of the knee was normal. There was no instability, no joint line tenderness, no crepitation, and full range of motion. He had considerable atrophy and weakness of the quadriceps muscle. Physical examination of the hip and the spine were normal. There was an area of exquisite pinpoint tenderness medially above the joint line, overlying the adductor canal (Fig. 1). Neurologic examination of both lower extremities was normal, as was his general physical examination.

Plain radiographs were normal. MRI was performed (Fig. 2).

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

Imaging Interpretation

An axial T1-weighted MR image (Fig. 2A) of the distal thigh revealed a 1- x 1-cm intermediate signal intensity focal lesion in the subcutaneous fat tissues over the adductor canal. An axial T1-weighted fat-saturated MR image (Fig. 2B) after gadolinium contrast injection showed the lesion enhanced with slight irregular contour. A coronal T2 gradient echo image (Fig. 2C) showed a lesion of increased signal intensity with the presence of chemical shift artifact seen as a low signal intensity over the inferior edge.

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Fig. 1 A clinical photograph shows a bluish discoloration at the point of maximal tenderness.

Differential Diagnosis

Glomus tumor
Schwannoma
Traumatic neuroma
Hemangioma
Leiomyoma cutis
Dermatofibrosarcoma protuberans

The mass was marginally excised and was sent for histologic examination (Fig. 3).

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

Histology Interpretation

Gross examination of the lesion revealed a pinkish mass measuring 15 mm in length and 10 mm in diameter. Microscopically, it consisted of an encapsulated mass of monotonous, cuboidal cells with rounded nuclei and a scant eosinophilic cytoplasm (Fig. 3).

Diagnosis

Extradigital glomus tumor.

Discussion and Treatment

The differential diagnosis of the lesion includes several disorders that may present with similar symptoms, clinical findings, and radiographic features, including tumors of neural and vascular origin and other dermal/subcutaneous neoplasms.

Schwannomas are benign tumors that arise from the neural crest-derived Schwann cell [12]. Symptoms are related to local compression of the involved nerve. They are well-circumscribed, encapsulated masses that are attached to a nerve but can be separated from it. Tumors are firm and gray and may have areas of cystic changes. Characteristic cells are elongated and possess oval nuclei. Although they clinically resemble glomus tumors,

Fig. 2A–C (A) An axial T1-weighted MR image (TR = 526; TE = 20) of the distal thigh shows a 1- x 1-cm intermediate signal intensity focal lesion (arrow) in the subcutaneous fat tissues over the adductor canal. (B) An axial T1-weighted fat-saturated MR image (TR = 864; TE = 16) after gadolinium contrast injection at the same level as in (A) shows the lesion enhanced with slight irregular contour. (C) A coronal T2 gradient echo image (TR = 675; TE = 27) shows a lesion of increased signal intensity (arrow) with the presence of chemical shift artifact seen as a low signal intensity over the inferior edge.

Fig. 3A–B (A) The lesion consists of a mass of polygonal cells that are well encapsulated with areas of cystic changes (Stain, hematoxylin and eosin; original magnification, $\times 10$). (B) The cells are monotonous and cuboidal; they have rounded nuclei and eosinophilic cytoplasm (Stain, hematoxylin and eosin; original magnification, $\times 40$).

symptoms are related to an adjacent nerve, which could not be recognized in the present case. Histologic evaluation is also distinctive.

Traumatic neuromas are nonneoplastic proliferations occurring in response to nerve injury [2]. In the absence of correctly positioned distal segments, axons may continue to grow, resulting in a mass of tangled axonal processes. Within this mass, small bundles of axons appear randomly oriented; each, however, is surrounded by organized layers containing Schwann cells, fibroblasts, and perineural cells. Injured neural tissue was not observed in the present case.

Hemangiomas are benign tumors of vascular origin [10, 24, 34]. A subgroup of hemangiomas, the cavernous hemangioma, can bear a remarkable similarity to glomus tumors. They are localized deep in the dermis/subcutaneous tissues, are 1 to 2 cm in size, and have a nodular pattern with a central blue-purple portion. Some may even be tender to touch, but not as exquisite as glomus tumors.

They, however, appear first in childhood. Histologically, they are composed of dilated vascular spaces filled with blood and surrounded with flattened endothelial cells. Diagnosis is clinical and is confirmed by histology.

Leiomyomas are benign smooth muscle tumors that most commonly arise in the uterus but may also present in the erector pili muscles found in the skin [32]. Skin leiomyomas, known as leiomyoma cutis, are frequently painful and may be multiple. They are usually smaller than 2 cm in greatest dimension and are composed of fascicles of spindle cells. They can be readily distinguished histologically.

Benign fibrous histiocytoma, also known as dermatofibroma, are usually seen in adults and often occur on the legs of young to middle-aged women [8, 24]. On gross inspection, these neoplasms are firm, tan-to-brown papules that may flatten with time. The majority of lesions are less than 1 cm in diameter. They may be tender. Dermatofibromas are formed by benign, spindle-shaped fibroblasts arranged in a well-defined, nonencapsulated mass within the middermis. Extension into the subcutaneous fat is frequently observed. They bear similarity to glomus tumors with respect to age at presentation, location, and size. The patient concern, however, is usually cosmetic and not pain. Histology, again, confirms the diagnosis.

Dermatofibrosarcoma protuberans is a rare, recurring, and locally aggressive tumor that usually presents as indurated plaque with protuberant nodules, varying from flesh color to reddish-brown [9, 24]. Initially, it often presents as a scarlike lesion that later develops into nodular, firm, and irregular masses. The tumor is painless. The tumor histologically shows cartwheel-like arrangements of fibroblasts. Distinction from glomus tumors is clinical and histologic. The importance of dermatofibrosarcoma protuberans in the differential is the need for wide margin resection as compared with the other entities. Recurrences do occur and often necessitate a second surgical procedure.

Glomus tumors, also called glomangiomas, are uncommon benign tumors that arise from the normal glomus body located in the subcutaneous tissue [20, 33, 35]. The glomus body is a neuromyoarterial apparatus that regulates blood flow to the skin [33, 35]. They are mostly concentrated in the digits, palms, and soles of the feet, especially under the nail [20, 33, 35]. Classically, they present with a triad of symptoms: pain, pinpoint tenderness, and hypersensitivity to cold [20, 33]. An area of slightly bluish discoloration is frequently found at the site of the lesion [20]. When the patients' complaints are not considered as a triad, the diagnosis can be easily missed [35]. Patients often go undiagnosed or misdiagnosed for many years because the lesions are small, not readily palpable, and have varying presentations [20, 33, 35]. MRI is invaluable for the diagnosis in extradigital glomus tumors [20, 33], but a negative MRI result should not prevent surgical

exploration [6]. Placing a radiographic marker directly over the exact point where the patient experiences pain improves success in surgical localization [33]. The typical appearance of a glomus tumor by MRI is decreased signal intensity on T1-weighted images and increased signal intensity on T2-weighted images.

Grossly, glomus tumors are small, rounded, firm nodules that are slightly elevated and have a red-blue discoloration. Histologically, glomus tumors show aggregates of small, regular, cuboidal cells that arrange about vessels. They have been described in three subtypes [33]. (1) The glomus tumor proper consists of sheets of round cells surrounding capillaries of varying shape. Glomus cells are small, uniform, and rounded with centrally placed nuclei. (2) Glomangioma is characterized by numerous dilated cavernous blood spaces whereby clusters of glomus cells are embedded within the vessel walls. (3) Glomangiomyoma has a gradual transition from typical glomus cells to elongated smooth muscle cells.

Although they are well recognized as a cause of pain in the digits, glomus tumors have erroneously been believed less common in extradigital locations [17, 33]. Extradigital presentations comprised up to 67% of glomus tumors in the recent literature [15, 33]. Their presence in extradigital locations is a diagnostic challenge as they are often missed and confused with other more common problems. Localized pain and tenderness can be detected in 86% of these patients, but cold intolerance occurs in less than 2% [33]. Even when present, the treating physician may not recognize it [29].

An extended duration has been associated with the diagnosis of digital and extradigital glomus tumors. Many of these years are spent visiting multiple physicians and other health professionals without a definitive diagnosis or treatment plan [3, 7, 13, 15, 21–23, 26, 27, 30, 31, 33, 35, 38]. Patients seek medical attention early on, but proper diagnosis and treatment are often late [20, 22, 26, 28, 30]. Most patients are evaluated repeatedly and have their conditions misdiagnosed [15, 19, 26, 28, 33]. According to one report, glomus tumor was considered by the initial physician in only 19% of patients and in less than 50% upon referral to a specialist [17]. When the index of suspicion for a glomus tumor is low, the physician constructs and investigates a list of differential diagnoses that is based on the anatomic site, rather than the nature of the complaint. Upper extremity pain is investigated and treated for radiculopathy [14], shoulder pain for impingement [14], knee pain for meniscal disorders [18], and back pain for spinal cord disorders [3, 15, 31]. Once all these investigations fail, a “functional” or psychiatric basis is considered [1, 4, 7, 19, 36]. Various specialties can be involved in the care of these patients [33]. An average of 2.5 physicians evaluated the patients before the correct

diagnosis was established [35]. A high index of suspicion remains the only clue.

Although pain is the most frequent symptom present, few reports actually provide a feeling of how bad this pain can be. Taken in the context of the number of years that pass until the patient is cured, this description can be shocking. One reported patient described the severity of his pain as being far worse than what he had experienced during angina attacks and coronary bypass surgery [14], while others have demanded amputation or contemplated suicide because of pain [4]. Friction with clothes, stockings, or bedclothes can provoke a severe attack, even while asleep [19, 25, 28].

The most definitive treatment of glomus tumor is surgical excision [17, 20, 33, 35]. Treatments other than this do little to ease the pain. Various nonoperative and alternative modalities have been tried and have failed [4, 14, 18, 28, 30, 31, 33, 35, 38]. Errors in diagnosis have led to inappropriate minimally invasive [26, 38] and traditional surgery [1, 5, 7, 14, 18, 19, 30, 35, 36] that would not relieve symptoms. Nine percent of patients with extradigital glomus tumors underwent at least one invasive procedure before the proper diagnosis was discovered [33]. Recurrence is related mostly to inadequate surgical excision and has been reported mostly in digital tumors as high as 33% [33]. The risk of malignancy and metastatic potential are increased in the presence of malignant histologic features (atypia, increased mitotic activity, and high nuclear grade), large size (> 2 cm), and depth (deep to the muscle fascia or visceral location) [11]. In the presence of these features, a wider margin of resection should be planned for.

Several authors described muscle disuse atrophy in glomus tumors. Marked wasting has been described in the shoulder [37], thigh [1, 4, 7, 16, 18], calf [16, 19], and gluteal muscles [13]. This was reversed partially after surgical resection [4, 16, 18].

Our patient had severe pain, limitation of motion, and weakness of the quadriceps muscle. He had localized hyperesthesia and acute pinpoint tenderness that clinched the diagnosis. His lesion was surgically excised, and his pain was immediately relieved after the resection. Eighteen months later, the patient was still pain free with no evidence of recurrence. The muscle atrophy and weakness had recovered with physical therapy.

Early diagnosis of glomus tumors, especially in the atypical sites, would help save patients from unnecessary suffering and prevent unnecessary procedures from being performed. One should include it in the differential diagnosis of any localized end point tenderness associated with extreme pain, especially on exposure to cold. Patients suffer and extra costs are generated when the index of suspicion for glomus tumor, digital or extradigital, is not high enough.

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