Malignant Granular Cell Tumor of the Thigh

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abstract

Malignant granular cell tumor is a rare neural tumor characterized by abundant granular-appearing tumor cells. These tumors account for <2% of all granular cell tumors. Unlike its benign counterpart, a malignant granular cell tumor presents primarily in the lower limb and is notably larger. Both the uncommon occurrence of malignant granular cell tumors and its similarities in feature with their benign counterparts make diagnosis of this particular malignancy difficult. By 1998, Fanburg-Smith et al developed a diagnostic criteria in which granular cell tumors were divided into 3 categories—benign, atypical, and malignant—based on 6 histological characteristics of the tumor: necrosis, spindling, vesicular nuclei with large nucleoli, increased mitotic activity, high nuclear-to-cytoplasmic ratio, and pleomorphism.

This article presents a case of a large malignant granular cell tumor in the right thigh of a 69-year-old woman. Gross examination of the mass showed the well-demarcated, tan, white tumor measuring 18.2 cm long and 7.6 cm wide at its largest width. Histological examination of the mass, performed by an oncological pathologist, demonstrated foci of tumor necrosis, scattered apoptotic cells, prominent nucleoli, increased nuclear-to-cytoplasmic ratio, increased mitotic activity, and areas of spindling with significant atypia.

To our knowledge, this is the largest reported case of malignant granular cell tumor in the lower limb diagnosed using the histological criteria established by Fanburg-Smith et al. This case stresses the importance of thorough evaluation in instances of atypical granular cell tumor presentations.
Malignant granular cell tumor is a rare, aggressive neural tumor that was first reported by Ravich et al in 1945. Although granular cell tumors are not uncommon, the malignant variation of this tumor represents only 1% to 2% of all granular cell tumors, accounting for <100 reported cases. Benign and malignant granular cell tumors share many characteristics, including higher incidence in women and similar histological features. The uncommon occurrence of malignant granular cell tumors and the shared features with its benign counterpart make diagnosis of malignant granular cell tumors difficult.

In 1998, Fanburg-Smith et al developed a diagnostic criteria in which granular cell tumors were divided into 3 categories—benign, atypical, and malignant—based on 6 histological characteristics of the tumor: necrosis, spindling, vesicular nuclei with large nucleoli, increased mitotic activity, high nuclear-to-cytoplasmic ratio, and pleomorphism. Tumors that exhibited ≥3 of these characteristics prominently throughout the tumor were characterized as malignant. Prior to this study, the diagnosis of malignant granular cell tumors may have been overestimated due to the tumors' abilities to mimic other benign and malignant tumors that demonstrate granular features.

Even with the development of these diagnostic criteria, correctly diagnosing malignant granular cell tumor remains challenging. We present a case of an unusually large malignant granular cell tumor of the thigh, which on core biopsy did not fulfill the criteria of malignant granular cell tumor. On resection, diligent sampling and studying revealed all 6 of Fanberg-Smith et al's criteria. This case highlights the underlying difficulties with which one is faced when confronted with a large atypical granular cell tumor.

CASE REPORT

A 69-year-old woman presented with a 3-month history of a palpable mass in her right thigh. She reported some pain in the area of the mass after prolonged sitting but reported no history of recent trauma to the leg, fevers, chills, or weight loss. The patient reported a history of breast cancer treated with partial mastectomy 14 years ago. On physical examination, a nontender firm mass was palpated in the posterolateral aspect of the distal right thigh. The skin around the mass was intact and no erythema was noted. There was full range of motion in the right lower extremity without pain.

Computed tomography (CT) with contrast of the chest, abdomen, and pelvis showed no evidence of metastatic disease. Computed tomography of the right leg demonstrated a heterogeneous soft tissue mass between the long and short heads of the biceps femoris muscle (Figure 1). Radiologically, the mass extended 14 cm longitudinally and measured 6.7 × 5.4 cm transversely. Positron emission tomography (PET)-CT demonstrated intense uptake, with a standardized uptake value of 15.8, in the distal right thigh without osseous involvement. No additional abnormal fluoride uptake was seen on PET-CT. Magnetic resonance imaging (MRI) revealed increased signal intensity on the T2-weighted image (Figure 2A) and decreased signal intensity on the T1-weighted image (Figures 2B, C).

Core needle biopsy of the mass showed abundant granular cytoplasm with several foci that demonstrated nuclear pleomorphism. The degree of atypia could not be fully appreciated in the original core biopsy. Study of the core biopsy showed tumor cells to be positive for S-100 and periodic acid-Schiff, but dem-
Case Report

A diagnosis of granular cell tumor was made.

The decision to resect with a marginal excision was made, as a malignant diagnosis was not inferred on the core biopsy. Gross examination of the mass showed the well-demarcated, tan, white tumor measuring 18.2 cm long and 7.6 cm wide at its largest width (Figure 3). Histological examination of the mass, performed by an oncological pathologist (J.R.), demonstrated foci of tumor necrosis, scattered apoptotic cells, prominent nucleoli, increased nuclear-to-cytoplasmic ratio, increased mitotic activity, and areas of spindling with significant atypia (Figure 4). Immunohistochemical panel revealed tumor cells in multiple fields showing positivity for S-100 and focal positivity for p53. Ki-67 generally showed <2% positivity with areas of increased (>10%) proliferative activity (Figure 5). The margins of the tumor were interpreted as negative. After thorough evaluation of the pertinent parameters, the final diagnosis was malignant granular cell tumor. One month postoperatively, the patient was well and informed of the need for surveillance for local recurrence and distant disease.

Discussion

Malignant granular cell tumor is a rare soft tissue tumor that is characterized by cells showing coarse granular eosinophilic cytoplasm similar to that seen in benign granular cell tumors. Of all granular cell tumors, <2% can be diagnosed as malignant. The difficulty in diagnosing malignant granular cell tumors lies in its overlapping features with benign granular cell tumors, as well as with other benign and malignant tumors that present with granular-appearing tumor cells.3,4 Similar to benign granular cell tumors, malignant granular cell tumors have a higher incidence in women between ages 40 and 60 years and usually present as painless masses.2

Although malignant and benign granular cell tumors share many clinical characteristics, the 2 distinct clinical characteristics of malignant granular cell tumors are larger average size and frequent localization to the lower limbs.5,6 Malignant granular cell tumors typically present as larger painless masses, with a median size of 4 to 5.0 cm, as compared to benign tumors, which in most cases are <3 cm.2,3,5 A review of literature by Blacksin et al7 reports that, unlike benign granular cell tumors, which commonly occur in the head, neck, and tongue, malignant granular cell tumors primarily occur in the lower extremity. In a study by Tsuchida et al,5 the authors reported the incidence of a malignant granular cell tumor presenting in the lower limb to be 26.8%, while Strong et al6 reported the incidence of a benign granular cell tumor occurring in the lower limb to be 6.4%. Although size and location should raise suspicion for a malignant granular cell tumor, definitive diagnosis is only given after histological criteria of malignancy is met.

In light of the difficulties found in diagnosing malignant granular cell tumors, Fanburg-Smith et al3 developed a criteria based on 6 histological characteristics that divided granular cell tumors into benign, atypical, and malignant. The key histological features include necrosis, spindling, vesicular nuclei with large nucleoli, increased mitotic activity (>2 mitoses/10 high-power field at 200× magnification), high nuclear-to-cytoplasmic ratio, and pleomorphism. Malignancy was defined as a tumor that met ≥3 of the criteria, whereas atypical tumors were those that presented with 1 or 2 characteristics. The pertinent features must be prominent within the tumor and not simply a focal change. Benign tumors demonstrated only focal pleomorphism.3 Our case demonstrated positivity in all 6 characteristics on multiple slides.

Figure 3: Intraoperative photograph showing a large mass measuring >15 cm (A). Gross photograph showing a fairly well circumscribed homogeneous finely granular tan cut section of the tumor mass (B).

Figure 4: Low-magnification micrograph (40× magnification) showing diffusely infiltrating tongues and cords of the neoplasm in a desmoplastic background (A). High-magnification micrograph (200× magnification) showing characteristic spindle cell configuration with nuclear enlargement, atypia, and prominent nuclei (B). Figure 5: Ki-67 stain showing an area of high proliferative activity manifested by nuclear staining involving >10% of cells.
Although not part of the diagnostic criteria for malignant granular cell tumor, immunohistochemical analysis may assist in the confirmation of the disease. Fanburg-Smith et al\(^3\) report that benign, atypical, and malignant granular cell tumors demonstrated positivity in S-100 protein in almost all cases, while positivity in Ki-67 and p53 were more typically found in malignant granular cell tumor. These characteristics were found positive in the excised mass.

To our knowledge, this case demonstrates one of the largest cases of malignant granular cell tumor of the lower limb in the English literature. Wieczorek et al\(^8\) reported a case of malignant granular cell tumor that extended along the tibial nerve, but the actual full dimensions of the tumor were not given, nor did the tumor demonstrate intramuscular involvement. Another case by Donhuijzen et al\(^6\) reported a malignant granular cell tumor spanning 20 cm in the thigh, but was written prior to the development of the diagnostic criteria of malignant granular cell tumors.

Currently, the gold standard for diagnosing soft tissue tumors is through an open biopsy,\(^{10-12}\) but due to the costliness, complications, and inconvenience, a simpler procedure like core needle biopsy is often performed. In a recent study by Kasraein et al,\(^11\) the authors analyzed the diagnostic accuracy of open, core needle, and fine needle biopsies standardized by using the same mass for all 3 biopsies. They demonstrated that sensitivity of core needle biopsy in determining malignancy was 79.4%, while other studies showed a sensitivity ranging from 82% to 100%. In analyzing these and other findings, it can be determined that, although core needle is a safer and more cost-effective way of diagnosing soft tissue tumors, identification of malignancy might not be apparent, as in our case, because of the potential for sampling error. This factor, compounded with the histological similarities between benign granular cell tumor and malignant granular cell tumor, can lead to difficulties in arriving at a diagnosis of malignant granular cell tumor in a limited core biopsy sample.

To avoid under-diagnosing a malignant granular cell tumor, it is important to take into account all clinical, radiographic, and histological features. The original biopsy of our patient demonstrated a granular cell tumor without specific mention of malignancy. Nonetheless, the tumor presented unlike most benign granular cell tumors, as it was extremely large in size and presented in the lower limb. Presentation of unusual characteristics of granular cell tumor, as in our case, should lead one to consider the potential of malignancy. When faced with atypical but inconclusive features, a second biopsy may be necessary. Another alternative is to perform an excision of the mass with adequate surgical margins, as was done in a report by Tsuchida et al\(^7\) of a malignant granular cell tumor originally diagnosed as benign.

**References**