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Malignant granular cell tumor of the foot—multimodality imaging findings and literature review☆

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ABSTRACT

We describe how the combination of imaging and histologic findings was essential in establishing a preoperative diagnosis of an extremely rare malignant granular cell tumor (GrCT) occurring in the lower extremity of a 17-year-old man. Magnetic resonance imaging demonstrated a large infiltrative tumor of heterogeneous intermediate signal intensity on both T1- and T2-weighted sequences. Subsequent computed tomography (CT) and fluorodeoxyglucose positron emission tomography CT scans of the patient revealed distant nodal and skeletal metastases.

1. Introduction

Granular cell tumors (GrCTs) were first described by Abrikossoff in 1926 [1] and originally termed as "granular cell myoblastomas." Fischer and Wechsler subsequently demonstrated histiogenesis of this tumor from Schwann cells [2]. Histologically, these tumors are characterized by discrete or locally infiltrative proliferation of large cells with small central nuclei and abundant granular cytoplasm. These cells typically stain positive for S-100 protein and often for neuron specific enolase and various myelin proteins, thereby supporting a neurogenic origin [3].

Clinically, GrCTs are rare, accounting for 0.5% of all soft tissue tumors. The tumor is benign in the majority of cases, and these are often associated with excellent outcomes following surgical resection [4]. Malignant variants comprise 0.5–2% of all GrCT and are extremely rare. Patients with these tumors often have poor surgical outcomes and are associated with high potential for local recurrence and distant metastasis [3].

Although Fanburg-Smith et al. [3] have reported histologic criteria for malignant GrCTs, these are not without their limitations [5]. This notwithstanding, histopathologic correlation with the magnetic resonance imaging (MRI) features of GrCT has been made by several authors in an attempt to distinguish the malignant variants of this tumor from their benign counterparts [4–8]. We present a case of a patient with a malignant GrCT of the lower extremity with regional nodal and distant skeletal metastases, in which the combined imaging findings from MRI, computed tomography (CT) and fluorodeoxyglucose (FDG) positron emission tomography (PET) CT served as important adjuncts to histopathologic results from core needle biopsy in the patient's preoperative treatment planning.

2. Case report

A 17-year-old Chinese man presented to the Musculoskeletal Tumor Clinic with the primary complaint of persistent left foot swelling since sustaining an apparent injury to his left foot while participating in sports 5 months prior to his presentation. He was otherwise well, with no significant foot pain at the time of clinical presentation.

Physical examination revealed an irregular and hard mass that was most prominent over the dorsal, medial, and lateral aspects of the patient's midfoot. It was difficult to ascertain the true dimensions of the mass clinically. There was no abnormal discoloration of the skin overlying the mass itself.

Plain radiographs showed extensive mixed sclerotic and lytic appearance of the talus. There was also significant sclerosis of the navicular and cuboid bones, as well as the anterior process of the calcaneus (Fig. 1). Soft tissue swelling without abnormal soft tissue mineralization was also observed over the dorsal, medial, and lateral aspects of the patient's midfoot.

Corresponding MRI images demonstrated an ill-defined, infiltrative soft tissue mass in the patient's midfoot and anterior hindfoot regions, which showed heterogeneous intermediate signal intensity on both T1- and T2-weighted sequences (Fig. 2a and b). There was

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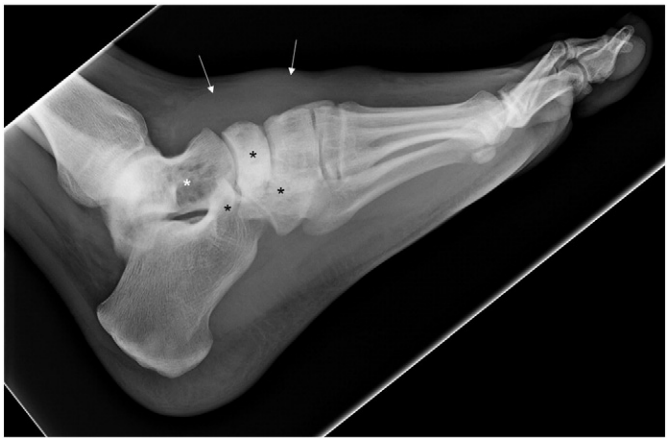

Fig. 1. A 17-year-old man with a malignant GrCT of the left foot. Lateral radiograph of the left foot demonstrates sclerosis of the navicular and cuboid bones as well as the anterior process of the calcaneus (black asterisks). There is mixed sclerotic–lytic change of the talus (white asterisk). Soft tissue swelling was also present over the dorsal aspect of the midfoot (white arrows).

also evidence of mixed low-to-intermediate T1-weighted hypointense signal replacing the normal marrow fat signal of the bones that were seen to be involved on the prior radiographs, namely, the talus, navicular, and cuboid bones. Patchy intermediate T2-weighted signal seen within these bones and those within the anterior process of the calcaneus were deemed suspicious for tumor involvement. Based on the radiographic and MRI findings, the main differential diagnoses for the patient's infiltrative left foot mass included pigmented villonodular synovitis, synovial sarcoma, and a chronic mycobacterial or fungal infection.

Subsequent PET-CT showed intense FDG avidity (maximum standardized uptake value of 13.82) of the left midfoot and anterior hindfoot, corresponding to the site of the soft tissue mass and areas of bony involvement as seen on radiographs and MRI (Fig. 3). PET-CT also revealed FDG avid lymph nodes measuring up to 1.6 cm in the left inguinal region as well as 1.9 cm within the left popliteal fossa, and these were deemed highly suspicious for nodal metastases. Scattered sclerotic lesions with abnormal FDG avidity were detected in the sternum, lumbosacral spine (Fig. 4), and right calcaneus. There was also a lytic expansile lesion in the anterior aspect of the left sixth rib with intense avidity on PET-CT (Fig. 5).

Ultrasound-guided core needle biopsy of the left foot mass was subsequently performed using a 14G Quick-Core biopsy needle (Cook Medical, Bloomington, IN, USA) via a dorsal approach. The patient declined further biopsy of the sites of distant skeletal and nodal involvement. Under light microscopy, the core biopsies from the primary tumor depicted a proliferation of rounded polygonal cells with eosinophilic, granular cytoplasm. These cells showed cytologic atypia, scattered pleomorphism, tumor cell necrosis, and a mitotic rate of about 5–6 per 10 high-power fields (Fig. 6a and b). Immunostains of the tumor cells were positive for S-100, Sox-10, and CD68, with a 15–20% Ki-67 labeling index. These findings were consistent with a malignant variant of a GrCT, as supported by the increased mitotic activity, tumor cell necrosis, and cytologic atypia [3]. Fluorescence in situ hybridization assay used to detect the presence of rearrangement of the EWSR1 gene locus was negative, which helped us to exclude a granular cell variant of a clear cell sarcoma.

Following discussion at the multidisciplinary tumor board, preoperative radiotherapy followed by surgical amputation of the patient's foot was recommended for local treatment of the primary tumor. However, the patient declined surgery and radiotherapy, electing to proceed with a trial of systemic chemotherapy consisting of crizotinib and pazopanib. Follow-up PET-CT performed following 4 cycles of systemic chemotherapy demonstrated a mixed response, in terms of reduction in size and

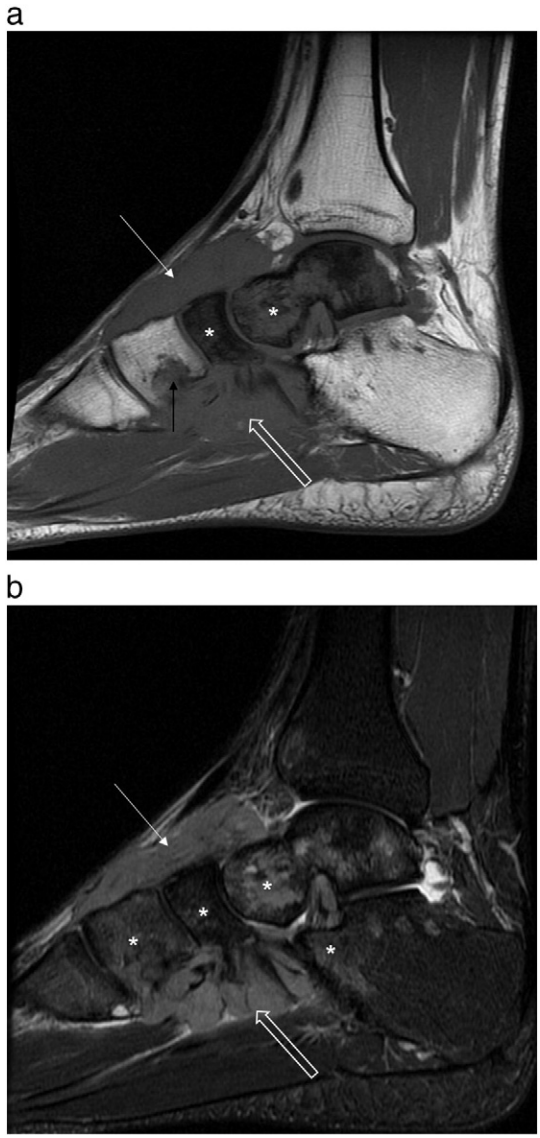

Fig. 2. (a) Sagittal T1-weighted image of a 17-year-old man with a malignant GrCT of the left foot. The soft tissue mass over the dorsal aspect (white arrow), which infiltrates the deep plantar compartment (open white arrow), demonstrates diffuse intermediate T1-weighted signal intensity. Mixed low-to-intermediate T1-weighted hypointensity replacing the normal fatty marrow signal of the talus and navicular bones (white asterisks) is suspicious for tumor involvement. Tumor infiltration of the medial cuneiform is also noted (black arrow). (b) Sagittal T2-weighted fat-suppressed image of a 17-year-old man with a malignant GrCT of the left foot. There is intermediate T2-weighted signal intensity of the infiltrative mass over the dorsal aspect of the midfoot (white arrow), which infiltrates the deep plantar compartment of the midfoot and anterior hindfoot (open white arrow). Patchy intermediate T2-weighted marrow signal intensity suspicious for tumor involvement is most pronounced within the talus and is also seen in the anterior process of the calcaneus, navicular, and medial cuneiform bones (white asterisks).

FDG uptake by the primary tumor in the left foot, while an increase in the number and size of the multifocal skeletal lesions consistent with progression of metastatic disease was noted.

3. Discussion

GrCT may be found in any part of the body, with 40–60% of lesions found in the head and neck region and the tongue being most frequently involved [9]. A significant proportion of these tumors are also thought to occur in the extremities, with Tsuchida et al. describing 16 out of 41 (39%) malignant GrCTs involving the upper and lower extremities in their case report and review of the literature [6]. Tsuchida and his