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CASE REPORT

Malignant granular cell tumor of the median nerve: a case report with a literature review of 157 cases

Shinji Tsukamoto[1] · Maiko Takeda[2] · Kanya Honoki[1] · Shohei Omokawa[1] · Yasuhito Tanaka[1]

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Abstract

Malignant granular cell tumors are an extremely rare, high-grade sarcoma with a schwannian phenotype and are composed of malignant granular cells with cytoplasmic lysosomal inclusion. To date, 157 cases of malignant granular cell tumors have been reported. We report the first case of a malignant granular cell tumor arising from the digital nerve to the median nerve in the palm, and we review the 157 previously reported cases and summarize the clinical profile, treatment, and outcome of this tumor. The median age, tumor size, and follow-up periods were 51 years, 6 cm, and 24 months respectively. With respect to the oncological result, 53 patients (33.8%) had no evidence for disease, 31 (19.7%) were alive with the disease, and 51 (32.5%) died because of the disease. Our case report indicates that rare malignant tumors can arise from the digital nerve to the median nerve in the palm, an anatomical site that is usually affected by benign lesions. Exhaustive discussions between surgeons and pathologists are necessary for the treatment of this rare malignant tumor.

Keywords Malignant granular cell tumor · Granular cell tumor · Median nerve · Nerve sheath tumor

Introduction

Malignant granular cell tumors constitute an extremely rare high-grade sarcoma with a schwannian phenotype and are composed of malignant granular cells with cytoplasmic lysosomal inclusion [1]. One hundred and fifty-seven cases of malignant granular cell tumors have been reported so far [1–103]. These tumors arise in a variety of sites, including the head and neck, digestive tract, trunk, chest, mediastinum, urinary bladder, and extremities [1–103]. Malignant granular cell tumors of the palm have not been previously reported in the literature, whereas 16 cases of malignant granular cell tumors arising from the peripheral nerves have been reported to date [16, 19, 24, 40, 41, 45, 50, 52, 54, 66, 67, 74, 80, 83, 101, 103]. To our knowledge, malignant granular cell tumors arising from the digital nerve to the median nerve have not been previously reported. In this paper, we present the first case of a malignant granular cell tumor arising from the digital nerve to the median nerve. We review the 157 previously reported cases, which is the largest number of malignant granular cell tumors to have ever been reviewed, and summarize the clinical profile, treatment, and outcome of this tumor.

Case report

A 67-year-old woman with a history of chronic thyroiditis noticed a mass of about 1 cm in her right palm 6 years previously. Two years ago, she visited her former hospital, and a magnetic resonance imaging (MRI) scan was performed, which revealed a 4- × 1-cm fusiform mass that displayed intermediate intensity on T1-weighted imaging (Fig. 1a) and slightly high intensity on T2-weighted imaging (Fig. 1b). The entire tumor was located between the flexor tendons of the index and middle fingers, with a slight invasion of the flexor tendon, along the digital and median nerves, and had the appearance of a schwannoma on MRI. She had no sensory or motor deficits of the digital and median nerves.

✉ Shinji Tsukamoto
shinji104@mail.goo.ne.jp

[1] Department of Orthopaedic Surgery, Nara Medical University, 840, Shijo-cho, Kashihara-city, Nara 634-8521, Japan

[2] Department of Diagnostic Pathology, Nara Medical University, Kashihara, Nara, Japan

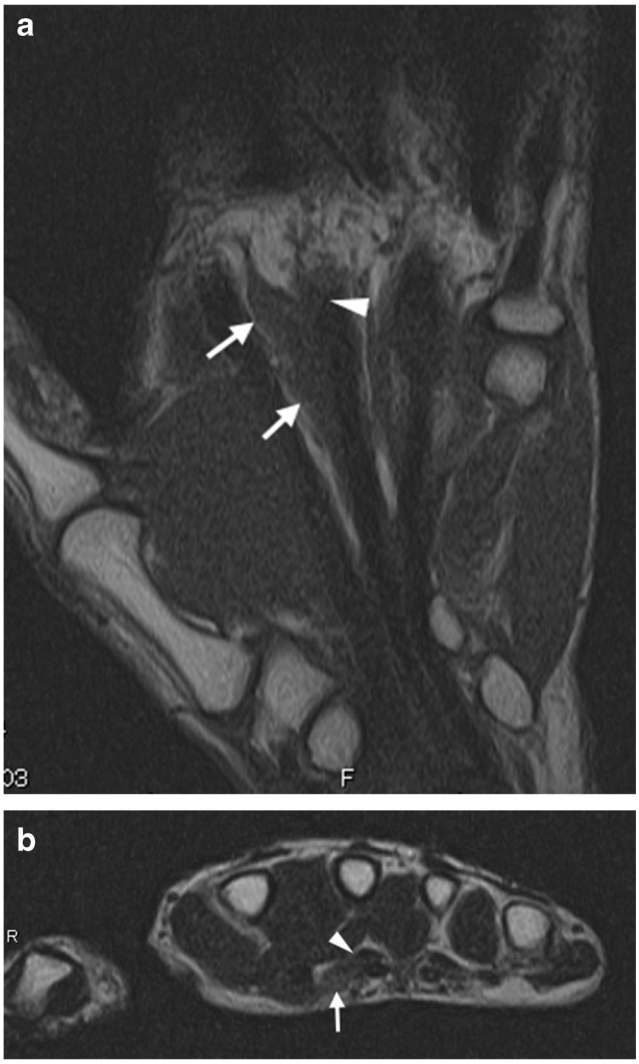

Fig. 1 Magnetic resonance images taken in the previous hospital, 1 and 5 years before the operation. **a** Coronal T1-weighted (TR/TE = 400/15) and **b** axial T2-weighted (TR/TE = 3,500/90) images. The lesion was a 4- × 1-cm fusiform mass, displaying intermediate intensity on T1-weighted images (*arrows*) and slightly high intensity on T2-weighted images (*arrow*). The tumor was located between the flexor tendons of the index and middle fingers, with a slight invasion of the flexor tendon (*arrowhead*), along the digital and median nerves

A marginal resection was performed at her previous hospital, 7 months ago. The tumor was removed, including the digital nerves on the ulnar side of the index finger and the radial side of the middle finger, as the tumor was attached to these two nerves (Fig. 2). The lesion consisted of sheets and nests of round to short spindle cells with granular and eosinophilic cytoplasm. The tumor cells had mild to moderate nuclear atypia and occasionally prominent nucleoli, although nuclear pleomorphism was mild. Mitotic figures were rare, and necrosis was absent. The tumor was histopathologically diagnosed as a granular cell tumor with atypical features (Fig. 3). Subsequently, the patient again noticed a mass in her

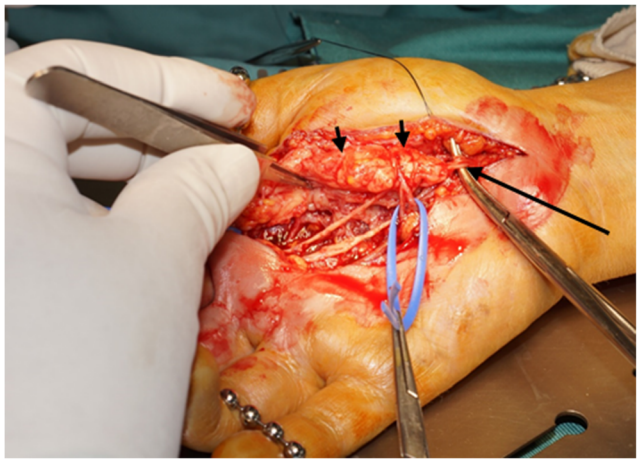

Fig. 2 Operative photograph taken in the previous hospital showing that the tumor (*short arrows*) was attached to the digital nerves on the ulnar side of the index finger and the radial side of the middle finger (*long arrow*)

palm 3 months after the operation. Six months after the operation, her MRI showed a lobulated tumor, measuring 6.4 × 4.4 × 3.0 cm, and displaying homogeneous intermediate intensity on T1-weighted imaging (Fig. 4a), heterogeneous high intensity on T2-weighted imaging (Fig. 4b), and intense enhancement on fat-suppressed T1-weighted imaging, after contrast medium injection (Fig. 4c). Perilesional edema was visible on fat-suppressed T1-weighted imaging, after contrast medium injection (Fig. 4c). The tumor appeared to be connected to the median nerve. F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) showed increased FDG uptake in the right palm, with no other abnormal uptake

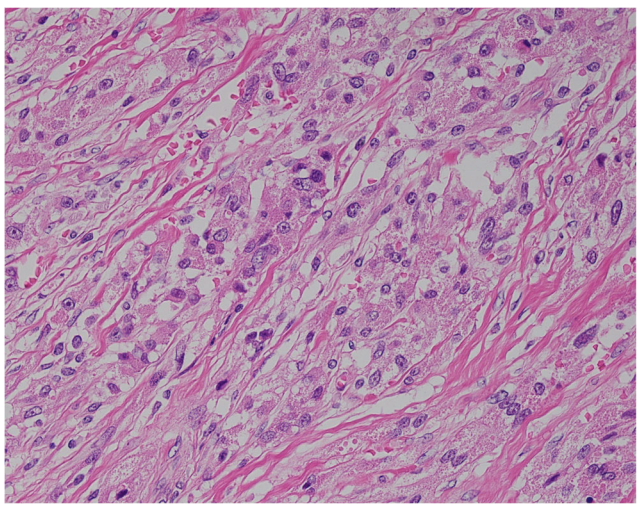

Fig. 3 Histopathological features of the tumor at the first operation (hematoxylin and eosin; ×400 magnification). The lesion consisted of sheets of round to short-spindle atypical cells, with granular and eosinophilic cytoplasm

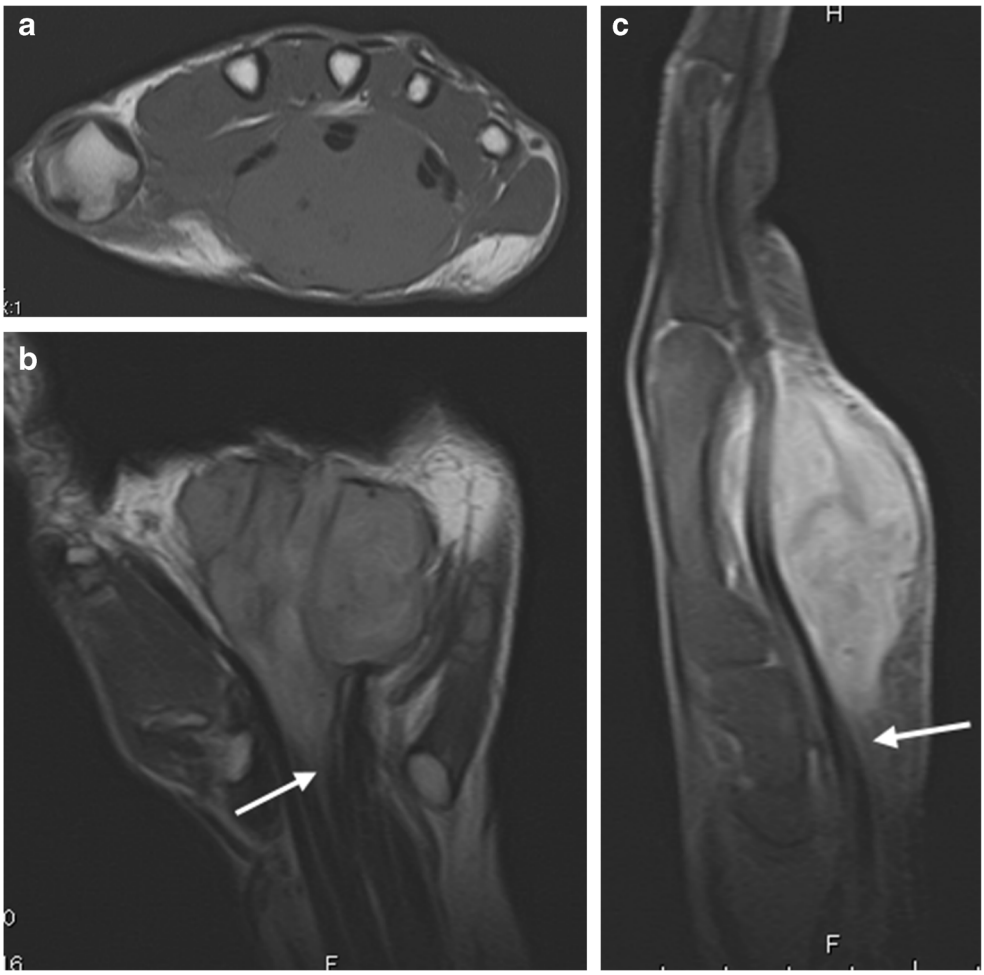

Fig. 4 Magnetic resonance images that were taken 6 months after the operation in the previous hospital. **a** Axial T1-weighted (TR/TE = 510/15), **b** coronal T2-weighted (TR/TE = 2,950/90), and **c** sagittal fat-suppressed T1-weighted images after contrast medium injection (TR/TE = 400/15). The lobulated tumor measured 6.4 × 4.4 × 3.0 cm and displayed homogeneous intermediate intensity on T1-weighted images, heterogeneous high intensity on T2-weighted images, and intense enhancement after contrast medium injection. A perilesional edema was visible on fat-suppressed T1-weighted images after contrast medium injection. The tumor appeared to be connected to the median nerve (*arrows*)

(Fig. 5). A malignant granular cell tumor was suspected, owing to the history of local recurrence, rapid recent growth, and large tumor dimension, and the patient was referred to our hospital.

Upon clinical examination, a fixed, elastic hard mass was palpated. Contrast-enhanced computed tomography showed a lobulated tumor, measuring 5.2 × 5.0 × 3.5 cm, with relatively distinct boundaries and heterogeneous enhancement (Fig. 6). A needle biopsy was performed, and the tumor was histopathologically consistent with recurrence of the granular cell tumor. Therefore, an intralesional resection and a free peroneal flap with a vascularized nerve graft were performed. A free flap, rather than a pedicled flap, was selected, to prevent the tumor from spreading into the forearm, which can occur in cases of malignant granular cell tumors. The tumor was removed, including the median nerve, ulnar artery, and all digital nerves except for those on the ulnar side of the little finger; all of the flexor tendons were preserved. Postoperatively, anastomotic thrombosis occurred; the thrombus was immediately removed, and the blood vessels were anastomosed again. Unfortunately, the flap was lost owing to total necrosis. A skin graft was successfully performed, after two debridements.

The surgically removed specimen consisted of a yellowish-white, irregular, and firm mass, measuring 5.2 × 5.0 × 4.0 cm. Histopathologically, the ill-defined lesion was located below the subcutaneous tissue, was composed of proliferating atypical oval epithelioid or short-spindle cells with hyperchromatic or vesicular nuclei, prominent nucleoli, and fine granular eosinophilic cytoplasm, admixed with larger pleomorphic cells that were arranged in nests or cords and embedded in a fibrocollagenous stroma. Mitotic figures were occasionally encountered (3–4/10 high-power fields at ×200 magnification). Foci of the necrotic area were identified, and some involved nerve plexuses were observed at the tumor periphery (Fig. 7). Immunohistochemically, the tumor cells were positive for S-100 protein and CD68 and negative for cytokeratins (CAM5.2, AE1/AE3), EMA, smooth muscle actin, desmin, CD34, and h-caldesmon. The Ki-67 (MIB1) labeling index was 10% (Fig. 8), and the final pathological diagnosis was a malignant granular cell tumor. Below-elbow amputation was needed for resection with a wide margin; however, the

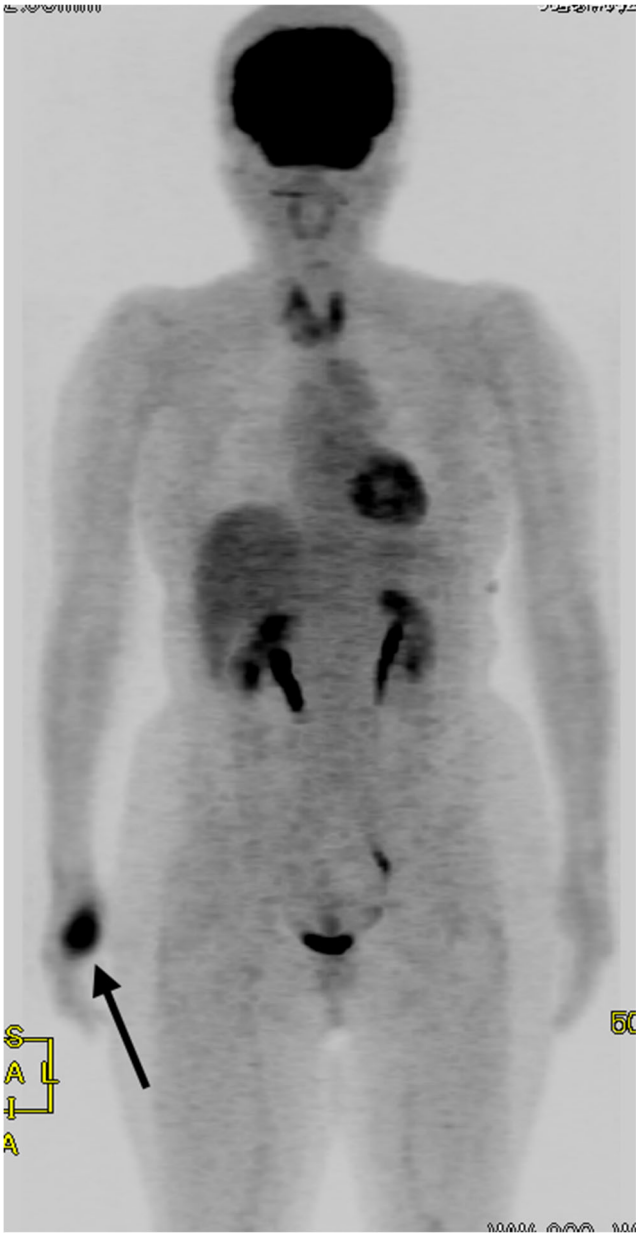

Fig. 5 F-18 fluorodeoxyglucose (FDG) positron emission tomography images showing increased FDG uptake in the right palm (*arrow*) and no uptake in other locations. The maximum standardized uptake value of the lesion was 6.9

patient refused. Five months after the operation in our hospital, an MRI of the hand revealed local recurrence and pazopanib was administered, because of a case report of a patient with a metastatic malignant granular cell tumor who had a dramatic response to pazopanib [85]. However, pazopanib treatment was ceased 2 weeks after initiation because of liver dysfunction. Radiotherapy was started 6 months after the operation, and subsequent PET and contrast-enhanced computed tomography scans showed neither distant nor lymph node metastases.

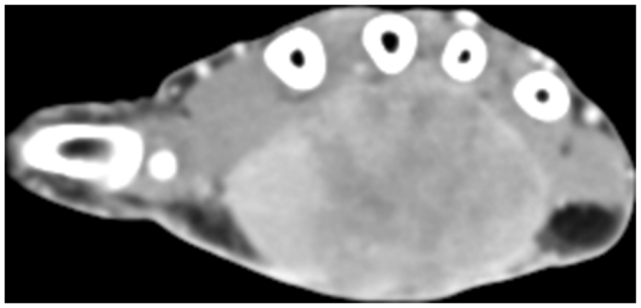

Fig. 6 Contrast-enhanced computed tomography showing a lobulated tumor measuring 5.2 × 5.0 × 3.5 cm, with relatively distinct boundaries and heterogeneous enhancement

Discussion

We report to our knowledge the first case of a malignant granular cell tumor arising from the digital nerve to the median nerve in the palm. So far, 157 cases of malignant granular cell tumors have been reported, based on our extensive search of the English- and Japanese-language literature [1–103]. We summarized the clinical profiles, treatments, and outcomes of these cases in Table 1 [1–103]. Moreover, we summarized 16 cases of malignant granular cell tumors that arose from named peripheral nerves in Table 2 [16, 19, 24, 40, 41, 45, 50, 52, 54, 66, 67, 74, 80, 83, 101, 103]. The population of malignant granular cell tumors that arose from named peripheral nerves was female-predominant at a ratio of 1.7:1 and the median age was 49.5 years (interquartile ratio [IQR] 36.0–63.0). The most frequent primary site was the trunk (6 cases, 37.5%) followed by the upper extremities (5 cases, 31.3%), and the lower extremities (5 cases, 31.3%). The median tumor diameter was 5.5 cm (IQR 3.1–9.8). Regarding clinical symptoms, 8 patients (50.0%) had noted a mass, 9 (56.3%) had pain, and 5 (31.3%) had palsy. Fifteen patients (93.8%) underwent tumor excision, 4 (25.0%) underwent radiation, and 4 (25.0%) underwent chemotherapy. The median follow-up period was 16.0 months (IQR 11.0–38.5). Four patients (33.3%) had no evidence for disease, 4 (33.3%) were alive with the disease, and 4 (33.3%) died because of the disease. Four patients (33.3%) experienced local recurrence, 3 (25.0%) lymph node metastasis, and 7 (58.3%) distant metastasis.

The pathological discrimination of malignant from benign granular cell tumors is not yet well established. The most accepted histological criteria for diagnosing malignant granular cell tumors were established by Fanburg-Smith et al. [1]. These researchers proposed the following six histological criteria for the diagnosis of atypical or malignant granular cell tumors in their study of 73 cases of granular cell tumors: necrosis, spindling of the tumor

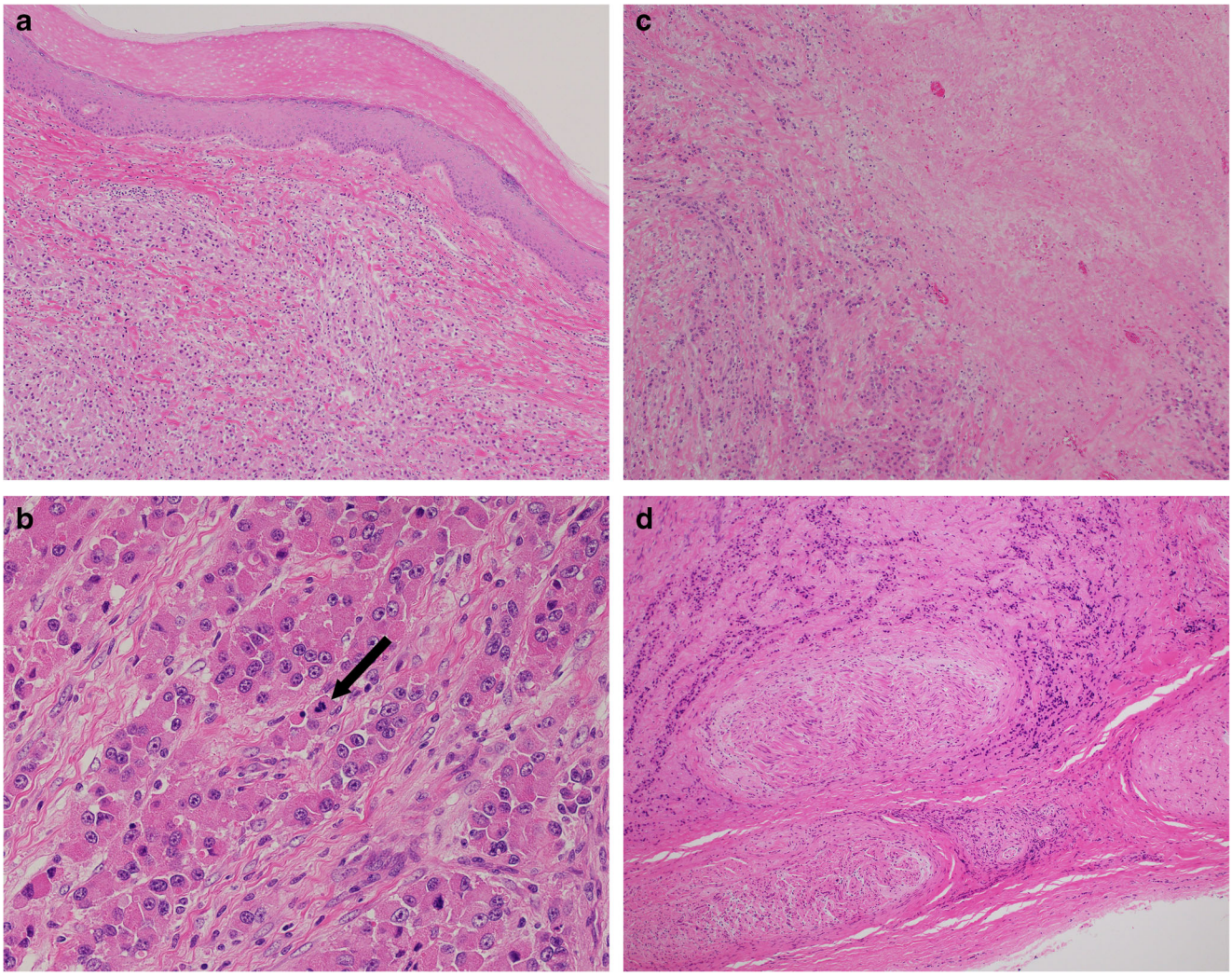

Fig. 7 Histopathological features of the recurrent tumor (hematoxylin and eosin; **a**, **c**, **d**: ×100, **b**: ×400 magnification). **a** The tumor was an ill-defined lesion, located beneath the subcutaneous tissue. **b** The tumor was composed of proliferating, atypical oval or short spindle cells, with occasional mitosis (*arrow*). **c** Necrosis foci were found. **d** Nerve plexuses in the periphery were involved

cells, vesicular nuclei with large nucleoli, an increased mitotic rate (>2 mitoses/10 high-power fields at ×200 magnification), a high nuclear-to-cytoplasmic ratio, and pleomorphism. They selected the fulfillment of 3 out of 6 pathological criteria as the cut-off for malignancy because cases with 2 or fewer criteria had never metastasized or resulted in death [1]. However, they also stated the possibility that this cut-off might not be low enough.

Histopathologically, the original tumor contained some malignant features, although we were unable to diagnose it as malignant. The recurrent tumor met all six Fanburg-Smith criteria for classification as malignant; therefore, it was diagnosed as malignant. In this case, after recurrence, the original lesion was reviewed and diagnosed as malignant, whereas malignant granular cell tumor cases that progressed from a benign granular cell tumor after recurrence have been reported [49, 51, 78].

Enzinger and Weiss highlighted several factors for suspecting malignant granular cell tumors, including a history of local recurrence, rapid recent growth, and a large tumor diameter (more than 5 cm in size) as several cases presented malignant clinical courses despite their histologically mild atypia [104]. In our case, because the tumor recurred postoperatively and increased in size to more than 5 cm within 6 months, its malignant potential was suspected. However, we were unable to perform an amputation without histological confirmation of a malignant tumor. Although it is apparent that wide resection, irrespective of regional lymph node dissection, is the conventional treatment, the therapeutic effects of radiotherapy and chemotherapy are debatable [93]. Exhaustive discussions between surgeons and pathologists are necessary for the treatment of this rare malignant tumor. The median tumor size of the malignant granular cell tumors listed in Table 1 is

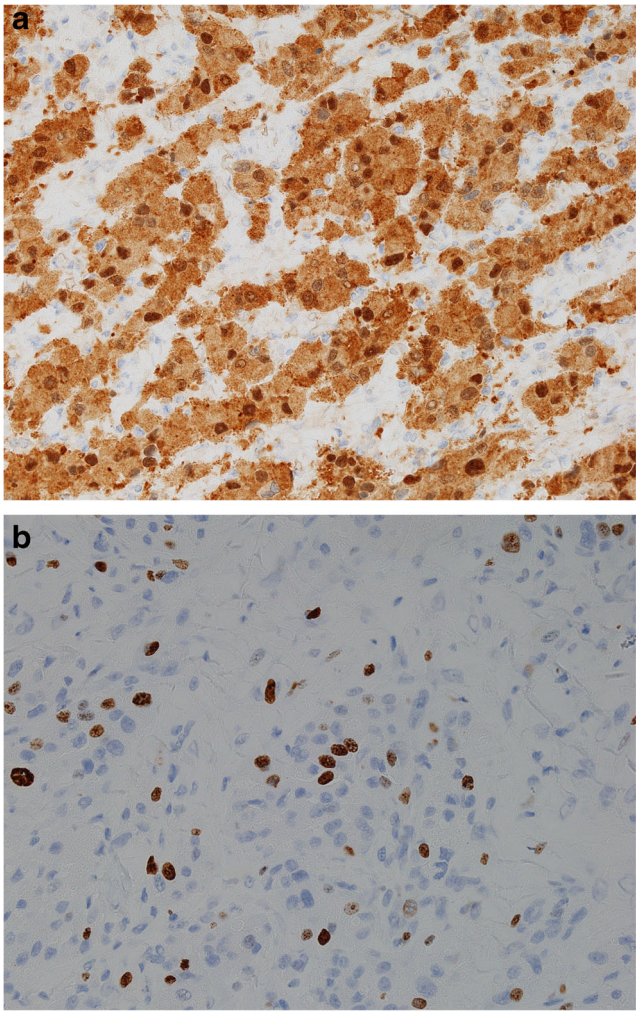

Fig. 8 Immunohistochemically, the tumor cells were positive for S-100. The Ki-67 labeling index was 10% (**a**: S-100, **b**: Ki-67, ×400 magnification)

6 cm. Therefore, tumors that are larger than 5 cm in size should raise the suspicion of malignancy, as Enzinger and Weiss suggested [104].

Magnetic resonance imaging characteristics of malignant granular cell tumor were frankly infiltrating the adjacent bone, bone marrow edema, and necrosis within the lesion [63]. In our case, MRI of the recurrent tumor showed that the lobulated tumor displayed homogeneous intermediate intensity on T1-weighted images, heterogeneous high intensity on T2-weighted images, and invasion of adjacent structures on fat-suppressed T1-weighted images after contrast medium injection (Fig. 4). MRI at initial presentation in the previous hospital showed slight invasion of the flexor tendon, which may have given a clue to the suspected malignancy (Fig. 1). Contrast-enhanced computed tomography characteristics of malignant granular cell tumor were central hypodense areas consistent with necrosis or a heterogeneous mass with

Table 1 Literature review of 157 malignant granular cell tumors

Characteristics	Data (%)
Age (years)[a]	
Median	51
IQR	38.0–62.5
Sex	
Male	58 (36.9)
Female	99 (63.1)
Tumor site	
Head	11 (7.0)
Neck	9 (5.7)
Trunk	43 (27.4)
Chest	3 (1.9)
Mediastinum	3 (1.9)
Breast	5 (3.2)
Gastrointestinal tract	9 (5.7)
Genitourinary system	5 (3.2)
Axilla	4 (2.5)
Upper arm	9 (5.7)
Forearm	7 (4.5)
Finger	2 (1.3)
Buttock	9 (5.7)
Thigh	26 (16.6)
Lower leg	5 (3.2)
Foot and ankle	3 (1.9)
Multiple subcutaneous tissue	3 (1.9)
Unknown	1 (0.6)
Tumor size (cm)[b]	
Median	6.0
IQR	3.0–10.0
Symptom	
Mass	
Yes	64 (40.8)
No	39 (24.8)
Unknown	54 (34.4)
Pain	
Yes	35 (22.3)
No	68 (43.3)
Unknown	54 (34.4)
Palsy	
Yes	6 (3.8)
No	97 (61.8)
Unknown	54 (34.4)
Treatment	
Excision	
Yes	138 (87.9)
No	10 (6.4)
Unknown	9 (5.7)
Chemotherapy	
Yes[c]	27 (17.2)
No	90 (57.3)
Unknown	40 (25.5)
Radiation	
Yes	28 (17.8)
No	89 (56.7)
Unknown	40 (25.5)
Follow-up period (months)[d]	
Median	24
IQR	12–48
Outcome	
No evidence of disease	53 (33.8)
Alive with disease	31 (19.7)
Died of disease	51 (32.5)
Died of unrelated disease	3 (1.9)
Unknown	19 (12.1)
Local recurrence	
Yes	55 (35.0)

Table 1 (continued)

Characteristics	Data (%)
No	79 (50.3)
Unknown	23 (14.6)
Lymph node metastasis	
Yes	47 (29.9)
No	90 (57.3)
Unknown	20 (12.7)
Distant metastasis	
Yes	71 (45.2)
No	65 (41.4)
Unknown	21 (13.4)

IQR interquartile range

[a] Age unknown in 4 patients

[b] Size unknown in 19 patients

[c] Includes 2 patients treated with pazopanib and 1 patient treated with imatinib

[d] Follow-up period unknown in 16 patients

areas of cystic changes, as in our case [80, 95]. Increased FDG uptake by a malignant granular cell tumor has been reported, with maximum standardized uptake values ranging from 5.8 to 20.5 [81, 82, 90].

Tumors arising from peripheral nerves include schwannoma, melanotic schwannoma, neurofibroma, perineurioma, granular cell tumor, dermal nerve sheath myxoma, solitary circumscribed neuroma, ectopic meningioma/meningothelial hamartoma, nasal glia heterotopia, benign triton tumor, hybrid nerve sheath tumors, malignant peripheral nerve sheath tumor, malignant granular cell tumor, and ectomesenchymoma [105]. Most soft-tissue tumors of the hand are benign [106]. Our case report demonstrates the possibility of this rare malignant tumor arising from the digital nerve to the median nerve in the palm, an anatomical site that is usually affected by benign lesions.

Table 2 Literature review of malignant granular cell tumors of the peripheral nerve

References	Age, sex	Location	Size (cm)	Symptoms	Treatment	Follow up (months)	Follow-up findings
Usui et al. [16]	34, male	Radial nerve in the upper arm	10	Mass	Ex	19	LNM, DM, DOD
Weisman et al. [19]	33, female	Laryngeal nerve in the neck	2	Mass, pain	Ex	24	R, NED
Shimamura et al. [24]	43, female	Sciatic nerve in the buttock	9	Low back pain, peroneal nerve palsy	Ex, Ra, Chemo	13	DM, DOD
Hurrell et al. [101]	81, male	Sciatic nerve in the thigh	3.5	Mass and pain	Ex	NA	NA
Saperstein et al. [40]	51, female	Sciatic and tibial nerve in the popliteal fossa	12	Numbness and pain in the leg and foot	Ex, Chemo	12	R, LNM, DM, DOD
Simsir et al. [41]	30, male	Fifth cranial nerve in the infratemporal fossa	10	Mass, facial nerve paralysis	Ex, Ra	12	R, AWD
Sonobe et al. [45]	54, male	Radial nerve in the forearm	3	Mass	Ex,	60	DM, AWD
Wieczorek et al. [50]	64, female	Tibial nerve in the leg	2.5	Numbness and pain in the lower leg	None	16	DM, AWD
Hyodo et al. [52]	48, female	Cervical sympathetic nerve trunk	8.6	Mass, hyperesthesia in the neck and shoulder	Ex	36	NED
Di Tommaso et al. [54]	42, male	Lateral femoral cutaneous nerve	6	Pain in the thigh	Ex, Chemo	7	DM, AWD
Meling et al. [66]	60, female	Suboccipital nerve	4	Mass	Ex, Ra	1	LNM, NED
Imao et al. [103]	51, female	C5 root	5	Mass, pain in the neck and upper arm, motor and sensory deficit	Ex, Ra, Chemo	52	R, DM, DOD
Papachristou et al. [67]	74, male	Ulnar nerve in the forearm	4.5	Ulnar nerve dysfunction, mass	Ex	NA	NA
Go et al. [74]	46, female	Brachial plexus	7.8	Pain, motor and sensory deficit	Ex	41	NA
De Luca et al. [80]	64, female	Sympathetic nerve in the posterior mediastinum	15	Dyspnea, fatigue, cough	Ex	NA	NA
Aviles et al. [83]	14, female	Radial nerve in the forearm	1.5	Pain, numbness	Ex	10	NED

Ex excision, *Ra* radiation, *Chemo* chemotherapy, *DOD* died of disease, *R* recurrence, *LNM* lymph node metastasis, *DM* distant metastasis, *AWD* alive with disease, *NED* no evidence of disease, *NA* not available

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Author statement All authors had access to the data and a role in writing the manuscript.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

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