Imaging findings of NTRK-rearranged spindle cell neoplasms: A case series

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Abstract. NTRK-rearranged spindle cell neoplasms (NTRK-RSCNs) are a new category of soft tissue tumors with *NTRK* gene fusions. The present study aimed to investigate the radiological features of NTRK-RSCNs and their association with histopathological findings. The present study included six patients with NTRK-RSCNs, whose fusion genes were confirmed using next-generation sequencing. All patients underwent surgery, and their diagnosis and clinical outcomes were investigated. In addition, the magnetic resonance imaging (MRI) features of all tumors and histopathological findings of the resected specimens were assessed. The present study included three women and three men, with a mean age of 22 years (range, 2-43 years). The *NTRK* gene fusions included four *NTRK1* and two *NTRK3* fusions. Three patients were preoperatively diagnosed with solitary fibrous tumors. One patient with *NTRK3* fusion experienced local recurrence and distant metastases, whereas the other five patients had no local recurrence or metastasis. MRI revealed that all tumors were highly vascular with intra- and peritumoral flow voids of differing degrees. Furthermore, a partially ill-defined border, suggesting infiltration of tumors into the surrounding tissues, particularly fat tissue, was observed in five patients, which was confirmed by histopathological findings. In conclusion, NTRK-RSCNs are highly vascular tumors that can infiltrate the surrounding tissues. These findings suggested that NTRK-RSCNs should be considered in the differential diagnosis of highly vascular-rich mesenchymal tumors, including solitary fibrous tumors and alveolar soft part sarcomas. Furthermore, wide resection may be preferred to completely resect this type of tumor, considering its invasive nature.

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Introduction

NTRK-rearranged spindle cell neoplasms (NTRK-RSCNs) are soft tissue tumors that harbor mainly *NTRK1* or *NTRK3* fusion genes, other than infantile fibrosarcoma (1). NTRK-RSCNs comprise a broad range of tumors, including morphological heterogeneity and histological grade. Histologically, NTRK-RSCNs resemble inflammatory myofibroblastic tumors, solitary fibrous tumors (SFTs), and malignant peripheral nerve sheath tumors (2,3). Recently, lipofibromatosis-like neural tumors were described, characterized by local aggressiveness and co-expression of Pan-TRK, CD34, and S100 (4), which are involved in NTRK-RSCNs in the presence of the *NTRK1* fusion gene. Regarding histological grade, NTRK-RSCNs range from benign to low- and high-grade lesions (1).

The frequency of NTRK-RSCNs is reported to be 0.68% in sarcoma cases, analyzing 1915 cases at Memorial Sloan Kettering Cancer Center (5). Assays commonly performed to identify *NTRK* fusions include Pan-TRK immunohistochemistry, fluorescence *in situ* hybridization, DNA sequencing using targeted cancer panels, and RNA sequencing. In clinical settings, Pan-TRK immunohistochemistry and DNA sequencing are commonly used; however, these assays can miss the detection of *NTRK* fusions at a frequency of approximately 20% (5). These methods tend to miss the detection of *NTRK3* fusions, and the specificity and staining of Pan-TRK are reported to be low and faint in sarcoma cases (5). *NTRK3* fusion-positive mesenchymal tumors are more aggressive than *NTRK1* fusion-positive mesenchymal tumors (2). Therefore, the clinical features and characteristics of imaging findings

Table I. Patients' clinical characteristics, fusion gene and prognosis.

Case	Age, years	Sex	Location of primary tumor	Diagnosis by resected tumor	Fusion gene	Treatment	Follow- up duration, months	Prognosis
1	23	F	Lower leg	NTRK-rearranged spindle cell neoplasm	LMNA-NTRK1	Surgery	16	CDF
2	2	M	Knee	Sarcoma, intermediate malignancy	TPM3-NTRK1	Surgery	125	CDF
3	16	F	Buttock	SFT, grade 3	YWHAE-NTRK3	Surgery, chemotherapy	39	DOD
4	13	M	Knee	SFT, grade 1	TPR-NTRK1	Surgery	146	CDF
5	43	F	Knee	SFT, grade 2	PPFIBP-NTRK3	Surgery	125	NED
6	35	M	Perineal	Dedifferentiated liposarcoma, grade 2	LMNA-NTRK1	Surgery	31	CDF

F, female; M, male; SFT, solitary fibrous tumor; CDF, complete disease free; DOD, dead of disease; NED, no evidence of disease.

are important to assess NTRK-RSCNs and treat patients with advanced NTRK-RSCNs, because NTRK inhibitors have shown dramatic and durable activity against *NTRK* fusion-positive tumors (6).

Several histopathological studies have focused on gene fusion and prognosis, but no previous case series has reported the radiological features of NTRK-RSCNs. Therefore, the present study aimed to clarify the radiological features of NTRK-RSCNs to improve the diagnostic rate of this rare tumor and compare them with histopathological features.

Patients and methods

Patients. A retrospective review of spindle cell tumors morphologically resembling NTRK-RSCNs treated in our institutions The University of Tokyo Hospital (Tokyo, Japan) and The Cancer Institute Hospital of the Japanese Foundation for Cancer Research (Tokyo, Japan) between January 2003 and December 2019 revealed that six patients were diagnosed with NTRK-RSCNs and had NTRK gene fusions, which was confirmed using next-generation sequencing. One case has been published previously (Case 1) (7); we have included it here to enhance our evidence of radiological and histopathological features. We examined the patients' clinical information, including patient age, sex, location of the tumor, clinical follow-up, and features of magnetic resonance imaging (MRI) and compared the histopathological features. This study was approved by the institutional review board of The University of Tokyo Hospital (approval number 11019). Written informed consent was obtained from the patients or the parents of patients for all of the participants. All procedures described in this study were performed according to the ethical standards of the Declaration of Helsinki of 1975, revised in 2000, and the national law.

Magnetic resonance imaging (MRI) acquisition and analysis. MRI examinations were performed using 1.5-Tesla magnets from different two centers. MRI evaluations included T1-weighted fast spin-echo, short tau inversion recovery, and T2-weighted fast spin-echo images in at least two planes (usually the axial and coronal planes). All six patients were also studied using dynamic contrast-enhanced sequences.

All MRI scans were reviewed by a senior radiologist (YT) and orthopedist (HK) to assess inter-observer reproducibility. Tumor location, size, local invasion, vascularity, MRI signal intensities, and presence of necrosis, fatty or fibroblastic component (defined as low signal intensity on T1- and T2-weighted image and possible subtle enhancement by gadolinium administration), and peritumoral edema were noted. When there was disagreement between observers, they re-evaluated and discussed the images to determine the existence of each characteristic. Tumor growth patterns were classified into three types, as previously reported (8) pushing type, entirely well-defined tumor; focal type, tumor with irregular borders and infiltration of surrounding tissues representing <25% of tumor circumference; and diffuse type, tumor with irregular borders and infiltration of surrounding tissues representing 25% of tumor circumference.

Histopathological analysis. Surgical specimens stained with hematoxylin and eosin were retrospectively reviewed by expert pathologists. Mitotic count/10 high-power fields, cellularity, presence of necrosis, infiltration into surrounding tissues, and surgical margin were evaluated. Surgical margins were classified into three categories-R0, microscopically negative margin; R1, macroscopically complete with positive microscopic margin; and R2, macroscopically incomplete margin. Immunohistochemistry of CD34, S100, and MIB1 was also analyzed.

Results

Patient characteristics. Patient characteristics are presented in Table I. This study included three women and three men, with a mean age of 22 (range, 2-43) years. The tumors were in the knee (n=3), lower leg (n=1), buttock (n=1), and perineum (n=1). One patient (Case 5) had a recurrent tumor after treatment at another hospital, and the other five patients had primary tumors. One patient was diagnosed with NTRK-RSCN because the

Table II. Imaging findings of the tumor.

Case	Depth	Maximal diameter, cm	T1	T2	Degree of contrast enhancement	Pattern of enhancement	Peritumoral enhancement	Fatty component	Fibroblastic component	Central necrosis	Lobular architecture
1	Deep	11	High	High	Intense	Homogeneous	Yes	No	Yes	No	No
2	Deep	11.3	Iso	High	Intense	Heterogeneous	No	No	No	Yes	Yes
3	Deep	8.6	Iso	High	Intense	Heterogeneous	No	No	No	Yes	No
4	Deep	4	Iso	High	Intense	Homogeneous	Yes	No	Yes	No	No
5	Superficial	11	Iso	High	Intense	Heterogeneous	No	No	No	Yes	No
6	Superficial	10.5	Iso	High	Intense	Homogeneous	No	Yes	No	No	No

patient was treated in 2019, and the entity of NTRK-rearranged mesenchymal tumors was suggested. However, three patients were diagnosed with SFTs, one patient had dedifferentiated liposarcoma because of the positivity of MDM2 immunohistochemical staining and fatty component, and one patient had sarcoma with intermediate malignancy. Four and two tumors harbored *NTRK1* and *NTRK3* fusions, respectively. All patients underwent surgery, and no recurrence was observed, except in one patient. Five patients were disease free or had no evidence of disease, and one patient with recurrence and distant metastasis (Case 3) was treated with chemotherapy; however, the patient did not survive.

MRI findings. The imaging characteristics, including the location, size, and properties of the tumors, are summarized in Tables II and III. Four tumors were located in the deep area, and two were located in the subcutaneous tissue. The mean diameter was 9.4 (range, 4-11.3) cm. These tumors were isointense or slightly high in intensity compared to the skeletal muscle on T1-weighted images and high intensity on T2-weighted images. All tumors were intensely enhanced by gadolinium (Figs. 1-5), and peritumoral enhancement was observed in two patients. Regarding intratumoral features, one tumor had a fatty component (Fig. 5), two fibrotic component, three central necrosis (Fig. 4), and one lobular architecture.

The growth pattern of these tumors was focally and globally infiltrative in five patients, especially infiltration into the surrounding fat tissue (Figs. 1, 3, 4 and 5), and one tumor had distinct tumor margin (Fig. 2). Five tumors had flow voids (Figs. 1, 2 and 5)-three cases at the intra- and peripheries (Figs. 1 and 5) and two cases at the periphery (Fig. 2). Three tumors had more than five flow voids, and these tumors had a relatively large diameter of the flow voids.

Histopathology and correlation with imaging characteristics. Representative histopathological findings and surgical margin are presented in Tables IV and V. Five patients were both CD34 and S100 positive, and one patient was CD34 positive. Mitotic counts equal to or greater than 10 were observed in two patients, whereas others had few mitoses. Cellularity was high in all four patients. In all patients, invasion of the surrounding tissues was observed, especially in fat tissue compatible with MRI findings. Invasion into the surrounding tissues from the main nodule was also observed in histological evaluation (Figs. 1, 3, 4 and 5). Local recurrence was observed in one patient (Case 3) after R1 resection, and no local recurrence was observed with marginal or wide margin resection. Vascular invasion was observed in one patient (Case 3) with distant metastasis.

Discussion

NTRK-RSCNs are extremely rare tumors, and identification of these tumors is important because NTRK inhibitors are highly effective and durable (6). NTRK-RSCNs include various fusion types, and their histological features and grades vary (1). According to a recent report, DNA-sequencing target panel and Pan-TRK immunohistochemistry, commonly available methods, could overlook these tumors (5); therefore, it is important to understand the clinical features of these tumors.

Table III. Imaging findings of the tumor growth pattern and flow-voids.

Case	Growth pattern	Edema	Infiltration into fatty tissue	Tail sign	Distribution of flow-voids	Number of flow-voids	Maximal diameter of flow-void, mm
1	Focal-type	Limited	Yes	No	Intra and peripheral	≥5	8
2	Diffuse-type	Limited	Yes	No	Intra and peripheral	≥5	4
3	Pushing-type	Absent	No	No	Peripheral	≤5	1.5
4	Focal-type	Absent	Yes	Yes	None	NA	NA
5	Focal-type	Limited	Yes	No	Peripheral	≤5	1
6	Focal-type	Absent	Yes	No	Intra and peripheral	≥5	4

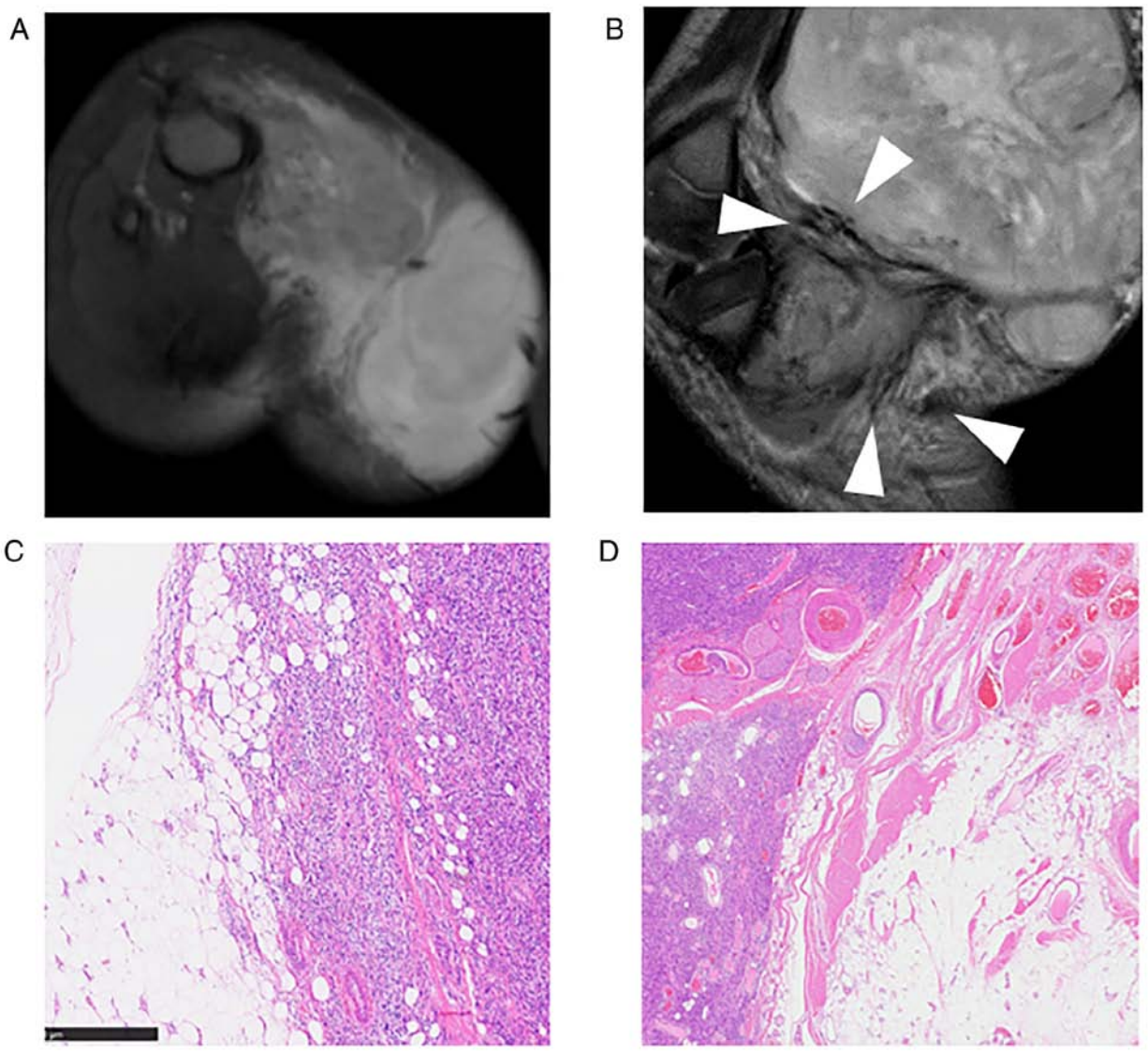

Figure 1. Findings of a 2-year-old boy (Case 2) with an NTRK-rearranged spindle cell neoplasm at his knee. (A) Axial T1-weighted image with gadolinium enhancement shows infiltrative growth into the subcutaneous tissue. (B) Sagittal T2-weighted image shows intra- and peritumoral flow voids (white arrow heads). (C) Histological findings of the resected specimen focusing on the periphery of the tumor, with the tumor showing infiltrative growth pattern of the tumor into the subcutaneous fat and (D) prominent angiogenesis at intra- and peritumoral regions.

There are only two case reports describing the imaging characteristics of these tumors (7,9). In this study, we characterized the MRI appearance of NTRK-RSCNs, which suggested that NTRK-RSCNs could be one of the differential diagnoses of highly vascular-rich mesenchymal tumors, such as SFT and alveolar soft part sarcoma (ASPS). Furthermore, we observed

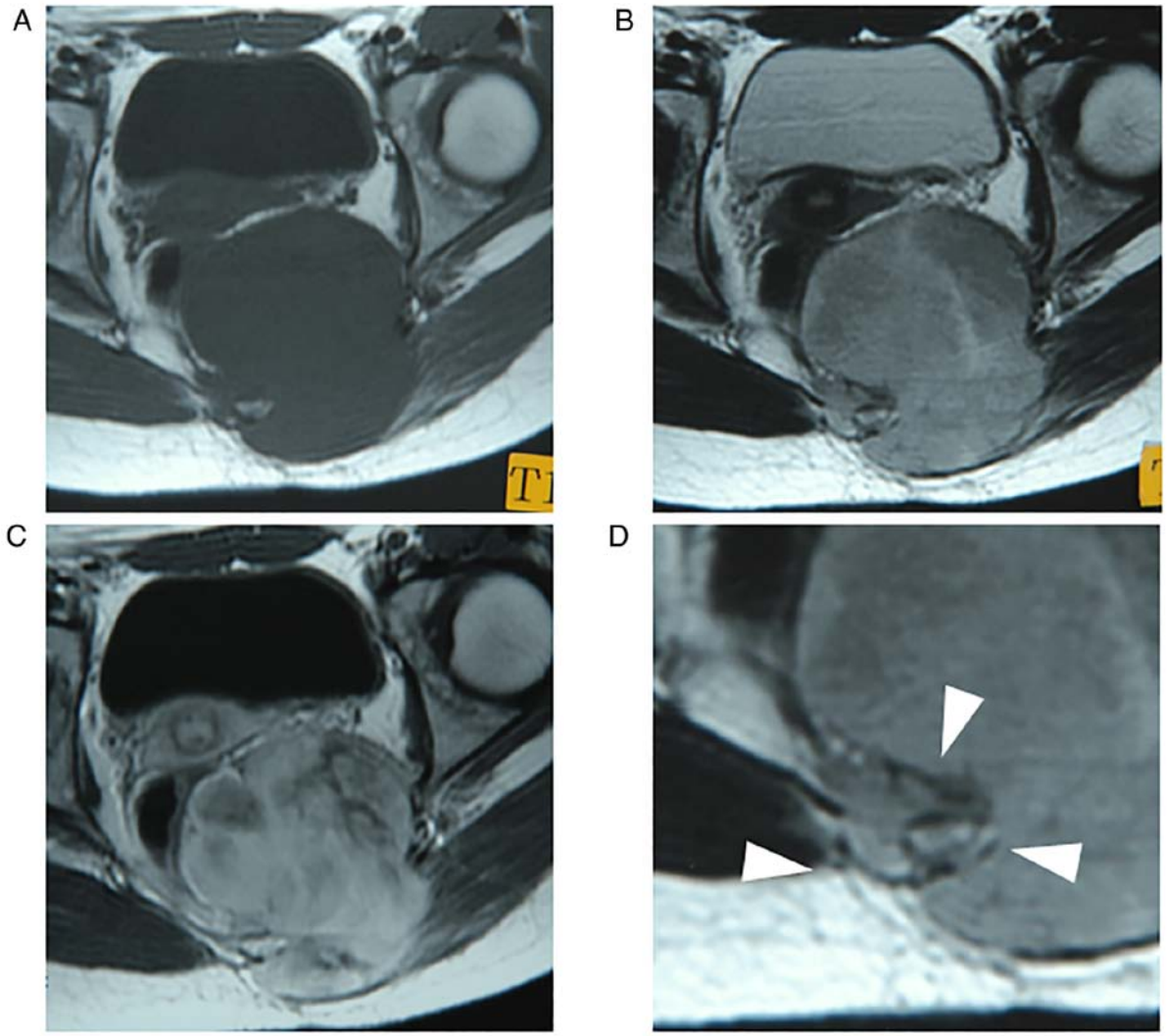

Figure 2. Findings of a 16-year-old girl (Case 3) with an NTRK-rearranged spindle cell neoplasm at her buttock. (A) Axial T1-weighted image shows well-demarcated low signal intensity mass circumscribing the coccyx and protruding anteriorly, compressing the rectum. The tumor is depicted as (B) homogeneous high intensity mass with axial T2-weighted image and (C) well enhanced by gadolinium. (D) Axial T2-weighted image shows peritumoral flow voids (white arrow heads).

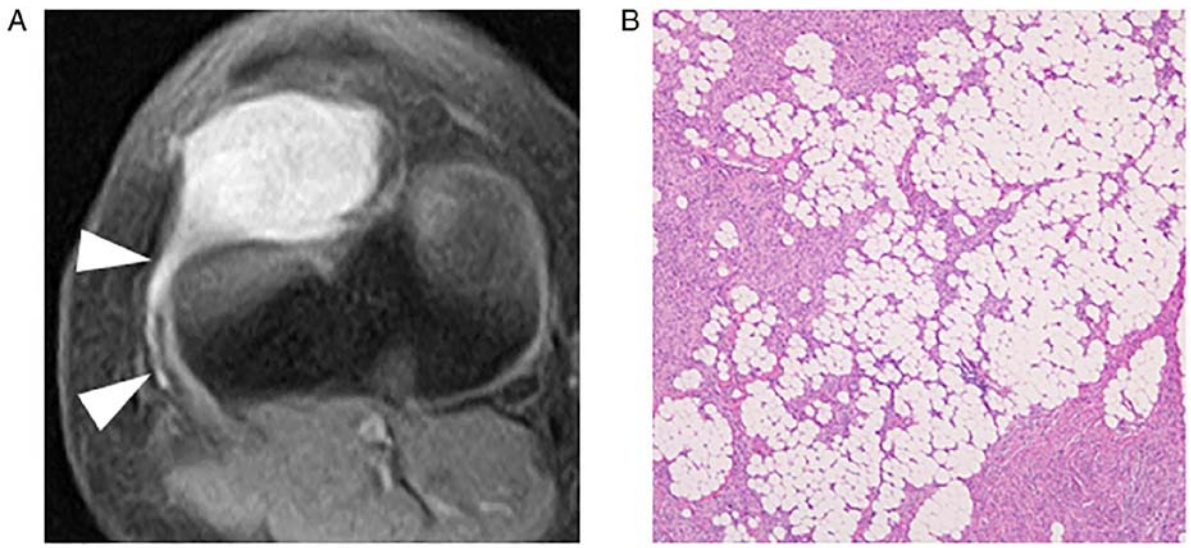

Figure 3. Findings of a 13-year-old girl (Case 4) with an NTRK-rearranged spindle cell neoplasm at the infrapatellar fat pad. (A) Axial T1-weighted image with gadolinium enhancement shows the tumor infiltrate along with the tibia under the joint capsule and ligament (white arrow heads). (B) Histologically, the tumor cells infiltrate into the subcutaneous fat.

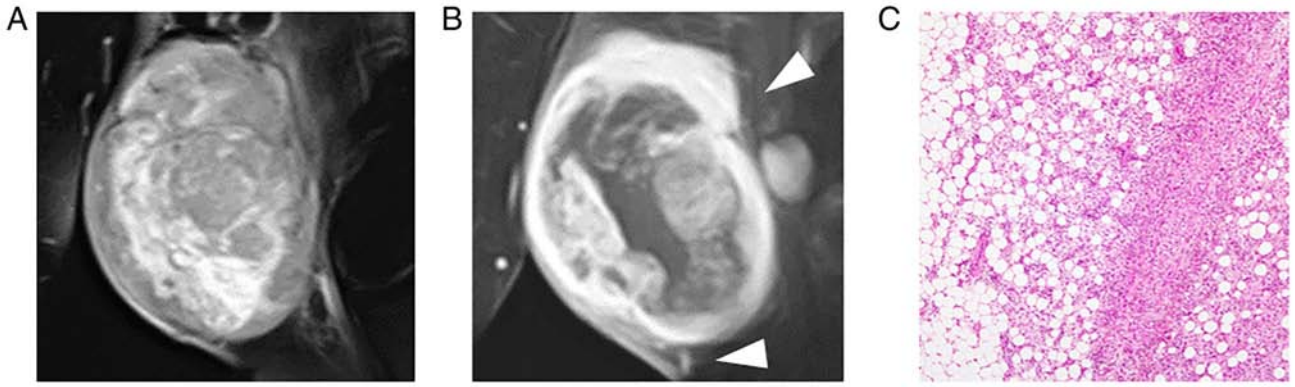

Figure 4. Findings of a 43-year-old woman (Case 5) with an NTRK-rearranged spindle cell neoplasm at the subcutis of her knee. (A) Coronal T2-weighted image shows ovoid mass with heterogeneous high signal intensity. (B) The periphery of the tumor was well enhanced by gadolinium, and the center of the tumor was not enhanced, indicating the necrotic region. The boundary of the tumor from the subcutaneous fat is partly vague and has an infiltrative growth pattern (white arrow heads). (C) Histological finding of the resected specimen focusing on the periphery of the tumor, with the tumor showing infiltrative growth pattern into the surrounding subcutaneous fat, reflecting the magnetic resonance imaging findings.

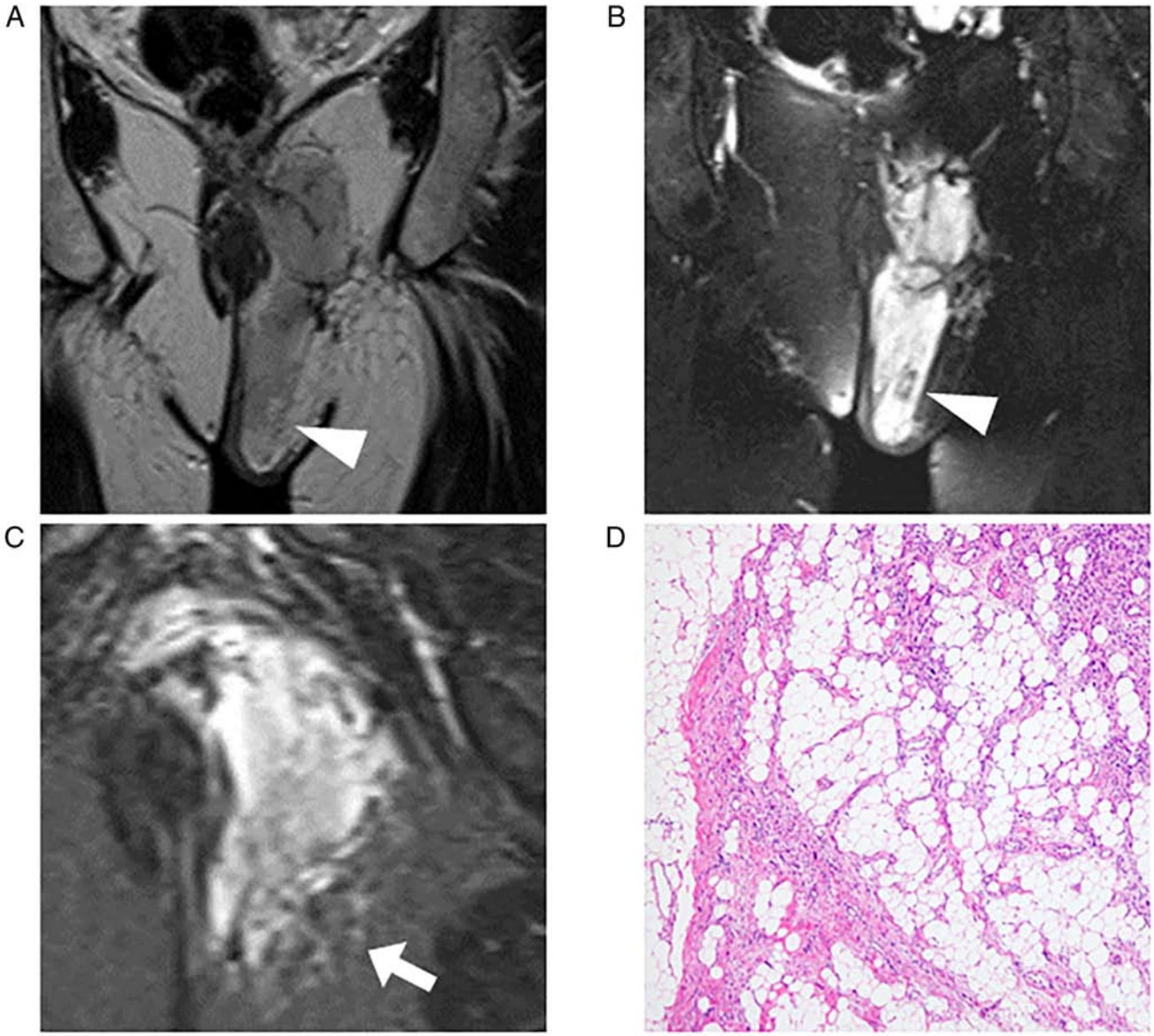

Figure 5. Findings of a 35-year-old man (Case 6) with an NTRK-rearranged spindle cell neoplasm at the perineal region. (A) Coronal T1-weighted and (B) fat-saturated T2-weighted images show ovoid mass, which has infiltrative growth at the cranial side of the tumor and contains fat component (white arrowhead). (C) Axial T2-weighted image shows intra- and peritumoral flow void (white arrow). (D) Histologically, the tumor shows infiltration into the surrounding subcutaneous fat.

Table IV. Histopathological findings.

Case	Mitosis	Cellularity	Necrosis	Infiltration into fat tissue	Vascular invasion
1	0-1	High	No	+	-
2	10	High	No	+	-
3	10-15	High	<50%	+	+
4	0-2	Intermediate-high	No	+	-
5	5-10	Intermediate	<50%	+	-
6	0-5	High	No	+	-

Table V. Surgical margin.

Case	Intended surgical margin	Invasion from the main nodule	Microscopic surgical margin
1	Wide	Fat tissue, muscle	R0
2	Wide	Fat tissue	R1
3	Marginal	Fat tissue, muscle, intermuscular fat tissue	R1
4	Wide	Fat tissue	R0
5	Wide	Fat tissue	R0
6	Wide	Fat tissue, muscle, intermuscular fat tissue	R0

that NTRK-RSCNs can infiltrate the surrounding tissues, especially fat tissues, by comparing imaging characteristics and histopathological features. These findings could help surgeons plan the extent of resection of these tumors.

Imaging features of NTRK-RSCNs have been mentioned so far in only two case reports (7,9). This case series of six patients with NTRK-RSCNs reveals that these tumors have a highly vascular nature, presence of intra- or peritumoral vessels is characteristic feature of these tumors, and the findings are compatible with that of a previous case report (7,9). The number of flow voids and the diameter of flow-void vessels were different in each patient, and five out of the six patients showed intra- or peritumoral flow voids. As for other mesenchymal tumors with a highly vascular nature, SFTs and ASPS have been reported. McCarville *et al* reported that ASPS imaged with MRI in 19 patients had flow voids in all patients and that 95% (18/19 patients) of patients had both intra- and peripheral flow voids (10). Compared to the results of this report, NTRK-RSCNs could be less vascular than ASPS, although they tend to be highly vascular tumors. Crombé *et al* reported that ASPS had eight characteristic imaging features-deep location, high signal intensities on T1-weighted imaging, central area of necrosis, absence of fibrotic component, infiltrative growth pattern, absence of tail sign, presence of intra- and peritumoral flow voids, and number of flow voids ≥5. Moreover, 80% of ASPS pose at least seven out of the eight features (11). In our patients, the scores for these eight characteristics were 6, 7, 4, 3, 5, and 6 points in Cases 1-6, respectively. These results indicate that NTRK-RSCNs resemble ASPS in terms of highly vascular tumors, but NTRK-RSCNs tend to be less vascular than ASPS and have different imaging characteristics. SFT is an important differential diagnosis for NTRK-RSCNs because it shows monotonous spindle cell tumors and vascular-rich lesions with a hemangiopericytomatous appearance, which is also observed in NTRK-RSCNs (12). In our cases, three patients were first diagnosed with SFTs. Garcia-Bennett *et al* reported imaging findings of SFTs in nine patients and revealed that the common findings were well-defined polylobulated masses and the presence of vascular pedicles. However, invasion into adjacent structures was reported to be only 22% (13), and other reports of imaging findings of SFTs demonstrated that the ratio was 9% (14). In contrast, NTRK-RSCNs in our cases showed infiltration into the adjacent tissues on MRI, and infiltration into the surrounding tissues was confirmed by histopathological analysis. The finding of infiltration into adjacent tissues was consistent with previous reports (2,4,15). This infiltrative feature can be a differential point of imaging between SFTs and NTRK-RSCNs. SFT is histologically diagnosed using its specific molecular marker, STAT6, because of the *NAB2-STAT6* fusion gene (16). In cases where imaging findings show a highly vascular mass and histological findings show spindle cell tumor without STAT6 immunostaining, the screening of *NTRK* gene fusion, including Pan-TRK, fluorescence in situ hybridization, DNA-sequencing targeted panel, and RNA sequencing, should be considered to discover NTRK-RSCNs. Recently, spindle cell tumors with CD34 or S100 immunostaining positive could pose other RTK-related fusions, including *ALK*, *BRAF*, *ROS1*, and *RET* (14,17). It is unknown whether these tumors are vascular-rich lesions; therefore, further investigation should be performed.

We recognized the clinically important feature, that is, focal infiltration of the tumor into adjacent structures, in imaging and histopathological findings, which was recently observed in previous case reports (7,9). In five of the six patients, infiltration into fatty tissue was observed on MRI, which was confirmed by histological findings. In Case 3, histological infiltration of the surrounding tissue, including

fat tissue, intermuscular fat, and muscle, was observed despite imaging findings with the pushing type and no invasive pattern into fat tissue. This patient had metastasis after surgery, with relatively higher mitosis compared with other patients, and vascular invasion was observed histologically. Although it is difficult to conclude from our findings, due to limited cases, that imaging findings could not predict the malignant potential of this tumor, NTRK-RSCNs could have malignant potential although the imaging findings were well circumscribed. Furthermore, histological findings with high mitotic count should be considered a sign of malignant potential of this tumor, as described by previous reports (2,17), and vascular invasion should be carefully investigated, which could be a poor prognostic factor, similar to other soft tissue sarcomas (18). Intended wide resection with negative histological margins resulted in no recurrence in four patients, although one patient with a marginal margin had no recurrence. Considering the infiltrative nature of this tumor, wide resection is recommended. Effective chemotherapeutic NTRK inhibitors, including entrectinib and larotrectinib, are usually used in advanced cases, whereas the efficacy and safety of neoadjuvant larotrectinib treatment have been reported in the management of children with locally advanced TRK fusion sarcomas (19). To reduce the loss of function after extended tumor resection, neoadjuvant treatment with NTRK inhibitors for NTRK-RSCNs is promising, and further analysis is required.

The present study has some limitations. The has a retrospective design and analyzed a small number of patients. The entity of NTRK-RSCNs includes a broad range of histological features and grades, and local aggressiveness and metastatic potential differ depending on the tumor. However, our imaging findings of highly vascular tumors might be a common feature of this tumor driven by the same driver *NTRK* gene fusions. Despite these limitations, to the best of our knowledge, this is the first case series reporting the MRI findings of NTRK-RSCN lesions in soft tissues.

In conclusion, this study mainly presented two important imaging findings of NTRK-RSCNs-high vascularity and focal invasiveness into the surrounding tissues, especially fat tissue. NTRK-RSCNs could be candidates for the differential diagnosis of highly vascular mesenchymal tumors, including SFT and ASPS. Furthermore, the focal invasiveness of the tumor shown by MRI was confirmed by histopathological analysis, and NTRK-RSCNs could be resected with wide margin to avoid local recurrence. These findings provide useful information for the diagnosis and treatment of NTRK-RSCNs and would aid in improving the detection and curative rates of these tumors.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Author's contributions

HK wrote the paper and performed the literature review. HK and KA confirmed the authenticity of all the raw data. HK, YT, KA, KY, NM and ST contributed to the conception and design of the manuscript, and critically revised the manuscript. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was approved by the institutional review board of The University of Tokyo Hospital (approval no. 11019). Written informed consent was obtained from the patients or the parents of patients for all individual participants included in the study at The University of Tokyo Hospital and The Cancer Institute Hospital of the Japanese Foundation for Cancer Research.

Patient consent for publication

Written informed consent was obtained from the patient for publication of this report and accompanying images.

Competing interests

The authors declare that they have no competing interests.

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