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CASE REPORT

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NTRK rearranged spindle cell neoplasm of the uterine cervix: a rare case report and literature review

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Abstract

Background Neurotrophic tyrosine receptor kinase (NTRK) rearranged spindle cell neoplasm is an emerging group of molecularly defined rare soft tissue tumors, often presenting with a monotonous spindle cell morphology, infiltrative growth, and co-expression of S-100 and CD34 proteins by immunohistochemistry (IHC). Accurate diagnosis necessitates the combination of morphology, immunohistochemistry, and molecular test results, with next-generation sequencing (NGS) as the gold standard. We present a rare case of NTRK rearranged spindle cell neoplasm of the uterine cervix and review the literature to highlight the current understanding of the diagnosis and treatment of this rare disease.

Case presentation A 49-year-old perimenopausal woman presented with menorrhagia for more than a month. A biopsy of the cervix revealed a cervical spindle cell neoplasm with a tendency to be an isolated fibrous tumor. A total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed and the surgical pathology suggested NTRK rearranged spindle cell neoplasm, while NGS confirmed TFG-NTRK3 fusion gene. Postoperatively, the patient refused larotrectinib maintenance therapy for economic reasons and had no sign of recurrence or metastasis at 31 months of follow-up.

Conclusion We presented the first case of cervical spindle cell neoplasm with TFG-NTRK3 gene rearrangement and retrieved 22 cases of NTRK rearranged spindle cell neoplasm of the uterine cervix from literature. The most prevalent type of gene fusion was TPM3-NTRK1, and almost all cases demonstrated S-100 and CD34 positivity by IHC. Surgery remains the initial treatment of choice and tyrosine receptor kinase (TRK) inhibitors may serve as a promising target therapy for patients with recurred or metastatic disease.

Keywords Neurotrophic tyrosine receptor kinase (NTRK), Spindle cell neoplasm, Cervical sarcoma, Case report

Background

The concept of neurotrophic tyrosine receptor kinase (NTRK)-rearranged spindle cell tumors was first introduced in the 2020 edition of the WHO Classification of Soft Tissue and Bone Tumors and defined as a new group of rare soft tissue tumors diagnosed at the molecular level (except infantile fibrosarcoma), which have a broad spectrum of morphology and histological gradations, often show co-expression of S-100 and CD34 by immunohistochemistry (IHC), and the use of molecular means can detect the *NTRK* gene [1]. The *NTRK* gene

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contains *NTRK1*, *NTRK2*, and *NTRK3,* encoding three highly homologous TRKA, TRKB, and TRKC receptor proteins respectively [2]. The TRK family is an important signaling pathway that regulates cell communication and tumor growth. *NTRK* gene fusion is the linkage of the 3' sequence of *NTRK* to the 5' sequence of a partner gene through intrachromosomal or interchromosomal rearrangements, generating TRK fusion proteins in a persistently active state, which in turn triggers a sustained cascade of downstream signaling pathways that promote tumorigenesis [3–5].

NTRK rearrangement uterine sarcoma is a recently discovered extremely rare gynecologic malignancy that occurs mainly in premenopausal women, with most tumors originating from the cervix, and early-stage patients are treated predominantly with surgery. Here we reported firstly a case of TFG-NTRK3 fusion cervical sarcoma and collected the existing reported cases of NTRK fusion cervical tumors for literature review to highlight diagnosis, initial treatment, prognosis, as well as promising recurrence therapy for the extremely rare disease.

Case presentation

A 49-year-old female patient had excessive menstruation for 1 month, HPV test suggested type 52 positive, colposcopy observed the disappearance of the normal morphology of the cervix, the cervical surface of the cervix was visible in the diameter of about 5 cm of redundant organisms, the mass was partially lobulated, the surface was smooth, there was no obvious abnormal vascularity, it was pink in color, brittle, and rich in blood supply. Biopsy pathology suggested spindle cell tumor, inclined to isolated fibroma. Tumor markers showed no obvious abnormalities, and pelvic magnetic resonance examination showed an enlarged cervix and soft tissue mass. Subsequently, the patient underwent abdominal hysterectomy and bilateral salpingo-oophorectomy on May 26, 2021 at our center. Histopathological examination revealed macroscopic features of the tumor: the tumor tissue consisted of diffuse spindle-shaped cells in bundles, nests, or homogeneous shapes, and vascularity and nuclear atypia (mild to moderate) with active mitosis [>30/10 high power fields (HPF)] were observed, as well as perivascular collagenous fibrous degeneration and lymphocytic infiltration, although necrosis was not detected. Consequently, we diagnosed the patient as (cervical) spindle cell tumor. IHC revealed negative results for CK, EMA, P16, ER, actin, SMA, β-catenin, HMB45, melan A, Caldesmon, Desmin, MyoD1, and CD10. Weakly positive staining was observed for PR (approximately 10%), while positive staining was observed for Ki67 (approximately 30%) and scattered positive staining for CyclinD1. Positive staining was also observed for Vim, CD34, S-100, and TLE1 (Fig. 1). The pathology consultation conducted at the Affiliated Cancer Hospital of Fudan University indicated the presence of an NTRK-rearranged spindle cell tumor. Repeated IHC analysis revealed positive expression of CD34, pan-TRK, H3K27ME3, and S-100, while HMB45, STAT6, Desmin, and SMA exhibited negative expression. In comparison to our center's assays, the Affiliated Cancer Hospital of Fudan University added positively expressed pan-TRK, H3K27ME3, and

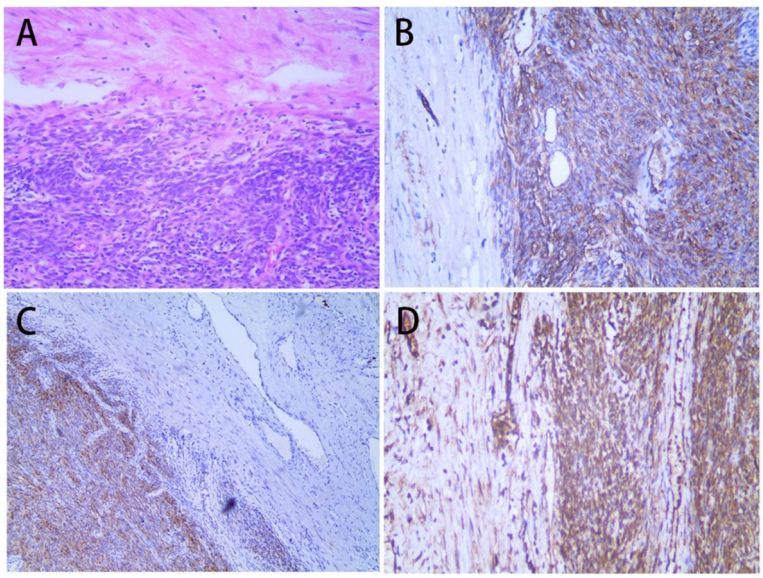

Fig. 1 Histopathological and immunohistochemical staining findings. **A** Tumor cells are arranged in a spindle pattern (100×; H&E staining); **B** Positive stain for CD34 (100 ×); **C** Positive stain for S-100 (100 ×); **D** Positive stain for vim (100 ×)

negatively expressed STAT6 to confirm the diagnosis. Molecular pathology analysis revealed the presence of t(1p22) (NTRK1) through fluorescence in situ hybridization (FISH), where approximately 15–25% of tumor cells exhibited distinct red and green signals. These signals were observed nearby, with a separation spacing equivalent to approximately 1–2 signal dots in diameter, suggesting the potential occurrence of NTRK1 gene-associated translocation. Additionally, soft tissue next-generation sequencing (NGS) identified the TFG-NTRK3 fusion gene. In conjunction with the consultation opinion, considering the patient's existing diagnosis of cervical spindle cell tumor with NTRK rearrangement, the patient may benefit from TRK inhibitors. Regrettably, these inhibitors remain inaccessible in mainland China at that time. Clinical trials associated with TRK inhibitors are also suggested, however, the patient did not meet the eligibility criteria for such trials. Encouragingly, the patient's subsequent follow-up has thus far indicated an absence of recurrence or metastasis without any adjuvant therapy.

Discussion

In this case report, we identified the first case of cervical spindle cell tumor with TFG-NTRK rearrangement and found, through a literature review of 23 reported cases of cervical spindle cell tumor with NTRK rearrangement (Table 1), the most common type of gene rearrangement was TPM3-NTRK1 [6–10]. Also, we found that IHC showed universal positivity for S-100 and CD34. For patients with NTRK-rearranged cervical spindle tumors, surgery remains the initial treatment, and tyrosine receptor kinase (TRK) inhibitors may be a therapeutic option for patients with recurrence or metastasis, which needs to be confirmed by further studies.

NTRK rearrangement sarcoma is a spindle cell tumor originating from the uterus, with a mean age of onset of 35 years (23–60 years), of which 85% occur in the cervix, with a mean tumor diameter of 6.9 cm (1.5–23.0 cm) [17]. Most patients can be identified and detected at early stages, and 91% of patients have tumors confined to the uterus at the time of diagnosis, with the following clinical manifestations: irregular vaginal bleeding, cervical mass, and so on. Certainly, as a highly aggressive tumor, within the reported 23 patients with existing NTRK-rearranged cervical spindle cell tumors, 15 patients survived to date without recurrence or metastasis (60.9%), with mean overall survival time of 19.3 months, 3 had an unknown prognosis (13.0%), and 6 developed metastases (26.1%), including the vagina, lungs, pancreas, and brain [6].

The pathological features of NTRK rearrangement tumors are relatively distinctive: (i) typical sarcoma features: spindle cell bundles arranged in a fishbone-like or cushion-like pattern. (ii) abundant vascularity: the tumor contains various types of blood vessels, and the thick-walled vessel walls often show vitreous degeneration and fibrosis. (iii) nuclear heterogeneity: the cells are mild to moderately heterogeneous, with occasional scattered syncytial heterogeneous cells. The nuclei were ovoid with inconspicuous nucleoli. Among 23 cases reported, five cases (21.7%) showed mild atypia, five cases (21.7%) showed moderate atypia, and four cases (17.4%) showed severe atypia in the available reports. Also included were 4 cases (17.4%) with mild to moderate atypia and 5 cases (21.7%) with unknown atypia. Nuclear divisions were usually more active at 7/10HPF (1–50/10HPF), with a mean number of nuclear divisions of 13/10HPF available for reporting. (iv) Inflammatory cells: mostly focal lymphocytic infiltration. IHC revealed 91.3% positive for S-100 protein (21/23), 87.0% positive for CD34 protein (20/23), and usually negative for SOX10, vascular markers, and various smooth muscle markers (SMA, desmin, Caldesmon). The indicator H3K27ME3 was added by the consulting hospital for our patient as being a histone-specific modification site, suggesting the possibility of malignancy. Immunohistochemical testing for STAT6 was also added to identify and exclude isolated fibromas [18, 19]. Therefore, we can assume that if the sarcoma consists of diffuse spindle cells with negative expression of multiple tissue factors, the possibility of NTRK gene fusion tumors can be considered and the detection of Pan-TRK staining can be added. Pan-TRK antibodies can be used for routine screening of NTRK gene fusion with an overall sensitivity of 87.9% and specificity of 81.1%, respectively [20]. However, there exist some tumors without NTRK fusions that also express pan-TRK; therefore, the detection of NTRK fusions still requires molecular pathology analyses such as FISH, RT-PCR, and NGS. The European Society of Medical Oncology (ESMO) guidelines [21] suggest that FISH and RT-PCR may be appropriate for detecting tumors with a high incidence of NTRK genes. As for tumors with a low incidence of NTRK gene fusions, pan-Trk IHC is performed for screening, and if positive, then RNA-NGS is recommended to confirm the presence of specific genetic alterations. In other words, the NGS method is the gold standard for detecting NTRK gene rearrangements at this stage [12]. However, in clinical practice work, the decision to carry out NTRK gene fusion testing is also affected by the cost of treatment and the accessibility of TRK inhibitors, especially in resource-limited areas, IHC can be used as a screening tool for NTRK rearrangement tumors, which can then be detected by FISH or RT-PCR, and NGS when conditions allow.

After the pathology consultation at the Affiliated Cancer Hospital of Fudan University, this patient was

Table 1 Pathological features, treatment methods and prognosis of the included cases

First author	Case (number)	Tumor site	Gene fusion type	Initial treatment	Mitotic count(0/10 HPFs)	Atypia	Lymphatic metastasis	IHC markers	State	Overall survival time(month)
Chiang et al. [6] (2018)	1	cervix	RBPMS-NTRK3	total abdominal hysterectomy with bilateral salpingo-oophorectomy + chemotherapy	15	moderate	NO	Pan-TRK, S100, SMA, H3K27me3(+), ER, PR, desmin, SOX10, CD34(-)	metastatic (vagina)	7
	2	cervix	LMNA-NTRK1	total abdominal hysterectomy with bilateral salpingo-oophorectomy +chemotherapy	12	moderate	NO	Pan-TRK, S100, SMA, H3K27me3(+), ER, PR, desmin, SOX10, CD34(-)	metastatic (lung, pancreatic and brain)	78
	3	cervix	TPM3-NTRK1	total abdominal hysterectomy with bilateral salpingo-oophorectomy	30	severe	NO	Pan-TRK, S100, SMA, H3K27me3(+), ER, PR, desmin, SOX10, CD34(-)	survive	2+
Wells et al. [8] (2019)	4	cervix	TPM3-NTRK1	radical abdominal hysterectomy, bilateral salpingectomy	2	severe	NO	CD34, S100, p16, Ki67, CD10(+), SOX10(-)	survive	4+
Croce et al. [7] (2019)	5	cervix	TPM3-NTRK1	NA	3	mild	NO	TRK, S100, CD34 (+); ER, PR, desmin (-)	NA	NA
	6	cervix	TPM3-NTRK1	NA	3	moderate	NO	TRK, S100, CD34 (+); ER, PR, desmin (-)	survive	2+
	7	cervix	TPM3-NTRK1	NA	5	moderate	NO	TRK, S100, CD34 (+); ER, PR, desmin (-)	survive	33+
	8	cervix	TPM3-NTRK1	NA	50	mild	NO	TRK, S100, CD34 (+); ER, PR, desmin (-)	survive	12+
	9	cervix	TPM3-NTRK1	NA	50	mild	NO	TRK, S100, CD34 (+); ER, PR, desmin (-)	metastatic	30
	10	cervix	TPM3-NTRK1	NA	1	mild	NO	TRK, S100, CD34 (+); ER, PR, desmin (-)	survive	108+
	11	cervix	EML4-NTRK3	NA	3	moderate	NO	TRK, S100, CD34 (+); ER, PR, desmin (-)	metastatic	52
Gatalica et al. [11] (2019)	12	cervix	TPM3-NTRK1	NA	NA	NA	NA	pan-TRK(+)	NA	NA
Rabban et al. [9] (2020)	13	cervix	TPM3-NTRK1	polypectomy	0	mild to moderate	No	Pan-TRK, S100, H3K27me3, Rb, p53(+), desmin, SMA, SOX10, calde-smon(-)	survive	6+

Table 1 (continued)

First author	Case (number)	Tumor site	Gene fusion type	Initial treatment	Mitotic count(0/10 HPFs)	Atypia	Lymphatic metastasis	IHC markers	State	Overall survival time(month)
	14	cervix	TPR-NTRK1	hysterectomy, bilateral salpingectomy, and pelvic lymph node dissection	5–18	mild to moderate	No	Pan-TRK, S100, H3K27me3, Rb, p53(+); desmin, SMA, SOX10, Caldesmon(-)	survive	19+
	15	cervix	SPECC1L-NTRK3	hysterectomy, bilateral salpingectomy, pelvic lymph node dissection + chemotherapy + pelvic radiotherapy+ larotrectinib	16–20	mild to moderate	LVSI	Pan-TRK, S100, H3K27me3, Rb, p53(+), desmin, SMA, SOX10, Caldesmon(-)	metastatic	16
Boyle et al. [10] (2020)	16	cervix	TPM3-NTRK1	hysterectomy + adjuvant pelvic radiotherapy + brachytherapy	8	NA	NA	Pan-TRK, CD10, vimentin, CyclinD1, CD34(+), Cytokeratins, desmin, SMA, caldesmon, ALK1, S100, SOX10(-)	survive	11+
Wong et al. [12] (2020)	17	cervix	NTRK3	hysterectomy and bilateral salpingo-oophorectomy	15	mild	NO	Pan-TRK, S100, CD34, SMA(+), keratins, ER, PR, SOX10, desmin, Cyclin D1(-)	NA	NA
Hodgson et al. [13] (2021)	18	cervix	SPECC1L-NTRK3	hysterectomy, bilateral salpingo-oophorectomy and omentectomy	0	mild to moderate	NA	S100, CD34, SMA, ER, PR, H3K27me3(+), pancytokeratin, epithelial membrane antigen, desmin, myogenin, SOX10, Melan-A, ALK1, neuro-Filament (-)	survive	8+
Munkhdelger et al. [14] (2021)	19	cervix	DLG2-NTRK2	tumor excision +larotrectinib +chemotherapy	NA	severe	NA	Collagen IV, P16(+); CK7, CK19, EMA, S-100, SMA, ER, PR, CD56 (-)	survive	23+

Table 1 (continued)

First author	Case (number)	Tumor site	Gene fusion type	Initial treatment	Mitotic count(0/10 HPFs)	Atypia	Lymphatic metastasis	IHC markers	State	Overall survival time(month)
Dang X et al. [15] (2022)	20	cervix	EML4-NTRK3	hysterectomy and bilateral salpingo-oophorectomy + pelvic lymph node dissection +chemotherapy	>10	severe	NO	S100, CD34, Pan-TRK, vimentin(+); SOX10, desmin, ALK, Caldesmon, MyoD1, Myogenin (-)	metastatic (brain, lung and vagina)	12
Xiaoqi Li [16] (2023)	21	Cervix	EML4-NTRK3	hysterectomy and bilateral salpingo-oophorectomy + pelvic lymph node dissection +chemotherapy	NA	NA	No	S-100, H3K27ME3, pan-TRK (+), SOX10, ER, PR, CD10, SMA, Desmin, Caldesmon, Ki-67(-)	survive	20+
	22	Cervix	NTRK3—	hysterectomy and bilateral salpingo-oophorectomy + pelvic lymph node dissection	NA	NA	No	S-100, CD34, NTRK1, pan-TRK, H3K27ME3(+), SOX10(-)	survive	11+
Current Case	23	Cervix	TFG-NTRK3	total abdominal hysterectomy with bilateral salpingo-oophorectomy	NA	NA	No	CD34, pan-TRK(roche), H3K27ME3, S-100(+), HMB45, STAT6, Desmin, SMA(-)	survive	31+

suggested to have CD34, S-100, and pan-TRK (+), further FISH and NGS were performed. Based on the reliability of the results, this patient was definitively diagnosed as a cervical spindle cell tumor with TFG-NTRK3 rearrangement. In response to the possibility that the FISH probe only suggested NTRK1 gene-related translocation, we considered the following: firstly, the diagnosis of NTRK1 gene ectopia was not very clear as about 15–25% of the tumor cells were seen to have red and green separated signals under the microscope of FISH detection, with a large span of intervals, which was on both sides of the diagnostic value of 20%; secondly, the NGS showed a TFG-NTRK3 fusion but the FISH did not recognize the disruption of NTRK3 may be caused by the proximity of NTRK3 at 1q23.1 and TFG at 1q21.3, which failed to be recognized effectively and has been reported in the literature [12]. Finally, substandard FISH assay samples may also lead to NTRK3 false negatives. The types of gene rearrangements currently reported in the existing literature include TPM3-NTRK1 [6–10], TPR-NTRK1 [6, 9, 22], LMNA-NTRK1 [6], EML4-NTRK3 [7, 15, 16], RBPMS- NTRK3 [6], STRN-NTRK3 [23], SPECC1L-NTRK3 [9, 11, 13], DLG2-NTRK2 [14], etc., and among them, the most common type is TPM3-NTRK1(11/23).

As an extremely aggressive tumor, surgery has been reported in the literature as the most common and primary treatment for patients with early-stage NTRK rearrangement cervical sarcoma, but the extent of surgical resection is not uniform. More than half (13/23) of the patients reported in the existing literature underwent abdominal hysterectomy and bilateral salpingo-oophorectomy, with a maximum postoperative follow-up of 108 months. Prognostic information for this tumor is scarce, and resection of the greater omentum, adjuvant chemotherapy, adjuvant pelvic radiotherapy, or brachytherapy does seem not to benefit the patient's overall survival. In the present case, the patient had no recurrence or metastasis after 31 months of postoperative follow-up without any adjuvant therapy.

Targeted therapy for tumors has now transitioned from narrow-spectrum therapy for specific histological types to broad-spectrum therapy for specific biomarkers. Larotrectinib and enrectinib [3, 24], broad-spectrum anticancer drugs independent of tumor type, are first-generation inhibitors targeting TRK proteins, which play a role in inhibiting the growth and proliferation of tumor cells mediated by NTRK fusion by competing with ATP for binding to the structural domains of the kinase and impeding the phosphorylation of tyrosine residues, thereby blocking the downstream signaling pathway. Currently, larotrectinib and entrectinib are approved for marketing by the U.S. Food and Drug Administration (FDA) and the European Union [7, 25], and Drilon [26] and Doebele [27] have found that larotrectinib and entrectinib are safe and effective treatment options for NTRK-fusion positive solid tumor patients. Excitingly, larotrectinib was approved for marketing by the National Medical Products Administration (NMPA) in China in 2022. Although underreported, TRK inhibitors have shown significant clinical efficacy in both primary and recurrent NTRK-rearranged cervical sarcoma based on a few cases [9, 28], and TRK inhibitors have now been included in cervical cancer diagnostic and treatment guidelines for the treatment of NTRK-rearranged cervical sarcoma. Unfortunately, the drug is not covered by health insurance in mainland China, so this patient decided not to receive targeted therapy for financial reasons.

In conclusion, spindle cell tumors with NTRK gene rearrangement are rare mesenchymal-derived tumors of the uterus, and accurate diagnosis must combine morphology, immunohistochemistry, and molecular test results, with NGS as the gold standard. Moreover, the prognostic factors of patients with this type of tumor are still not warranted because of its rarity. This case is the first discovery of TFG-NTRK3 rearrangement cervical spindle cell tumor and the literature review suggested surgery concerning hysterectomy with bilateral salpingo-oophorectomy may serve as the standard initial treatment, while TRK inhibitors provide a promising choice for patients with advanced stage and recurrence or metastasis disease. Certainly, this study has its limitations. Firstly, the sample size was confined to a solitary patient, which constrains the generalizability of the findings. Secondly, the intricate etiology and pathogenesis of the disease remain ambiguous, leaving us unaware of the prognosis and recurrence pattern within this population. Therefore, future investigations with larger and more comprehensive sample sizes are imperative to overcome these limitations and enhance our comprehension of the disease.

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Authors' contributions
XXJ, SZ, and ZL: Study design. XXJ: Data extraction, case analysis, and manuscript writing. SZ: Case analysis. LW: Diagnosis approach design. ZL: Manuscript editing. All authors approved the final version of the manuscript.

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Data availability
Data is provided within the manuscript or supplementary information files. The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Approval was granted by the Ethics Committee of the Yunnan Cancer Hospital (KYLX2022003).

Consent for publication
Written consent was informed obtained from the patient under the 1975 Declaration of Helsinki.

Competing interests
The authors declare no competing interests.

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