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NTRK3-Rearranged Sarcoma of the Cervix: An Emerging Tumor Entity - Case Report and Review of the Literature

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ABSTRACT

NTRK-rearranged sarcoma of the cervix was recognized by the World Health Organization in 2020 as an emerging tumor entity under mesenchymal tumors of the lower female genital tract. Defined by characteristic NTRK gene fusions, this rare tumor is therapeutically targetable due to same. We report a case of a 23-year-old woman who presented with abnormal vaginal bleeding and a polypoid cervical mass. Histopathological examination of preliminary biopsy revealed spindle cell sarcoma demonstrating immunopositivity for Pan-TRK, CD34, and S100. Break-apart fluorescence in situ hybridization (FISH) confirmed the presence of an NTRK3 gene rearrangement. This patient represents one of the few reported cases of NTRK3-rearranged cervical sarcoma with lymph node metastasis in a young female. We also extensively review the existing literature and summarize the clinicopathological features, molecular profiles, and treatment implications of this report. Given the availability of effective TRK inhibitors, it is imperative to consider NTRK-rearranged sarcoma in the differential diagnosis of spindle cell sarcomas of the lower genital tract.

Keywords: NTRK3 sarcoma, Pan-TRK Immunohistochemistry, NTRK3 Break apart FISH, Cervical Sarcoma, Mesenchymal tumor of lower genital tract

INTRODUCTION

In 2020 the World Health Organization updated its classification of tumors of the female genital tract (1). In this classification, Neurotrophic factor tyrosine kinase receptor (NTRK)-rearranged spindle cell neoplasm was listed as an emerging tumor entity in mesenchymal tumors of the lower genital tract without an International Classification of Diseases of oncology (ICD-o) code. With merely 62 cases reported so far, NTRK-rearranged sarcoma of cervix ia yet to be explored (2,3). Owing to its recent recognition and rarity, the literature pertaining to the diagnostic and therapeutic challenges or prognosis is still very limited. Moreover, since cervical sarcoma have poor prognosis and the patients are more often young, prompt diagnosis and treatment are of utmost importance as presence of NTRK fusion genes may serve as a promising therapeutic target in these cases. We report a case of NTRK3-rearranged sarcoma of the cervix with lymph node metastasis in a young female and discuss the morphological immunohistochemical molecular features of these tumors. We also review the reported cases of NTRK-rearranged sarcoma of the uterus and discuss the clinicopathological features, therapeutic modalities, and prognosis of these cases.

CASE REPORT

A 23-year-old woman, Para 1 Live 1, presented with a short history of discharge per vaginum for 1 month and a single episode of heavy menstrual bleeding 50 days back. She had unremarkable menstrual, obstetric, medical, and family history. While her general physical/per abdominal examination was normal, she had a 5 x 6 cm polypoid growth on the cervix with minimal involvement of the upper wall of the vagina on per speculum examination. Uterus was anteverted and normal in size and rectal mucosa/bilateral parametria were free.

Pelvic ultrasound was suggestive of a mass lesion involving the lower uterine segment and cervical canal, while contrast-enhanced MRI also suggested an extension into the vagina. Whole body PET CT reported no metastasis elsewhere and confirmed an FDG uptake limited to the cervix and upper vagina (Figure 1, PET, MRI, and Intraop). The patient underwent Type B Radical hysterectomy + Bilateral salpingectomy + Bilateral pelvic Lymphadenectomy + Excision of enlarged paraaortic lymph nodes + Bilateral ovarian transposition following a provisional diagnosis of adenosarcoma on biopsy. Gross examination of the specimen demonstrated a grey-white homogenous tumor, measuring

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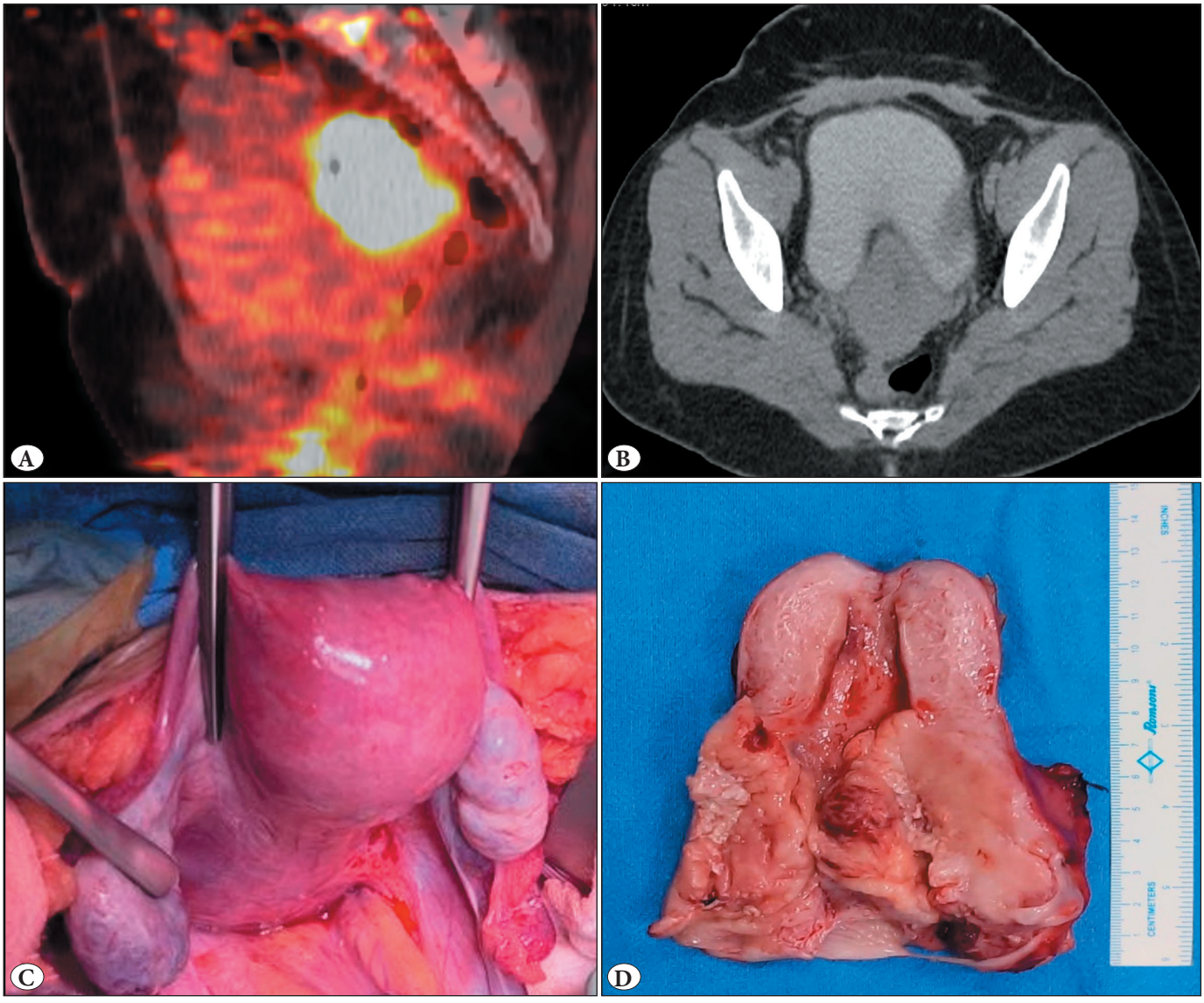


Figure 1: A) Shows FDG avid soft tissue density mass of 5.0 x 5.4 cm size involving the cervix and upper vagina on PET CT with no metastasis detected on MRI **(B)**. **C)** Intraoperatively, it was noted that though the body of the uterus was normal, there were dense adhesions between the uterus and bladder, **D)** cervix shows a large 5x4 cm fleshy growth reaching to the lower uterine segment.

9x7.6x5 cm, infiltrating deeply into the cervix, reaching up to the serosa, and involving the vagina.

Microscopy revealed a variably cellular tumor comprising spindly shaped cells arranged in bundles, long fascicles, and short fascicles. An occasional herringbone pattern could also be appreciated. These cells had scant cytoplasm, oval to elongated nuclei showing mild to moderate pleomorphism, clumped chromatin, and inconspicuous nucleoli. There was no necrosis and mitosis was 20-21/10 HPF with occasional atypical mitotic figures. Occasionally some normal endocervical glands were seen entrapped in the tumor tissue. Perivascular hyalinization with areas of focal necrosis and thin as well as thick blood vessels was also noted. Both thin-walled and thick-walled vessels were seen throughout the tumor. 1/16 resected pelvic lymph nodes was positive for metastasis from cervical sarcoma. Based on the above morphology a differential diagnosis of cervical adenosarcoma, uterine leiomyosarcoma (LMS), fibrosarcoma, malignant peripheral nerve sheath tumor, or still emerging NTRK-rearranged sarcoma of the cervix was considered since the predominant cervical location of the tumor, young age, and mildly pleomorphic spindled cells entrapping unremarkable endocervical glands were not a classical presentation of the commonly known sarcomas of the cervix.

On immunohistochemistry, the tumor cells were immunopositive for Pan-Trk (diffuse, moderately intense, and cytoplasmic), CD34, S100, Cyclin D1 (Focal) and negative for SMA, Desmin, CD10, BCOR, STAT6, ALK HMB45, Estrogen receptor, and progesterone receptor. FISH For NTRK3 rearrangement using a Break apart FISH probe from Cytotest was done. Out of 200 cells counted, 53 cells (25%) showed NTRK 3 rearrangement. Thus, a final diagnosis of NTRK-rearranged sarcoma of the cervix was rendered (Figure 2: HE, IHC and FISH). Since the patient could not afford NTRK inhibitor therapy she was treated with 6 cycles of Carboplatin (AUC 6)+ Paclitaxel 260 mg. She tolerated chemotherapy well and is currently disease-free for the last 2 years.

DISCUSSION

Mesenchymal tumors of the uterine cervix are a heterogenous group of neoplasms accounting for 0.2 -0.5% of all sarcomas and less than 1% of all cervical malignancies. NTRK fusion sarcomas of cervix are a still emerging group of sarcomas where use of NTRK inhibitors may be promising. The NTRK gene family includes the NTRK1, 2 and

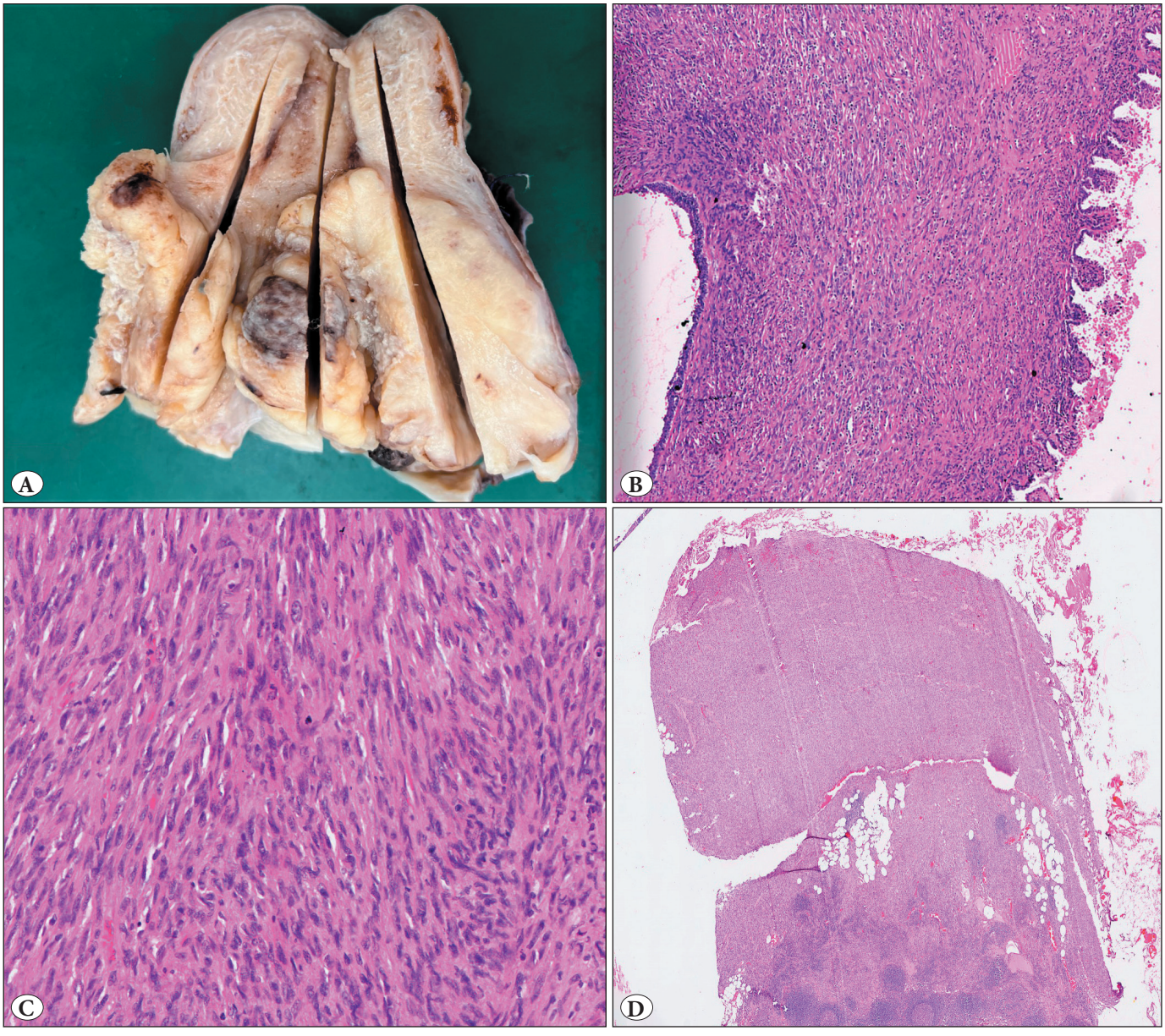


Figure 2: A) Gross photograph of the specimen showing grey-white fleshy growth in the cervix with no areas of hemorrhage or necrosis. **B, C)** Microphotograph of sections showing tumor comprising spindle-shaped cells with moderate pleomorphism and benign endocervical glands entrapped in the tumor. **D)** shows the same tumor metastatic to pelvic lymph node (40x,100x; HE)

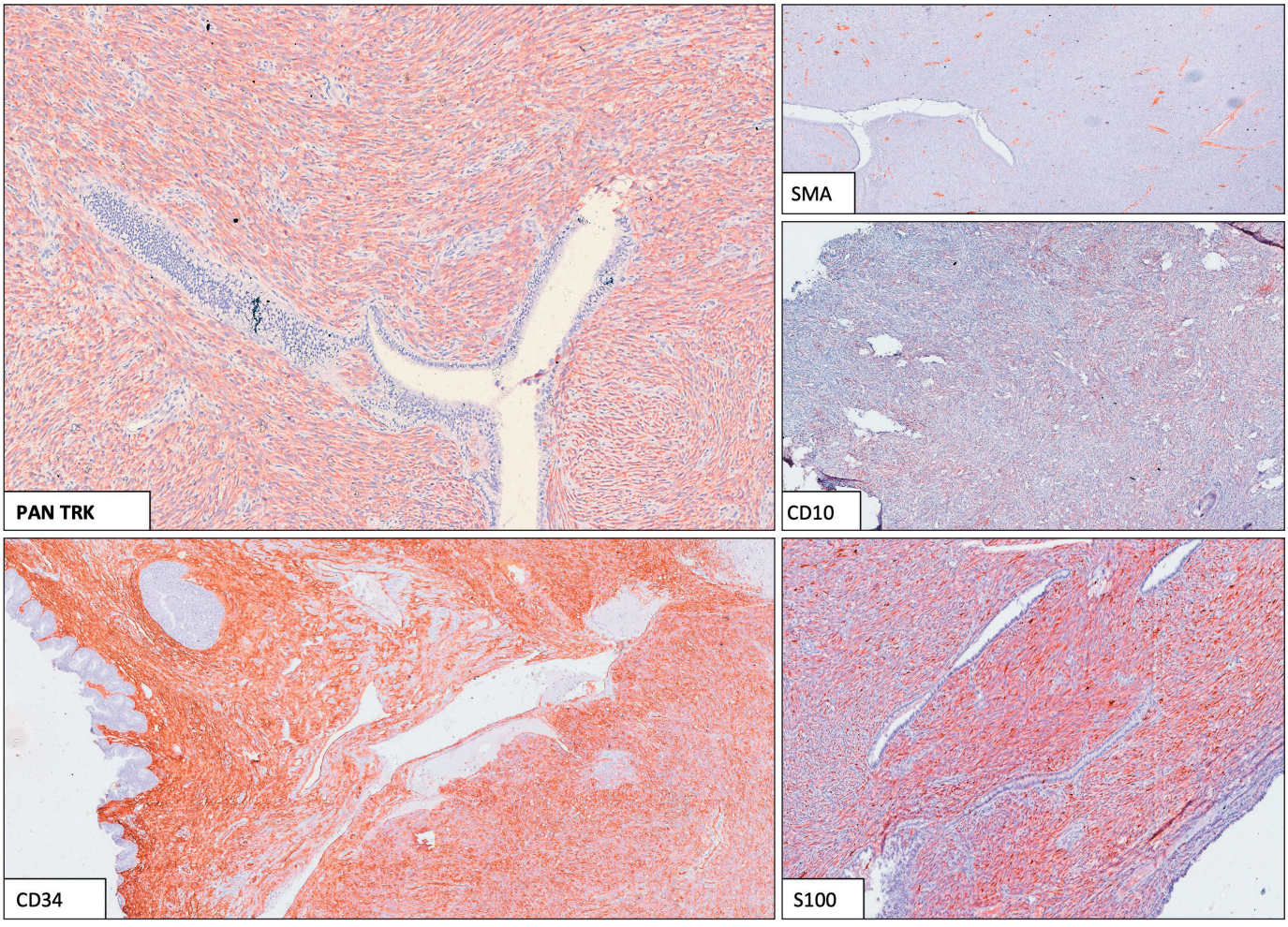


Figure 3: Images of Immunohistochemistry performed on the tumor showing immunopositivity for Pan TRK (diffuse), CD34 (diffuse) and S100 (focal) while the tumor cells are immunonegative for CD10 and Smooth muscle antigen (SMA). (100x;IHC)

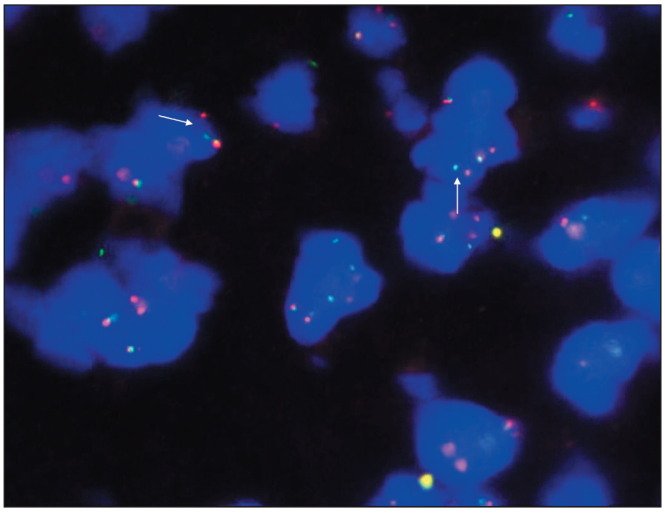


Figure 4: Image of interphase Fluorescent in situ hybridization (FISH) showing NTRK3 rearrangement. (arrows). An NTRK 3 break apart probe was used and more than 10% of the cells showing two distinct green and red signals in a well-visualized cell was considered positive.

3 genes that encode for receptor tyrosine kinases (TRK)A, B and C respectively. Chromosomal rearrangements leading to gene fusions and their recurrence serve as oncogenic drivers of tumor growth and survival across various malignancies. These fusion proteins further cause activation of downstream signaling pathways like the PI3K-Akt-mTor, Ras MAPK-ERK pathway leading to tumorigenesis (4). Fusions of NTRK genes have been identified in tumors like infantile fibrosarcoma, secretory carcinoma of the breast, congenital mesoblastic nephroma, mammary analogue of secretory carcinoma, and a broad range of mesenchymal tumors of superficial and deep soft tissues and bone have also been added to the list in the past few years (5). However not much is known about the recently described NTRK-rearranged sarcomas of the cervix.

NTRK fusion sarcomas of the cervix tend to occur in a younger age group (mean age 35 years; range 13-61 years) and present frequently with abnormal vaginal bleeding or a

polypoid mass in the cervix (6). On gross, these are yellow, white, or pink masses involving the cervix (Figure 2A). In concordance with the described literature, our patient was a 23-year-old young female who presented with a polypoid mass in the cervix.

Microscopically these tumors are variably cellular, consisting of spindle-shaped cells with scant cytoplasm, arranged in a patternless architecture to vague fascicles and /or herringbone pattern at places. They are described to have "Fibrosarcoma-like tumor morphology" in some cases. Infrequently there may be focal myxoid change in the stroma. The tumor cells, like in our case, have oval to elongated nuclei with mild pleomorphism, clumped nuclear chromatin, and inconspicuous to conspicuous nucleoli. Necrosis has been described in some cases (7). Variable mitotic activity ranging from 0 to 50/10HPF has been noted. Variable histologies like the presence of bizarre cells giving the lesion a "symplastic-like morphology" or presence of entrapped normal endocervical glands giving it an "adenosarcoma-like" appearance have also been described.

Rabban et al. have reported 3 cases of NTRK-rearranged sarcoma of the cervix with entrapment of normal endocervical glands amidst a tumor composed of spindle cells, and described areas of stromal overgrowth in the form of intraglandular stromal projection in their cases raising a diagnostic dilemma of adenosarcoma with sarcomatous overgrowth (7). The literature describes these tumors to have infiltrative margins, as in our case also. The tumor had reached the lower uterine segment as well as involved the upper vagina. Vascular invasion has been reported in only one case and lymphatic invasion in two cases so far (2). The presence of lymph node involvement was noted in one of the excised pelvic LN in our case (Figure 2A gross 2B Tm with entrapped endocervical glands 2C Margins and hyalinized blood vessels, 2D LN mets, inset (atypical mitosis and necrosis)).

On IHC the presence of CD34, S100, and PanTRK are described in these tumors. In the majority of reported cases PanTRK immunopositivity is correlated with NTRK fusions with a sensitivity of 75-100% and specificity of 93-100% (8). However, in 2021 Hondelink et al. stated that PanTRK IHC has a sensitivity of 18% and thus concluded that a molecular confirmation using FISH or RTPCR is essential for establishing a diagnosis (9). Our review of past cases suggested that though NTRK1 rearrangement is more common among these patients, NTRK3 rearrangements more frequently presented with distant metastasis to LN, lung, etc. and had a poorer prognosis.

The development of targeted therapy in several tyrosine kinase inhibitors (TKI) with varying degrees of activity against TRK A/B/C is the most promising prospect in the current era. Currently, Larotrectinib is the most specific TRK inhibitor used in the treatment of NTRK-positive tumors. Entrectinib is yet another orally available Pan TRK inhibitor with additional activity against ROS1 and ALK (10,11). Since these are expensive drugs and unavailable in developing countries like India, our patient was treated with adjuvant chemotherapy and radiotherapy. Table I summarizes the clinicopathological features and molecular abnormality in the cases reported so far (2-7,12-19).

Table I: Showing the clinicopathological profile of previously reported cases of NTRK rearranged sarcoma of cervix.

S. No.	Author	Age	Cl/F	Site	Salient Pathology	Stage	LVSI/Mets/Rec	Pan TRK	NTRK Fusion
1.	Chiang et al. (2)	46		Cervix		1b		+++	NTRK 1
2.	Yang et al. (3)	49		Corpus		IIb		+++	NTRK1
3.	Dang et al. (4)	33	BPV	Cervix	Fibro Sa Like	IIa	None	+++	NTRK3
4.	Goulding et al. (5)	13	BPV	Cervix		Ib	None		NTRK1
5.	Rabban et al. (7)	24	BPV	Cervix	Polypoid	NA		+++	NTRK1
6.		30	BPV	Cervix	Polypoid	NA		+++	NTRK1
7.		49	Asymp	Cervix	Infiltrative/ LVSI	NA	Pleural Mets	+++	NTRK3
8.	Boyle et al. (12)	42	BPV	Cervix	Polypoid	1b		+++	NTRK1
9.	Croce et al. (13)	39	-		Infiltrative/ LVSI	NA		+++	NTRK1
10.		44	-	Cervix		Ia		+++	NTRK1
11.		26	-	Cervix		Ia	Vagina Rec	+++	NTRK3

Table I Continued

12.		23	-	Cervix	Infiltrative	Ia	-	+++	NTRK1
13.		30		Cervix	Infiltrative Borders	Ia	-	+++	NTRK1
14.		60		Cervix		IIIb	Pelvis, Bladder	NA	NTRK1
15.		33		Cervix	Infiltrative Borders	Ia	-	+++	NTRK1
16.		23		Cervix	Local Infiltration	IIa	Omentum, Uv Tissue, Pelvis, Ovary, Liver	+++	NTRK1
17.	Costigan et al. (14)	35	Anemia	**Corpus**		Ib	-	-	NTRK1
18.		35	Dysmen	Cervix		Ia	-	+++	NTRK1
19.		47	Mass	Cervix		Ib	B/L Pelvic And Para Aortic LN	NA	NTRK1
20.		30	Polypoid, Enlarged Vascular	Cervix		IIb	-	++	NTRK1
21.		39	-	Cervix		NA	-	NA	NTRK1
A.		16	-	Cervix		Ia	-	+++	NTRK1
22.		26	-	Cervix		IIb	Pelvis	+	NTRK1
23.		26	-	Cervix		>Ib	Peritoneal LN	++	NTRK3
24.		26	-	Cervix		NA	Lung	+	NTRK3
25.		61	BPV	Cervix		Ib	-	++	NTRK3
26.		24	-	Cervix		Ia	-	+++	NTRK1
27.		42	BPV	Cervix		Ib	-	++	NTRK1
28.		42		Cervix		Ib		++	-
29.		46	BPV	Cervix		NA		+++	NTRK1
30.		26	-	Cervix		NA	-	+++	NTRK1
31.	Huang et al. (15)	NA		Cervix				Pos	NTRK1
32.		NA		Cervix				Pos	NTRK1
33.		NA		Cervix				Pos	NTRK1
34.		NA		Cervix				Pos	NTRK1
35.		NA		Cervix				Pos	NTRK1
36.		NA		Cervix				Pos	NTRK1
37.		NA		Cervix				Pos	NTRK1
38.	Wells et al. (16)	30	LSIL On Pap	Cervix		Ib		+++	NTRK1
39.	Moh et al. (17)	69	-	**Corpus**		Ib		--	NTRK2
40.	Gatalica et al. (18)	NA		Cervix		NA		Pos	NTRK1
41.		NA		**Corpus**		NA		Pos	NTRK3
42.	Present Case	23	BPV	Cervix	Polypoid Mass	LN	-	+++	NTRK3

Cl/F: clinical Features, **BPV:** Bleeding per vagina, **Asymp:** Asymptomatic, **Dysmen:** dysmenorrhea, **Fibro Sa:** fibrosarcoma like, **LVSI:** Lymphovascular invasion, **Mets:** metastasis, **Rec:** Recurrence, **LN:** lymph Node, **Pos:** Positive, **LSIL:** low grade squamous intraepithelial lesion, **Pap:** Papanicolaou stain, **NA:** Not available

+++ diffuse and strong immunopositivity ++ moderate immunopositivity + weak immunopositivity

CONCLUSION

To conclude, NTRK-rearranged sarcoma of the cervix is an emerging subset of cervical sarcoma with fibrosarcoma/adenosarcoma-like histomorphology. Use of common IHC like CD34, S100, and Pan TRK can be very helpful in identifying these tumors, though establishing a definite NTRK rearrangement on molecular testing is essential. Given the efficacy of TKI in the treatment of malignant TRK-rearranged tumors, a high index of suspicion and their accurate identification is clinically relevant.

Conflict of Interest
The authors have no conflict of interest.

Authorship Contributions
Concept: **RR, SM, SK,** Design: **RR,** Data collection and/or processing: **RR, BK,** Analysis and/or interpretation: **RR, SM, NB,** Literature search: **RR,SK,** Writing: **RR,** Approval: **SM.**

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