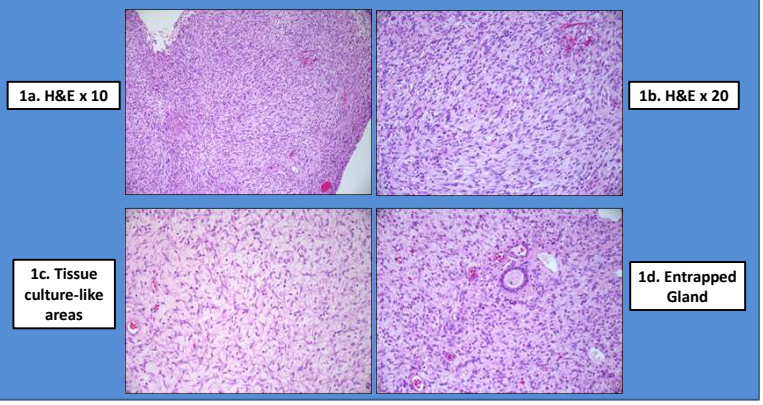
NEUROTROPHIC TYROSINE RECEPTOR KINASE ASSOCIATED SPINDLE CELL NEOPLASMS:

THREE CASES OF AN EMERGING ENTITY

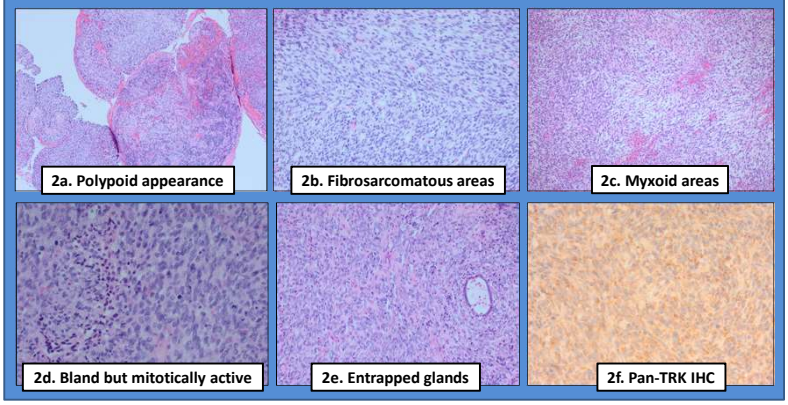
Authors: Grant L[1], Ganesan R[1], Williams S[2], Pascoe J[2], Boyle W[1]. **Institution:** [1]Birmingham Women's Hospital. [2]University Hospitals Birmingham.

Introduction: Uterine sarcomas are rare and typically smooth muscle or endometrial stromal in origin. However, recent molecular advances have identified numerous, genetically defined entities. NTRK-rearranged spindle cell neoplasms are classified as emerging entities [1-2]. Only 26 uterine/cervical cases are reported in current literature [3]. Physiologically, NTKRs play a role in the differentiation, survival and proliferation of neural tissue. Pathologically, NTRK oncogenic-driver mutations with numerous partners are described (TPM3 is most common, others include LMNA, TPR, RBPMS, EML4, and SPECC1L). NTRK-translocations occur in numerous solid tumours but <1% sarcomas. Tumour morphology and grade varies (currently believed to be translocation-type independent) however, in the female genital tract these are currently defined as low grade [1, 4-5]. Here we describe three cases of this emerging entity, one of which demonstrated dramatic therapeutic response to NTRK inhibitor (Larotrectinib).

Case 1: 42 year old presented with irregular vaginal bleeding and posterior cervical mass:

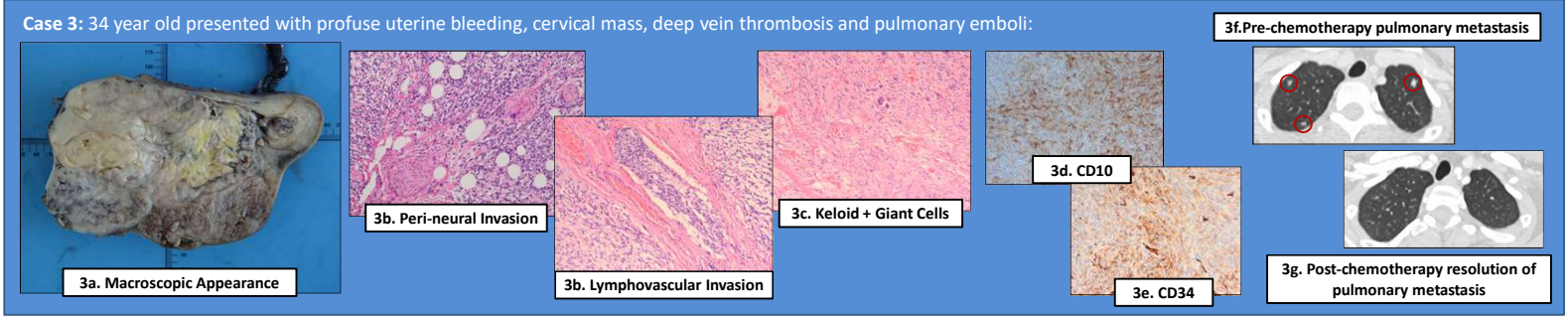


Case 2: 32 year old presented with ectopic pregnancy and incidental anterior cervical mass:



Case	MACROSCOPY:	MICROSCOPY:	ADDITIONAL STUDIES:
1.	Posterior cervical biopsy. Two polypoid fragments of cream coloured tissue measuring up to 25mm in aggregate	Uniformly, densely cellular tumour comprising short interconnecting fascicles of fairly monomorphic, mildly atypical spindle cells with bland plump nuclei showing even chromatin. Scattered individually hyperchromatic atypical nuclei with copious amounts of eosinophilic cytoplasm "resembling ganglion cells". Mitotic count 4/10hpfs. No necrosis. Background stroma is pale, eosinophilic and finely vacuolated with occasional myxoid areas imparting a tissue culture-like appearance. Capillary sized blood vessels and dense lymphocytic and plasma cell infiltrate are present throughout Trapped endocervical glands show no evidence of peri-glandular cuffing. There is no lymphovascular or peri-neural invasion.	- Pan-NTRK, CD10 and vimentin positive. - Minority of cells cyclin D1 positive. - MNF116, CAM 5.2, AE1/3, desmin, SMA, caldesmon, ALK, S100, SOX10, CKIT, DOG1, CD21, CD23 and CD34 negative. - PR negative. ER positive in <1% cells. - Molecular **NTRK1 (exon 9)-TMP3 (intron 6)** translocation demonstrated.
2.	Radical hysterectomy showing cervical effacement by fleshy, whiteish tumour 80mm in size showing areas of congestion and haemorrhage and surfaced by purulent material..	Uniformly densely cellular spindle cell tumour showing fascicular and storiform architecture. Many areas showed cells with more rounded nuclei. Mitotic activity was brisk including multiple atypical forms. Tumour infiltrating lymphocytes were present, more copious peripherally and in oedematous areas. Trapped endocervical glands show no evidence of peri-glandular cuffing. There is no lymphovascular or peri-neural invasion.	- Pan-NTRK diffusely positive. - S100, cyclin D1, CD31, CD34 and EMA show patchy positivity. - AE1/3, CD10, desmin, SMA, caldesmon,, MyoD1, Myogenin, ERG, ALK, CKIT, DOG1, P63, P16, PR and ER negative. - Molecular **TPR (exon 21)-NTRK1 (exon 10)** translocation demonstrated.
3.	Radical hysterectomy showing 146mm large solid cervical/lower uterine segment mass that extends into the paracervical stroma.with multiple, bilateral similar appearing pelvic and peritoneal deposits.	Solid, multi-lobulated, patternless/fasicular/storiform ovoid-spindled cells with relatively uniform nuclear morphology. Occasional scattered cells have enlarged nuclei. Scattered cells also have a "vaguely rhabdoid" appearance. Frequent mitotic figures and areas of coagulative tumour necrosis are seen. There is focal deposition of osteoid-like keloid material with some osteoclast-like giant cells. Trapped endocervical glands show no evidence of peri-glandular cuffing. Lymphovascular and peri-neural invasion is present.	- Pan-NTRK shows widespread cytoplasmic positivity. - S100, CD10 and CD34 show patchy positivity. - AE1/3, CAM 5.2, desmin, SMA, caldesmon, HMB45, CD117, calretinin. STAT6, cyclin D1, PR and ER negative. - Molecular **SPECC1L (exon 6)-NTRK3 (exon 14)** translocation demonstrated.

Case 3: 34 year old presented with profuse uterine bleeding, cervical mass, deep vein thrombosis and pulmonary emboli:



Discussion: Clinically: NTRK-rearranged neoplasms tend to occur in younger patients (mean 35, range 23-60 years). Most present with vaginal bleeding or a cervical mass [1-2]. **Macroscopically:** they are typically firm, fleshy polypoid lesions, centred in cervical stroma, ranging from 3-12cm. Similar uterine and vaginal lesions can occur [1-2]. **Microscopically:** they are typically moderate to hypercellular, fibrosarcomatous-like, fasicular and storiform with occasional hypocellular, myxoid areas. Keloid-like collagen, peri-vascular hyalinisation and staghorn vessels are described. Gland trapping appears common. Cytologically, they comprise relatively uniform mild-moderately atypical spindle cells with scant cytoplasm and inconspicuous nucleoli. Scattered symplast-like and vacuolated epithelioid cells may occur. Mitotic count is variable (1–50 mitoses/mm^2). Necrosis may be present. Tumour infiltrating lymphocytes can simulate inflammatory myofibroblastic tumour. Lymphovascular invasion (case 3) has not been described before [1-5]. **Immunohistochemically:** most NTRK-rearranged tumours show (nuclear or cytoplasmic) Pan-TRK staining, whilst relatively sensitive it is non-specific (seen in 6% leiomyosarcomas and 91% high grade endometrial sarcomas). Tumours may show S100, CD34, CD31 and cyclin D1 positivity. **CD10,** SMA, desmin, Sox-10, BCOR, ER, or PR are typically negative [3].

References: : 1. WHO Classification of Tumours Editorial Board. Female genital tumours 5th ed. Lyon (France): International Agency for Research on Cancer; 2020.. 2. Croce et al. 2021. NTRK and other recently described kinase fusion positive uterine sarcomas: A review of a group of rare neoplasms. Genes Chromosom Cancer. 60(3):147-159. 3. Pubmed 2022 "uterine NTRK neoplasm" Available at: https://pubmed.ncbi.nlm.nih.gov/?term=uterine+ntrk+neoplasm&sort=date Accessed: 11/05/22. 4. Nilforoushan et al. 2021. NTRK-Fusion Sarcoma of the Uterine Cervix: Report of 2 Cases with Comparative Clinicopathologic Features. Int J Gynaecol Pathol. 00: 1-7. 5. Goulding et al. 2021. Case: report: NTRK1-rearranged cervical sarcoma with fibrosarcoma like morphology presenting in a 13-year-old managed with a neo adjuvant TRK-inhibitor and surgical excision. Gynecol Oncol Rep. 10;37:100845.6. National Institute of Clinical Excellence. Larotrectinib for treating NTRK fusion-positive solid tumours. Guidelines. Published May 27 2020.

Molecularly: demonstration of an NTRK-rearrangement is required for diagnosis. **Prognosis:** These are staged as other cervical sarcomas. Most are confined to the uterus (stage I). The course varies, but at least some are aggressive ± metastasize. Prognostic data is lacking however older patients do appear to have higher risk of progression [1-2]. **Therapeutically:** there is growing evidence for **NTRK-inhibitors** as oncologic agents. Both larotrectinib and entrectinib have shown dramatic, durable effects against both locally advanced and metastatic NTRK-rearranged tumours regardless of tumour site, histological classification or NTRK-fusion type. For all tumour types: Larotrectinib objective response rate (ORR) was 76%, complete response (CR) 22%. Entrectinib ORR was 57%, CR 7% with a median duration of 10.4 months [5]. Following accelerated FDA approval NICE now recommends managed access Larotrectinib for NTRK-fusion positive solid tumours if disease is "locally advanced, metastatic or surgery could cause severe health problems" and/or "they have no satisfactory treatment options" [6]. Our patient (case 3) showed striking response of both pelvic and pulmonary metastasis (that had previously progressed on conventional chemotherapy) after 4-6 weeks Larotrectinib treatment.

Aim: Improve clinical, morphological and diagnostic awareness of these tumours with hope for more robust clinical trials and future evidence based therapies:

- Typically, "**young**" patients who present with **bleeding** and an **incidental tumour**.
- **Variable morphology** can be diagnostically challenging.
- **High index of suspicion** required for **molecular testing** due to diagnostic and therapeutic implications (i.e. **Larotrectinib therapy**)