NTRK1 Rearranged uterine sarcoma- a study of two cases

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Introduction

Uterine sarcomas are rare malignant tumours of uterus. They are tumours with a wide range of appearances, immunophenotype and molecular alterations. With the use of elaborate molecular techniques, including next generation sequencing, new genetic rearrangements have been described. a heterogeneous group of tumours with differing morphologies, immunophenotypes and molecular alterations. With the advent of modern molecular techniques, such as next generation sequencing, newly defined genetic abnormalities are being reported in this group of neoplasms. Rearrangements of the neurotrophic tyrosine kinase receptor (NTRK) genes *NTRK1*, *NTRK2*, and *NTRK3*, which encode tropomyosin receptor kinases TrkA, TrkB, and TrkC, respectively, have been identified in a wide spectrum of malignancies including uterine mesenchymal tumours.[1] *NTRK* fusions have recently been reported in 14 cases of uterine sarcoma.[1,2]

Cases

We report two cases of NTRK rearranged uterine sarcomas presenting as masses in the uterine cervix.

Case1:

A 32-year female presented with abnormal vaginal bleeding during pregnancy and was taken for surgery for ectopic pregnancy where a polypoidal tumour was discovered within the cervix.

Case2:

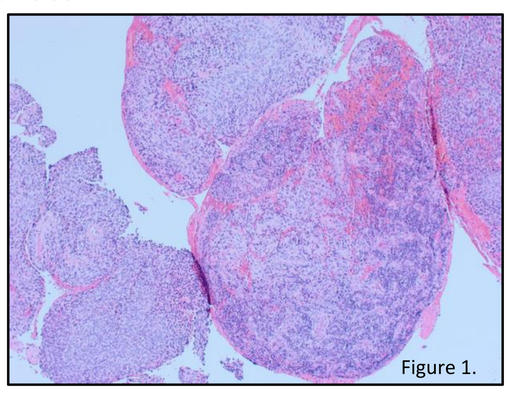
A 42 year female presented with abnormal vaginal bleeding and a polypoidal lesion was discovered in the posterior cervix.

Histopathology:

Biopsy from both polyps showed tumour composed of dense monomorphic spindle cells arranged in fascicles and storiform pattern. The cells had plump nuclei with fine chromatin and moderate amount of eosinophilic cytoplasm. Entrapped benign tubular glands were noted throughout the tumour. Tumour infiltrating lymphocytes and plasma cells were present. Mitotic activity was variable and ranged from 8 mitoses per 10 high power fields (hpfs) in one case to 48 per 10 hpfs in the other. Atypical mitoses were also present. None of the tumours showed coagulative type tumour necrosis. Morphological differential diagnosis was adenosarcoma with sarcomatous overgrowth versus high grade sarcoma and immunohistochemistry was requested.

Immunohistochemistry

Case1: The tumour was weakly positive for CD99 and showed patchy positivity with EMA.
Case2: This tumour was diffusely positive for pan-Trk, positive staining with CD10 and Vimentin, weak cytoplasmic staining with CD34 and focal positivity with Cyclin D1.
Both tumours were negative for smooth muscle markers, hormone receptors and S100.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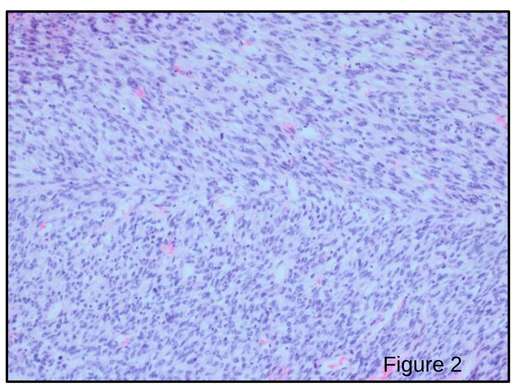
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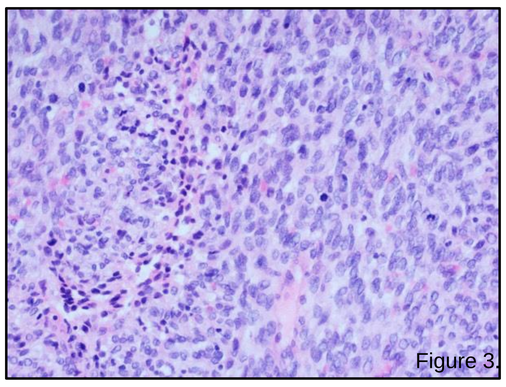


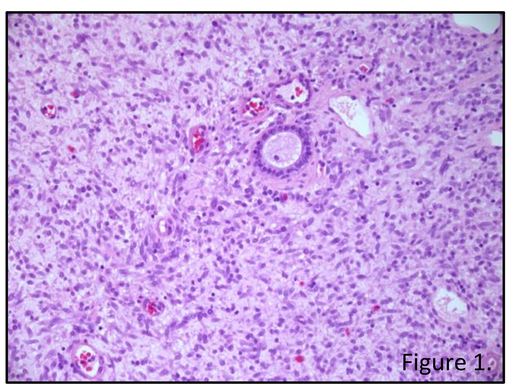
Figure 3.

CASE1

Figure 1. Polypoidal fragments of tumour (x40 magnification)

Figure 2. Neoplastic cells in fascicles- fibrosarcoma-like morphology (x200 magnification)

Figure 3. Bland appearing neoplastic cells showing brisk mitotic activity(x200 magnification)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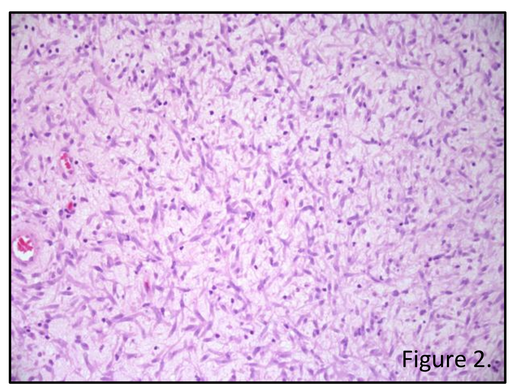
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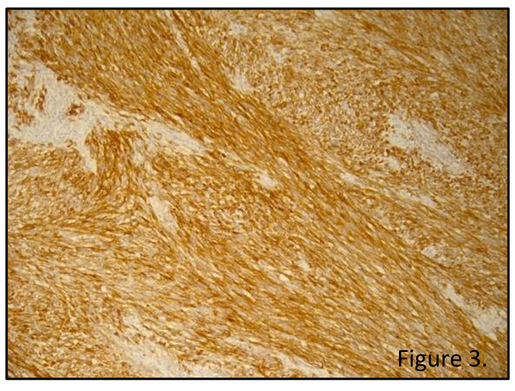
Figure 3.

CASE 2

Figure 1. Small inactive gland entrapped by neoplastic spindle cells with hyperchromatic nuclei. There is no periglandular stromal condensation (x200 magnification)

Figure 2. Neoplastic cells within loose myxoid matrix with scattered chronic inflammatory cells imparting a tissue culture-like appearance (x200 magnification)

Figure 3. Neoplastic cells showing diffuse positive staining with pan-Trk immunostaining (x200 magnification)

FISH Analysis

FISH analysis of both tumours specimen was performed using the Zytovision ZytoLight SPEC NTRK1 dual-colour break-apart probe (Z-2167-200) which detects translocations involving the chromosomal region 1q22-q23.1 harbouring the NTRK1 gene. NTRK1 translocation was detected in both tumours. Final diagnosis in both cases was NTRK1 rearranged cervical sarcoma, high grade.

Next Generation Sequencing

Next generation sequencing was performed using a 28 gene NGS panel. It revealed Tropomysin3 (TPM3)gene-NTRK1 rearrangement of NTRK1 rearrangement.

Follow up

Both patients underwent hysterectomy following diagnosis followed by adjuvant radiotherapy and brachytherapy. Both are tumour free after 11 months and 3 months post surgery.

Discussion

NTRK fusion sarcomas of uterine cervix show a unique constellation of gross, microscopic and immunohistochemical features. The tumours present as a cervical polyp or mass in women between 20-40 years of age.[2] These tumours are pale white and have smooth borders on gross appearance. Morphologically, they are composed of a fibrosarcoma-like fascicular proliferation of spindle cells with mild to moderate atypia and mitotic activity that varies highly between tumours.[3,4] These are generally FIGO stage IA or IB with few exceptions.[2]
Benign entrapped glands are a feature of these tumours which can lead to misdiagnosis as uterine sarcomas including adenosarcomas. Diffuse positive staining with Pan-Trk immunohistochemsitry, leads to diagnosis. FISH analysis for NTRK gene re arrangement is valuable as demonstration of the abnormality allows targeted therapy.

Conclusion

In summary, we present two cases of NTRK1 rearranged sarcoma of uterine cervix. NTRK sarcomas are members of a recently described group of uterine fibrosarcoma-like mesenchymal tumours. Pan-Trk immunohistochemistry is a rapid and effective screening tool for these tumours. Due to lack of specificity, FISH analysis and molecular testing is required for diagnosis. If NTRK rearrangement is detected, these patients are eligible for targeted therapy with tropomyosin receptor kinase inhibitors (TRKI). The accurate identification of these rare tumours is clinically relevant given the tissue type-agnostic efficacy of tropomyosin receptor kinase inhibitors in the treatment of malignant tumours with NTRK mutations.

References

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