

Case report

NTRK-1 fusion in endocervical fibroblastic malignant peripheral nerve sheath tumor marking eligibility for larotrectinib therapy: A case report

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1. Introduction

< 1% of all reported cervical malignancies are sarcomas, with rhabdomyosarcomas making up the majority of this group. (Wright et al., 2005) Malignant peripheral nerve sheath tumors (MPNST), previously referred to as neurofibrosarcomas, account for five to 10% of sarcomas at any primary site, with only a handful of cervical MPNSTs reported in the literature. (Sangiorgio et al., 2018) Endocervical fibroblastic MPNST (neurofibrosarcoma) has been reported as a novel entity possibly related to endocervical CD34 fibrocytes, however, given the small sample size it is difficult to test this theory in a large case series. (Mills et al., 2011) It is not clear that the shared terminology of MPNST is applicable for these cervical neoplasms.

The lifetime risk of MPNST in the general population is 0.001% but is markedly increased in patients with neurofibromatosis type 1—up to eight to 13%. (Fadare, 2006) Recent genetic insights have found the tumor suppressors NF1, TP53 and CDKN2a along with the PRC complex proteins EED and SUZ12 to be common genetic changes in NF1 related MPNST along with some RAS pathway changes in fewer cases. (Brohl et al., 2017; Lee et al., 2014) Radical resection remains the mainstay of treatment for MPNST, with adjuvant radiation therapy allowing a significant reduction in the local recurrence of disease. Chemotherapy is currently reserved for systemic disease. Recent targeted therapy may

represent an option for the refractory setting and also in patients who may be poor surgical candidates.

2. Case report

A 30-year-old nulliparous, healthy woman presented to the cancer center for evaluation and management of a presumed MPNST without history of neurofibromatosis. She presented for a routine healthcare maintenance visit and was discovered to have an abnormal Pap test which revealed low-grade squamous intraepithelial lesion (LSIL) with human papillomavirus (HPV) co-testing positive. She underwent a colposcopy with biopsies returning as cervical intraepithelial neoplasia (CIN) 2. She underwent a cold-knife conization. The surgical specimen and endocervical curettage showed atypical spindle cells positive for p16, Ki-67, CD10, CD34, and S100 (polyclonal) (Figs. 1–3), suggesting endocervical fibroblastic MPNST (up to two mitoses were visualized per 10 high-powered fields and some nuclei showed pseudoinclusions). The tumor was deemed low grade, which is another characteristic that would be unlikely in classic NF1 associated MPNST. Pathology was reviewed at three comprehensive cancer centers with two in agreement with endocervical fibroblastic MPNST (neurofibrosarcoma) and one favoring “atypical spindle cell proliferation involving the cervical stroma and extending to the tissue edges; a low grade sarcoma cannot

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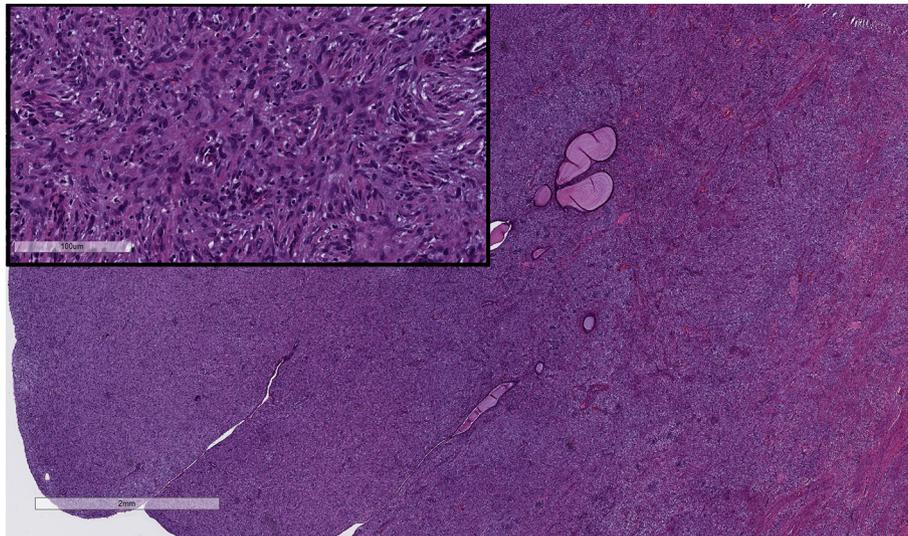


Fig. 1. Digital image of a low power view of the hematoxylin and eosin stain of the cervical sarcoma that involves the cervical stroma. Insert: Digital image of a high power view of the hematoxylin and eosin stain of the cervical sarcoma which is composed of cellular spindle cells.

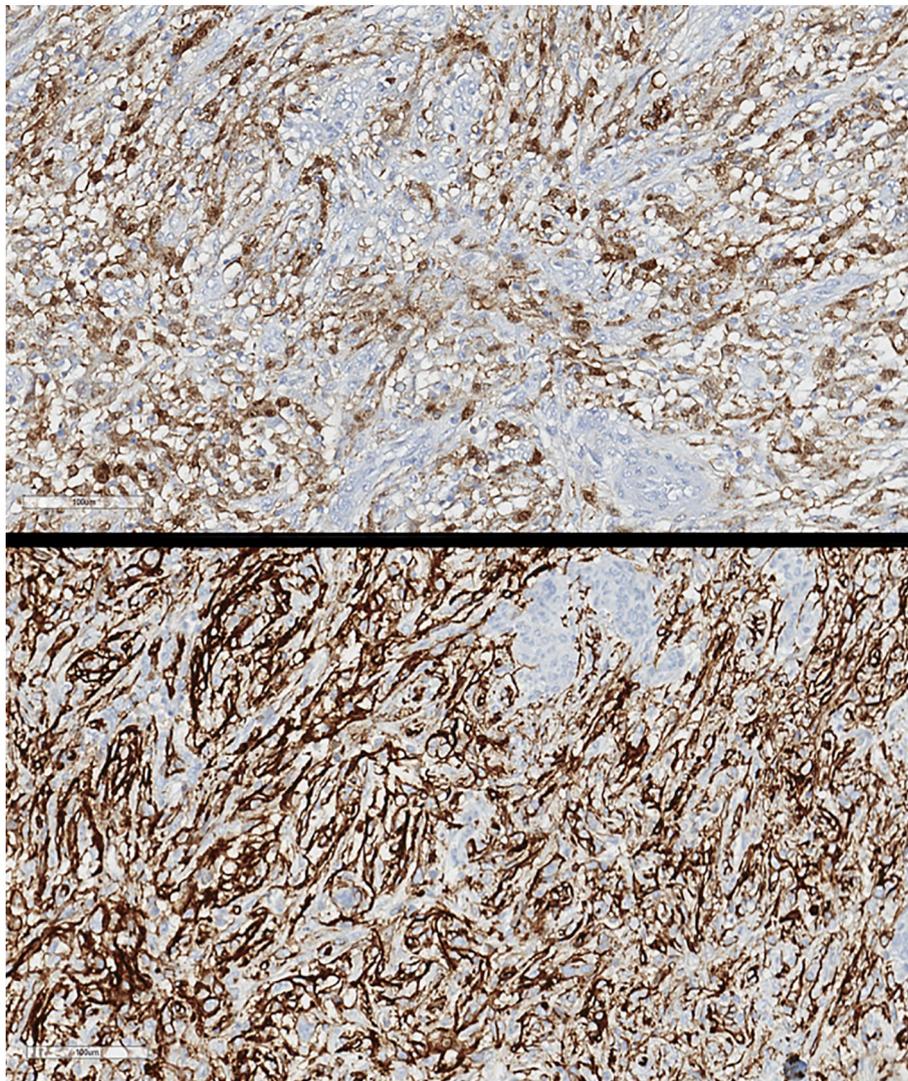


Fig. 2. Digital image of a high power view of S-100 (polyclonal) stain of the tumor cells and CD34 stain of the tumor cells. The positive cells are stained brown exhibiting neural differentiation (S-100) and fibroblastic differentiation (CD34). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

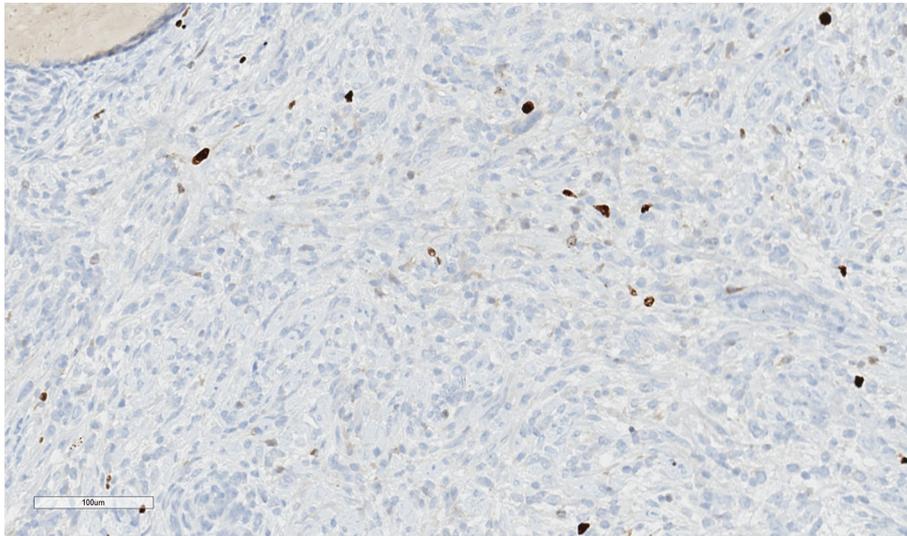


Fig. 3. Digital image of a high power view of Ki-67 stain of the tumor cells. Only scant tumor cells are stained brown indicating low proliferation index. A benign endocervical gland is noted at the left upper corner. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

be excluded.” The patient had no prior abnormal Pap test and did not have any first-degree relatives with history of gynecologic cancer; however, she was adopted and had limited knowledge of family health. Outside first opinion was for a hysterectomy, however, she desired fertility preservation and, thus, presented to our institution for a second opinion.

On presentation, the patient was asymptomatic and had a negative comprehensive review of systems. On bimanual exam, the cervix and tumor was 3–4 cm in diameter. The uterus was freely mobile and there was no obvious vaginal or parametrial disease. Pelvic MRI suggested the mass was closer to 3 cm in greatest tumor dimension, and PET scan was negative for metabolically active lymph nodes or evidence of metastatic disease. Across the comprehensive cancer center opinions, there were concerns that this lesion could be progressing or of a size not amenable to surgery; there was some apprehension that delaying surgery could lead to a missed chance for complete resection. The patient was diagnosed with stage IB1 primary sarcoma of the cervix. In agreement with outside institutions, fertility preservation was not recommended given the rare and potentially aggressive histologic subtype along with the suspected tumor size.

The patient underwent exam under anesthesia, exploratory laparotomy, radical abdominal hysterectomy, bilateral salpingectomy, and bilateral ovarian transposition. No tumor was grossly visible near the vaginal margin or in the parametria. The patient tolerated the procedure well and was discharged on post-operative day three following an uneventful hospital course. Final pathology revealed a 2.5 × 2 × 2 cm, grade 1–2 (FNCLCC) endocervical fibroblastic MPNST involving the lower uterine segment without evidence of necrosis or angiolymphatic invasion. Subsequent immunohistochemistry (IHC) was negative for SOX-10; the cancer center did not have the ability to perform IHC for NTRK-1 internally or externally. The surgical margins were free of tumor. No adjuvant therapy was recommended given the final surgical pathology.

Based on suspicion for association between CD34 and S100 (polyclonal) positivity with neurotrophic receptor tyrosine kinase (NTRK) gene expression, specimens were sent for Foundation Heme somatic testing (Foundation Medicine, Cambridge, MA), in whose comprehensive genomic profiling assay the NTRK1 gene rearrangement is incorporated. This revealed genetic alterations including *TPM3-NTRK1* fusion. With this promoting partner domain, the tyrosine kinase A becomes constitutively active, leading to increased neuronal cell proliferation, differentiation, and survival. (Klein et al., 1991; Wooten et al., 2001) As of late November 2018, larotrectinib became the second FDA-approved targeted therapy for a specific gene mutation, developed

as an inhibitor for NTRK in both adult and pediatric tumors. The approval was based on results from a combined 55 patients with the identified gene fusion across three clinical trials, which demonstrated a 75% overall response rate. (Laetsch et al., 2018) This targeted oral therapy could represent a viable treatment option for this patient if she were to experience a recurrence; the patient is four months with no evidence of disease at latest office visit.

Patient consent was obtained for publication of case details and accompanying images.

3. Discussion

Our patient's case adds to the many whereby histologic characterization and nomenclature can be enhanced by molecular testing resulting in potentially improved treatment options. While this lesion demonstrates several good prognostic factors for MPNST, including small tumor size (< 5 cm) and negative surgical margins, we favor this lesion being characterized more by the biology it seems to share with other NTRK translocated sarcomas, such as an infantile fibrosarcoma which can be managed conservatively. (Orbach et al., 2016) This case complements the review done by Suurmeijer et al. describing 25 cases of tumors all with co-expression of S100 and CD34 without SOX10 expression. In those bearing the NTRK1 gene fusion, these kinases were highly expressed, suggesting this recurrent gene fusion comprises a molecular subtype of tumors with S100 and CD34 immunoreactivity. (Suurmeijer et al., 2018) While these lesions are typically locally invasive and can be targeted with NTRK inhibitors effectively (Morton and Truman, 1986), the molecular change has a spectrum of clinical behavior including metastatic ability. (Davis et al., 2019) Even metastatic NTRK translocated sarcomas have demonstrated some improvement from NTRK targeted therapies. Thus, patients with cervical fibrosarcomas may benefit from *TPM3-NTRK1* fusion testing. (Doebbele et al., 2015) Our patient's positive Ki-67 immunohistochemistry reflects an increased proliferation index and may represent a poorer prognostic factor, and there remains a possibility that she could develop recurrent disease refractory to first-line chemotherapy. The recent FDA approval of larotrectinib as a targeted therapy for this tyrosine kinase presents a new second-line modality for refractory disease previously poorly managed with chemotherapeutic agents. (Laetsch et al., 2018; Drilon et al., 2018) Larotrectinib (Vitrakvi) is currently indicated for treatment of solid tumors that possess NTRK gene fusion without resistance mutation and have metastasized or recurred after surgical resection, or in patients for whom a surgical procedure would result in severe morbidity.

Author contributions

Ali Wells, BS: manuscript preparation, literature review.
 Adrienne Mallen, MD: manuscript preparation, literature review.
 Marilyn M. Bui, MD, PhD: manuscript review, preparation of pathology images.
 Damon Reed, MD: consulting physician, manuscript preparation and review.
 Sachin M. Apte, MD, MBA: primary physician and investigator, manuscript review.

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