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Case report

Detection of a somatic GREB1-NCOA1 gene fusion in a uterine tumor resembling ovarian sex cord tumor (UTROSCT)

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ABSTRACT

Uterine tumor resembling ovarian sex cord tumor (UTROSCT) is a rare uterine neoplasm of uncertain malignant potential. We present the case of a 69-year-old woman who underwent hysterectomy for postmenopausal bleeding and was found to have a myometrial UTROSCT. RNA-sequencing identified a somatic GREB1–NCOA1 fusion, supporting the diagnosis. Next-generation sequencing is increasingly being adopted in diagnostic pathology laboratories. This report highlights the value of RNA-sequencing in identifying rare fusion events to support pathologic diagnoses.

1. Introduction

Uterine tumor resembling ovarian sex cord tumor (UTROSCT) is a mesenchymal neoplasm with predominantly sex cord-like differentiation, classified by the World Health Organization as a subset of endometrial stromal and related neoplasms. Fewer than 100 cases of UTROSCT have been published since the entity was first described (Schraag et al., 2017), and it is clearly a rare entity, although the true incidence is difficult to estimate due to its rarity and the historical absence of a reliable diagnostic marker. UTROSCT usually occurs in middle-aged women (average age of 50 years) who present with abnormal bleeding or pelvic pain (Blake et al., 2014; Clement and Scully, 1976). Hysterectomy with or without bilateral salpingo-oophorectomy is considered standard treatment for these neoplasms. While typically considered to be of low malignant potential, a recent series documented extrauterine metastasis in 8 of 34 patients (Moore and McCluggage, 2017). Although referral bias is likely to be present, the non-negligible rate of malignant behavior underscores the need for accurate diagnostic tools for such patients.

Sex cord-like elements are present in a variety of uterine neoplasms. They can be a focal pattern within endometrioid adenocarcinoma, or can be mimicked by adenosarcoma, carcinosarcoma, or smooth muscle tumors. Once these mimickers are excluded, uterine tumors with a bona fide sex cord-like element have been divided into two groups: group I tumors, known as endometrial stromal tumors with sex cord-like elements (ESTS克莱), and group II tumors, comprising classic UTROSCTs. A recent systematic review showed that subcategorization is often not reported, but that group I tumors have the greater malignant potential of the two, with disease-free survival at 2 years being 23.8% for group I, but 100% for group II (Blake et al., 2014). Group I tumors contain focal sex cord-like elements (although > 10% by definition), and these tumors appear to be closely related to low-grade endometrial stromal sarcomas, sometimes harboring characteristic genetic rearrangements such as JAZF1–SUZ12. Group II tumors appear to be a separate entity (Blake et al., 2014; Clement and Scully, 1976). Molecular features of UTROSCT were elusive until RNA sequencing (RNA-seq) revealed recurrent NCOA1 rearrangements (Dickson et al., 2019; Goebel et al., 2020), usually partnering with estrogen receptor 1 (ESR1) or growth regulation by estrogen in breast cancer (GREB1).

Here we report a case of a 69-year-old woman with a uterine tumor. The histopathologic findings were initially equivocal, but RNA-seq identified a diagnostic GREB1–NCOA1 fusion, supporting classification as UTROSCT.

2. Case summary

The patient provided consent for publication. A 69-year-old woman with past medical history significant for breast cancer (stage I ER/PR-positive, HER-2–negative invasive ductal carcinoma diagnosed in 2010) presented with postmenopausal bleeding and underwent hysteroscopy...
and D&C in 2016, with removal of a benign endometrial polyp. She had a recurrent episode of postmenopausal bleeding in February 2019. A transvaginal ultrasound at that time demonstrated a thickened endometrium at 1.2 cm, as well as an isoechic 3.9 cm mass within the myometrium without mass effect on adjacent endometrium. Repeat D&C in early 2019 revealed no evidence of malignancy. The patient remained symptomatic and desired definitive management. In July 2019, she underwent robotic-assisted total laparoscopic hysterectomy and bilateral salpingo-oophorectomy. Operative findings were notable for normal uterus, tubes and ovaries, vaginal strictures and atrophy, a 2 cm inclusion cyst on the anterior uterine serosa, and adhesions from ascending and descending colon to pelvic sidewalls.

Gross examination of the bivalved uterus showed a 5.2 × 4.1 × 3.2 cm tan-white, well delineated, focally necrotic-appearing mass. Histology showed a stromal tumor within the myometrium, with several histologic components (Fig. 1). One component consisted of cells with small to medium-sized, round to oval nuclei and inconspicuous cytoplasm, resembling cells of low-grade endometrial stromal sarcoma, with a mitotic rate of approximately 1 per 10 high-power fields. Other more peripheral areas showed similar cells arranged in cords, tubules and other pseudoglandular configurations, resembling patterns that can be seen in granulosa cell tumors of the ovary, also with aggregates of foamy macrophages. Each component was noted to make up close to 50% of the volume of the tumor. The growth habitus appeared expansile, but on microscopic examination, the sex cord elements peripherally infiltrated the myometrium. Margins and serosa were negative, and lymphovascular invasion was absent. Immunostains showed tumor cells to be positive for CD10, pancytokeratin (sex cord elements only), progesterone receptor, calretinin, and vimentin, very weakly positive for estrogen receptor, and negative for smooth muscle actin. Inhibin showed multifocal but strong positivity, mainly in the sex cord-like component.

Several diagnoses were considered. Less likely entities included carcinosarcoma, adenosarcoma and dedifferentiated endometrioid adenocarcinoma. More probable entities included low-grade endometrial stromal sarcoma, endometrial stromal tumor with sex cord-like elements (ESTS克莱) or uterine tumor resembling ovarian sex cord tumors (UTROSCT). Fluorescence in situ hybridization was negative for JAZF1, PHF1, or YWHAE rearrangements. RNA-seq (Dickson et al., 2019) identified a fusion between GREB1 (NCBI Reference Sequence: NM_014668.3; exon 7 of 33) and NCOA1 (NM_003743.4; exon 13 of 21) (Fig. 2). The presence of a somatic GREB1-NCOA1 fusion supported a definitive diagnosis of UTROSCT.

The patient recovered from surgery without complication and was seen at 2 and 6 weeks postoperatively. No adjuvant therapy was felt to be indicated. She was without apparent disease at an 8-month postoperative interval.

3. Discussion

The current World Health Organization (WHO) classification includes UTROSCT under the category of “endometrial stromal and related tumors”. However, these tumors do not resemble ovarian sex cord-stromal tumors nor uterus stromal neoplasms at a molecular level, despite their morphologic resemblance (Croce et al., 2016; Staats et al., 2009). Recently, a small number of studies have identified molecular alterations strongly associated with UTROSCT. A recent study showed recurrent NCOA2/3 gene fusions in 4 UTROSCTs (ESR1-NCOA3, n = 2; ESR1-NCOA2, n = 1; GREB1-NCOA2, n = 1) (Dickson et al., 2019). A subsequent report characterized the features of 4 GREB1-rearranged uterine sarcomas (GREB1-NCOA1, GREB1-NR4A3, GREB1-SS18, and GREB1-NCOA1), as well as 4 classic UTROSCT harboring ESR1-NCOA3 (Lee et al., 2019). The GREB1-rearranged sarcomas were said to have limited sex cord differentiation, but
our case with NCOA1-GREB1 showed reasonably strong sex cord features.

In response to those initial studies, Goebel et al. sought to further describe the molecular characteristics of this rare tumor using a larger cohort of 26 UTROSCT cases. A majority of cases showed NCOA1, NCOA2, or NCOA3 gene fusions (18/22). The most commonly identified fusion partners were ESR1 or GREB1 (17/22). Further, a subset of the UTROSCTs were analyzed for alterations characteristic of low-grade stromal neoplasms (JAZF1-SUZ12 translocations and PHF1 rearrangements), all of which were negative (Goebel et al., 2020).

ESR1 (estrogen receptor 1) is a ligand-dependent transcription factor and GREB1 (growth regulation by estrogen in breast cancer) is expressed in all ESR1-expressing tissues, and is a mediator of estrogen activity (Dickson et al., 2019). NCOA1-3 genes encode a family of nuclear receptor co-activators (p160/Src family) that, when bound to nuclear receptors, stimulate transcription in a hormone-dependent manner. Their role in steroid hormone-dependent uterine function and has been described (Szwarc et al., 2014). It has been surmised that these fusions cause uterine disease because ESR1 and GREB1 are highly expressed in uterine tissue. The putative fusion oncoproteins retain the active promoter region of ESR1/GREB1 fused to the nuclear receptor co-activator domain of NCOA1–3. This would result in dysregulated expression of the nuclear receptor co-activator domain of NCOA1–3 (Dickson et al., 2019). Functional studies supporting this hypothesis have not been reported.

Making a distinction between UTROSCT and ESTS克莱尔可能导致不同的病理学背景。鉴于在诊断、数据采集方面的潜在差异，以及通过随机前瞻性观察数据，可以更有效地监测。测试更先进的行为，ESTS克莱尔，特别是对II型（UTROSCT）肿瘤的术后影像可能需要被实施，因为临床观察是适用的。

In conclusion, the present case showed a somatic GREB1-NCOA1 fusion, supporting the diagnosis of UTROSCT. This newly recognized molecular event can aid in distinguishing these rare, apparently innocent tumors from more aggressive morphologic mimics.

Hagemann: Conceptualization, Writing - review & editing, Data curation, Investigation, Methodology, Project administration, Supervision.

References


