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Case report

A recurrent endometrial stromal sarcoma harbors the novel fusion *JAZF1-BCORL1*

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1. Introduction

Endometrial stromal sarcomas (ESS) account for <10% of all uterine sarcomas and <1% of all uterine malignancies (Chan et al., 2008). ESS are classified by the World Health Organization (WHO) as low grade (LG-ESS) and high grade (HG-ESS) if they resemble proliferative-phase endometrial stroma, but infiltrate the surrounding myometrium (Chan et al., 2008). LG-ESS has an indolent but ultimately destructive course and can also present a diagnostic challenge if variant morphology such as smooth muscle or sex cord differentiation is present (Xue and Cheung, 2011). In the latter case, immunohistochemistry, such as the presence of hormone receptors can be helpful. LG-ESS harbors *JAZF1-SUZ12* in approximately 50% of cases, but can harbor other fusions with a variety of 5′ and 3′ partners (Chiang et al., 2011; Conklin and Longacre, 2014). We report here a case of LG-ESS harboring a novel genomic rearrangement of *JAZF1-BCORL1* as identified by RNA sequencing in the context of comprehensive genomic profiling and possible implications for benefit from targeted therapy.

2. Case

A 59 year old nulligravida presented in 2009 with complaints of a prolapsing firm vaginal mass of 6 months duration. She had no other associated symptoms, and underwent resection of the vaginal mass. The histologic diagnosis was consistent with a LG-ESS. After referral to Gynecologic-Oncology, she underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy and standard staging followed by adjuvant therapy with megestrol acetate. She remained asymptomatic until 2014, when she presented with progressively worsening abdominal pain. A large abdominal mass, was identified on CT scan. In September 2014 she underwent resection of the abdominal mass, infracolic omentectomy, partial colectomy and end colostomy, and resection of the bladder dome. Histologic assessment was consistent with recurrent endometrial stromal sarcoma (Fig. 1a–c). Formalin-fixed paraffin embedded tumor tissue from this recurrent tumor resection was submitted for comprehensive genomic profiling.

3. Methods

Comprehensive genomic profiling of the abdominal tumor specimen was performed in a CLIA-certified, CAP-accredited lab (Foundation Medicine, Cambridge, MA) to identify potential therapeutic options. Hybridization capture from 405 cancer-related genes and 31 genes commonly rearranged in cancer (FoundationOne Heme®) was applied to ≥50 ng of DNA and 265 genes were sequenced from RNA extracted from formalin-fixed, paraffin embedded recurrent ESS tumor tissue and sequenced to high, uniform coverage (median exon coverage > 500×). Sequence reads were mapped to the reference human genome (hg19) and all classes of genomic alterations (base substitutions, small indels, rearrangements, copy number alterations) were determined as previously described (Frampton et al., 2013).

4. Results

Comprehensive genomic profiling revealed a genomic rearrangement between *JAZF1* exons 1–3 and exons 5–12 of *BCORL1* (Fig. 1d). Additionally, a splice-site mutation within *NF1* and homozygous deletion of *CDKN2A/B* were identified.

5. Discussion

LG-ESS is a low grade malignancy that morphologically mimics the stromal cells of the endometrium, and is a distinct clinicopathologic entity from high grade endometrial stromal sarcoma and undifferentiated uterine sarcoma (UUS) (Conklin and Longacre, 2014). The incidence of ESS in the United States is approximately 300–600 year, and surgery

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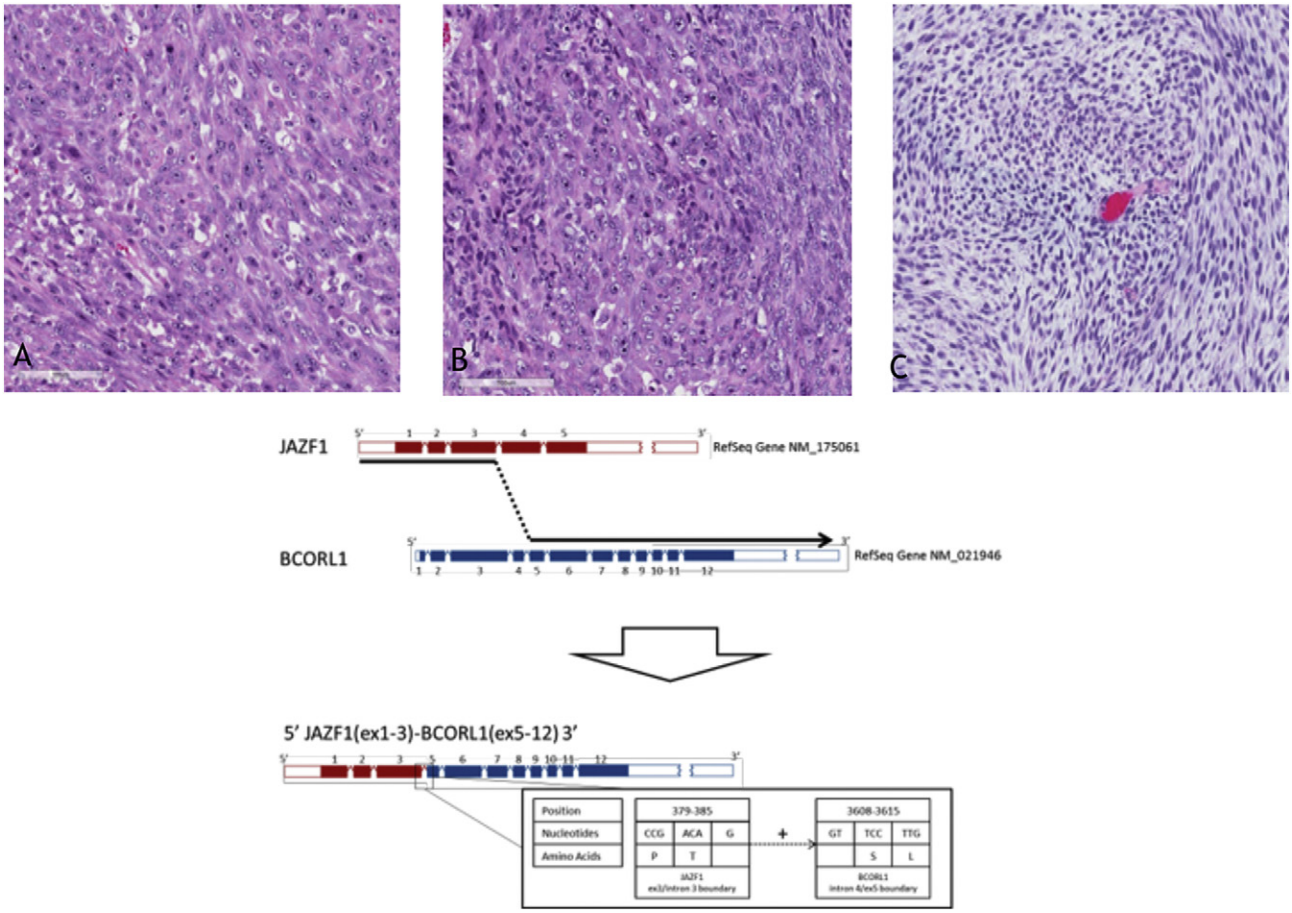

Fig. 1. Recurrent endometrial stromal sarcoma harbors the novel *JAZF1-BCORL1* fusion. A–C) Photomicrographs of recurrent tumor at 100× demonstrating LG-ESS. D) *JAZF1-BCORL1* genomic rearrangement.

can provide effective control for some cases.(Puliyath and Nair, 2012) For the up to 50% of ESS cases that locally recur, as well as those initially presenting with metastatic disease, the median survival is in the neighborhood of 5 years[4]. After first line treatment with endocrine agents, cytotoxic chemotherapy regimens provide limited benefit in recurrent or metastatic disease and rigorous study of new approaches is challenging given the rarity of this condition (Dahhan et al., 2009).

The recurrent genomic alterations associated with ESS, when identified in the course of clinical care, can resolve diagnostic dilemmas. In some instances, it may be difficult to differentiate ESS from uterine leiomyosarcoma or other sarcomas based solely on the histology or immunohistochemical characterization (Xue and Cheung, 2011). Rearrangements between the gene *JAZF1* (Just Another Zinc Finger 1) and *SUZ12* (*JJAZ1*) were the first characterization of a recurrent genomic driver of ESS (Li et al., 2007). The *JAZF1-SUZ12* fusion is also found in the physiologic context of endometrial stroma via RNA splicing without gene fusion, as well as in endometrial stromal nodules (ESN), a circumscribed non-invasive nodule of endometrial stroma (Li et al., 2008).

We report here the first instance of a *JAZF1-BCORL1* fusion in an ESS. The selection strategy used in the FoundationOne Heme hybrid capture-based profiling assay allowed for the de novo identification of *JAZF1-BCORL1* fusion in this case without prior knowledge of existence of this fusion via paired end sequencing of cDNA generated from total tumor RNA (He et al., manuscript in preparation. By mapping read pairs generated from cDNA sequencing to the reference human genome (hg19) it was possible to identify fusion partners between a selected target region *BCORL1* and untargeted region *JAZF1*.

Many of the genes found in ESS fusions regulate chromatin remodeling, and regulate or are subunits of chromatin remodeling complexes, in particular polycomb repressive complexes (PRC1 and PRC2) (Laugesen and Helin, 2014). In particular, SUZ12 is a subunit of PRC2, and the complex has histone tri-methyltransferase (H3K27) activity, and the catalytic subunit is EZH2. In vitro modeling demonstrates expression of the *JAZF1-SUZ12* fusion has an anti-apoptotic effect in an *SUZ12* wild type depleted background. If hyper-activation of PRC2 occurs in an advanced ESS harboring *JAZF1-SUZ12*, treatment with an inhibitor of EZH2 could confer clinical benefit (Knutson et al., 2012). Alternatively, if the *JAZF1-SUZ12* fusion depresses function of the PRC2 complex, such a phenotype may create a sensitivity of ESS to bromodomain extra-terminal (BET) inhibitors (De Raedt et al., 2014). Further (?) preclinical investigation is greatly needed to clarify the possibilities for benefit from either inhibitor for ESS cases.

The *JAZF1-BCORL1* fusion in this cases may also derange polycomb complex function, as BCORL1 (BCL6 co repressor like 1) binds BCL6, and the co-repressor complexes interact with PRC1. As a corollary, any benefit from therapies affecting polycomb complex function in advanced ESS could be dependent on the specific fusion harbored by a given ESS case, ie *JAZF1-SUZ12* vis a vis *JAZF1-BCORL1*.

The other genomic alterations harbor by this ESS also offer the possibility of benefit from targeted therapy. NF1 loss of function alterations may predict response to MEK or mTOR pathway inhibition (Lodish and Stratakis, 2010). Similarly the homozygous deletion of the CDKN2A locus which encodes p16 might also predict benefit from therapies targeting components of the cell cycle such as CDK4/6 inhibitors (Flaherty et al., 2012).

The utilization of genomic profiling in this case definitively identified a novel rearrangement that is possibly similar in function to the 'canonical' *JAZF1-SUZ12* fusion in ESS. Currently, there is no FDA approved

fluorescence in situ hybridization (FISH) diagnostic reagent kit available for identifying such fusions in ESS, and use of a break-apart FISH assay would not likely identify the fusion partners. Moreover, even with FISH assays specific for a given genomic rearrangement, the panorama of multiple genomic rearrangements in LG-ESS and HG-ESS may necessitate the serial use of multiple FISH assays in clinical cases to correctly identify the specific fusion. In contrast, the use of an integrated genomic profiling assay can identify the driver fusion in a given case among the many fusions known to be associated with ESS. Future investigations may indicate whether ESS can respond to targeted therapy and whether benefit could be dependent on the fusion harbored by an individual case.

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Conflict of interest

JAE, KG, JSR, TR, JC, VAM, and SMA are employees of and have equity interest in Foundation Medicine Inc. No other conflict of interest is stated.

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