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BCOR Expression in Mullerian Adenosarcoma: A Potential Diagnostic Pitfall

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Abstract

Adenosarcoma can mimic high-grade endometrial stromal sarcoma with *ZC3H7B-BCOR* fusion that may show entrapped glands and often exhibits diffuse BCOR expression. We encountered diffuse BCOR expression in rare adenosarcomas and sought to define its frequency among a larger cohort of these tumors. BCOR immunohistochemistry was performed on archival formalin-fixed paraffin-embedded tumor tissue in 13 of 14 adenosarcomas with and without stromal overgrowth arising in the uterus or ovary. Staining intensity and percentage of positive tumor nuclei in the mesenchymal component were evaluated. Eleven cases with sufficient tumoral tissue were subjected to fluorescence in situ hybridization for the detection of *BCOR*, *BCORL1*, *NUTM1*, *ZC3H7B*, and *JAZF1* rearrangement. Three cases were subjected to targeted RNA sequencing. BCOR was expressed in 9 of 13 (70%) tumors, including 6 with and 3 without stromal overgrowth. Moderate to strong staining in >70% of cells was seen throughout one low- and six high-grade tumors, five of which had stromal overgrowth. No staining was seen in three low- and 1 high-grade tumor with stromal overgrowth. One tumor demonstrating extensive sex cord-like differentiation and diffuse BCOR expression harbored *JAZF1* and *BCORL1* rearrangements. No *BCOR* or *BCORL1* rearrangement was identified in the remaining tumors. BCOR expression is seen in most adenosarcomas with and without stromal overgrowth. *BCORL1* rearrangement is seen in rare tumors with diffuse BCOR expression. Assessment of *BCOR* or *BCORL1* rearrangement status is required in adenosarcomas demonstrating BCOR expression.

Keywords

BCOR ; *BCORL1* ; *JAZF1* ; adenosarcoma; endometrial stromal sarcoma

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INTRODUCTION

Mullerian adenosarcoma is a rare biphasic tumor that occurs in all age groups but most frequently affects postmenopausal women and arises most commonly in the uterine corpus followed by the uterine cervix, ovary, fallopian tube, or vagina (1). Most lesions are easily recognizable by their characteristic phyllodes-like architecture, periglandular stromal condensation and low-grade cytology (2). However, high-grade cytologic features, heterologous elements, and stromal overgrowth may occur and cause diagnostic confusion when architectural features characteristic of adenosarcoma are obscured (3). There is particularly substantial morphologic overlap between adenosarcoma with homologous stromal overgrowth and high-grade endometrial stromal sarcoma harboring *ZC3H7B-BCOR* gene fusion, especially when entrapped endometrioid glands may be found in the latter (4, 5). In practice, we have also anecdotally encountered variable BCOR expression, a diagnostic marker helpful in the evaluation of high-grade endometrial stromal sarcomas, among adenosarcomas (6).

While *BCOR* genetic abnormalities play important roles in the development of high-grade endometrial stromal sarcoma in the form of gene rearrangement or internal tandem duplication, they so far do not appear to contribute to the highly heterogeneous genetic landscape of adenosarcomas. *MDM2*/*CDK4* gene amplifications are the most common genetic abnormality and have been detected in 16–28% of lesions (7–9). Additional alterations with variable detection rates across studies include *TERT* and *MYBL1* amplifications; *FGFR2*, *KMT2C*, *DICER1*, *ATRX*, and *TP53* mutations; and *ESR1-NCOA2* and *ESR1-NCOA3* fusions (7–9). Some of these genetic aberrations have also been found in other uterine tumor types, such as *DICER1* mutations in cervical rhabdomyosarcoma (10, 11), and *ESR1-NCOA2* and *ESR1-NCOA3* fusions in uterine tumor resembling ovarian sex cord tumor (12–14).

To date, BCOR expression appears to be a robust diagnostic marker of high-grade endometrial stromal sarcomas harboring *YWHAE* rearrangement and *BCOR* genetic abnormalities (6). However, BCOR staining patterns have not been evaluated in adenosarcomas, which may be confused with high-grade endometrial stromal sarcoma in the setting of stromal overgrowth (4). In this study, we sought to define the frequency of BCOR expression among adenosarcomas with and without stromal overgrowth and correlate BCOR staining with *BCOR* and *BCORL1* gene rearrangement status by fluorescence in situ hybridization (FISH).

MATERIALS AND METHODS

Case selection

All available hematoxylin-and-eosin stained slides and pathology reports of adenosarcomas diagnosed between 2013 and 2019 were collected from the pathology archives of Memorial Sloan Kettering Cancer Center, New York, NY, USA and University of Medicine, Pharmacy, Sciences and Technology of Targu Mures, Targu Mures, Romania using the search term “adenosarcoma.” The slides were reviewed by a gynecologic pathologist for confirmation of diagnosis based on the presence of the following features: (1) biphasic morphology with

benign epithelial and malignant mesenchymal components, (2) phyllodes-like architecture, and (3) periglandular stromal condensation. Tumor size, FIGO stage, histologic grade, presence of heterologous elements, and presence of stromal overgrowth were recorded. Tumors were assigned low-grade if the mesenchymal component showed only mild to moderate cytologic atypia and low mitotic activity (index of <10 mitotic figures per 10 high power fields), resembling a low-grade endometrial stromal sarcoma or low-grade fibrosarcoma. Tumors were considered high-grade if the mesenchymal component exhibited severe cytologic atypia and brisk mitotic activity (index of ≥10 mitotic figures per 10 high power fields). Stromal overgrowth was recorded when it comprised at least 25% of the overall tumor area. Clinical features, including patient age, disease presentation, treatment, and outcome, were also extracted from available medical records.

Immunohistochemistry

Immunohistochemical staining for BCOR was performed on all tumors as previously described (6). Briefly, five μm whole tumoral sections mounted on charged glass slides were stained with a commercially available monoclonal antibody, clone C-10 (sc-514576; Santa Cruz, Dallas, TX, USA) at 1:150 dilutions (1.7 μg/ml) generated against the N-terminus (1–300 amino acid) of BCOR. Staining was performed on the Leica Bond-3 autostainer (Leica, Buffalo Grove, IL). Immunohistochemical stains were evaluated by two pathologists (SC, VM). Intensity of staining (negative, weak, moderate, strong) and estimated percentage of positive tumor nuclei in the mesenchymal component of all tumors tested were recorded.

FISH

Eleven tumors with sufficient material were subjected to break-apart FISH analysis for *BCOR* and *BCORL1* gene rearrangement (15). For tumors with confirmed *BCOR* or *BCORL1* rearrangement, break-apart FISH for possible fusion partners, *NUTM1*, *ZC3H7B*, and *JAZF1* gene rearrangements was also undertaken. FISH was performed on formalin-fixed paraffin-embedded whole tumoral sections mounted on charged glass slides using custom bacterial artificial chromosomes (BAC) probes flanking *BCOR* (RP11–21D3, RP11–1105N2, RP11–37K20, RP11–973F20) *BCORL1* (RP11– 671B10, RP11–246J10, RP11–460L15, RP11–383B16), *NUTM1* (RP11–1141P10, RP11–477L8, RP11–1084A12), *ZC3H7B* (RP11–1078O11, RP11–110H11), and *JAZF1* genes, obtained from BAC/PAC sources of Children's Hospital of Oakland Research Institute (CHORI, http://bacpac.chori.org) (Oakland, CA, USA). Briefly, slides were pre-treated, de-paraffinized and hybridized with denatured BAC probes. Slides underwent post-hybridization incubation, washing, and counterstaining with DAPI. Two hundred tumor nuclei were examined using a Zeiss fluorescence microscope (Zeiss Axioplan, Oberkochen, Germany), controlled by Isis 5 software (Metasystems). Gene rearrangement was confirmed when at least 20% of tumor nuclei showed a break-apart signal.

Targeted RNA sequencing

Three tumors were subjected to the Archer FusionPlex Custom Solid Panel (ArcherDC Inc., Boulder, CO), a next-generation targeted RNA sequencing assay utilizing the Anchored Multiplex PCR technology that detects gene fusions and oncogenic isoforms in selected

protein-coding exons of 62 genes (16). Tumor RNA was extracted from five μm, formalin-fixed, paraffin-embedded tumoral sections followed by cDNA synthesis and library preparation. Final targeted amplicons were sequenced on an Illumina MiSeq. Data were analyzed using the Archer Software (version 4.0.10; ArcherDX Inc.).

RESULTS

Clinicopathologic features

Fourteen adenosarcomas, including twelve uterine and two ovarian, with available tumoral material were identified (Table 1). Median patient age was 64 (range, 23 to 77) years. Patients with uterine tumors presented with vaginal bleeding or a uterine mass, while patients with ovarian primaries presented with a pelvic mass. All were treated surgically with three and one patient receiving chemotherapy and chemoradiation, respectively. Nine and three patients presented with FIGO stage IA and IB uterine disease. Five patients recurred at 6 to 21 months, and all were alive with disease at last follow up. Six patients had no evidence of disease at 7 to 72 months after initial diagnosis. Patients with ovarian primaries presented with FIGO stage IC and IIB disease, the latter who recurred two months after initial presentation.

Median tumor size was 6.3 (range, 1.7 to 13.0) cm (Table 2). Five tumors were low-grade, and nine were high-grade (Figure 1A–C). Stromal overgrowth was seen in eight high-grade tumors and not in any of the low-grade tumors. Variant features, defined as sex cord-like differentiation and heterologous elements, were present in eight tumors. Sex cord-like differentiation was seen in four tumors, two of which were high-grade (Figure 2). Heterologous rhabdomyosarcomatous elements were seen in three high-grade tumors with stromal overgrowth, including one also demonstrating rare teratoid elements. Ossification and lipomatous differentiation were seen in two low-grade tumors.

Immunohistochemical findings

Nuclear BCOR staining was present in the mesenchymal component of 9 of 13 (70%) tumors, including 6 high-grade tumors with stromal overgrowth as well as 1 high- and 2 low-grade tumors without stromal overgrowth (Table 2). Moderate to strong BCOR expression in at least 70% of cells was seen in the mesenchymal component of one low- and six high-grade tumors; three in the latter group demonstrated stromal overgrowth (Figure 1D–F). Weak staining in 20% of cells was seen in the mesenchymal component of one low- and one high-grade tumor, the latter exhibiting stromal overgrowth. No staining was seen in three low- and one high-grade tumor with stromal overgrowth.

Among seven patients with high-grade uterine adenosarcomas with BCOR expression, two with FIGO stage IA disease recurred at 6 and 20 months after initial presentation, while the remaining five were alive with no evidence of disease at 7 to 35 months follow-up. The patient with a FIGO stage IIB ovarian high-grade adenosarcoma demonstrating BCOR immunoreactivity recurred two months after initial presentation. Of the two patients with BCOR-positive uterine low-grade adenosarcoma, both recurred 6 and 21 months after presentation.

FISH findings

Among 11 tumors subjected to *BCOR* and *BCORL1* FISH, only one tumor (case 10) with strong BCOR expression in ≥95% of tumor cells harbored a *BCORL1* gene rearrangement in the mesenchymal component only. Additional FISH analysis identified *JAZF1* as the fusion partner in the mesenchymal component only, and no rearrangements of *BCOR*, *NUTM1*, or *ZC3H7B*. No *BCOR* or *BCORL1* rearrangement was detected in the remaining 10 tumors subjected to FISH (Table 2).

Next generation sequencing findings

No gene fusions were identified in the three tumors that were subjected to targeted RNA sequencing (Table 2).

Genotype-phenotype correlation

The gross and histologic features of case 10 were re-reviewed after FISH confirmation of a *JAZF1-BCORL1* fusion. A 7.3 cm tan polypoid mass involved the endometrium with no gross involvement of the underlying myometrium. The tumor was biphasic with an atypical spindle cell proliferation associated with bland often cystic endometrioid glands, some of which imparting a phyllodes-like appearance (Figure 2A). Periglandular stromal condensation was readily seen on low magnification, separated by scattered foci of edematous and fibrotic stroma (Figure 2B). Most of the periglandular spindle cells had intermediate-size round to oval nuclei with clumped chromatin, small nucleoli, and scant eosinophilic cytoplasm (Figure 2C). Mitotic index was 12 mitotic figures per 10 high power fields in this region. In rare scattered foci, the periglandular spindle cells showed enlarged pleomorphic nuclei with clumped chromatin, prominent nucleoli, occasional intranuclear inclusions, and a moderate amount of eosinophilic to foamy cytoplasm (Figure 2D). These cells also formed sheets, nests, cords, trabeculae, and rare tubules devoid of an epithelial component (Figure 2E). Mitotic index in these areas was 30 mitotic figures per 10 high power fields. One area also showed fascicular growth of a fibromyxoid spindle cell component (Figure 2E). BCOR expression was strong and diffuse throughout the tumor, including sex cord-like foci (Figure 2F) with confirmation of *BCORL1* rearrangement by FISH (Figure 3).

DISCUSSION

Nuclear BCOR expression is frequently observed in the mesenchymal component of Mullerian adenosarcomas, including both low- and high-grade lesions with and without stromal overgrowth. Moderate to strong staining in at least 70% of tumor cells in the sarcomatous component is present in 45% of tumors and does not appear associated with grade, stromal overgrowth, or clinical outcomes. This extent of BCOR expression does not correspond with the presence of *BCOR* rearrangement in adenosarcomas, suggesting that using BCOR expression alone as a surrogate marker of *BCOR* fusion-positive high-grade endometrial stromal sarcoma may represent a potential diagnostic pitfall. Rare adenosarcomas with BCOR overexpression may, however, harbor *BCORL1* gene fusion. These findings suggest that molecular assessment of *BCOR* and *BCORL1* rearrangement

status may be helpful in the diagnostic evaluation of any uterine sarcoma demonstrating BCOR overexpression.

We recently reported the clinical utility of BCOR expression in the diagnostic evaluation of high-grade endometrial stromal sarcomas and undifferentiated uterine sarcomas (6, 15). BCOR expression has a sensitivity of 86% (95% CI, 70–95%) and specificity of 100% (95% CI, 97–100%) in the detection of high-grade endometrial stromal sarcomas with *YWHAE-NUTM2* fusion, *ZC3H7B-BCOR* fusion, and *BCOR* internal tandem duplication, with positive and negative predictive values of 100% and 97%, respectively (6, 15). Diffuse moderate to strong BCOR expression has not been seen in endometrial stromal nodules, low-grade endometrial stromal sarcomas, leiomyomas, and most leiomyosarcomas (6). Our new findings, however, demonstrate that BCOR overexpression may also be seen in a large subset of Mullerian adenosarcomas lacking *BCOR* rearrangements. This is particularly problematic in the diagnostic evaluation of any uterine spindle cell sarcoma with fibromyxoid features in which adenosarcoma with stromal overgrowth and *ZC3H7B-BCOR* fusion-positive high-grade endometrial stromal sarcoma are the main differential diagnoses. In this setting, BCOR overexpression may not be used to support a provisional diagnosis of high-grade endometrial stromal sarcoma with probable *ZC3H7B-BCOR* fusion. The mechanism of BCOR expression in adenosarcoma is unclear and requires further investigation.

One of our cases demonstrating BCOR overexpression, however, harbored a *JAZF1-BCORL1* fusion which has not been previously described in adenosarcomas. This tumor exhibited features diagnostic of adenosarcoma and was biphasic with both periglandular stromal condensation and phyllodes-like architecture. While sex cord-like differentiation is common among adenosarcomas (17), this tumor was unusual by the degree of cytologic atypia and mitotic activity observed in the sex cord-like foci. *JAZF1-BCORL1* fusion with rearrangement between *JAZF1* exons 1–3 and exons 5–12 of *BCORL1* has been recently reported in a tumor classified as recurrent low-grade endometrial stromal sarcoma (18). However, published histologic images demonstrate sheets of spindle cells with nuclear enlargement, prominent nucleoli, and ample eosinophilic cytoplasm without perivascular whorling and associated with myxoid matrix. These findings are somewhat unusual for low-grade endometrial stromal sarcoma, and histologic review of the primary uterine tumor to assess features of adenosarcoma or high-grade endometrial stromal sarcoma may be of interest. It is feasible that our case represents a high-grade endometrial stromal sarcoma recapitulating adenosarcoma-like architecture. It is also possible that identical gene fusions are observed across various uterine mesenchymal tumor types, i.e. *ESR1* rearrangement with *NCOA2* or *NCOA3* fusion partners in uterine tumors resembling ovarian sex cord tumor (12–14) and adenosarcomas (7, 9).

BCORL1 (BCL6 corepressor-like 1) encodes a transcriptional corepressor homolog to BCOR and results in transcriptional repression by interacting with class II histone deacetylase and C-terminal-binding protein (19). Amino acid sequence homology between BCORL1 and BCOR likely accounts the observed BCOR overexpression. *BCORL1* rearrangements have been previously described as rare events in ossifying fibromyxoid tumors (*CREBBP-BCORL1* fusion) (20) and hepatocellular carcinoma (*BCORL1-ELF4*

fusion) (21). Inactivating mutations of *BCORL1* have also been reported in subsets of acute myeloid leukemia (22, 23), myelodysplastic syndrome (24), chronic myelomonocytic leukemia (25), aplastic anemia (26), and intracranial germ cell tumors (27).

JAZF1 (JAZF zinc finger 1) encodes a nuclear factor that represses transcription by interacting with nuclear orphan receptor TR4 (28). Mutations have only been reported in endometrial stromal tumors in which *JAZF1* rearrangement is found most frequently with *SUZ12* followed by *PHF1* in endometrial stromal nodules and low-grade endometrial stromal sarcomas (29). The JAZF1-SUZ12 fusion product appears to disrupt the polycomb repressive complex 2 and decreases H3K27me3, thereby resulting in an oncogenic-like protein involved in endometrial stromal sarcoma tumorigenesis (30–32).

In summary, we demonstrate BCOR expression in a large proportion of Mullerian adenosarcomas of any grade and with or without stromal overgrowth. Lesions with BCOR overexpression lack *BCOR* gene rearrangement, suggesting that the use of BCOR overexpression in isolation may be misleading. Rare lesions with BCOR overexpression may harbor *JAZF1-BCORL1* fusion, expanding the genetic spectrum of adenosarcomas. Molecular assessment of *BCOR* and *BCORL1* rearrangement status is recommended in the diagnostic evaluation of any uterine sarcoma demonstrating BCOR overexpression to confirm *BCOR* fusion-positive high-grade endometrial stromal sarcoma and the rare adenosarcoma harboring *BCORL1* fusion.

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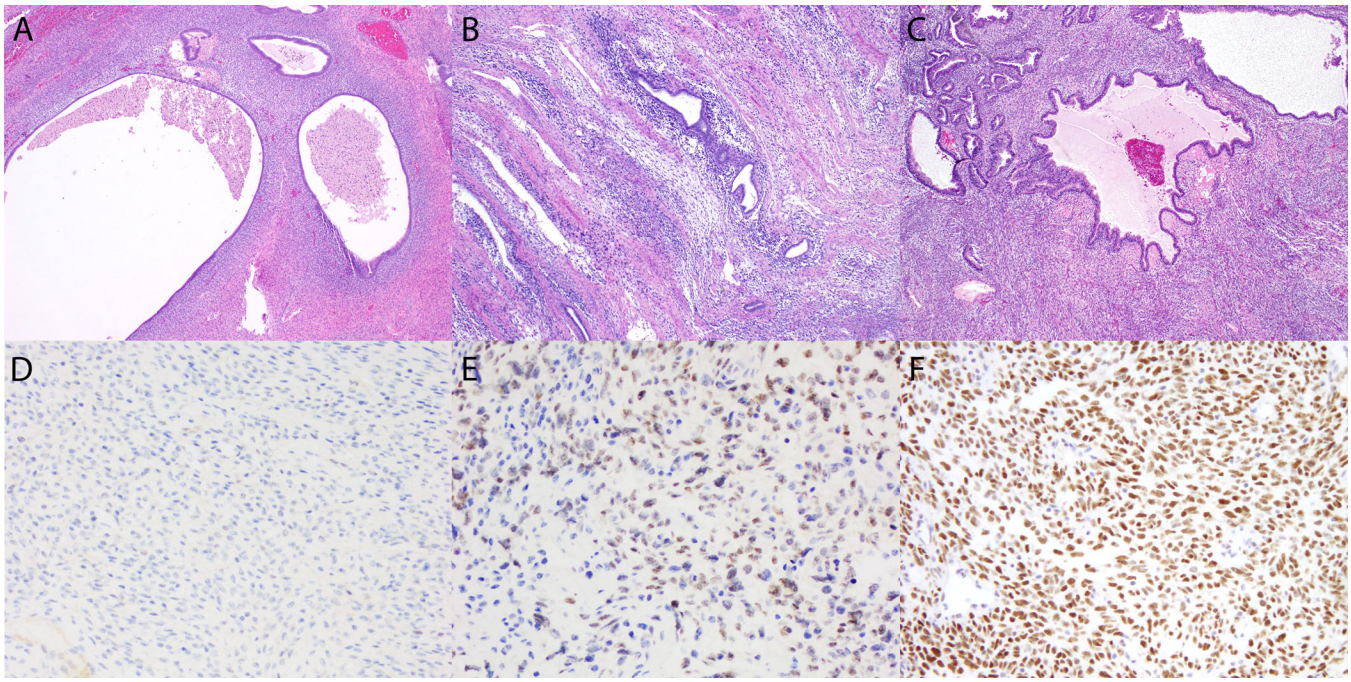

Figure 1.

BCOR expression in adenosarcoma. (A-C) Periglandular stromal condensation is seen in (A) low-grade and (B, C) high-grade tumors, one which exhibited stromal overgrowth (not pictured). (D) BCOR expression is absent in the low-grade tumor. (E, F) Strong BCOR expression is seen in the mesenchymal component of both high-grade tumors.

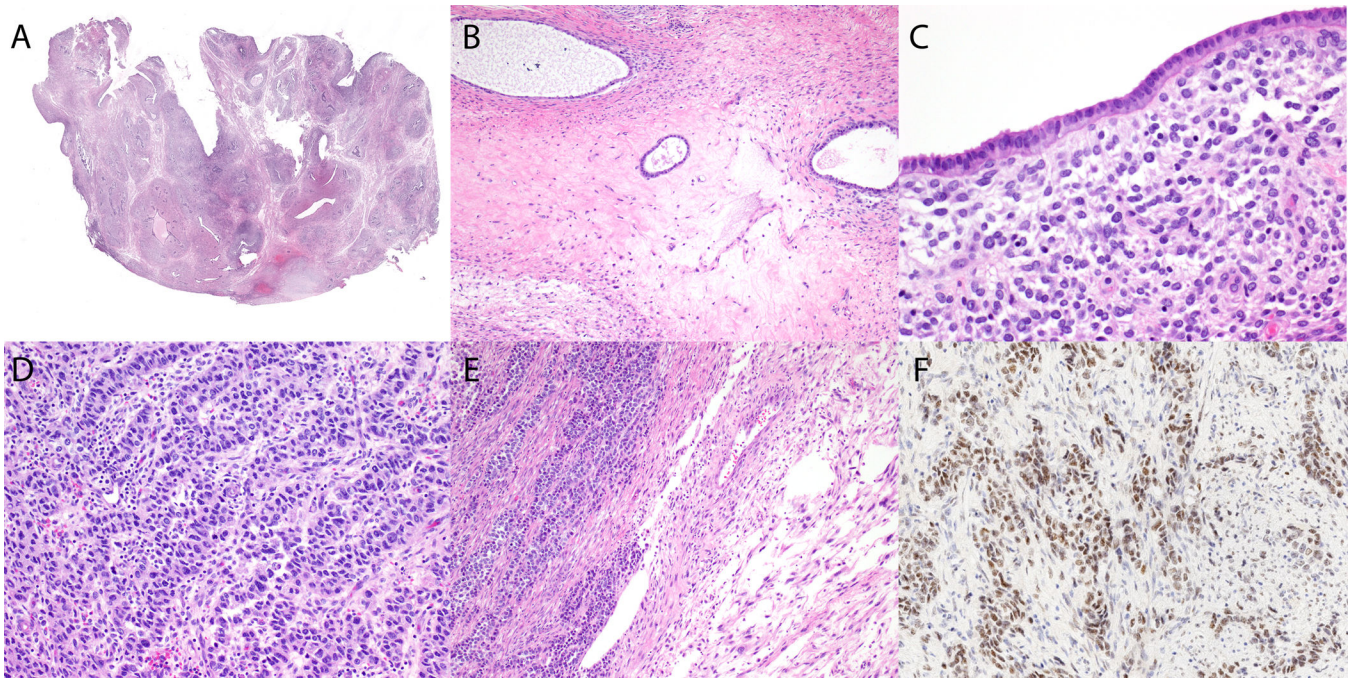

Figure 2.

High-grade adenosarcoma with *JAZF1-BCORL1* fusion. (A) Phyllodes growth pattern and periglandular stromal condensation is visible on low magnification. (B) Periglandular stromal condensation surrounds cystically dilated glands and is associated with fibrotic stroma. (C) Stromal cells adjacent to the cytologically bland epithelium have mild to moderate nuclear atypia. (D, E) Cells with marked cytologic atypia form cords and trabeculae adjacent to (E) a fibromyxoid spindle cell component. (F) Strong BCOR expression is seen in the sex cord-like foci.

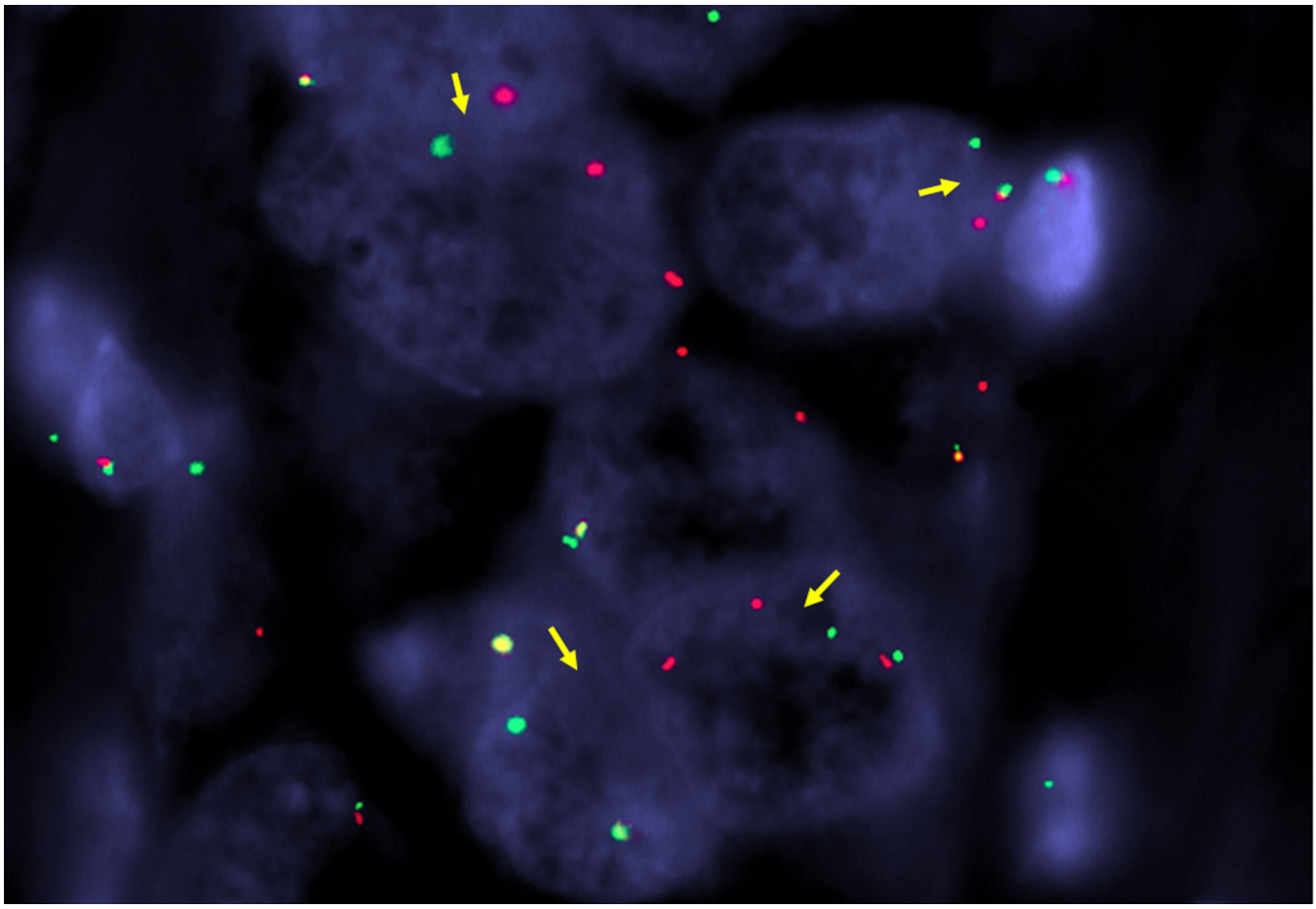

Figure 3.

BCORL1 rearrangement in adenosarcoma. Separation of green telomeric and red centromeric signals (arrows) flanking the gene confirm *BCORL1* rearrangement by fluorescence in situ hybridization.

Table 1.

Clinical features

Case	Age, y	Signs and symptoms	Site	FIGO stage	Treatment	Recurrence, mo	Last follow-up, mo
1	35	Vaginal bleeding	Uterus	IA	Surgery, chemotherapy	6	Alive with disease, 24
2	77	Vaginal bleeding	Uterus	IA	Surgery, chemoradiation	11	Alive with disease, 38
3	32	Vaginal bleeding	Uterus	IA	Surgery		No evidence of disease, 30
4	56	Vaginal bleeding	Uterus	IA	Surgery, chemotherapy	11	Alive with disease, 18
5	57	Vaginal bleeding	Uterus	IA	Surgery		No evidence of disease, 26
6	77	Vaginal bleeding	Uterus	IA	Surgery	20	Alive with disease, 24
7	56	Vaginal bleeding	Uterus	IB	Surgery	21	Alive with disease, 21
8	70	Pelvic mass	Ovary	IIB	Surgery	2	Alive with disease, 2
9	23	Vaginal bleeding	Uterus	IB	Surgery, chemotherapy		No evidence of disease, 19
10	69	Vaginal bleeding	Uterus	IA	Surgery		No evidence of disease, 7
11	70	Vaginal bleeding	Uterus	IB	Surgery		No evidence of disease, 72
12	69	Pelvic mass	Ovary	IC	Surgery		Lost to follow up
13	75	Uterine mass	Uterus	IA	Surgery	6	Alive with disease, 12
14	58	Uterine mass	Uterus	IA	Surgery		No evidence of disease, 35

Table 2.

Pathologic features

Case	Size, cm	Grade	Stromal Overgrowth	Variant features	BCOR expression	Fusion status
1	1.7	Low	No		Strong, >95%	Negative
2	3.2	Low	No	Lipomatous and sex cord differentiation	Negative	Negative
3	5.7	Low	No		Negative	Negative
4	5.6	High	Yes		Negative	Negative
5	3.1	High	Yes		Moderate, 70%	Negative
6	13.0	High	Yes		Weak, 20%	Negative
7	7.8	Low	No	Ossification	Weak, 20%	Negative
8	10.6	High	Yes	Rhabdomyosarcoma	Strong, >95%	Negative
9	6.8	High	Yes	Rhabdomyosarcoma, teratoid elements	Moderate, >95%	Negative
10	7.3	High	No	Sex cord differentiation	Strong, >95%	*JAZF1-BCORL1*
11	3.5	Low	No	Sex cord differentiation	Negative	Negative
12	14.9	High	Yes	Sex cord differentiation	Not performed	Negative
13	13.0	High	Yes	Rhabdomyosarcoma	Strong, >95%	Negative
14	3.8	High	Yes		Strong, >95%	Negative

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