BCOR Internal Tandem Duplication in High-grade Uterine Sarcomas

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Abstract: Endometrial stromal sarcomas (ESSs) are mesenchymal uterine tumors characterized by recurrent genetic events, most commonly chromosomal rearrangements, that create oncogenic gene fusions. High-grade endometrial stromal sarcomas (HG-ESSs), as defined in the 2014 World Health Organization Classification, typically contain oncogenic *YWHAE-NUTM2* fusions; however, although not well characterized, there are tumors morphologically overlapping with HG-ESS that do not contain the *YWHAE-NUTM2* fusions. These fusions are also found in certain pediatric primitive sarcomas, including clear cell sarcoma of the kidney and soft tissue undifferentiated round cell sarcoma of infancy. A subset of these same pediatric sarcomas lack *YWHAE-NUTM2* fusions and instead have internal tandem duplications (ITDs) involving exon 15 of *BCOR* (*BCOR* ITD). We investigated the presence of *BCOR* ITD by targeted sequencing in a series of 31 uterine sarcomas, comprising 5 low-grade ESS, 13 uterine sarcomas diagnosed as HG-ESS, and 13 undifferentiated uterine sarcomas. *BCOR* ITD were present in 1 uterine sarcoma diagnosed as HG-ESS and 2 undifferentiated sarcomas with uniform nuclear features, all of which lacked any of the recurrent chromosome translocations known to occur in ESS. These 3 high-grade sarcomas with *BCOR* ITD affected young patients (average age, 24) and morphologically were composed of nonpleomorphic spindle cells admixed with epithelioid and round cell areas. Focal myxoid stroma was present in 2 cases. Mitotic activity was brisk, necrosis was present, and there was lymphovascular involvement in all cases. The 3 uterine sarcomas with *BCOR* ITD exhibited diffuse cyclin D1 immunohistochemical expression and there was diffuse BCOR expression in the 2 cases tested. Long-term follow-up in 2 patients revealed 1 to be tumor-free after 22 years and the other to die of disease after 8 years. In conclusion, *BCOR* ITD is an oncogenic alternative to *YWHAE-NUTM2* fusion in high-grade uterine sarcomas with uniform nuclear features. We propose that neoplasms with the morphology described and *BCOR* ITD be regarded as a unique subtype of high-grade uterine sarcoma, possibly within the family of endometrial stromal neoplasia.

Key Words: sarcoma, *BCOR*, internal tandem duplication endometrial stromal sarcoma, undifferentiated uterine sarcoma

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Endometrial stromal sarcomas (ESSs) are an uncommon heterogenous group of gynecologic mesenchymal neoplasms that morphologically resemble, to variable degrees, proliferative-phase endometrial stroma. According to the 2014 World Health Organization (WHO) Classification, there are categories of low-grade ESS and high-grade endometrial stromal sarcoma (HG-ESS), as well as a category of undifferentiated uterine sarcoma.[1] Low-grade ESS are more common than high-grade, and generally show a characteristic histomorphology that usually results in straightforward diagnosis, although there are several morphologic variations that may result in diagnostic problems.[2] Low-grade ESS are genetically characterized by recurrent rearrangements of genes involved in transcriptional repression and chromatin remodeling, including *JAZF1*, *SUZ12*, *EPC1*, and *PHF1*,[2] and demonstration of these rearrangements is useful in diagnosis in problematic cases. HG-ESS, on the contrary, has historically been more difficult to define, due to lack of reliable morphologic and immunophenotypic diagnostic criteria; however, based on recent studies it is a morphologically, immunophenotypically, and genetically definable tumor.[3]

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Accurate diagnosis of HG-ESS is clinically relevant in as much as its clinical course is intermediate in aggressiveness between the generally indolent low-grade ESS and undifferentiated uterine sarcoma. The latter are clinically aggressive high-grade neoplasms that lack a demonstrable line of differentiation, so this is, in essence, a diagnosis of exclusion. Although most undifferentiated uterine sarcomas are composed of highly pleomorphic cells, there is a subset that exhibits monomorphic nuclear features resulting in morphologic overlap with HG-ESS.[4,5]

The diagnosis of HG-ESS was historically based on mitotic rate >10 per 10 high-power fields (HPFs) within a tumor that morphologically resembled proliferative phase endometrial stroma.[2] This definition was not clinically relevant and led to temporary elimination of "HG-ESS" as a diagnostic category in the 2003 WHO Classification. In that classification, a uterine sarcoma with high-grade nuclear features (uniform or pleomorphic), regardless of presumed stromal differentiation, was classified as undifferentiated endometrial sarcoma, a single category encompassing tumors with stromal differentiation and undifferentiated neoplasms, both of which behave more aggressively than low-grade ESS (as reviewed in Lee and Nucci).[2] This changed with the discovery of highly recurrent t(10;17)(q22;p13) translocations in a morphologically characteristic subset of high-grade tumors that exhibit endometrial stromal differentiation, as evidenced by their coexistence with areas that morphologically were identical to low-grade ESS; these translocations create oncogenic *YWHAE-NUTM2A/B* fusions (previously referred to as *YWHAE-FAM22A/B*), which serve as reliable molecular diagnostic markers and these neoplasms are now classified as HG-ESS.[6] Clinicopathologic studies of such molecularly defined HG-ESS identified morphologic features and diagnostically useful immunohistochemical markers, such as cyclin D1 and CD117 overexpression;[7,8] this resulted in the reintroduction of HG-ESS in the 2014 WHO classification.[2] More accurate diagnosis of such cases ultimately resulted in refinement of management protocols for HG-ESS, which may benefit from chemotherapeutic regimens containing anthracycline.[9]

Interestingly, the *YWHAE-NUTM2A/B* fusions found in HG-ESS[6] are also found in ~12% of clear cell sarcomas of the kidney (CCSK), a rare and highly aggressive sarcoma that affects young children.[10,11] The round cell component of CCSK and HG-ESS are similar histologically, although there is no clinical or anatomic overlap between the 2 entities; CCSK occurs exclusively in the pediatric population and arises within the kidney,[11] whereas HG-ESS is a uterine tumor that affects middle-aged or older women.[3] An alternative recurrent genetic aberration was recently identified in CCSK, an internal tandem duplication (ITD) involving the 3' end of the transcriptional repressor gene *BCOR*.[12–14] *BCOR* ITDs are present in 85% to 95% of CCSK and are mutually exclusive with *YWHAE-NUTM2A/B* in this neoplasm.[15,16] Further emphasizing the biologic overlap between *BCOR* ITD and *YWHAE-NUTM2A/B*, both molecular alterations have been recently described in a mutually exclusive manner in a subset of soft tissue undifferentiated round cell sarcomas of infancy, which may thus be considered the soft tissue counterpart of CCSK.[17] All these molecularly heterogenous entities share a transcriptional signature that includes overexpression of *BCOR*, which can be detected by immunohistochemistry.[18]

Considering the histologic and genetic similarities between HG-ESS, CCSK, and soft tissue undifferentiated round cell sarcoma of infancy, we sought to investigate the presence of *BCOR* ITD by targeted sequencing in a series of 26 high-grade uterine sarcomas, including 13 cases diagnosed as HG-ESS on morphologic grounds and 13 as undifferentiated uterine sarcomas. We included 5 CCSK as *BCOR* ITD-positive controls. In addition, we screened a group of 5 low-grade ESS lacking known chromosomal rearrangements for the presence of *BCOR* ITD.

MATERIALS AND METHODS

Tumor Samples

The study series included 36 tumors obtained from the files of Brigham and Women's Hospital (Boston, USA), Vancouver General Hospital (Vancouver, Canada), Belfast Health and Social Care Trust (Belfast, UK), Birmingham Women's Hospital (Birmingham, UK), Maria Sklodowska-Curie Institute—Oncology Center (Warsaw, Poland), and Stanford Hospital (Stanford), under institutional review board approval. As summarized in Table 1, the tumor types included were HG-ESS (n = 13), undifferentiated uterine sarcoma (n = 13), low-grade ESS (n = 5), and CCSK (n = 5) as *BCOR* ITD-positive controls. The diagnoses of HG-ESS and undifferentiated uterine sarcoma were made by specialized gynecologic pathologists involved in this study. Among the HG-ESS, 8 cases harbored *YWHAE-NUTM2* rearrangements (previously published data),[3] whereas in 5 cases *YWHAE-NUTM2* rearrangement was not present, as determined by reverse transcription polymerase chain reaction (PCR) and/or fluorescent in situ hybridization. Eleven undifferentiated uterine sarcomas exhibited uniform nuclear features, whereas 2 showed nuclear pleomorphism. Twenty-four tumor samples were snap-frozen and 12 were formalin-fixed paraffin-embedded (FFPE). Two nontumor DNA samples were used as controls. Hematoxylin and

TABLE 1. Summary of Study Case Series

Tumor Type (Morphologic Diagnosis)	n	*BCOR* ITD (n)
Low-grade endometrial stromal sarcoma	5	0
HG-ESS	13	
YWHAE-NUTM2-rearranged	8	0
Not *YWHAE-NUTM2*-rearranged	5	1
Undifferentiated uterine sarcoma	13	
With uniform nuclear features	11	2
With nuclear pleomorphism	2	0
CCSK	5	4
	36	7

eosin and diagnostic immunohistochemical stains were reviewed. BCOR immunohistochemistry was performed in 2 cases with available material (clone C-10, sc-514576, 1:150 dilution; Santa Cruz, Dallas, TX). Clinical charts of the 3 BCOR-ITD cases were reviewed with approval of the Institutional Review Board at each institution.

Genomic PCR and Targeted Sequencing

DNA was extracted using the QIAamp DNA Mini Kit (QIAGEN) for fresh frozen tissue samples, and the QIAamp DNA FFPE Tissue Kit (QIAGEN) for FFPE samples, according to the manufacturer's instructions. PCR was performed on DNA from frozen samples with PCR SuperMix (11306; Invitrogen), as follows: 1 cycle at 94°C for 2 minutes, 35 cycles of 94°C for 0.5 minutes, 55°C for 0.5 minutes, 68°C for 1 minutes, and a final extension at 68°C for 5 minutes. Primers flanking *BCOR* exon 15 for frozen tumor samples were from Ueno-Yokohata et al.[12]: F: GGACCAGAAGACCAGGATGA, R: TCCGAAAGCAGTAGCCAGTT (expected amplicon size: 566 bp); the following *BCOR* exon 15 primers were used for FFPE samples: F: CGGCAGGTTTC TGCAAGTCTC, R: ACTGTACATGGTGGGTCCA (expected amplicon size: 198 bp). PCR products were evaluated by ethidium bromide staining on a 1% agarose gel alongside 1 kb Plus DNA Ladder (Invitrogen). The PCR products were purified using 2 units of exonuclease (M0293S; New England Bio Labs) and 0.4 units of shrimp alkaline phosphatase (78390; Affymetrix) incubated for 18 minutes at 37°C and 15 minutes at 80°C. Cleaned product was Sanger-sequenced and annotated in relationship to NM_001123385.1 reference sequence (corresponding to Ensembl ID ENST0000037844.8).

RESULTS

BCOR ITDs were identified in 3 of 26 high-grade uterine sarcomas, 2 cases which were diagnosed as undifferentiated uterine sarcoma with uniform nuclear features and 1 diagnosed as *YWHAE-NUTM2*-negative HG-ESS (Table 1). *BCOR* ITDs were predicted on gel electrophoresis before sequencing due to size difference (Fig. 1). All 3 mutations were heterozygous and resulted in tandem duplications of different sizes affecting exon 15, the 3' end of *BCOR* that encodes the C-terminal end of the protein. These mutations are predicted to result in protein changes akin to those previously reported in cases of CCSK[12,13] (Fig. 1 and Table 2): in case 1, there was a tandem duplication of 31 amino acids with substitution of the first Leu residue by Ser; in case 2, the duplication involved 29 amino acids with a junctional 3-bp insertion resulting in insertion of an ectopic Val residue; and in case 3, 30 amino acids were duplicated, with an internal Glu to Val substitution. None of the 5 low-grade ESS nor the 8 *YWHAE-NUTM2*-rearranged HG-ESS had *BCOR* ITD. Four of 5 CCSK had *BCOR* ITD.

The clinicopathologic features of the 3 uterine sarcomas with *BCOR* ITD are summarized in Table 2. All cases affected young patients (ages 18, 23, 32). The case diagnosed as HG-ESS occurred in an 18-year-old woman who presented with menorrhagia and was found to have a 7 cm submucosal polypoid mass filling the endometrial cavity, with additional intramural nodular masses. The

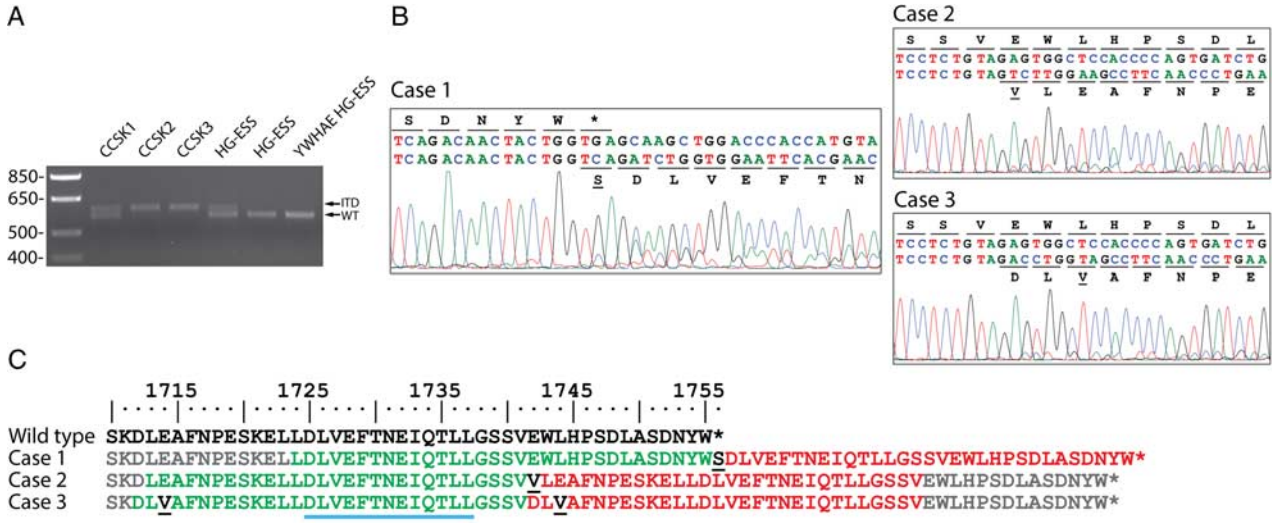

FIGURE 1. *BCOR* ITD in high-grade uterine sarcomas. A, Gel electrophoresis of PCR products following reverse transcription PCR using primers designed to amplify *BCOR* exon 15 (566 bp expected fragment size for wild-type *BCOR*). Note bands of larger size in lanes 2 to 5, consistent with *BCOR* ITD. Samples in this gel include 3 CCSK (CCSK1 in a female patient, CCSK2 and CCSK3 in males), 2 *YWHAE-NUTM2*-negative HG-ESS (labelled "HG-ESS"), and 1 *YWHAE-NUTM2*-rearranged HG-ESS (labelled "YWHAE HG-ESS"). B, Electropherograms of *BCOR* PCR product from cases 1, 2, and 3, confirming tandem duplications of *BCOR*. C, Predicted BCOR protein sequence resulting from *BCOR* ITD. Duplicated segments are colored in green and red; underlined black font highlights amino acid substitutions/insertions resulting from the duplicated sequence. The blue line indicates the commonly duplicated region reported by Ueno-Yokohata et al.[12]

TABLE 2. Clinicopathologic Features and *BCOR* Mutations in 3 High-grade Uterine Sarcomas With *BCOR* ITD

ID	Morphologic Diagnosis	Age (y)	Morphology	Immunohistochemistry	*BCOR* ITD	Follow-up (y)
1	HG-ESS	18	Permeative growth. Myxoid bland spindle cells and high-grade spindle cell sarcoma with focal epithelioid cells. Prominent vascular network. Lymphovascular invasion	Cyclin D1 (diffuse) BCOR (diffuse) CD10 (negative) Desmin (focal) SMA (negative) h-caldesmon (negative)	p.(Leu1724Ser, Asp1725_Trp1755dup)	NED 22
2	Undifferentiated uterine sarcoma	23	Permeative growth. High-grade spindle and round cell sarcoma with uniform nuclear features. Lymphovascular invasion	Cyclin D1 (diffuse) BCOR (diffuse) CD10 (focal) Desmin (negative) SMA (negative) h-caldesmon (negative)	p.(Leu1713_Val1741dup, Val1741_Glu1742insVal)	NA
3	Undifferentiated uterine sarcoma	32	Myxoid spindle cell sarcoma and round cell areas. Uniform nuclear features. Prominent vascular network. Lymphovascular invasion	Cyclin D1 (diffuse) CD10 (focal) Desmin (negative) SMA (negative) h-caldesmon (negative)	p.(Asp1712_Val1741dup {Glu1714Val})	DOD 8

DOD indicates dead of disease; NED, no evidence of disease; NA, not available; SMA, smooth muscle actin.

patient underwent abdominal hysterectomy and bilateral salpingo-oophorectomy with bilateral pelvic lymph node dissection. Histologically, the tumor showed a range of appearances (Fig. 2): large areas were composed of densely packed ovoid to spindle cells with scant cytoplasm and large round to ovoid atypical but relatively uniform nuclei with clear chromatin, growing in sheets and fascicles (Fig. 2A). Focally, these atypical cells showed epithelioid morphology with more abundant cytoplasm. Other areas were less cellular with smaller, bland spindle cells set in a prominent myxoid stroma. The tumor invaded the myometrium with a permeative and destructive growth pattern (Fig. 2B). Vasculature was focally prominent. There were 40 mitoses per 10 HPF and multiple foci of necrosis. There was lymphovascular invasion, and metastatic tumor was present in 1 obturator pelvic lymph node. The tumor cells expressed desmin focally and cyclin D1 and BCOR diffusely (Figs. 2C, D). CD10, smooth muscle actin, and h-caldesmon were negative. The patient received systemic chemotherapy (mesna, doxorubicin, ifosfamide, and dacarbazine) and is alive with no evidence of disease 22 years later.

The 2 cases diagnosed as undifferentiated uterine sarcoma with *BCOR* ITD affected patients aged 23 and 32 years. Morphologically, both tumors were composed of highly cellular proliferations with predominantly spindled cells arranged in short fascicles (Fig. 2E), with scant cytoplasm. The nuclear contours were irregular but the nuclear size and shape was uniform throughout with no marked nuclear pleomorphism appreciated at low-magnification examination. Both tumors invaded the myometrium with a permeative and destructive growth pattern. The stroma was predominantly collagenous, with prominent myxoid foci in 1 case. The vascular network was prominent, with numerous small vessels with prominent walls, but the vessels were not as delicate and curvilinear as in *YWAHE-NUTM2*-rearranged HG-ESS. Mitotic activity was >10 mitoses per 10 HPF. There was multifocal tumor necrosis, and foci of lymphovascular invasion at the periphery of both tumors. Both cases expressed CD10 focally, while cyclin D1 staining was diffuse. One case tested showed diffuse BCOR expression. Desmin, smooth muscle actin, and h-caldesmon immunostaining was negative in both tumors. One patient was lost to follow-up, and the other 1 had tumor recurrence 7 years posthysterectomy, with a tumor mass in the inguinal soft tissues; morphologically, the tumor recurrence consisted of a dense proliferation of neoplastic small round cells, morphologically resembling an undifferentiated round cell sarcoma with multiple areas of necrosis (Fig. 2F). The patient died 1 year after this recurrence, 8 years after initial diagnosis.

DISCUSSION

Herein we report the presence of *BCOR* ITD in 3 high-grade uterine sarcomas affecting young patients furthering our understanding of the genetic landscape of uterine sarcomas and potentially identifying another distinct subtype of high-grade uterine sarcoma within the category of undifferentiated uterine sarcoma. Over the past few years, the classification of uterine sarcomas has greatly benefited from genetic insights. In particular, the discovery of *YWHAE-NUTM2A/B* fusions resulted in reintroduction of the clinically relevant diagnostic category of HG-ESS in the WHO 2014 Classification.[2] In this study, we have identified *BCOR* ITD as an alternative genetic alteration to *YWHAE-NUTM2* in a small number of high-grade uterine sarcomas. *BCOR* ITD was present in 1 of 5 cases diagnosed as HG-ESS but lacking *YWHAE-NUTM2A/B* fusions, and in none of 8 *YWHAE-NUTM2A/B*-rearranged HG-ESS. Although the numbers are small, these findings suggest that *BCOR* ITD in uterine sarcomas is both less common than and mutually exclusive with *YWHAE-NUTM2* rearrangement.

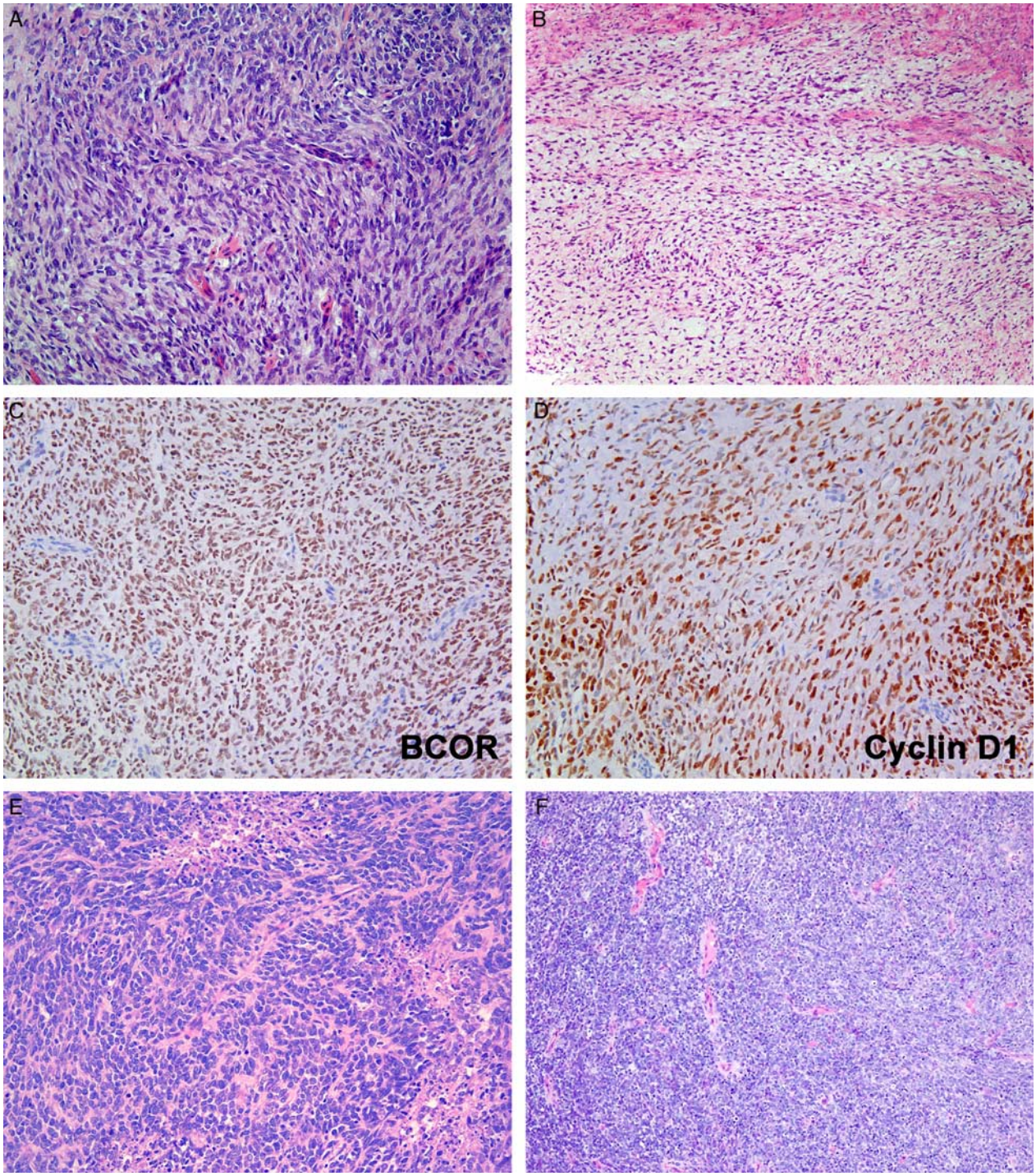

FIGURE 2. Morphology and immunohistochemistry of high-grade uterine sarcomas with *BCOR* ITD. A, Case 1, "HG-ESS," high-grade spindle cell component. B, Case 1, "low-grade" component with ovoid to spindle cells with scant cytoplasm arranged in fascicles with myxoid stroma, permeating the myometrium in a destructive growth pattern. Strong, diffuse nuclear expression of BCOR (C) and cyclin D1 (D) in case 1. E, Case 2 has undifferentiated spindle and round cell morphology, with high mitotic activity and foci of necrosis. F, Case 3 is an undifferentiated round cell sarcoma with prominent branching blood vessels.

BCOR ITD was identified in 2 cases that were diagnosed as undifferentiated uterine sarcomas. Undifferentiated uterine sarcoma (previously termed undifferentiated endometrial sarcoma) is the term now preferred to designate uterine mesenchymal neoplasms that lack specific lines of differentiation. It is thus a diagnosis of exclusion and, as such, likely a heterogenous category that may include sarcomas that are biologically

equivalent to a subset of HG-ESS. On review, the 2 undifferentiated uterine sarcomas with *BCOR* ITD described herein showed features that might raise the possibility of endometrial stromal differentiation, such as areas with cytologically bland ovoid-to-spindle cells or a "finger-like" permeative growth pattern, although these features are not specific for endometrial stromal neoplasia. Of note, both tumors displayed monomorphic nuclei, a feature that sets them apart from undifferentiated uterine sarcomas that exhibit significant nuclear pleomorphism, which likely represent biologically different entities. Given the diffuse cyclin D1 expression, which is rare in undifferentiated uterine sarcomas,[7] and the molecular findings of *BCOR* ITD, these 2 cases seem biologically related to HG-ESS, although they lack definitive morphologic or immunohistochemical features of endometrial stromal differentiation. On the basis of these observations, we propose that undifferentiated uterine sarcomas with uniform nuclear features and diffuse cyclin D1 expression should be tested for *BCOR* ITD and, if *BCOR* ITD is present, the neoplasm should be classified as a *BCOR* ITD-positive high-grade uterine sarcoma. Ongoing clinicopathologic and immunohistochemical studies will clarify if these neoplasms are best classified as HG-ESS or represent a distinct variant of truly undifferentiated (ie, nonendometrial stromal) uterine sarcoma.

Clinically, the 3 sarcomas with *BCOR* ITD affected patients under the age of 35. All 3 tumors showed lymphovascular invasion. Of the 2 patients with long-term follow-up, 1 died of recurrent disease 8 years after diagnosis, whereas the other had no evidence of disease 22 years after diagnosis and anthracycline-based chemotherapy. Although the numbers are small, the clinical behavior appears to be more in keeping with *YWHAE-NUMT2*-positive HG-ESS with a prognosis that is intermediate between low-grade ESS and undifferentiated uterine sarcoma. As such, the identification of *BCOR* ITD-positive high-grade uterine sarcoma is likely to be clinically important.

BCOR alterations have been previously observed in uterine sarcomas in the form of *ZC3H7B-BCOR* rearrangements, resulting from t(X;22)(p11q13). *BCOR* translocation-mediated rearrangements have been reported in 2 cases classified as ESS in 1 study[19] and 3 cases classified as HG-ESS in another.[20] These tumors exhibited extensive myxoid stroma, together with brisk mitotic activity and high-grade nuclear features. These morphologic features are similar to those observed in the neoplasms we describe with *BCOR* ITD, suggesting that different *BCOR* genetic alterations result in similar biologic and phenotypic consequences in uterine sarcomas. This interpretation is supported by recent studies in pediatric round cell sarcomas, which suggest that a variety of *BCOR* genetic alterations lead to similar transcriptional signatures that include overexpression of *BCOR* and other genes, resulting in overlapping biologic programs.[18]

The presence of *BCOR* ITD in uterine sarcomas highlights the genetic overlap between sarcomas of the gynecologic tract, CCSK, and soft tissue undifferentiated round cell sarcoma of infancy.[17] Intriguingly, all these entities feature *YWHAE-NUTM2* fusions or *BCOR* ITD in a mutually exclusive manner, suggesting that these genetic alterations are in some respects oncogenic equivalents. The high-grade component in each of these tumor types is morphologically similar, being composed of small round or ovoid neoplastic cells with scant cytoplasm and atypical nuclei with regular contours, with a prominent vascular network. Diffuse expression of cyclin D1, observed in a subset of these uterine sarcomas and CCSK, provides an additional point of biologic overlap.[7,21] However, there are striking demographic differences between these uterine sarcomas and pediatric undifferentiated round cell sarcomas, which may reflect contributions of the cellular environment to the transformation process during oncogenesis.

During the preparation of this manuscript, a multiinstitutional study analyzed the diagnostic value of BCOR immunohistochemistry in 31 genetically heterogenous high-grade uterine sarcomas diagnosed as HG-ESS.[22] On the basis of strong diffuse BCOR expression, the authors identified 1 case with *BCOR* ITD that was clinically and morphologically very similar to the 3 cases presented herein. In addition, 23 HG-ESS with *YWHAE-NUTM2* rearrangements and 3 HG-ESS with *BCOR* translocation-mediated rearrangement also expressed BCOR strongly and diffusely. Given the lack of BCOR expression in low-grade ESS and other uterine mesenchymal tumors, the authors concluded that BCOR is a sensitive immunohistochemical marker for *YWHAE-NUTM2*-associated HG-ESS and uterine sarcoma with BCOR alterations. Our data support the conclusions of that study and confirm the contribution of *BCOR* ITD to the pathogenesis of *YWHAE-NUTM2*-negative uterine high-grade sarcomas.

In conclusion, *BCOR* ITD is an alternative genetic event to *YWHAE-NUTM2* fusion in a subset of high-grade uterine sarcomas. High-grade uterine sarcomas with *BCOR* ITD usually affect young patients and may be clinically aggressive. The data presented herein expand the contribution of genetic studies to accurate classification of uterine sarcomas, and further illustrate the remarkable, although poorly understood, genetic overlap between high-grade uterine sarcomas and infantile undifferentiated round cell sarcomas. We propose that neoplasms with the morphology described herein and *BCOR* ITD be regarded as a unique subtype of high-grade uterine sarcoma, possibly within the family of endometrial stromal neoplasia.

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