Int J Clin Exp Pathol 2024;17(8):245-251
www.ijcep.com /ISSN:1936-2625/IJCEP0157116

Case Report

High-grade endometrial stromal sarcoma with *BCOR* rearrangements: clinicopathological analysis of five cases and literature reviews - an extension in understanding of morphological characteristics

Xuan Zuo[1,2], Wei Jiang[1,2], Yan-Mei He[1,2], Wei Kuang[1,2], Lei Li[1,2]

[1]*Department of Pathology, West China Second University Hospital, Sichuan University, Chengdu, Sichuan, China;* [2]*Key Laboratory of Birth Defects and Related Diseases of Women and Children (Sichuan University), Ministry of Education, Chengdu, Sichuan, China*

Received April 9, 2024; Accepted July 23, 2024; Epub August 15, 2024; Published August 30, 2024

Abstract: Five cases of FISH verified *BCOR* rearranged high-grade endometrial stromal sarcoma were retrospectively analyzed. The patient age ranged from 33 to 65 years (median, 48.4 years). Most patients presented with irregular vaginal bleeding (3/5) and uterus mass (2/5). Only one patient developed an abdominal wall metastasis and other patients remained in good condition during the follow-up. Pathological findings revealed that the tumors exhibited morphological diversity in terms of cell shape, arrangement pattern and tumor stroma, compared to previous summarized histology of *BCOR* rearranged high-grade endometrial stromal sarcoma. Detailed description of such morphology changes expanded our understanding of the histology of *BCOR* rearranged high-grade endometrial stromal sarcoma. Due to the non-specificity of morphology in such malignancies, molecular testing is needed for confirmation in all patients.

Keywords: *BCOR* rearrangement, high-grade endometrial stromal sarcoma, non-classic histomorphology, molecular test

Introduction

Endometrial stromal tumors (ESTs) are a spectrum of neoplasms which exhibit benign to malignant biological behaviors. These neoplasms can be divided into four groups: endometrial stromal nodule (ESN), low grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS) and undifferentiated uterus sarcoma (UUS). Despite being the second most common uterine mesenchymal malignancy, the overall incidence is low and only represents 7-25% of all uterine mesenchymal tumors [1]. Recently, several related gene alternations were discovered in HG-ESS. Gene fusion between *YWHAE* and *NUTM2A/B* was first reported [2] and then *ZC3H7B-BCOR* fusion [3] and *BCOR* internal tandem duplication (*BCOR*-ITD) [4] were identified. Researchers have summarized some morphological characteristics of *BCOR* rearranged HG-ESS. However, studies remain limited because of the rarity of such neoplasms. Herein, we report 5 cases of high-grade endometrial stromal sarcoma with *BCOR* rearrangement and hope to deepen our understanding of the clinicopathological features of such neoplasms.

Materials and methods

Case selection

All five cases were retrieved by searching the archive at West China Second University Hospital (Sichuan, China) using the keywords: high-grade endometrial stromal sarcoma and *BCOR*. Patient information and clinicopathological characteristics were gathered from system records. Precise diagnoses were made by gynecological pathologists, based on hematoxylin and eosin (H&E)-stained sections and

https://doi.org/10.62347/GDKO4005

immunochemistry. Diagnoses were all confirmed by fluorescence in situ hybridization (FISH). Follow-up data were available for all patients.

Immunochemistry

Formalin-fixed paraffin-embedded tissue blocks which contained the most representative lesions with scarce necrosis were selected for immunochemistry. A panel of diluted antibodies, including desmin, caldesmon, SMA, cyclin D1, BCOR, CD10, ER, PR, and Ki67, were used for analysis on an EnVision Automated Immunostainer. The expression status was evaluated by a semiquantitative system based on both staining intensity and percentage of positive cells. Staining intensity was divided into four grades: no staining (-), weak staining (+), moderate staining (++), and strong staining (+++).

Fluorescence in situ hybridization

All cases were verified by *BCOR* Dual-Color Break Apart FISH analysis. *BCOR* Break Apart FISH probe (Xp11.4) was designed by HealthCare Biotechnology (WuHan, China). Experiments were performed following the manufacturer's protocol. A break-apart pattern with a separation of red and green signals > 3 signal diameters was used as the criteria for a translocation. A minimum of two hundred nuclei from tumor cells with clear nuclear staining were counted at 100× magnification. A positive score was interpreted when over 30% of counted nuclei showed a break-apart pattern.

Results

Clinical features

In our cohort, patient age at tumor onset ranged from 33 to 65 years, and the average age was 48.4 years. Four patients were referred to our hospital because of suspicion of malignancy after myomectomy. Patients sought medical help for irregular vaginal bleeding (3/5) and a rapidly growing uterus mass (2/5). Tumors originated mainly in the uterine corpus (4/5), and one originated in the lower segment of the uterus. All neoplasms were confirmed to be *BCOR*-rearranged high-grade endometrial stromal sarcoma. Three patients had early-stage disease (FIGO I or II), and one had advanced-stage disease (FIGO IV). The other patient only asked for consultation and failed to obtain information about staging. The patient with advanced FIGO stage disease was treated with concurrent chemoradiotherapy.

Histopathological findings

For three patients, macroscopic examinations were not possible since there were no visible lesions after myomectomy. For the remaining two patients, the lesions had unclear boundaries and gray-to-white gelatinous cut surfaces with focal necrosis and hemorrhage. The lesion of one patient had a polyp-like appearance and protruded into the cervix tube. The lesion of the other patient occupied the entire uterine cavity and penetrated the serosa with a mucous-like cut surface.

Microscopically, the tumor cells were typically ovoid to spindle shaped with scant eosinophil cytoplasm and were mostly arranged in the fasciculus with focal myxoid degeneration (**Figure 1A**, **1B**). Although they showed some similar features, the lesions of each patient exhibited morphological differences as well. First, the tumor cells partially became epithelioid (**Figure 1C**) or star-shaped (**Figure 1D**). Apparent nuclear atypia and prominent nucleoli were occasionally present (**Figure 1E**). Second, alterations in the growth pattern and supporting stroma also occurred. Microcystic and reticular arranged tumor cells (**Figure 1F**) and collagen-rich stroma with plaque formation (**Figure 1G**) were observed. Moreover, a filamentary-like structure was observed in one patient (**Figure 1H**). Greater than 15/10 HPFs mitosis were observed on average. Hemorrhage and necrosis with tumor cells survival only around vessels were frequently observed. In addition, vascular hyalinosis and infiltration of plasma cells were present for a few patients (**Figure 1I**).

Immunohistochemical phenotypes

The immunohistochemical profiles are summarized in **Table 1**. Tumor cells generally exhibited typical staining phenotypes and were positive for CD10, CyclinD1 and BCOR and negative for ER, PR and myogenic markers, such as caldesmon, SMA and desmin. The expression patterns of important markers are illustrated in **Figure 2**.

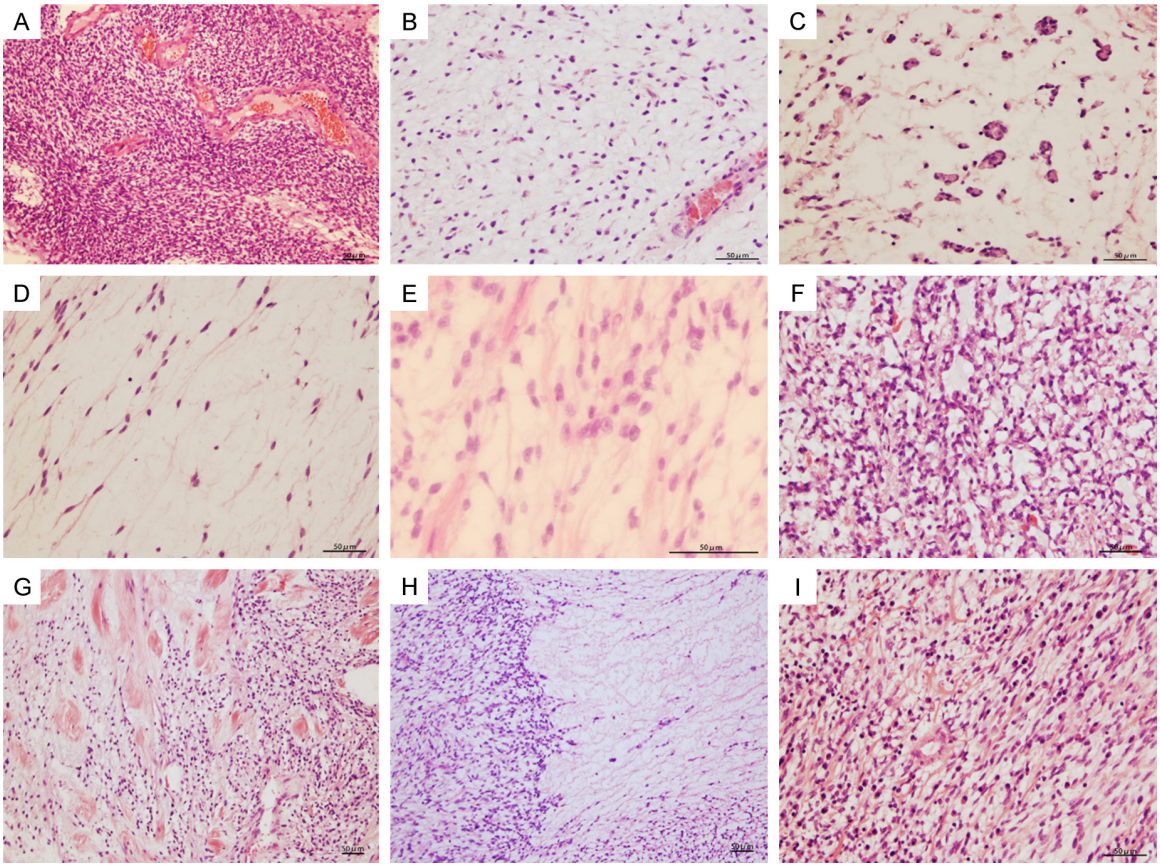

Figure 1. Morphological features of *BCOR* rearrangement HG-ESS. Magnification power: (A) 100×; (B-D) 200×; (E) 400×; (F) 200×; (G, H) 100×; (I) 200×.

Table 1. Immunophenotype of *BCOR* rearranged, high-grade endometrial stromal sarcomas

Case	CD10	CyclinD1	BCOR	Caldesmon	Desmin	SMA	ER	PR
1	F, +	+++	+++	-	-	-	F, +	-
2	+++	++	++	-	-	-	-	-
3	+++	++	NA	-	-	-	++	+
4	+++	++	+	-	-	-	-	-
5	+++	++	NA	-	-	-	-	-

Abbreviations: +, weak positive; ++, moderate positive; +++, strong positive; -, negative; F, focal; NA, not available.

Gene rearrangements

BCOR rearrangements were verified in all five patients by double-color break-apart FISH analysis. All cases exhibited typical break-apart signals showing separated green and red signals in more than 30% of the counted cells (**Figure 3**).

Follow-up data

Only one patient developed an abdominal wall metastasis 2 years after primary surgery. The other patients showed no signs of recurrence during the follow-up time from 6 to 24 months.

Discussion

BCOR rearrangements in uterine high-grade endometrial stromal sarcoma were first discovered by Panagopoulos in 2013 [5]. Since then, many studies have focused on *BCOR*-related alterations in HG-ESS. Most of them were reported as case reports [6, 7], and a few were reported as cohort studies. With the increasing number of cases, most scholars believe that

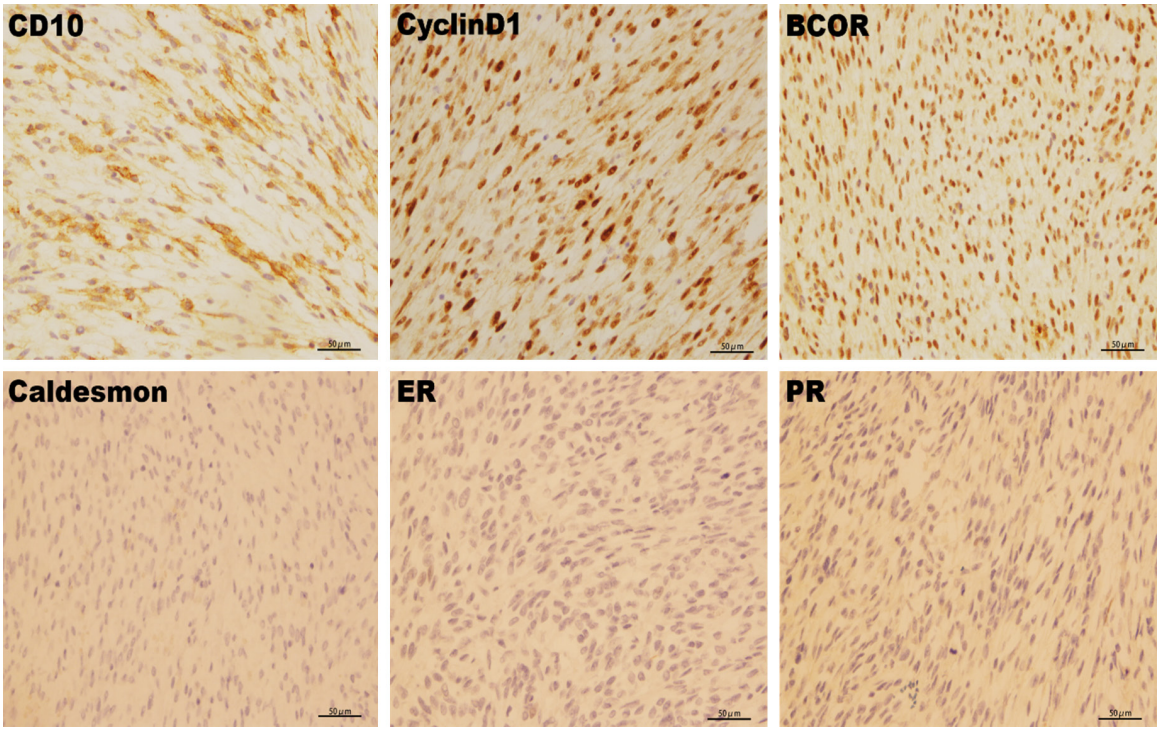

Figure 2. Representative expression pattern of important markers in the diagnosis of HG-ESS. CD10, Cyclin D1 and BCOR are diffuse positive. Caldesmon, ER and PR are all negative (Magnification power: 200×).

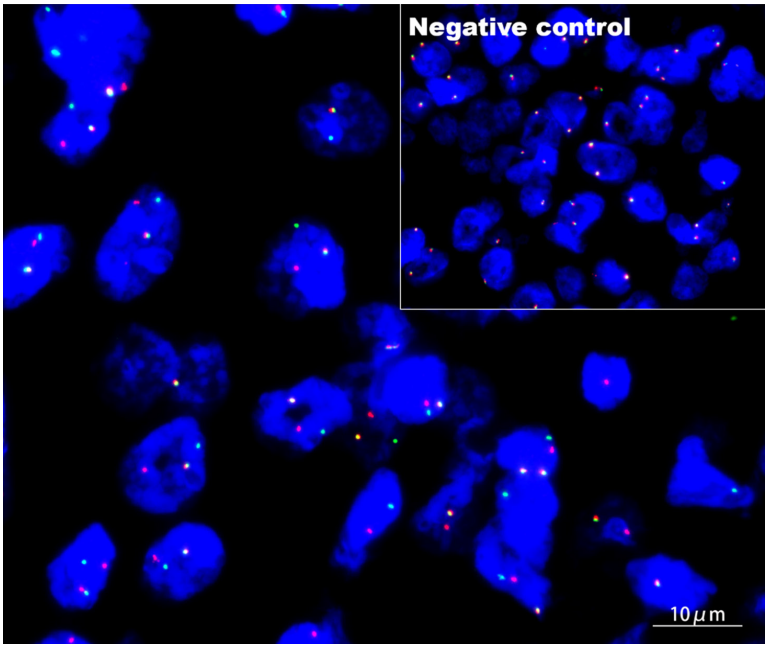

Figure 3. FISH analysis confirmed gene rearrangements in *BCOR* by dual-color break-apart gene probes (The upper right box shows the negative contrast of the FISH test. Magnification power: 400×).

significant genetic alterations in HG-ESS are associated with distinct histological characteristics [8]. For instance, *YWHAE-NUTM2* fusion tumors consisted of high-grade round and low-grade spindle cell components. The *BCOR-ZC3H7B* fusion HG-ESS frequently exhibits spindle cells arranged in a uniformly fascicular pattern, with mild to moderate atypia and myxoid or collagenous stroma [3].

The patients in our study displayed histological similarities and differences compared to those with the *BCOR-ZC3H7B* fusion HG-ESS. Consistent with recent studies, as listed in **Table 2**, morphological diversity was mostly observed in terms of cell type, arrangement, and tumor stroma. Recognizing these changes is highly important for avoiding misdiagnosis. The underlying reason for these histological changes has not yet been fully studied. Douglas et al. [9] indi-

Table 2. HG-ESSs with molecular alterations and histology features in reported cases

No.	Reported *BCOR* fusions	Characteristic morphology			
		Cell shape	Pleomorphism	Stromal change	Mitosis
1 [3, 19]	*ZC3H7B-BC*OR	Spindle, Ring like	Mild	Myxoid and collagenous	Active
2 [9]	*BCOR-L3MBTL2*	Spindle	Moderate	Nonspecific	Active
3 [9]	*EP300-BCOR*	Spindle	Moderate	Nonspecific	Active
4 [9]	*BCOR-NUTM2G*	Small round	Moderate	Myxoid	Active
5 [9]	*BCOR-RALGPS1*	Spindle and Epithelioid	Moderate	Myxoid and collagenous	Active
6 [9]	*BCOR-MAP7D2*	Spindle and Epithelioid	Mild-moderate	Myxoid and collagenous	Active
7 [9]	*RGAG1-BCOR*	Spindle and Epithelioid	Moderate-severe	Myxoid and collagenous	Active
8 [9]	*ING3-BCOR*	Spindle	Mild-moderate	Myxoid	Active
9 [9]	*BCOR-NUGGC*	Spindle	Mild-moderate	Myxoid	Active
10 [9]	*KMT2D-BCOR*	spindle and Small	Moderate-severe	Myxoid	Active
11 [9]	*CREBBP-BCOR*	Spindle and Epithelioid	Mild-moderate	Myxoid	Active
12 [16]	*BCOR-LPP*	Spindle	Mild-moderate	Nonspecific	Active

cated that these differences might be a result of non-*BCOR-ZC3H7B* gene fusions. We suggest that this may be a reflection of the pluripotent nature of endometrial stromal cells since smooth muscle and myofibroblast differentiation are commonly observed in other endometrial stromal hyperplastic lesions (such as adenomyomatous polyps of the uterus and endometrial adenosarcoma). However, due to limitations in the detection methods and case numbers, we were unable to further explore the pathological reasons behind these changes.

Despite these morphological changes, immunochemistry can still provide great help. Patients showing classic morphological features are consistently diffuse positive for BCOR, Cyclin D1, and CD10 [10]. BCOR overexpression has served as an important hallmark of HG-ESS according to previous studies [11]. However, in patients who exhibit histological diversity, its expression can become less representative. Other auxiliary biomarkers, such as CD10 and CyclinD1, are helpful in differential diagnosis.

Due to the non-specificity of morphological features, myxoid leiomyosarcoma and inflammatory myofibroblastic tumor (IMT) need to be routinely excluded. Patients with myxoid leiomyosarcoma express smooth muscle markers, such as desmin, caldesmon or SMA, and are negative for CD10 and BCOR. Moreover, patients with myxoid leiomyosarcoma frequently harbor *PLAG1* rearrangements [12]. IMTs are positive for ALK and other smooth muscle cell markers, and patients with IMT harbor *ALK* rearrangements. Together with histological features, such as predominantly fusiform cells arranged in an edematous to myxoid background and infiltration of acute to chronic inflammatory cells, an exclusive diagnosis of IMT can be successfully made [13]. In addition, histological atypia induced by cell degeneration may display similar morphology, and changes related to cell degeneration are characterized by cell ballooning or condensing.

BCOR rearrangements are commonly discovered in HG-ESS patients with myxoid changes [14]. This is considered as a driver gene in tumorigenesis. Recent studies have revealed that the *BCOR* rearrangement HG-ESS frequently harbors *CDK4* and *MDM2* amplification [9, 15, 16]. CDK4 is a regulator of cell cycle progression [17], and its amplification indicates activation of the CDK4/cyclin D1 pathway, which explains the overexpression of cyclin D1 and its biological aggressiveness in such malignancies [18]. Amplification of *MDM2*, a primary negative regulator of P53, can enhance the inhibitory effect of *TP53* transcription, resulting in wild-type expression of P53. Molecular analyses provide insights into the mechanisms related to tumor oncology and may help to identify potential molecular targets for chemotherapies.

Conclusion

According to the detailed description of morphology in these 5 *BCOR*-rearranged HG-ESS,

we need to realize that *BCOR*-rearranged HG-ESS may not be easily recognized by classic histological characteristics. Pathologists need to be aware of its morphological diversity and should carefully consider uncommon features. Morphological characteristics, immunophenotype and molecular alterations should be interpreted as an integration. Only then, can patients receive precise treatment and achieve a better prognosis.

Disclosure of conflict of interest

None.

Address correspondence to: Lei Li, West China Second University Hospital, Sichuan University, No. 1516, Section 1, Chenglong Avenue, Jinjiang District, Chengdu, Sichuan, China. Tel: +86-18602888809; E-mail: lipath@163.com

References

[1] Micci F, Heim S and Panagopoulos I. Molecular pathogenesis and prognostication of "low-grade" and "high-grade" endometrial stromal sarcoma. Genes Chromosomes Cancer 2021; 60: 160-167.

[2] Ullah A, Arbindi H, Zola F, Mattox SN, Velasquez Zarate L, Munroe J, Heneidi S, Sharma S, Ghamande S and Kleven DT. Pleomorphic high grade endometrial stromal sarcoma with YWHAE gene amplification may be a novel variant with poor prognosis. Int J Clin Exp Pathol 2022; 15: 72-78.

[3] Lewis N, Soslow RA, Delair DF, Park KJ, Murali R, Hollmann TJ, Davidson B, Micci F, Panagopoulos I, Hoang LN, Arias-Stella JA 3rd, Oliva E, Young RH, Hensley ML, Leitao MM Jr, Hameed M, Benayed R, Ladanyi M, Frosina D, Jungbluth AA, Antonescu CR and Chiang S. ZC3H7B-BCOR high-grade endometrial stromal sarcomas: a report of 17 cases of a newly defined entity. Mod Pathol 2018; 31: 674-684.

[4] Thiryayi SA, Ettler H, Goebel EA, Prefontaine M, Paton TA, Wong A, Yee D, Agro E, Mayers J, Lerner-Ellis J and Turashvili G. BCOR internal tandem duplication associated uterine sarcoma: expanding the clinicopathologic spectrum. Int J Gynecol Pathol 2022; 41: 503-507.

[5] Panagopoulos I, Thorsen J, Gorunova L, Haugom L, Bjerkehagen B, Davidson B, Heim S and Micci F. Fusion of the ZC3H7B and BCOR genes in endometrial stromal sarcomas carrying an X;22-translocation. Genes Chromosomes Cancer 2013; 52: 610-618.

[6] Ling F, Ruan S, Chen H, Xiong X, Zhao D, Haybaeck J and Zhang C. Highly invasive and metastatic high-grade endometrial stromal sarcoma with BCOR gene alterations: a case report. In Vivo 2022; 36: 1971-1976.

[7] Zhi W, Zheng X and Jin Y. ZC3H7B-BCOR high-grade endometrial stromal sarcoma with a mucoid grossly feature: a case report and literature review. Int J Womens Health 2022; 14: 1701-1708.

[8] Kim Y, Kim D, Sung WJ and Hong J. High-grade endometrial stromal sarcoma: molecular alterations and potential immunotherapeutic strategies. Front Immunol 2022; 13: 837004.

[9] Lin DI, Hemmerich A, Edgerly C, Duncan D, Severson EA, Huang RSP, Ramkissoon SH, Connor YD, Shea M, Hecht JL, Ali SM, Vergilio JA, Ross JS and Elvin JA. Genomic profiling of BCOR-rearranged uterine sarcomas reveals novel gene fusion partners, frequent CDK4 amplification and CDKN2A loss. Gynecol Oncol 2020; 157: 357-366.

[10] Alkanat NE, Uner A and Usubutun A. High-grade endometrial stromal sarcoma: morphologic and clinical features, the role of immunohistochemistry and fluorescence in situ hybridization in diagnosis. Int J Surg Pathol 2023; 31: 521-531.

[11] Chiang S, Lee CH, Stewart CJR, Oliva E, Hoang LN, Ali RH, Hensley ML, Arias-Stella JA 3rd, Frosina D, Jungbluth AA, Benayed R, Ladanyi M, Hameed M, Wang L, Kao YC, Antonescu CR and Soslow RA. BCOR is a robust diagnostic immunohistochemical marker of genetically diverse high-grade endometrial stromal sarcoma, including tumors exhibiting variant morphology. Mod Pathol 2017; 30: 1251-1261.

[12] Arias-Stella JA 3rd, Benayed R, Oliva E, Young RH, Hoang LN, Lee CH, Jungbluth AA, Frosina D, Soslow RA, Antonescu CR, Ladanyi M and Chiang S. Novel PLAG1 gene rearrangement distinguishes a subset of uterine myxoid leiomyosarcoma from other uterine myxoid mesenchymal tumors. Am J Surg Pathol 2019; 43: 382-388.

[13] Zhu Y, Ding Y, Song GX, Li X, Ding R, Fan QH and Gong QX. Clinicopathological features of inflammatory myofibroblastic tumor. Zhonghua Bing Li Xue Za Zhi 2021; 50: 194-200.

[14] Akaev I, Yeoh CC and Rahimi S. Update on endometrial stromal tumours of the uterus. Diagnostics (Basel) 2021; 11: 429.

[15] Kommoss FK, Chang KT, Stichel D, Banito A, Jones DT, Heilig CE, Fröhling S, Sahm F, Stenzinger A, Hartmann W, Mechtersheimer G, Sinn HP, Schmidt D, Kommoss F, von Deimling A and Koelsche C. Endometrial stromal sarcomas with BCOR-rearrangement harbor MDM2 amplifications. J Pathol Clin Res 2020; 6: 178-184.

[16] Kommoss FKF, Chiang S, Köbel M, Koelsche C, Chang KT, Irving JA, Dickson B, Thiryayi S, Rouzbahman M, Rasty G, von Deimling A, Lee CH and Turashvili G. Endometrial stromal sarcomas with BCOR internal tandem duplication and variant BCOR/BCORL1 rearrangements resemble high-grade endometrial stromal sarcomas with recurrent CDK4 pathway alterations and MDM2 amplifications. Am J Surg Pathol 2022; 46: 1142-1152.

[17] Chou J, Quigley DA, Robinson TM, Feng FY and Ashworth A. Transcription-associated cyclin-dependent kinases as targets and biomarkers for cancer therapy. Cancer Discov 2020; 10: 351-370.

[18] Thiel JT, Daigeler A, Kolbenschlag J, Rachunek K and Hoffmann S. The role of CDK pathway dysregulation and its therapeutic potential in soft tissue sarcoma. Cancers (Basel) 2022; 14: 3380.

[19] Ondič O, Bednářová B, Ptáková N, Hájková V, Šteiner P, Šidlová H, Presl J, Bouda J, Alaghehbandan R and Michal M. ZC3H7B-BCOR high-grade endometrial stromal sarcoma may present as myoma nascens with cytoplasmic signet ring cell change. Virchows Arch 2020; 476: 615-619.