

BCOR Expression in Endometrial Stromal Sarcoma: A Single-Center Study

Hira Nasir*, Aribah Atiq, Azra Bashir, Akhtar Sohail Chughtai, Omar Chughtai, Faria Waqar Khan

Department of Histopathology, Chughtai Institute of Pathology, Lahore, Pakistan

*Corresponding author's email address: nasirhira86@gmail.com

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Abstract: Endometrial stromal sarcoma (ESS) is a rare uterine neoplasm of mesenchymal origin that requires careful subcategorization due to its distinct prognostic implications. Recent studies have identified BCOR (BCL6 corepressor) as a reliable immunohistochemical marker with potential diagnostic value in high-grade ESS, aiding differentiation from other uterine sarcomas. **Objective:** To evaluate the diagnostic utility of BCOR expression in endometrial stromal sarcomas and to highlight its role in distinguishing high-grade ESS as a unique pathological entity for targeted treatment strategies. **Methods:** This prospective single-center study included 30 histologically confirmed cases of endometrial stromal neoplasms. Cases with insufficient tissue for immunohistochemistry or missing paraffin blocks were excluded. Formalin-fixed, paraffin-embedded tissue samples were subjected to BCOR immunohistochemical staining, and nuclear expression in tumor cells was assessed. Statistical analysis was performed to determine the association between BCOR expression and histological subtype. **Results:** Nuclear BCOR expression was detected in 3 (10.0%) of the 30 endometrial stromal neoplasms. All positive cases corresponded exclusively to high-grade ESS. Among nine cases of high-grade ESS, 3 (33.3%) exhibited BCOR expression, demonstrating a significant association with this subtype ($p = 0.005$). No BCOR expression was observed in endometrial stromal nodules, low-grade ESS, or undifferentiated uterine sarcomas. **Conclusion:** BCOR expression is a specific marker for high-grade ESS, facilitating its distinction from low-grade ESS, stromal nodules, undifferentiated uterine sarcomas, and other uterine pathologies. Incorporating BCOR immunostaining in diagnostic protocols may enhance diagnostic precision and guide individualized therapeutic approaches.

Keywords: Endometrial stromal sarcoma, BCOR, Immunohistochemistry, High-grade endometrial stromal sarcoma

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Introduction

Endometrial stromal sarcomas are the second most common uterine neoplasms of mesenchymal origin, with diverse morphological, immunohistochemical, and molecular features, preceded by leiomyosarcomas (1). They constitute approximately 7–25% of all uterine mesenchymal neoplasms (2) and less than 1% of overall malignancies arising in the female genital tract (3).

Norris and Taylor first studied endometrial stromal sarcomas in 1966(4). These tumors were primarily classified as low-grade or high-grade based on mitotic activity (4). With time, several changes have been made (5). In 2020, endometrial stromal tumors were subcategorized as an endometrial stromal nodule, low-grade endometrial stromal sarcoma, high-grade endometrial stromal sarcoma, and undifferentiated uterine sarcoma by the most recent World Health Organization (WHO) classification, and this subcategorization is primarily dictated by underlying genetic changes (5,6).

An endometrial stromal nodule is a benign, well-circumscribed, and non-infiltrative tumor that exhibits morphological resemblance to the proliferative phase of the endometrium (7). Low-grade endometrial stromal sarcoma is a malignant spindle cell neoplasm that has permeative margins with tongue-like infiltration (8). In contrast, undifferentiated uterine sarcoma is a Diagnosis of exclusion (9). It exhibits myometrial invasion, severe nuclear pleomorphism with little similarity to endometrial stroma, and no specific line of differentiation (9).

Two cell populations characterize high-grade endometrial stromal sarcomas: one is high-grade and exhibits a round cell morphology. At the same time, the other is low-grade and displays a spindle cell morphology with a fibromyxoid background. These tumors show YWHAE-NUTM2 fusion (10).

In recent years, however, endometrial stromal sarcoma with a ZC3H7B-BCOR fusion has been proposed, which is also high-grade and shows

morphologic overlap with myxoid leiomyosarcoma (11). The identification of BCOR gene abnormalities suggests that BCOR immunohistochemistry can be a valuable tool for diagnosing and stratifying endometrial stromal sarcomas (12).

This study aims to determine the utility of BCOR expression in endometrial stromal sarcomas and to elucidate these tumors as a distinct entity, thereby facilitating more effective and targeted management approaches for patients.

Methodology

This prospective study was conducted at the Histopathology Department of the Chughtai Institute of Pathology in Lahore, Pakistan, over a period of 1 year, from January 10, 2023, to January 9, 2024, following approval from the institution's review board (CIP/IRB#1159).

Our study included thirty cases of endometrial stromal sarcoma overall. Among these, one belonged to an endometrial stromal nodule, nineteen were low-grade endometrial stromal sarcomas, nine were high-grade endometrial stromal sarcomas, and one was categorized as an undifferentiated uterine sarcoma. These tumors were divided according to the 2020 WHO classification (5,6) (Figure 1). Cases with scant tissue in which immunostains could not be performed or those cases in which paraffin blocks could not be retrieved were excluded from our study.

BCOR immunohistochemical (IHC) stain was applied to formalin-fixed paraffin-embedded tissue blocks of all 30 cases. Initially, the paraffin-embedded blocks were sliced to a thickness of 3µm. They were then taken on slides. On a hot plate set to 70°C, these slides were dried. The paraffin wax in the sections was eliminated. The slides were then dipped in xylene, and the alcohol concentration was reduced to facilitate tissue rehydration. Antigen retrieval was performed by placing the slides in a retrieval solution (high pH) at 97°C for 20 minutes. Subsequently, slides were put in an Autostainer Link 48 (DAKO). A blocking solution was used to



suppress the activity of peroxidase. Prediluted and ready to use, primary BCOR monoclonal antibody (clone BSB-128 from Bio SB) was utilized. The sample was incubated for 30 minutes, followed by 20 minutes of incubation with the enzyme-conjugated secondary antibody (HRP). To identify the primary antibody, a non-soluble chromogen compound called diaminobenzidine (DAB) was introduced for 10 minutes, and a counterstain known as haematoxylin was added. To determine the quality and efficacy of primary antibodies, an external control was incorporated into each batch of immunomarkers. Two consultant histopathologists then studied antibody expression with a special interest in gynepathology. BCOR expression was evaluated based on criteria recommended by earlier studies by Alkanat et al. (13) and Chiang et al. (14). Nuclear expression of BCOR in tumor cells was considered "positive". Cytoplasmic, membranous, or no expression of BCOR in tumor cells was considered "negative". The intensity of the tumor cells was identified as negative, weak, moderate, or strong. Statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 22.0. A p-value of ≤ 0.05 was considered statistically significant. The clinicopathological features were summarized with descriptive statistics, and the correlation between tumor type and BCOR expression in tumor cells was analysed using the Chi-square test.

Results

A total of 30 diagnosed cases of endometrial stromal neoplasms, aged between 26 and 82, with an average age of 53 years, were included in our study. Total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed in seventeen (56.7%) cases, followed by a laparotomy (33.3%). A total abdominal hysterectomy without bilateral salpingo-oophorectomy was performed in two cases (6.7%), and endometrial curettage was done in one case (3.3%). The most common primary site of neoplasm was the endomyometrium of the uterus (76.7%), followed by the ovary (20.0%). One neoplasm involved the omentum in addition to the endomyometrium (3.3%). Amongst thirty cases, one (3.3%) was an endometrial stromal nodule, nineteen (63.4%) were low-grade endometrial stromal sarcoma, nine (30.0%) were high-grade endometrial stromal sarcoma, and one (3.3%) was an undifferentiated endometrial stromal sarcoma. In four (13.3%) neoplasms, the tumor size was less than or equal to 5cm, fifteen (50.0%) were greater than 5cm, and eleven (36.7%) were fragmented. Lymphovascular invasion was identified in seven (23.3%) of the thirty cases. Moreover, four (13.3%) neoplasms were staged as pT1a, eleven (36.7%) as pT1b, three (10.0%) as pT2, one (3.3%) as pT3, and eleven (36.7%) were not staged due to their fragmented nature (Table 1).

Table 1: Demographic and Pathologic Parameters

Parameter	Categories	Frequency (n=30)	Percentage (%)
Age (years)	<50	23	76.7%
	≥ 50	07	23.3%
Procedure	Total Abdominal Hysterectomy with Bilateral salpingo-oophorectomy	17	56.7%
	Total Abdominal Hysterectomy	2	6.7%
	Endometrial Curetting	1	3.3%
	Laparotomy	10	33.3%
Tumor Site	Endomyometrium	23	76.7%
	Endomyometrium and omentum	1	3.3%
	Ovary	6	20.0%
Tumor Type	Endometrial Stromal Nodule (ESN)	1	3.3%
	Low-Grade Endometrial Stromal Sarcoma (LGESS)	19	63.4%
	High-Grade Endometrial Stromal Sarcoma (LGESS)	9	30.0%
	Undifferentiated Uterine Sarcoma (UUS)	1	3.3%
Lymphovascular Invasion (LVI)	Present	7	23.3%
	Absent	23	76.7%
Pathologic Tumor Stage	pT1a	4	13.3%
	pT1b	11	36.7%
	pT2	3	10.0%
	pT3	1	3.3%
	Fragmented	11	36.7%

Table 2: Correlation of BCOR expression in tumor cells with tumor subtype

TUMOR TYPE	BCOR EXPRESSION				p-VALUE
	Positive n=0 Mild No. (%)	Positive n=0 Moderate No. (%)	Positive n=3 Severe No. (%)	Negative n=27 No. (%)	
Endometrial stromal nodule	0 (0%)	0 (0%)	0 (0%)	1 (3.33%)	0.73
Low-grade endometrial stromal sarcoma	0 (0%)	0 (0%)	0 (0%)	19 (63.3%)	0.01
High-grade endometrial stromal sarcoma	0 (0%)	0 (0%)	3 (10.0%)	6 (20.0%)	0.005
Undifferentiated uterine sarcoma	0 (0%)	0 (0%)	0 (0%)	1 (3.33%)	0.73

We found that endometrial stromal nodules (3.3%), low-grade endometrial stromal sarcomas (63.3%), and undifferentiated stromal sarcomas (3.3%) were "negative" for BCOR expression. Three (10.0%) high-grade endometrial stromal sarcomas showed strong, nuclear BCOR expression in tumor cells. Six (20.0%) high-grade endometrial stromal sarcomas were "negative" for BCOR expression

(Figure 2). A significant correlation was observed between high-grade endometrial stromal sarcoma and BCOR expression, with a p-value of 0.005, indicating statistical significance. The relationship between tumor type and BCOR expression in the tumor cells of endometrial stromal sarcomas is explained in Table 2.

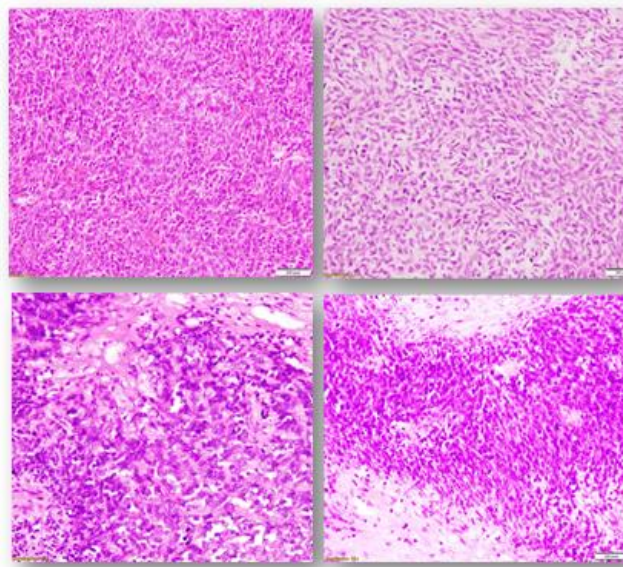


Figure 1: At 400x, histomorphology of (A) endometrial stromal nodule, showing monomorphic endometrial stromal neoplastic cells with bland nuclear features, (B) low grade endometrial stromal sarcoma, showing monotonous, spindle shaped neoplastic cells with mild cytologic atypia, (C & D) high grade endometrial stromal sarcoma, showing round to spindle shaped neoplastic cells with marked cytological atypia (Hematoxylin and eosin (H&E) stain, 40x)

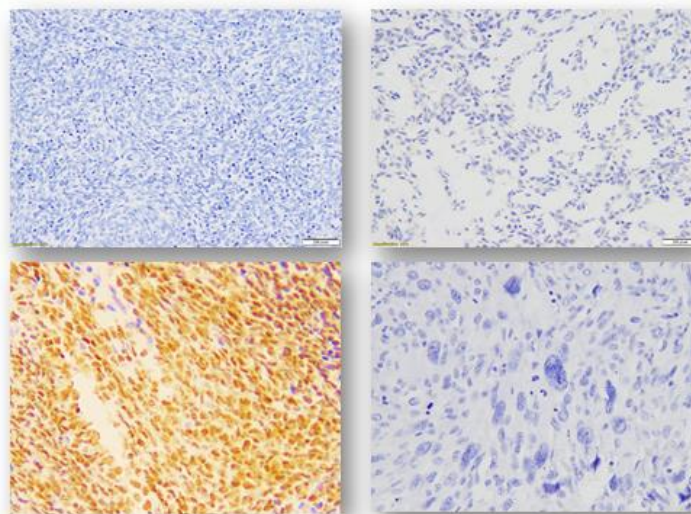


Figure 2: Immunohistochemical expression of BCOR in endometrial stromal neoplasms: (A) No expression of BCOR in an endometrial stromal nodule; (B) No expression of BCOR in low-grade endometrial stromal sarcoma; (C) Strong, nuclear BCOR expression in a high-grade endometrial stromal sarcoma; (D) No expression of BCOR in a high-grade endometrial stromal sarcoma

Discussion

The recognition and sub-categorization of endometrial stromal neoplasms is essential from a clinical, therapeutic, and prognostic perspective (15). BCOR genetic abnormalities can cause a variety of neoplasms, including endometrial stromal neoplasms (16). BCOR is located on the X chromosome at the Xp11.4 locus and is named for its role as a corepressor that interacts with BCL-6, enhancing transcriptional repression (16,17). Its expression in endometrial stromal neoplasms can be detected by immunohistochemical staining using a monoclonal antibody (18).

We applied BCOR immunohistochemical stain on thirty cases of endometrial stromal neoplasms that included endometrial stromal nodules, low-grade endometrial stromal sarcomas, high-grade

endometrial stromal sarcomas, and undifferentiated uterine sarcomas. Low-grade endometrial stromal sarcoma accounted for the majority (63.3%) in our study, while high-grade endometrial stromal sarcoma was the second most common type (20.0%). Subbaraya et al. in their study also identified low-grade endometrial stromal sarcoma as the most frequent type (50.0%), followed by high-grade endometrial stromal sarcoma at 30.0% (19). This aligns with the findings of Leath III et al., who reported that low-grade endometrial stromal sarcomas are the most common type (68.6%), followed by high-grade endometrial stromal sarcomas (29.5%) (20).

The BCOR staining pattern is nuclear in tumor cells, as determined by immunohistochemistry (21,22). In our research, three (10.0%) endometrial stromal neoplasms exhibited nuclear BCOR expression. In an earlier study by Alabiad, Mohamed Ali, et al., it was found that 13

(59.1%) endometrial stromal sarcomas showed nuclear BCOR expression, which is significantly higher than the results in our study (22). Moreover, BCOR expression was detected in 16.67% of endometrial stromal sarcomas in research conducted by Zou et al. Al (23).

We determined that BCOR expression was observed exclusively in high-grade endometrial stromal sarcomas. Amongst high-grade endometrial stromal sarcomas included in our study, 3 (33.3%) showed nuclear BCOR expression, while the remaining 6 (66.6%) were entirely negative. Lewis N. and their team chose seventeen high-grade endometrial stromal sarcomas for their research and applied BCOR in fourteen of these cases. BCOR expression was observed in 43.0% of these tumors, which is higher than the rate found in our study (24). In a separate study by Alkanat et al., 60.0% of high-grade endometrial stromal sarcomas showed BCOR expression (13). Research conducted by Abouelkhair and his colleagues in 2024 found that BCOR expression was positive in all cases of high-grade endometrial stromal sarcoma (12/12, 100%), results notably higher than ours (25).

In our study, endometrial stromal nodules, low-grade endometrial stromal sarcomas, and undifferentiated uterine sarcomas exhibited no BCOR expression in tumor cells. This is in concordance with the results by Alkanat et al. Al, who reported negative BCOR expression in all cases of low-grade endometrial stromal sarcoma (13). However, this contrasts with the study by Chiang et.al, which observed weak BCOR expression in 6% of endometrial stromal nodules and 6% of low-grade endometrial stromal sarcomas (14).

We noted the expression of CD10 and cyclin D1, in addition to BCOR, in endometrial stromal neoplasms. CD10 expression was seen in one (100%) endometrial stromal nodule, seventeen (89.5%) low-grade endometrial stromal sarcomas, and two (22.2%) high-grade endometrial stromal sarcomas. A previous study by Abouelkhair et al. showed that CD10 positivity was observed in all cases of endometrial stromal nodule (100%) and low-grade endometrial stromal sarcoma (100%). In comparison, it was entirely negative in high-grade endometrial stromal sarcomas (0.0%) (25). One low-grade endometrial stromal sarcoma and eight high-grade endometrial stromal sarcomas showed Cyclin D1 expression in our research. In 13 (43.3%) cases, a cyclin D1 immunohistochemical stain was not performed. However, in a 2018 study by Siavash Rahimi and his colleagues, Cyclin D1 expression was identified in all high-grade endometrial stromal sarcomas (6/6, 100%). It was observed to be negative in all low-grade endometrial stromal sarcomas (0/5, 0.0%) (26).

Amid the era of Next Generation Sequencing (NGS), significant efforts are ongoing to combine the morphological and immunohistochemical classification of endometrial stromal neoplasms with their molecular sub-classification (27). The goal of molecular classification of endometrial stromal neoplasms, like other tumors, goes beyond theoretical interest; it seeks to develop targeted therapies for each subtype (28). This understanding will be essential in developing treatment strategies for metastatic disease (28). In the future, we can expect new entities of endometrial stromal neoplasms to be defined based on molecular classification rather than histopathological classification (27,28).

Conclusion

BCOR has become a well-recognized immunohistochemical marker in recent years, possessing significant diagnostic utility for endometrial stromal sarcoma. The expression of BCOR in high-grade endometrial stromal sarcoma not only distinguishes it from other endometrial stromal neoplasms but also holds significance in differentiating this tumor from various other uterine sarcomas. Our study suggests that categorizing endometrial stromal sarcoma based on BCOR expression, in conjunction with CD10 and cyclin D1, may hold prognostic significance and could lead to different treatment strategies.

Declarations

Data Availability statement

All data generated or analysed during the study are included in the manuscript.

Ethics approval and consent to participate

Approved by the department concerned. (CIP/IRB#1159)

Consent for publication

Approved

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The authors declared the absence of a conflict of interest.

Author Contribution

HN

Manuscript drafting, study design, data entry, data analysis

AA

Conception of study, Review of literature

AB

Conception of Study

ASC

Conception of Study

OC

Conception of Study

FWK

Conception of Study

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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