



Case Report

A Case Report of *ZC3H7B-BCOR* High-grade Endometrial Stromal Sarcoma Expressing CD117 and DOG1: A Molecularly Confirmed Diagnostic Pitfall

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Abstract

High-grade endometrial stromal sarcoma (HGESS) is a rare sarcoma with aggressive biological behavior. Here we report a case of molecularly confirmed *ZC3H7B-BCOR* HGESS in extrauterine, with morphologic and immunohistochemical findings resembling a gastrointestinal stromal tumor. The patient, a 51-year-old woman, presented with extensive pelvic and abdominal masses. Histologically, the tumor displayed fascicles of spindle cells with myxoid stroma and abundant mitosis. Immunohistochemical staining revealed that the tumor cells were diffusely positive for cluster of differentiation 117 (CD117) and discovered on gastrointestinal stromal tumor 1 (DOG1). Gastrointestinal stromal tumor was initially diagnosed, and DNA sequencing was performed for targeted therapy. Unexpectedly, no mutations in KIT proto-oncogene, receptor tyrosine kinase (*CKIT*) or platelet-derived growth factor receptor, alpha polypeptide (*PDGFRA*) were identified, but amplification of murine double minute 2 (*MDM2*) and cyclin-dependent kinase 4 (*CDK4*) was found. Further, *ZC3H7B-BCOR* fusion was detected via RNA sequencing. Additional immunostaining showed that CD10 was diffusely positive, the estrogen receptor was negative, and the progesterone receptor was weakly positive. *ZC3H7B-BCOR* HGESS was definitively diagnosed. In conclusion, the coexpression of CD117 and DOG1 may present a potential diagnostic pitfall in the evaluation of pelvic/abdominal masses, which should be paid great attention.

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Abbreviations: BCOR, b-cell lymphoma-6 corepressor; CD, cluster of differentiation; CDK, cyclin-dependent kinase; CKIT, KIT proto-oncogene, receptor tyrosine kinase; DNA, deoxyribonucleic acid; DOG, discovered on gastrointestinal stromal tumor; ER, estrogen receptor; ERBB, human epidermal growth factor receptor; GIST, gastrointestinal stromal tumor; HGESS, high-grade endometrial stromal sarcoma; LYN, lck/yes-related novel protein-tyrosine kinase; MDM, murine double minute; NGS, next-generation sequencing; PDCD1LG2, programmed cell death 1 ligand 2; PDGFRA, platelet-derived growth factor receptor, alpha polypeptide; PR, progesterone receptor; RECQL, recQ like helicase; RNA, ribonucleic acid; *ZC3H7B*, zinc finger CCCH-type containing 7B.

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Introduction

High-grade endometrial stromal sarcoma (HGESS) is a rare mesenchymal tumor that typically occurs in the uterus but occasionally arises at other gynecologic or pelvic locations.¹ With the extensive application of molecular techniques, the diagnosis of HGESS has shifted from a morphology-based scheme to a paradigm that amalgamates molecular features, each with its own immunophenotype.² Besides *YWHAE-NUTM2A/B* fusion HGESS, *BCOR*-rearranged HGESSs, such as *ZC3H7B-BCOR*,³ *BCOR ITD*,⁴ and *EPC1-BCOR*,⁵ are new entities of HGESS. The histomorphology of HGESS expands from high-grade oval-shaped cells to high-grade oval or spindle-shaped cells. HGESS with *ZC3H7B-BCOR* fusion is the most common type among the new entities. Recognition of this rare tumor is of great clinical importance because of its aggressive biological behavior and susceptibility to recurrence and metastasis.^{3,6} Gastrointestinal stromal tumor (GIST) is one of the most common mesenchymal tumors in the abdominopelvic cavity. The diagnosis of GIST is mainly based on the combination of morphology with a cluster of differentiation 117 (CD117)- and/or discovered on gastrointestinal stromal tumor 1(DOG1)-positive immunophenotype. About 85% of GISTs have gain-of-function mutations in the KIT proto-oncogene, receptor tyrosine kinase (*CKIT*) or platelet-derived growth factor receptor, alpha polypeptide (*PDGFRA*) oncogene. Therefore, patients with GIST could benefit from targeted therapy with receptor tyrosine kinase inhibitors.⁷

Here, we report a case of molecularly confirmed *ZC3H7B-BCOR* HGESS in primary extrauterine, with morphologic and immunohistochemical findings resembling a GIST. The manuscript was prepared according to the CARE guideline and the checklist was completed.

Case presentation

The patient was a 51-year-old woman who presented with multiple abdominal masses and had undergone debulking

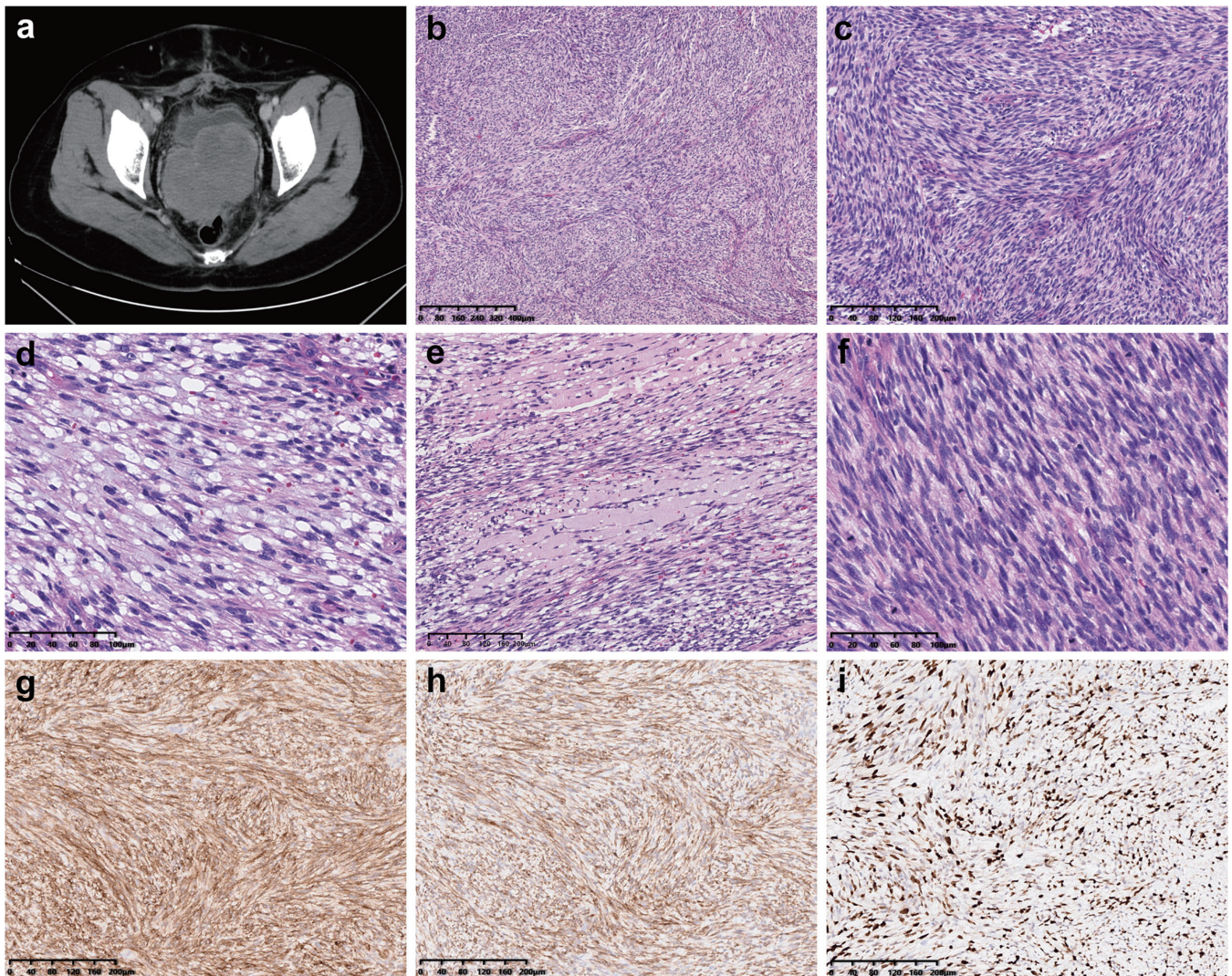


Fig. 1. Radiological imaging and histopathological findings. (a) Computed tomographic scan showed extensive pelvic and abdominal masses, with the largest tumor being 9.6 cm × 6.1 cm in size. (b) At low-power magnification, the tumor consisted of spindle cells arranged in haphazard fascicles and had moderate cellularity. (c) The tumor cells showed moderate eosinophilic cytoplasm, elongated nuclei and inconspicuous nucleoli. (d) Some areas had myxoid stroma. Cytoplasmic vacuolation sometimes generated a signet-ring-like appearance. (e) Myxoid lake was formed in the focal abundant myxoid area. (f) Mitotic figures were easily observed in the tumors. Immunostaining showed that the tumor cells were (g) diffusely and strongly positive for CD117 and (h) moderately positive for DOG1. (i) The proliferative index of ki-67 was about 60%. CD, cluster of differentiation; DOG, discovered on gastrointestinal stromal tumor.

surgery at a local hospital. Postoperatively, a pathological diagnosis of GIST was made. Pathological consultation was then performed for further diagnosis and treatment. She had a history of subtotal hysterectomy with double adnexectomy for uterine leiomyoma 9 months ago and without a family history of tumors. A computed tomographic scan showed extensive pelvic and abdominal masses, with the largest tumor measuring 9.6 cm × 6.1 cm, which invaded the rectum and left ureter (Fig. 1a).

By reviewing the histology, the tumor was composed of spindle cells arranged in haphazard fascicles without hyalinized collagenous stroma (Fig. 1b). The tumor cells had moderate eosinophilic cytoplasm, elongated nuclei and inconspicuous nucleoli (Fig. 1c). The intracellular and extracellular myxoid matrix could be found (Fig. 1d), and some even formed a myxoid lake locally (Fig. 1e). Cytoplasmic vacuolation sometimes generated a signet-ring-like appearance.

There were abundant mitotic figures (>30/5 mm²) (Fig. 1f). No hemorrhage or necrosis was observed. Immunohistochemical staining showed diffusely and moderately to strongly positive staining for CD117 (Fig. 1g) and DOG1 (Fig. 1h), variably focal staining for smooth muscle actin and negative staining for desmin, CD34, S-100 and SRY-box transcription factor-10. The proliferation index of Ki-67 (Fig. 1i) was about 60%. The tumor was initially diagnosed as a GIST. Unexpectedly, no *CKIT* or *PDGFRA* driver mutations were detected, but amplification of murine double minute 2 (*MDM2*) and cyclin-dependent kinase 4 (*CDK4*) was detected via next-generation sequencing (NGS) of DNA before imatinib treatment. Furthermore, *ZC3H7B-BCOR* was detected via sequential NGS of RNA (Fig. 2a), which was used to determine whether it was a specific type of sarcoma. Histology, immunohistochemistry, and molecular tests were performed on the same tissue block, and the genetic alterations identified by NGS of DNA

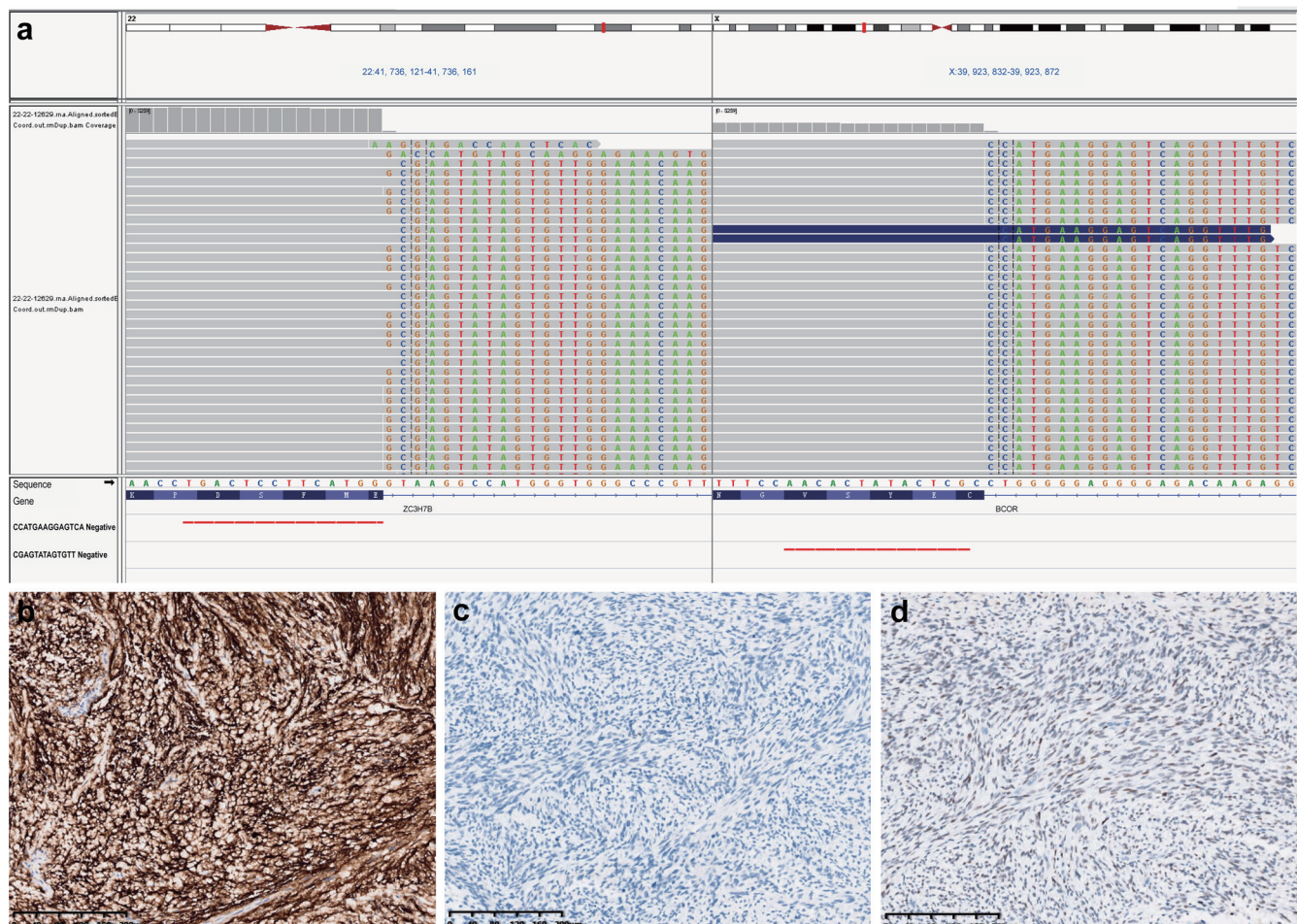


Fig. 2. RNA sequencing results and additional immunostaining findings. (a) Pictorial representation of the ZC3H7B-BCOR translocation via Integrated Genome Viewer. RNA sequencing results showed that BCOR gene exon 10 was fused to ZC3H7B gene exon 7. Immunostaining showed that the tumor cells were (b) diffusely and strongly positive for CD10, (c) negative for ER and (d) weakly focal positive for PR. BCOR, b-cell lymphoma-6 corepressor; CD, cluster of differentiation; ER, estrogen receptor; PR, progesterone receptor; RNA, ribonucleic acid; ZC3H7B, zinc finger CCCH-type containing 7B.

and RNA are summarized in Table 1. Additional immunostaining showed that CD10 (Fig. 2b) was diffusely positive, while the estrogen receptor (ER) (Fig. 2c) was negative and the progesterone receptor (PR) (Fig. 2d) was weakly positive. HGESS with ZC3H7B-BCOR fusion was definitively diagnosed.

The patient returned to the local hospital for therapy. She was alive 2 months after the initial presentation, but refused further follow-up.

The study was performed in accordance with the ethical standards of the institutions to which we are affiliated and the Declaration of Helsinki (revised in 2013).

Discussion

The diagnosis of this case was challenging due to complexities in morphology, immunohistology, and molecular testing.

Table 1. Genetic alterations in this ZC3H7B-BCOR high-grade endometrial stromal sarcomas

Method	Fusion	Amplification	Mutation
RNA NGS	ZC3H7B:exon10-BCOR:exon7	X	X
DNA NGS	X	CDK4	RECQL4 exon5 stop_gained
		MDM2	LYN exon9 missense_variant
		ERBB3	PDCD1LG2 exon5 missense_variant
			ERBB4 exon19 synonymous_varian
			RECQL4 exon14 splice_acceptor_variant

X indicated not found. BCOR, b-cell lymphoma-6 corepressor; CDK, cyclin-dependent kinase; DNA, deoxyribonucleic acid; ERBB, human epidermal growth factor receptor; LYN, lck/yes-related novel protein-tyrosine kinase; MDM, murine double minute; NGS, next-generation sequencing; PDCD1LG2, programmed cell death 1 ligand 2; RECQL, recQ like helicase; RNA, ribonucleic acid; ZC3H7B, zinc finger CCCH-type containing 7B.

While this case exhibited histological and immunohistochemical similarities with GIST, the prognosis and treatment strategies for these conditions are completely distinct.

The occurrence of HGESS with *ZC3H7B-BCOR* fusion in an extrauterine location is extremely rare, making it an unexpected finding. The morphological features of this case were similar to those of the previously reported *ZC3H7B-BCOR* fusion HGESS, characterized by uniform spindle cells arranged in haphazard fascicles with intermediate-sized ovoid to spindle nuclei, inconspicuous nucleoli, and frequent brisk mitotic activity. The cytoplasm ranges from scant to moderate and eosinophilic to more abundant and blue-gray. Myxoid stroma is frequently observed, with the occasional presence of collagen plaques.³ These features are often shared by myxoid leiomyosarcoma and GIST, which are common in the abdominopelvic cavity. The above morphologic characteristics, especially the myxoid matrix, as well as the female sex, should be considered HGESS.

A notable challenge in this case was the coexpression of CD117 and DOG1 in spindle tumor cells. Pathologists often use CD117 in combination with DOG1 as an approach to eliminate pitfalls in the diagnosis of GIST because CD117 may be expressed in various tumors, such as leiomyosarcoma, mesothelioma, dedifferentiated liposarcoma and solitary fibrous tumors.⁸ Unexpectedly, the dual expression of the group became the worst pitfall in this particular case. In the context of differential diagnosis, the expression of CD117 and DOG1 was examined in HGESS with *YWHAE-NUTM2A/B* fusion. Most (12/14) cases with high-grade round cells displayed moderate to strong membranous/cytoplasmic CD117 staining, while the remaining two cases with pure low-grade fibroblastic components were negative for CD117. Conversely, all 14 cases were negative for DOG1.⁹ Among the reported cases of *ZC3H7B-BCOR* fusion HGESS, only two cases were negative for CD117.^{6,10} The expression of DOG1 in the *ZC3H7B-BCOR* fusion HGESS is largely unknown. To our knowledge, DOG1 was only stained and was positive in our case. However, further studies are needed. When the tumor cells expressed CD117, no mutations involving *CKIT* were found, raising suspicion about the diagnosis. The marker CD10 is valuable because it's consistently positive in the *ZC3H7B-BCOR* fusion HGESS. *BCOR* was typically expressed in the *YWHAE-NUTM2A/B* fusion HGESS, but only half of the sarcomas with *BCOR* rearrangements displayed *BCOR* positivity. A panel of CD10, cyclin D1, ER, and PR is essential when considering HGESS.²

RNA NGS is preferred for its excellent performance in gene fusion detection when sarcoma is suspected. The identification of *ZC3H7B-BCOR* fusion through RNA NGS provided crucial insight and confidence to overthrow the diagnosis of GIST, characterized by spindle tumor cells expressing both CD117 and DOG1. Initially, DNA NGA was performed to determine whether the patient was suitable for targeted therapy. However, the absence of *CKIT* and *PDGFRA* mutations, along with the presence of *MDM2* and *CDK4* gene amplification, prompted the consideration of a special sarcoma. The incidences of *MDM2* and *CDK4* gene amplification have been reported in 45% and 38% of *BCOR*-rearranged cases respectively.¹¹ It's also worth highlighting that molecular detection becomes more essential in differential diagnosis as the distinction between low-grade and high-grade ESS is increasingly defined by genetics.

Conclusions

In summary, we presented a special *ZC3H7B-BCOR* HGESS in extrauterine expressing both CD117 and DOG1, which is a

diagnostic pitfall that needs to be considered because it may lead to misdiagnosis and incorrect clinical treatment.

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None.

Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

Writing the manuscript (YW, JY), assisting in data collection (PY), assisted in section staining (HZ), performing the molecular analysis (WL). All authors have made a significant contribution to this study and have approved the final manuscript.

Ethical statement

The study was performed in accordance with the ethical standards of the institutions to which we are affiliated and the Declaration of Helsinki (revised in 2013). Written informed consent was obtained from the patient for publication of this case report.

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