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CASE REPORT

High-grade endometrial stromal sarcoma with *ZC3H7B-BCOR* fusion

AP Aldera,[1,2] S Chiang,[3] M Snuderl,[4] G Jour,[4] RW James,[2] MH Botha[5]

[1] *Division of Anatomical Pathology, Faculty of Health Sciences, University of Cape Town, South Africa*
[2] *JDW Pathology Inc, South Africa*
[3] *Department of Pathology, Memorial Sloan Kettering Cancer Centre, United States of America*
[4] *Department of Pathology, NYU Langone Health, United States of America*
[5] *Department of Obstetrics and Gynaecology, Faculty of Medicine and Health Sciences, Stellenbosch University, South Africa*
Corresponding author, email: aldera@jdwpathology.co.za

High-grade endometrial stromal sarcoma (HG ESS) is a rare malignant mesenchymal tumour of the uterus which is prone to locoregional recurrence and has a poor prognosis. Recently, distinct molecular genetic subtypes have been described, most notably those harbouring *YWHAE-NUTM2A/B* fusion, *ZC3H7B-BCOR* fusion and *BCOR* internal tandem duplications. We present a case of a 50-year-old woman who initially presented with bowel obstruction and metastatic disease. Her clinical course was characterised by advanced stage and multiple recurrences. Histologically, the tumour showed typical ovoid to spindled cytomorphology with myxoid stroma, relatively uniform nuclear features, and brisk mitotic activity. Immunohistochemistry was negative for CD10, SMA and desmin, but showed strong and diffuse positive labelling with cyclin D1. Next-generation RNA sequencing showed a *ZC3H7B-BCOR* fusion. Awareness of this recently described molecular subcategory of HG ESS and its typical histological features is crucial in separating it from its pathological mimics and in establishing the correct diagnosis.

Keywords: uterine stroma sarcoma, BCOR, next-generation sequencing, molecular pathology

Introduction

High-grade endometrial stromal sarcoma (HG ESS) is an uncommon malignant mesenchymal neoplasm arising in the uterus. These tumours are very rare, and their true incidence is largely unknown. Several molecular subgroups have recently been identified, and more are likely to be described in the future.[1] These tumours have a prognosis which is intermediate between low-grade ESS and undifferentiated uterine sarcoma.[2] Awareness of this entity is important for pathologists and treating clinicians alike as timely and accurate recognition will facilitate expedient therapy. We present a diagnostically challenging case of HG ESS with proven *Z3CH7B-BCOR* fusion to highlight the key features of this tumour and increase awareness amongst our colleagues working with malignancies of the gynaecological tract.

Case report

A 50-year-old G1P1 presented in June 2020 to an emergency room, complaining of severe lower abdominal pain. On clinical examination, there was severe lower abdominal tenderness with localised peritonitis. Imaging revealed a mass in the pelvis.

She was booked for a diagnostic laparoscopy due to the severity of the pain and uncertain diagnosis by the general surgeon. During the procedure, a large, well-circumscribed pelvic tumour was found adherent to the anterior bladder peritoneum and posterior sigmoid colon. The procedure was converted to open laparotomy, during which an *en bloc* resection was performed with a partial sigmoidectomy and a partial bladder wall resection.

Postoperatively she recovered well, and the histology of this resection revealed a myxoid spindle cell neoplasm. The tumour was reported as moderately cellular with several mitotic figures. Beta-catenin immunohistochemistry showed nuclear translocation, and this tumour was diagnosed as a myxoid variant of intra-abdominal desmoid (aggressive) fibromatosis.

The patient presented with abnormal uterine bleeding seven weeks later and a hysteroscopy and endometrial sampling was performed. This was diagnosed as low-grade endometrial stromal sarcoma. She underwent a hysterectomy and bilateral salpingo-oophorectomy. A polypoid, firm tumour was found in the fundus of the endometrial cavity. This tumour was described as a spindle cell neoplasm with extensive haemorrhagic necrosis protruding into the endometrial cavity. There was proliferation of malignant spindled cells with notable myxoid stromal change. Mitotic activity was increased and counted up to five mitoses per 10 high-power fields. Peritoneal biopsies of abnormal areas showed a similar tumour. The uterine tumour and peritoneal metastases showed focal positivity with CD10, ER and SMA immunohistochemistry. Cyclin D1 was not done. The tumour was diagnosed as a low-grade endometrial stromal sarcoma with myxoid changes.

The histology results were discussed at a combined oncology forum and since the tumour was hormone-receptor negative and of low-grade histology, no further adjuvant therapy was recommended.

Eight months later, she again presented with symptoms and a repeat computer tomography (CT) scan showed clinically concerning lesions in the peritoneum with a few enlarged lymph nodes in the pelvis. The decision was made to repeat the CT scan a few weeks later and that confirmed progression of disease.

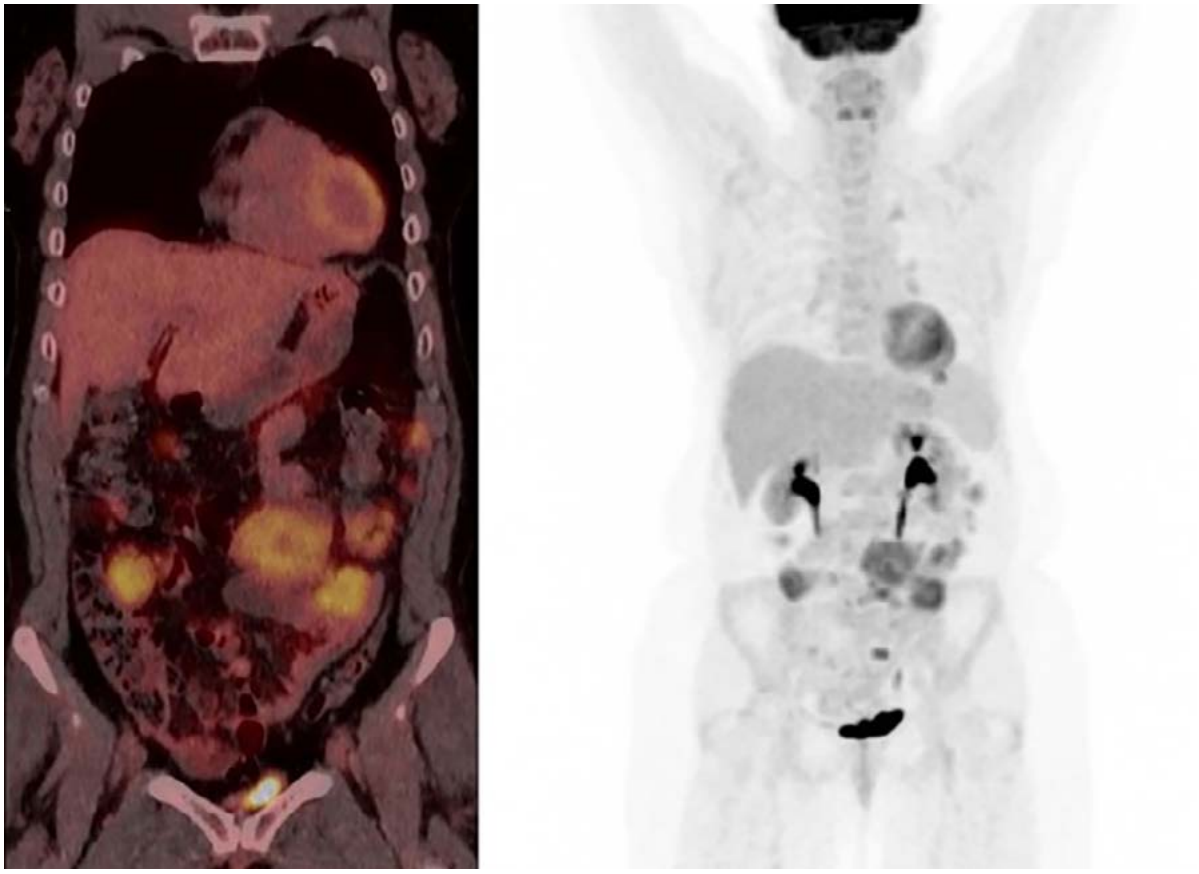

Figure 1: PET-CT revealed extensive progressive malignant disease one year after initial surgery

At this stage, she was referred for a second opinion to an oncology centre. A PET-CT scan revealed extensive tumour in the pelvis and upper abdomen (Figure 1) and further management was discussed at the multidisciplinary meeting. After extensive counselling with the patient and her family, the decision was taken to offer further surgery with the aim of i) trying to achieve tumour debulking, and ii) to obtain fresh histology due to the aggressive clinical course, which is unusual for a low-grade stromal sarcoma.

She underwent a third laparotomy one year after initial diagnosis and extensive tumour was found in the upper abdomen, infiltrating into the rectus sheath, small bowel, and omentum. A primary resection was possible with anastomosis of the small bowel. Approximately 20 cm of small bowel was removed. The patient made an uneventful postoperative recovery.

Histological evaluation of the most recent omental resection revealed a plexiform and lobulated tumour comprising ovoid to spindled cells arranged haphazardly and in short fascicles, embedded within a variably myxoid stroma (Figure 2). Other areas showed stromal hyalinisation. The tumoural cells displayed relatively uniform cytomorphology with ovoid nuclei, coarse chromatin, and inconspicuous nucleoli (Figure 3). Mitotic activity was brisk and there were areas of zonal ischaemic-type necrosis. There was a delicate background vascular network; these vessels did not contain pericytes or a muscular coat. Immunohistochemical interrogation revealed absent staining with CD10, SMA, desmin and *BCOR*. Cyclin D1 showed strong and diffuse nuclear labelling (Figure 4). The histological features and immunoprofile of the recurrent omental metastasis were similar to those in the initial mesenteric deposit, endometrial polyp, and hysterectomy specimens.

Targeted RNA next-generation sequencing (NGS) was performed on formalin-fixed paraffin-embedded tumour tissue obtained from the omental recurrence using a clinically validated fusion detection panel as previously described.[3] A *ZCH37B-BCOR* gene fusion was detected.

After the molecular diagnosis, the patient was rechallenged with combination chemotherapy of gemcitabine and docytaxel which

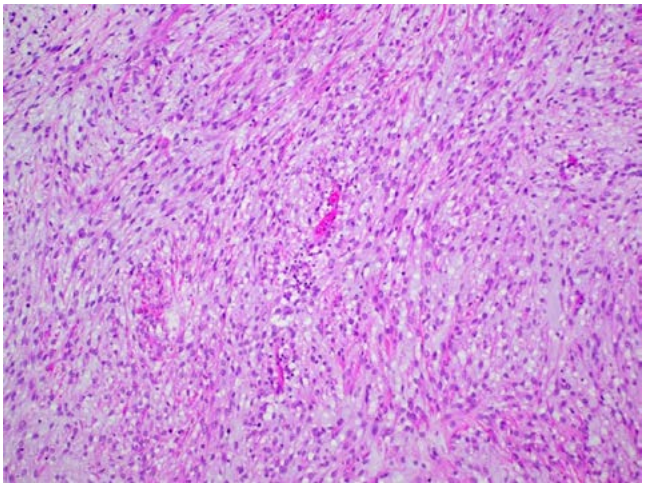

Figure 2: Monotonous spindled and fusiform cells are arranged haphazardly and in short fascicles, within a myxoid matrix (Haematoxylin and Eosin, 100x magnification)

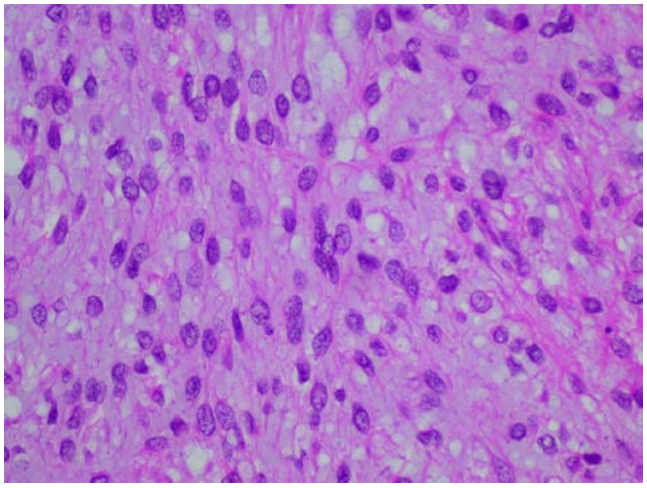

Figure 3: High-power magnification reveals spindled to fusiform cells with round to ovoid nuclei, coarse chromatin, and inconspicuous nucleoli (Haematoxylin and Eosin, 400x magnification)

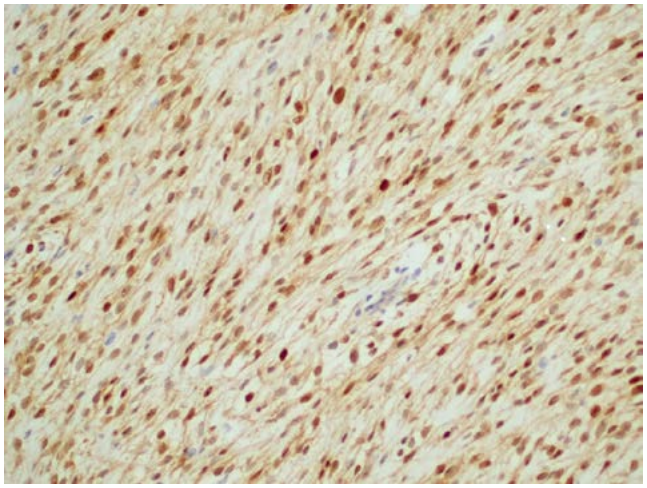

Figure 4: Cyclin D1 immunohistochemistry shows strong and diffuse nuclear positivity (200x magnification)

was later followed by carboplatinum and etoposide combined with gonadotropin-releasing hormone (GnRH) blockade. At most recent imaging, eight months after last surgery, there was stable disease.

Discussion

Endometrial stromal tumours (EST) comprise a group of mesenchymal neoplasms of the uterus which bear some histological resemblance to endometrial stroma. Endometrial stromal nodule, low-grade (LG) ESS, high-grade ESS and undifferentiated uterine sarcoma fall within this group.[1] HG ESS was first recognised by Kurihara et al. in 2008.[2] Several molecular subgroups of HG ESS have emerged over the past decade. Lee et al. described the first of these in 2012, harbouring a t(10;17) leading to *YWHAE-NUTM2A/B* fusion.[4] Recently, a novel group of HG ESS harbouring alterations in the BCL6 transcriptional corepressor gene (*BCOR*) have been described by two groups.[5-8] These genetic aberrations comprise both *ZC3H7B-BCOR* fusion, and less commonly, *BCOR* internal tandem duplications (ITD) in the last exons of the gene.[9,10] *BCOR* plays a role in epigenetic silencing via the polycomb repressive complex 1 and its role in cancer is being increasingly recognised. Aldera and Govender have provided a state-of-the-art summary of this gene and its role in neoplasia.[11]

BCOR-related ESS is a pathologically distinct group of tumours which should be separated from the *YWHAE-NUTM2A/B* group and other endometrial stromal tumours. In the largest case series to date, Lewis et al. describe the clinicopathological features of 17 cases.[6] These tumours occurred at a median age of 54 (range 28–71) years. FIGO Stage III disease was common (41%) and lymph node metastases were present in two of the five patients who underwent lymph node dissection at the time of initial surgery. Clinical follow up data was only available for five of the patients (two with Stage III and three with Stage I disease), all of which developed recurrences.

Histologically, BCOR-related ESS show relatively uniform ovoid to spindled cells which are arranged haphazardly or in fascicles and contain a variably myxoid stroma. The monotonous nature of the neoplastic cells, which is characteristic of translocation associated sarcomas, is a clue to the diagnosis. Mitotic figures are typically brisk but may be infrequent, and necrosis is often present. Immunohistochemistry has a role in establishing the diagnosis. BCOR-related ESS typically shows diffuse positive staining with CD10 (although it may be limited) and may focally express muscle markers such as SMA and h-caldesmon but is usually negative for desmin. Cyclin D1 is typically strongly and diffusely positive (unlike LG ESS). *BCOR* immunohistochemistry is also typically diffusely positive (with variable intensity) in a subset of *BCOR* fusion positive tumours, and strongly and diffusely positive in tumours harbouring *BCOR* ITD.[9] Cytogenetic and molecular techniques such as fluorescence in situ hybridisation (FISH) or NGS may be used to demonstrate gene fusion. *BCOR* ITD can be detected by Sanger or RNA sequencing methods.

It is important to distinguish these tumours pathologically from LG ESS and other mesenchymal tumours such as myxoid leiomyosarcoma. The latter may show considerable histological and immunohistochemical overlap with HG ESS. Typically, LG ESS comprises oval cells with no atypia which are concentrically arranged around arborising vessels (resembling endometrial spiral arterioles). These tumours are immunoreactive with CD10, ER and PR, and negative for cyclin D1 and *BCOR*. *JAZF1-SUZ12* fusions are typical, but a subset harbour *PHF1* fusions with various partner genes and other rare gene fusions. LG ESS has a better prognosis than HG ESS. Most patients present with Stage I disease and have an excellent prognosis.[12] Myxoid leiomyosarcoma may resemble BCOR-related ESS very closely, comprising spindled cells within a myxoid stroma. CD10, SMA, desmin, h-caldesmon and, rarely, cyclin D1 may show immunohistochemical positivity. *BCOR* immunohistochemistry is not specific for BCOR-related ESS or even HG ESS as a group, and may show positivity in up to 20% of myxoid leiomyosarcomas.[9] Recently, rearrangements in *PLAG1* have been found in up to 25% of myxoid leiomyosarcoma but have not yet been described in BCOR-related ESS.[13] Extensive sampling of the tumour and judicious use of a panel of antibodies is required to establish the correct diagnosis.

Limited data is available about the optimal treatment of BCOR-related ESS. However, it seems that most patients present with

advanced-stage disease, frequently develop locoregional recurrence and distant metastases, and response to adjuvant therapy is poor.[5,9,10] Early data from Momeni-Boroujeni et al. investigating RNA expression profiling has shown consistent overexpression of neurotrophic receptor tyrosine kinase 3 (*NTRK3*) and downregulation of oestrogen receptor 1 (*ESR1*) in their cohort of 11 HG ESS cases.[14] *NTRK3* overexpression raises the possibility of targeted therapies in these rare tumours. *ESR1* downregulation suggests that hormone therapy is less of an option for these patients, as opposed to LG ESS which are known to be responsive to hormone therapy. Further studies are required to fully delineate the genetic underpinnings of these unusual tumours, which may hopefully provide evidence for novel or targeted therapeutic strategies.

Conclusion

BCOR-rearranged ESS is a recently recognised group of malignant mesenchymal neoplasms of the uterus, which is prone to locoregional recurrence and has a poor prognosis. Awareness of this uncommon entity, recognition of the typical histological features, and the use of appropriate immunohistochemical and molecular techniques are important to distinguish this tumour from its pathological mimics and enable accurate and timely diagnosis.

Conflicts of interest

The authors declare no conflicts of interest.

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Ethical approval

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ORCID

AP Aldera https://orcid.org/0000-0002-9615-1692
S Chiang https://orcid.org/0000-0001-9698-0936
M Snuderl https://orcid.org/0000-0003-0752-0917
G Jour https://orcid.org/0000-0001-8916-8966
MH Botha https://orcid.org/0000-0002-6046-1453

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