Non-fusion mutations in endometrial stromal sarcomas: what is the potential impact on tumourigenesis through cell cycle dysregulation?

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► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/jclinpath-2020-206432).

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Received 4 February 2020
Revised 30 March 2020
Accepted 23 April 2020
Published Online First 8 May 2020

To cite: Patel SB, McCormack C, Hodge JC. *J Clin Pathol* 2020;**73**:830–835.

ABSTRACT

Targeted next-generation sequencing using the 50-gene Ion AmpliSeq Cancer Hotspot Panel v2 identified two significant point mutations in endometrial stromal sarcomas (ESS). Case 1 is a uterine mass from a quadragenarian woman with a karyotype lacking any known ESS rearrangements but demonstrated to have a *CTNNB1*-activating mutation (c.133T>C, p.[Ser45Pro]). Analysis of a uterine mass from case 2, a sexagenarian woman, revealed biallelic *CDKN2A*-inactivating mutations (c.172C>T, p.[Arg58Ter] and a deletion). Break-apart studies to identify *YWHAE*, *JAZF1* and *PHF1* rearrangements were negative in both tumours. We propose a model in which these point mutations may affect cell proliferation, converging at Wnt signalling and G1-S checkpoint control, that independently or in concert with a rare gene fusion result in ESS tumour development or progression.

INTRODUCTION

Endometrial stromal tumours are rare neoplasms of the female genitourinary tract characterised by recurrent gene fusions involving *JAZF1* or *PHF1* in low-grade endometrial stromal sarcomas (ESS) and endometrial stromal nodules (ESN) or *YWHAE* in high-grade ESS. While recurrent gene fusions are diagnostically useful features of these tumours, a significant minority lack such rearrangements.[1–6] The small subset of ESS with no detectable fusions may reflect insufficient testing sensitivity due to low prevalence fusions or variable fusion partners, or may represent a distinct molecular subgroup. It has been suggested that, unlike fusions, small nucleotide variants (SNVs) are not likely drivers of ESS based on finding only a few affected cancer genes with alterations outside of established cancer hotspots. However, this conclusion was derived from whole exome sequencing of only three ESS tumours that were predetermined to harbour fusion genes.[7] Thus, whether SNVs are significant drivers or have other functions in ESS lacking common gene fusions is an area that remains to be addressed.

Through targeted next-generation sequencing (NGS) in ESS, we identified one case with a well-established *CTNNB1*-activating mutation and a second case with biallelic *CDKN2A*-inactivating mutations. SNVs in *CTNNB1* are of interest because nuclear accumulation of its encoded protein catenin β1 has been observed in the majority of ESS, although no catenin β1 mutations were detected in 25 low-grade ESS[7–9] or in 8 undifferentiated uterine/endometrial sarcoma cases.[7–9] In contrast, a catenin β1 p.Ser33Asn mutation was identified in 1 of 10 ESN cases,[8 9] while the catenin β1 mutation p.Thr41Ala was found in one of eight ESS cases[10] (http://www.cbioportal.org/genie/index.do, accessed on 13 January 2018). Both of these reported that catenin β1 alterations are stabilising, but it is not known whether the associated tumours also harboured fusion genes. Our results raise the possibility that SNVs of *CNNTB1* and *CDKN2A* may play a role in ESS tumourigenesis that could be independent of gene fusions, potentially through perturbation of the cell cycle.

CLINICAL SUMMARY

Case 1

A quadragenarian woman with a history of uterine leiomyomas presented with sharp, intermittent left lower quadrant pain and 4 months of menometrorrhagia. Office ultrasound was remarkable for a left adnexal mass, and she was referred to the emergency department. CT scan at hospital admission showed bilateral adnexal masses concerning for malignancy and peritoneal carcinomatosis. She subsequently underwent dilatation and curettage, with intraoperative frozen section demonstrating a spindle cell lesion resulting in conversion to a diagnostic laparotomy. Multiple peritoneal nodules were appreciated. Frozen section of an omental mass was consistent with ESS, and a total abdominal hysterectomy with bilateral salpingo-oophorectomy was performed.

Case 2

A sexagenarian woman with a history of uterine leiomyomas presented with 6 months of progressive right lower quadrant pain and unintended weight loss. Office ultrasound demonstrated significant increase in the size of her fibroids compared with the previous year. Pelvic examination was remarkable for an enlarged and immobile nodular uterus and a palpable nodular anterior vaginal mass of approximately 10 cm in greatest dimension. MRI was concerning for a sarcoma, and CT showed bilateral pulmonary nodules, hepatic mass, lytic bone lesions and peritoneal carcinomatosis. She subsequently underwent a radical hysterectomy with bilateral salpingo-oophorectomy. Intraoperative findings included a 16 cm nodular uterus, peritoneal nodules, dense adhesions and multiple enlarged pelvic lymph nodes.

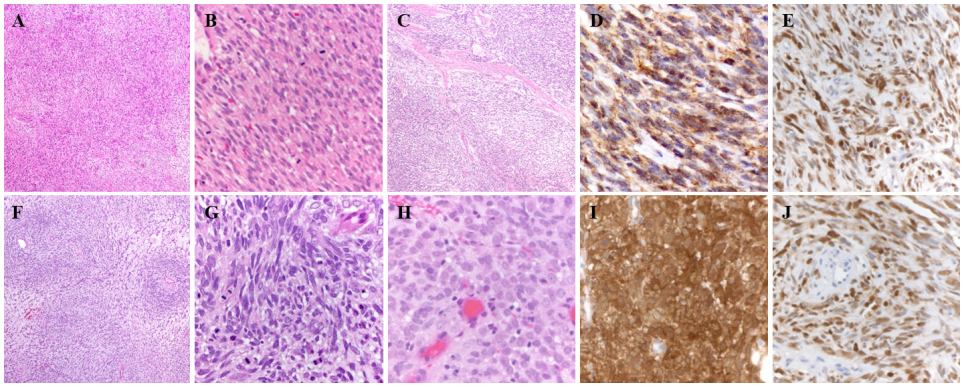

Figure 1 The tumour in case 1 (top panel) showed spindled cells in fascicular configuration (A) and numerous mitotic figures (B). Expanses of myxoid change were present (C). The tumour in case 2 (bottom panel) shows a densely cellular spindle cell neoplasm in fascicular and whorled configuration and areas of myxoid change (F). Nuclear atypia and mitotic figures are seen at high power (G). Epithelioid/rhabdoid features were seen focally (H). Both tumours showed strong nuclear and cytoplasmic β-catenin (D, I) and nuclear cyclin D1/BCL1 (E, J) immunoreactivity throughout the tumour.

Both patients were discharged after uneventful recovery. Follow-up is not available as their care was transferred to an outside hospital.

MATERIALS AND METHODS

Approval with waiver of consent was obtained from the Cedars-Sinai Medical Center institutional review board.

Histological and immunohistochemical staining

Surgical pathology reports and H&E and immunohistochemical stained slides were reviewed. Immunohistochemical studies performed on one or both cases included antibodies against catenin β1 (14; Cell Marque, 1:25), CD10 (56C6; Leica Biosystems, 1:100), KIT (Rabbit Polyclonal; Dako, 1:100), oestrogen receptor (SP-1; Ventana, 1:100), progesterone receptor (ie, 2; Ventana, 1:100), cyclin D1 (SP-4; Cell Marque, 1:100), actin (Alpha AM-1; Leica Biosystems, 1:200), keratin (AE1/AE3; Leica Biosystems, 1:100), myogenin (MYO18; Leica Biosystems, 1:100), S100 (16/F5; Leica Biosystems, 1:200) and desmin (DE-R- 11; Leica Biosystems, 1:200).

Genetic analysis

For NGS, H&E slides were reviewed to outline the target region and estimate tumour purity. Genomic DNA extraction, sequencing and variant analysis was performed as previously described.[11] In brief, DNA was extracted from unstained tissue sections with the QIAcube (Qiagen, Germany). The libraries were prepared with the 50-gene AmpliSeq Cancer Hotspot Panel v2 and run on the Ion Torrent Personal Genome Machine (Thermo Fisher Scientific). All high-confidence pathogenic variants were confirmed by bidirectional standard Sanger sequencing.

Chromosome G-banded analysis for case 1 was completed according to standard methods. Break-apart fluorescence *in situ* hybridisation (FISH) studies for both case 1 and case 2 using *YWHAE*, *PHF1* and *JAZF1* rearrangements were performed as previously described.[12]

RESULTS

Histopathological and immunohistochemical findings

The specimen for case 1 included an enlarged uterus with a 6.5 cm mass situated at the corpus and invading into the myometrium. H&E-stained sections showed a cellular neoplasm composed of spindled cells arranged in fascicles and prominent spiral arterioles (figure 1A). Spindled cells were reminiscent of endometrial stromal cells and had scant to modest oeosinophilic cytoplasm and elongated nuclei with fine uniform chromatin (figure 1B). Areas of myxoid stroma were noted throughout the tumour (figure 1C). There were >60 mf (mitotic figures)/10 HPF (high-power field) and areas suspicious for angiolymphatic invasion. Involvement of the omentum, urinary bladder, pelvic wall and large and small bowel was histologically confirmed. Tumour cells were negative for CD10, oestrogen receptor, progesterone receptor, actin, desmin, myogenin, keratin AE1/AE3 and S100, and positive for KIT (diffuse) and cyclin D1 (strong/diffuse; figure 1D). Catenin β1 showed strong and diffuse nuclear and cytoplasmic staining (figure 1E). The patient was diagnosed with high-grade ESS, although epithelioid cells were not present, and staged as pT4NxM1 (table 1).

The specimen for case 2 included a 16 cm nodular uterus with a 10.5 cm mass centred at the uterine corpus and invading the lower uterine segment, myometrium and serosa. H&E-stained sections showed highly cellular proliferation of spindled cells

Table 1 Histological and genetic features of endometrial stromal sarcoma cases

Clinical/histological				Immunohistochemistry			Sequencing				Cytogenetics			
Age	Grade	MF/HPF	Pathologic stage	CD10	Catenin β1	Cyclin D1	Gene	cDNA change	Protein change	VAF (%)	*YWHAE* FISH	*PHF1* FISH	*JAZF1* FISH	Karyotype
Case 1														
40s	High	60/10	T4NxM1	–	N/C	+	CTNNB1	133T>C	Ser45Pro	43	–	–	–	48,XX,+1,+1,i(1)(q10)x2[11]/46,XX[5]
Case 2														
60s	High	50/5	T4N1M1	+	N/C	+	CDKN2A	172C>T	Arg58Ter	79	–	–	–	Not assessed

cDNA, complementary DNA; FISH, fluorescence in situ hybridisation; MF/HPF, mitotic figures/high-power field; N/C, nuclear and cytoplasmic staining; VAF, variant allele frequency.

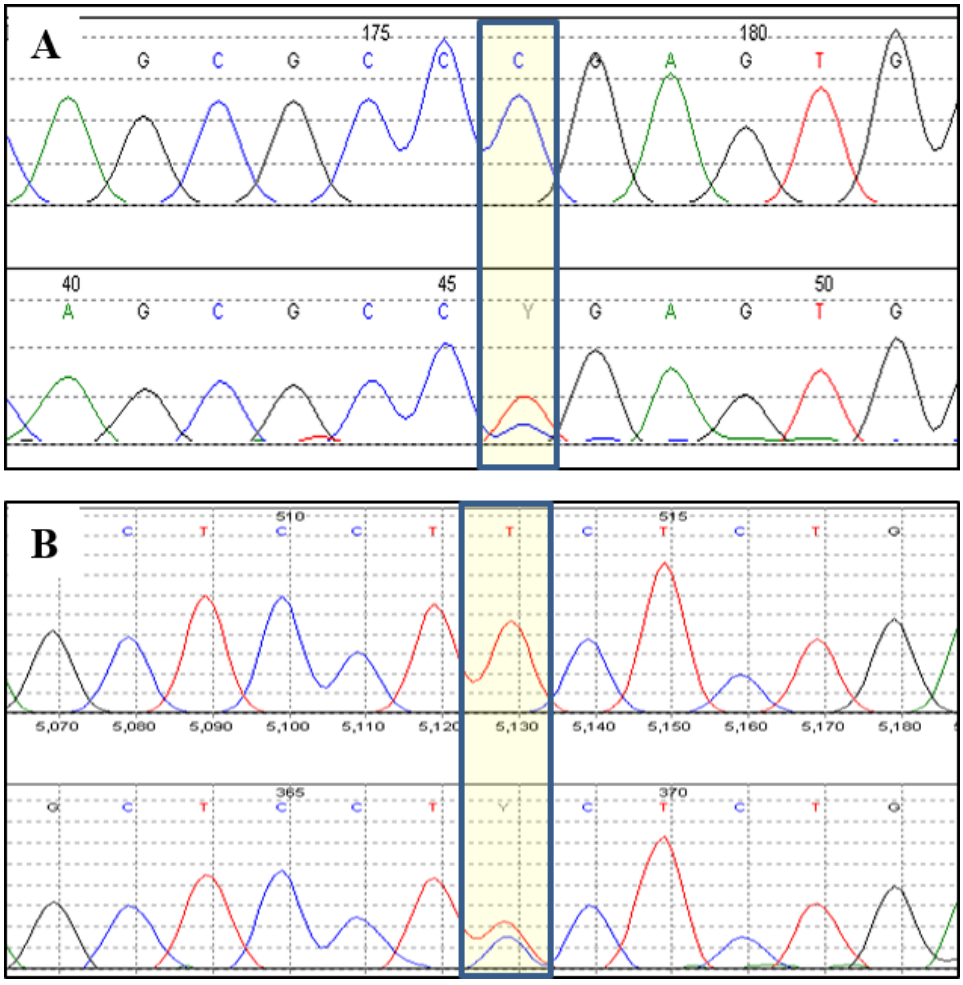

Figure 2 Genetic features of endometrial stromal sarcomas. Sanger sequencing confirmed the molecular alterations (A) *CTNNB1* c.133T>C and (B) *CDKN2A* c.172C>T discovered by next-generation sequencing in the tumours in case 1 and 2, respectively. Each electropherogram displays the reference sequence on top and the patient tumour sample sequence on the bottom.

arranged in fascicular and whorled configuration and expanses of myxoid stroma (figure 1F). Spiral arterioles with perivascular cuffing were prominent. Cells exhibited scant oeosinophilic cytoplasm and elongated hyperchromatic nuclei. Nuclear atypia and MF were seen at high power (figure 1G). There were >50 mf/5 HPF and angiolymphatic invasion was extensive. Epithelioid/rhabdoid cytological features were noted focally in the primary and metastatic tumour (figure 1H). Tumour cells were negative for desmin, oestrogen receptor, progesterone receptor, actin, keratin AE1/AE3 and KIT, and positive for CD10 (strong/diffuse) and cyclin D1 (moderate to strong/diffuse; figure 1I). Catenin β1 showed strong and diffuse nuclear and cytoplasmic staining (figure 1J). Involvement of the small and large bowel, urinary bladder, one ovary and multiple lymph nodes was histologically confirmed. The patient was diagnosed with high-grade ESS and staged as pT4N1M1 (table 1).

Molecular and cytogenetic findings

In both cases, the tumour cellularity in the macrodissected region used for sequencing was estimated at 85%. In case 1, a *CTNNB1* (catenin β1 or β-catenin) c.133T>C (p.[Ser45Pro]) mutation was detected at a variant allele frequency of 43%, suggestive of a clonal heterozygous mutation (table 1). In case 2, a *CDKN2A* (cyclin-dependent kinase inhibitor 2A or p16/INK4a) c.172C>T (p.[Arg58Ter]) mutation was identified at a variant allele frequency of 79%, indicating a concurrent deletion of the wild-type allele (table 1). Both are known hotspot mutations (online supplementary table 1) and were confirmed by Sanger sequencing (figure 2A,B). Break-apart FISH for *YWHAE*, *PHF1* and *JAZF1* loci showed two fused red and green signals within normal limits, indicating an absence of rearrangements involving these genes in both tumours (figure 3A–F). Consistently, case 1 had the karyotype 48,XX,+1,+1,i(1)(q10)x2[11]/46,XX[5] with no evident translocations suggestive of *YWHAE*, *PHF1* or *JAZF1* rearrangement (figure 3G).

The characterisation of both tumours as high-grade ESS is based on integrating the above morphological and genetic findings with the current WHO classification scheme,[13] which is further described (see online supplementary text).

DISCUSSION

The majority of ESS are characterised by recurrent gene fusions.[6] Neither of the ESS presented here had detectable fusions involving the most commonly involved genes by FISH. While the karyotype in case 1 was not suggestive of those or other low prevalence fusions, rearrangements can be cytogenetically cryptic. This tumour did have an isochromosome 1q, which appears to be a recurrent but non-specific alteration in ESS.[6] Rather than a common gene fusion, these tumours had hotspot mutations in established cancer genes, *CTNNB1* or *CDKN2A*.

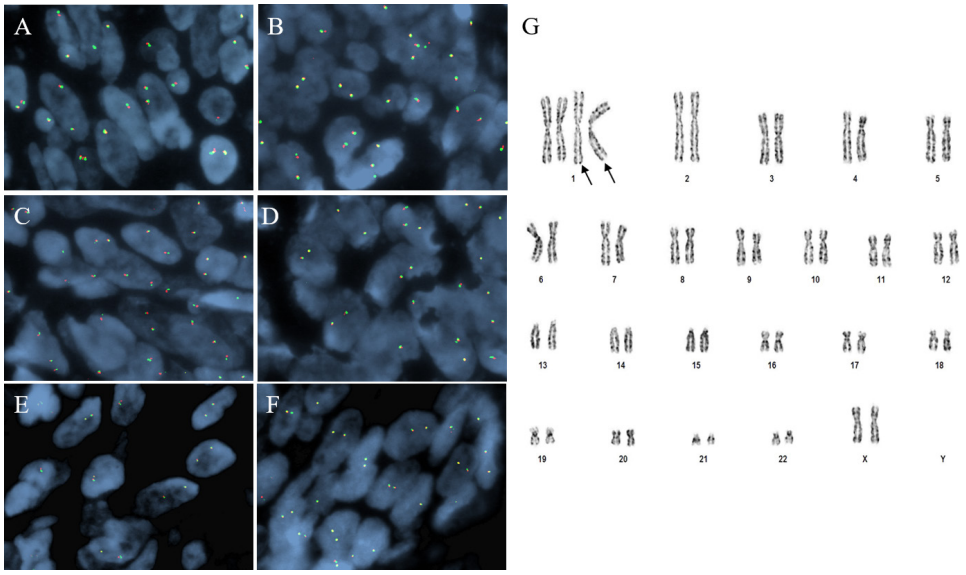

Figure 3 Cytogenetic features of endometrial stromal sarcomas (ESS). Break-apart fluorescence *in situ* hybridisation for *JAZF1* (A, B), *YWHAE* (C, D) and *PHF1* (E, F) showed normal results in the tumours from case 1 (left) and case 2 (right). Representative karyogram of the tumour in case 1, demonstrating absence of any translocations classically associated with ESS and presence of two copies of an isochromosome 1q as denoted by arrows (G).

Activating catenin β1 mutations are usually primary oncogene drivers (ie, mutually exclusive of other oncogene alterations) across various tumours, such as colorectal cancer[14] and hepatoblastomas.[15] In contrast, mutations in *CDKN2A* typically occur alongside primary oncogene drivers, like for other tumour suppressors. Thus, case 2 may have an oncogene driver that was not detected by our analysis, whereas for case 1 the catenin β1 mutation more likely represents a primary driver.

The activating mutation in case 1, catenin β1 p.[Ser45Pro], is associated with nuclear and/or cytoplasmic catenin β1 accumulation.[15–19] In case 2, the mutation in *CDKN2A*, encoding p16/INK4a, results in the truncation of the protein and has experimentally been characterised as a loss-of-function alteration.[20] *CDKN2A* mutations have not been detected in the 14 ESS cases analysed.[7 10 21]

Mutations in *CTNNB1* or *CDKN2A* may promote ESS tumourigenesis by affecting a common cell cycle regulatory pathway. In the physiological resting state, catenin β1 is primarily present at the plasma membrane and any free protein is phosphorylated and rapidly degraded (figure 4A). Normally, in the presence of Wnt signals, catenin β1 phosphorylation is inhibited resulting in the accumulation and nuclear import of catenin β1 (figure 4B).

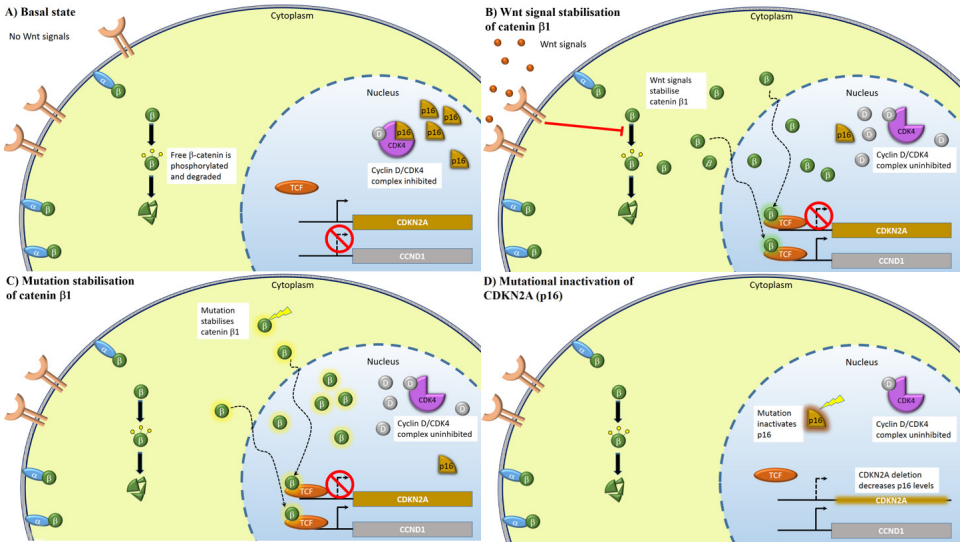

Figure 4 Potential tumourigenic mechanism of *CTNNB1* and *CDKN2A* mutations in endometrial stromal sarcoma (ESS) cases. (A) In the basal state, cytoplasmic catenin β1 is phosphorylated, ubiquitinylated and rapidly degraded, with only the membrane-bound form detectable. (B) Stabilisation occurs in the presence of (B) Wnt signals or (C) activating alterations, such as the catenin β1 mutation in case 1, leading to catenin β1 accumulation, nuclear translocation and T-cell factor (TCF) dimerisation. The dimeric transcription factor downregulates *CDKN2A* (encoding p16) and upregulates *CCND1* (encoding cyclin D1). (D) Decreased p16 activity may also result from loss-of-function mutations in the *CDKN2A* gene, as occurred in case 2. Ultimately, activation of catenin β1 and/or decreased p16 results in release of cyclin D/CDK4 inhibition, passage through the G1-S checkpoint and cell proliferation (not shown).

In the nucleus, catenin β1 then dimerises with T-cell factor (TCF) and activates/represses Wnt target genes, some of which participate in cell cycle regulation.[22] The expression of one such gene, cyclin D1 (*CCND1*), encoding an allosteric regulator of CDK4 required for passage through the G1-S checkpoint, is frequently upregulated in ESS. Mutations in catenin β1 can also result in catenin β1 stabilisation (figure 4C), as was exemplified by the *CNNTB1* mutation in case 1 with associated catenin β1 nuclear accumulation and cyclin D1 overexpression.

Cell cycle dysregulation may also be promoted through loss-of-function mutations in p16/INK4, an inhibitor of cyclin D/CDK4 by TCF/β-catenin[23] (figure 4D). Indeed, stabilising mutations of β-catenin in melanocytes resulting in the downregulation of p16 expression bypassed the requirement for *CDKN2A* mutations in melanoma mouse models.[23] In human melanomas, *CDKN2A* and *CTNNB1* mutations are largely mutually exclusive, suggesting that either pathway may contribute to tumourigenesis and/or tumour progression[24] (TCGA, Provisional dataset, http://www.cbioportal.org/, accessed on 10 June 2017).

While *CDKN2A* and *CTNNB1* mutations could represent primary drivers in ESS tumourigenesis, other possibilities need to be considered. First, because our analysis does not exclude very rare known alterations in ESS (eg, *BCOR* fusion to *ZC3H7B* or internal tandem duplication and MBTD1/CXorf67 fusion)[25 26] or currently undiscovered fusions, it is possible that *CDKN2A* and *CTNNB1* mutations may only cooperate with an undetected fusion driver for malignant transformation. Similar to ESS, *CTNNB1* mutations are present in a small but significant minority of another tumour type driven by recurrent fusions, synovial sarcomas; catenin β1 accumulates in many of these tumours even in the absence of discernible *CTNNB1* mutations.[27] In addition, blockade of Wnt signalling prevents SSX/SS18-fusion positive tumour development in animals.[27] Similarly, the defining translocation of follicular lymphoma, t(14;18), is prevalent in the healthy population, indicating that it is necessary but not sufficient for lymphomagenesis and that cooperation with other genetic or epigenetic alterations may be required.[28] Second, *CDKN2A* and *CTNNB1* mutations may be secondary events important for tumour survival and/or progression. Using synovial sarcoma again as a comparator, it has been reported that blockage of Wnt signalling inhibits growth of human synovial sarcoma cell lines.[27] Finally, it is possible the detected mutations have no biological effect, although their known oncogenic role in other tumour types makes this an unlikely possibility.

In summary, we present two cases of ESS that lack common gene fusions and instead have hotspot point mutations in known cancer genes (*CTNNB1* and *CDKN2A*). Given the frequent nuclear accumulation of catenin β1, cyclin D1 upregulation and p16 downregulation, these mutations could potentially represent mutually exclusive alternative initiating or cancer progression events in a small subset of ESS that either lack fusions or have rare fusions.[8 29 30] The *CTNNB1* and *CDKN2A* mutations may act through a common pathway involving cell cycle dysregulation. We emphasise that much remains to be learned about these rare tumours and further examination of those lacking the common fusion genes is necessary to elucidate the full spectrum of potential significant events.

Correction notice This article has been corrected since it appeared Online First. In the table, Karotype column, Grade 1 row has been reformatted.

Handling editor Mona El-Bahrawy.

Contributors SBP and JCH contributed to the conception and design of the study, data analysis and production of figures and manuscript text. CM contributed to data acquisition, production of figures and review of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES

1 Ali RH, Rouzbahman M. Endometrial stromal tumours revisited: an update based on the 2014 who classification. *J Clin Pathol* 2015;68:325–32.
2 Hrzenjak A. JAZF1/SUZ12 gene fusion in endometrial stromal sarcomas. *Orphanet J Rare Dis* 2016;11:15.
3 Conklin CMJ, Longacre TA. Endometrial stromal tumors: the new who classification. *Adv Anat Pathol* 2014;21:383–93.
4 Lee C-H, Nucci MR. Endometrial stromal sarcoma--the new genetic paradigm. *Histopathology* 2015;67:1–19.
5 Horng H-C, Wen K-C, Wang P-H, *et al*. Uterine sarcoma part II-Uterine endometrial stromal sarcoma: the tag systematic review. *Taiwan J Obstet Gynecol* 2016;55:472–9.
6 Micci F, Gorunova L, Agostini A, *et al*. Cytogenetic and molecular profile of endometrial stromal sarcoma. *Genes Chromosomes Cancer* 2016;55:834–46.
7 Choi YJ, Jung S-H, Kim MS, *et al*. Genomic landscape of endometrial stromal sarcoma of uterus. *Oncotarget* 2015;6:33319–28.
8 Jung C-K, Jung J-H, Lee A, *et al*. Diagnostic use of nuclear beta-catenin expression for the assessment of endometrial stromal tumors. *Mod Pathol* 2008;21:756–63.
9 Kurihara S, Oda Y, Ohishi Y, *et al*. Coincident expression of beta-catenin and cyclin D1 in endometrial stromal tumors and related high-grade sarcomas. *Mod Pathol* 2010;23:225–34.
10 AACR Project GENIE Consortium. Aacr project genie: Powering precision medicine through an international Consortium. *Cancer Discov* 2017;7:818–31.
11 Patel SB, Kadi W, Walts AE, *et al*. Next-Generation sequencing: a novel approach to distinguish multifocal primary lung adenocarcinomas from intrapulmonary metastases. *J Mol Diagn* 2017;19:870-880.
12 Hodge JC, Bedroske PP, Pearce KE, *et al*. Molecular cytogenetic analysis of Jazf1, PHF1, and YWHAE in endometrial stromal tumors: discovery of genetic complexity by fluorescence in situ hybridization. *J Mol Diagn* 2016;18:516–26.
13 Kurman RJ CM, Herrington CS, Young RH. *WHO Classification of Tumours of Female Reproductive Organs, World Health Organization Classification of Tumours*. Vol 6. Lyon, France: IARC Press, 2014.
14 Sparks AB, Morin PJ, Vogelstein B, *et al*. Mutational analysis of the APC/beta-catenin/TCF pathway in colorectal cancer. *Cancer Res* 1998;58:1130–4.
15 Huang H, Fujii H, Sankila A, *et al*. Beta-Catenin mutations are frequent in human hepatocellular carcinomas associated with hepatitis C virus infection. *Am J Pathol* 1999;155:1795–801.
16 Garcia-Rostan G, Tallini G, Herrero A, *et al*. Frequent mutation and nuclear localization of beta-catenin in anaplastic thyroid carcinoma. *Cancer Res* 1999;59:1811–5.
17 Miyaki M, Iijima T, Kimura J, *et al*. Frequent mutation of beta-catenin and APC genes in primary colorectal tumors from patients with hereditary nonpolyposis colorectal cancer. *Cancer Res* 1999;59:4506–9.
18 Rimm DL, Caca K, Hu G, *et al*. Frequent nuclear/cytoplasmic localization of beta-catenin without exon 3 mutations in malignant melanoma. *Am J Pathol* 1999;154:325–9.
19 Bonnet S, Gaujoux S, Launay P, *et al*. Wnt/β-catenin pathway activation in adrenocortical adenomas is frequently due to somatic CTNNB1-activating mutations, which are associated with larger and nonsecreting tumors: a study in cortisol-secreting and -nonsecreting tumors. *J Clin Endocrinol Metab* 2011;96:E419–26.
20 Parry D, Peters G. Temperature-Sensitive mutants of p16CDKN2 associated with familial melanoma. *Mol Cell Biol* 1996;16:3844–52.
21 Murray S, Linardou H, Mountzios G, *et al*. Low frequency of somatic mutations in uterine sarcomas: a molecular analysis and review of the literature. *Mutat Res* 2010;686:68–73.
22 Kimelman D, Xu W. Beta-Catenin destruction complex: insights and questions from a structural perspective. *Oncogene* 2006;25:7482–91.
23 Delmas V, Beermann F, Martinozzi S, *et al*. Beta-Catenin induces immortalization of melanocytes by suppressing p16INK4a expression and cooperates with N-ras in melanoma development. *Genes Dev* 2007;21:2923–35.
24 Cerami E, Gao J, Dogrusoz U, *et al*. The cBio cancer genomics portal: an open platform for exploring multidimensional cancer genomics data. *Cancer Discov* 2012;2:401–4.
25 Momeni-Boroujeni A, Chiang S. Uterine mesenchymal tumours: recent advances. *Histopathology* 2020;76:64–75.
26 Dewaele B, Przybyl J, Quattrone A, *et al*. Identification of a novel, recurrent MBTD1-CXorf67 fusion in low-grade endometrial stromal sarcoma. *Int J Cancer* 2014;134:1112–22.

27 Nielsen TO, Poulin NM, Ladanyi M. Synovial sarcoma: recent discoveries as a roadmap to new avenues for therapy. *Cancer Discov* 2015;5:124–34.
28 Janz S, Potter M, Rabkin CS. Lymphoma- and leukemia-associated chromosomal translocations in healthy individuals. *Genes Chromosomes Cancer* 2003;36:211–23.
29 Iwasaki S-ichi, Sudo T, Miwa M, *et al*. Endometrial stromal sarcoma: clinicopathological and immunophenotypic study of 16 cases. *Arch Gynecol Obstet* 2013;288:385–91.
30 Chang B, Lu LX, Tu XY, *et al*. [Endometrial stromal sarcoma: morphologic features and detection of JAZF1-SUZ12 and YWHAE FAM22 fusion genes]. *Zhonghua Bing Li Xue Za Zhi* 2016;45:308–13.