

# Frequent expression of KIT in endometrial stromal sarcoma with *YWHAE* genetic rearrangement

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**Endometrial stromal sarcomas with the *YWHAE-NUTM2A/B* genetic fusion characteristically contain high-grade round to epithelioid cell component that is strongly and diffusely cyclin D1-positive and it may or may not show an associated low-grade fibroblastic/myxoid cell component. They are clinically more aggressive than endometrial stromal sarcomas with the *JAZF1-SUZ12* genetic fusion and frequently demonstrate extrauterine extension at initial clinical presentation. In this setting, the tumor may be misdiagnosed as gastrointestinal stromal tumor. This study examines the expression of KIT and ANO1 in 14 *YWHAE-NUTM2A/B* tumors by immunohistochemistry. Staining localization was determined as membranous and/or cytoplasmic, and the staining intensity was assessed (negative, weak, moderate and strong). Of the 14 tumors, 6 contained only a high-grade round cell component, 2 only a low-grade fibroblastic component and 6 had both components in the slides evaluated. The high-grade round cell component displayed moderate to strong membranous/cytoplasmic KIT staining in all tumors (12 of 12). The low-grade fibroblastic cell component showed only weak cytoplasmic KIT staining in 3 of 8 tumors. In contrast, ANO1 was negative in all 14 neoplasms, irrespective of the component evaluated. Sanger sequencing analysis (exons 9, 11, 13 and 17) and Ampliseq Cancer Panel mutation screen (Ion Torrent) demonstrated no *KIT* mutations in three KIT-positive *YWHAE-NUTM2A/B* tumors. This study shows that the high-grade round cell component of *YWHAE-NUTM2A/B* endometrial stromal sarcoma consistently expresses KIT but lacks *KIT* hotspot mutations. KIT expression may represent a potential diagnostic pitfall in the evaluation of *YWHAE-NUTM2A/B* endometrial stromal sarcoma presenting with pelvic/abdominal mass, particularly in situations where its uterine origin is not definitive, and thus a panel of antibodies that includes ANO1 and cyclin D1 is necessary.**

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Endometrial stromal sarcoma with t(10;17)(q22;p13) resulting in *YWHAE-NUTM2A* or *YWHAE-NUTM2B* (*YWHAE-NUTM2A/B*) (previously known as *YWHAE-FAM22A* or *YWHAE-FAM22B*) genetic fusion is a recently described subset of endometrial stromal sarcoma classified as high-grade by

the upcoming World Health Organization (WHO) classification and exhibiting more aggressive clinical behavior when compared with classic low-grade endometrial stromal sarcomas.<sup>1–3</sup> Histologically, *YWHAE-NUTM2A/B* endometrial stromal sarcomas are characterized by round to epithelioid cells with scant to moderate faintly eosinophilic cytoplasm and high-grade cytologic features. The nuclei are larger in size and more irregular in contour compared with the tumor nuclei from classic low-grade endometrial stromal sarcoma and mitoses are readily identified (>10 mitoses per 10 high power fields). Also, characteristically, a fine arborizing

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capillary network is noted, which contributes to the nested appearance of the tumor. In half of the neoplasms, a second component of bland ovoid to spindle-shaped cells embedded in a fibroblastic to fibromyxoid background that morphologically and immunophenotypically resembles the fibroblastic/myxoid variant of low-grade endometrial stromal sarcoma is seen.<sup>4,5</sup> Immunohistochemically, the high-grade epithelioid component of *YWHAE-NUTM2A/B* endometrial stromal sarcoma is negative for CD10, estrogen receptor and progesterone receptor, and consistently expresses strong and diffuse nuclear cyclin D1,<sup>6</sup> whereas the low-grade fibroblastic component shows the opposite profile (akin to typical low-grade endometrial stromal sarcoma) being CD10, estrogen receptor and progesterone receptor positive with variable cyclin D1 nuclear staining (negative to weakly positive).

Patients with *YWHAE-NUTM2A/B* endometrial stromal sarcoma frequently have spread beyond the uterus at presentation. In these cases, the extrauterine disease may be extensive forming pelvic/abdominal mass(es) that may be responsible for the initial clinical signs/symptoms and the uterine origin can be overlooked. In such a scenario, an epithelioid gastrointestinal stromal tumor may be considered in the differential diagnosis, even more if the tumor is KIT (CD117, c-Kit) positive, as Amant *et al*<sup>7</sup> recently described in a *YWHAE-NUTM2A/B* endometrial stromal sarcoma by immunohistochemical evaluation. This potential diagnostic pitfall and our recent experience has prompted us to evaluate immunohistochemically the expression of the two frequently used diagnostic markers for gastrointestinal stromal tumors, namely KIT and ANO1 (also known as DOG1),<sup>8</sup> and to determine whether activating *KIT* mutation is present in KIT-expressing *YWHAE-NUTM2A/B* endometrial stromal sarcomas.

## Materials and methods

### Study Samples

Molecularly confirmed *YWHAE-NUTM2A/B* endometrial stromal sarcomas with available formalin-fixed, paraffin-embedded tumor block(s) from previously published series were included in this study.<sup>1,3</sup> Hematoxylin- and eosin-stained and -unstained slides that showed high-grade round/epithelioid cell component only,<sup>6</sup> low-grade spindle cell component only<sup>2</sup> or

both areas<sup>6</sup> were available for the study. This study was approved by the institutional research boards.

### KIT and ANO1 Immunohistochemistry

KIT and ANO1 expression was examined in 4  $\mu$ m whole tissue sections. KIT (Dako; A4502, 1:200, 30 min, room temperature) and ANO1 (Spring Bioscience; SP31, 1:200, 32 min, 37 °C) immunostaining were performed following heat-induced antigen retrieval using CC1 antigen retrieval buffer (Ventana Medical Systems, Tucson, AZ, USA). After incubation with the primary antibodies, sections were stained on the Ventana automated slide stainer (NEXES, Tucson, AZ, USA) using the Ventana diaminobenzidine (DAB) detection kit (Ventana Medical Systems). Membranous and cytoplasmic staining was evaluated, whereas intensity was categorized as negative, weak, moderate and strong. Internal stromal mast cell (for KIT) and/or KIT-positive gastrointestinal stromal tumor tissue (for KIT and ANO1) were used, with strong intensity being equivalent to mast cell and/or gastrointestinal stromal tumor control, moderate being relatively weaker but still easily appreciated at low magnification and weak being equivocal at low magnification.

### DNA Extraction and Sanger Sequencing of *KIT* Exons 9, 11, 13 and 17

Genomic DNA was extracted from formalin-fixed, paraffin-embedded tumor samples using Recover-All™ Total Nucleic Acid Isolation Kit for formalin-fixed, paraffin-embedded sample (Life Technologies) according to the manufacturer's protocol. The extracted DNA was quantified using NanoDrop spectrophotometer (Thermo Scientific). Polymerase chain reaction using primer sets for *KIT* exons 9, 11, 13 and 17 were performed using the extracted genomic DNA as described previously.<sup>9</sup> The primers are shown in Table 1.

### Ion Torrent Ampliseq Cancer Panel sequencing

For Ion Torrent analysis, extracted genomic DNA samples were further quantitated using the Qubit High Sensitivity DNA Assay Kit (Life Technologies). AmpliSeq Cancer Panel (Life Technologies) that covers 739 potential mutations in 46 genes including exonic regions of common somatic mutations in

**Table 1** Primer sequences used for *KIT* mutational analysis

<i>KIT</i> exon 9	Forward, 5'-ATTTATTTTCCTAGAGTAAGCCAGGG-3'; Reverse, 5'-ATCATGACTGATATGGTAGACAGAGC-3'
<i>KIT</i> exon 11	Forward, 5'-TCTGAGACTCACATAGCTTTGCATCC-3'; Reverse, 5'-CACAGAAAACCTATTGTTTTTCAGGTGG-3'
<i>KIT</i> exon 13	Forward, 5'-ATTTTGAAACTGCACAAATGGTCCTT-3'; Reverse, 5'-GCAAGAGAGAACAACAGTCTGGGTAA-3'
<i>KIT</i> exon 17	Forward, 5'-GCGTACTTTTGATTTTTATTTTTGGTG-3'; Reverse, 5'-AAATGTGTGATATCCCTAGACAGGATTT-3'

*KIT* (exons 2 and 9–18) and *PDGFRA* (exons 12, 14, 15 and 18) was used. Amplicon libraries were indexed using the Ion Xpress Barcode Adapter Kit and quantitated using the High Sensitivity DNA Chip on the Agilent BioAnalyzer (Agilent). Appropriate dilutions were performed based on amplicon concentration at the 130–210 bp range. Twenty pM of individual indexed amplicon libraries were pooled for emulsion PCR and sequencing on the Ion Torrent PGM platform using the 316 chip. Average base pair coverage was over 1000× for each tumor sample. Variant calling was performed using the Torrent Variant Caller v.2.2 against hg19 reference human genome.

## Results

### **KIT and ANO1 Immunostaining in *YWHAE-NUTM2A/B* Endometrial Stromal Sarcomas**

Of the 14 molecularly confirmed *YWHAE-NUTM2A/B* endometrial stromal sarcomas examined, the high-grade round/epithelioid cell component present in 12 cases displayed diffuse cytoplasmic/membranous KIT immunostaining (Figure 1 and Table 1). The staining intensity of the tumor cells ranged from moderate ( $n=8$ ) to strong ( $n=4$ ) (similar to that of the stromal mast cells in the adjacent myometrium) (Figure 1). The low-grade fibromyxoid component showed weak and typically patchy cytoplasmic KIT staining in three of eight neoplasms (Figure 2). ANO1 was negative in all 14 tumors examined, irrespective of the components evaluated (Table 2).

### **KIT Mutation Analysis**

Mutation analysis was performed in three of the four strongly KIT-positive *YWHAE-NUTM2A/B* endometrial stromal sarcomas with high-grade round/epithelioid cell component and available tumor material by Sanger sequencing. There were no mutations in exons 9, 11, 13 or 17 identified in any of the three tumors tested. AmpliSeq Cancer Panel screen showed only known single-nucleotide polymorphisms, including KIT M541L present at 49% frequency in one case,<sup>10</sup> but no candidate mutations (single-nucleotide variations, small insertions or deletions) involving *KIT* and *PDGFRA*. A known *TP53* somatic mutation (P190R)<sup>11</sup> was detected at very low frequency (2%) in the same case. No additional candidate mutations were identified involving other oncogenes/tumor suppressor genes surveyed by the panel.

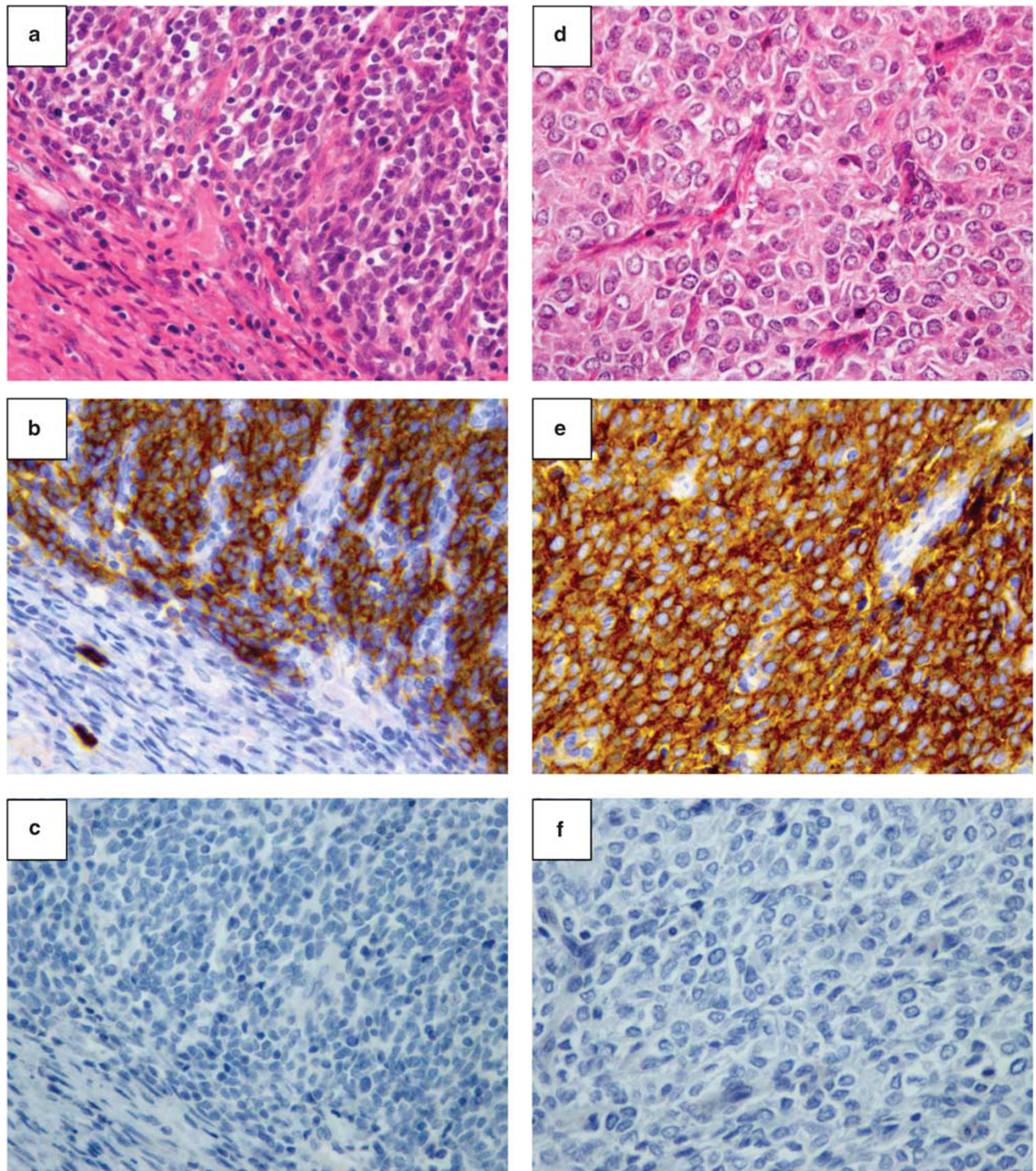
## Discussion

Although KIT is one of the standard immunostains used in the diagnosis of gastrointestinal stromal

tumors, this marker has been reported to be variably positive in other tumors including endometrial stromal sarcomas (including low- and high-grade tumors) and undifferentiated endometrial sarcomas. A low frequency of KIT immunopositivity, focal at most, had been reported in low-grade endometrial stromal sarcoma in six of eight prior studies (0–22%, average 5% in a total of 73 tumors tested).<sup>12–19</sup> In contrast, two studies reported a high frequency (50–82%) of KIT immunopositivity. One was a small study where only two tumors were examined, of which one tumor showed positive KIT staining.<sup>19</sup> The other study examined 39 low-grade endometrial stromal sarcomas and reported 82% (32 of 39) positivity in these tumors.<sup>20</sup> However, the positive tumors were also reported to show only very focal KIT immunostaining (<5% based on the representative KIT immunostaining image).<sup>20</sup> It is unclear what accounted for greater frequency of KIT positivity in this larger study as the primary antibody (Dako antibody for all) or the dilution used did not appear to be a contributing factor. Among the four studies evaluating KIT staining in high-grade endometrial stromal sarcomas/undifferentiated endometrial sarcomas, a total of 7 out of 18 tumors (39%) showed focal (<30%) positivity.<sup>12–14,16</sup> Several attempts have been made to correlate KIT positivity with prognosis in endometrial stromal sarcomas,<sup>17,19,21</sup> but no correlation has been found and these tumors (neither typical or those with *YWHAE-NUTM2A/B* fusion) do not show *KIT* mutations, as discussed below.

Similar to KIT, ANO1 (also known as DOG1) is another widely used diagnostic immunomarker for gastrointestinal stromal tumor, as its expression is observed in about 90% of these tumors.<sup>8</sup> Only one study to date examined its expression in low-grade endometrial stromal sarcomas, all 14 cases being negative.<sup>22</sup> However, it is important to note that a subset of uterine benign and malignant smooth muscle tumors and extrauterine uterine-type smooth muscle tumors (abdominal/retroperitoneal uterine-type leiomyoma, leiomyomatosis peritonealis disseminata) as well as other mesenchymal tumors including synovial sarcoma and chondroblastoma can show ANO1 immunopositivity;<sup>22–25</sup> hence, the expression of ANO1 is not restricted to gastrointestinal stromal tumors.

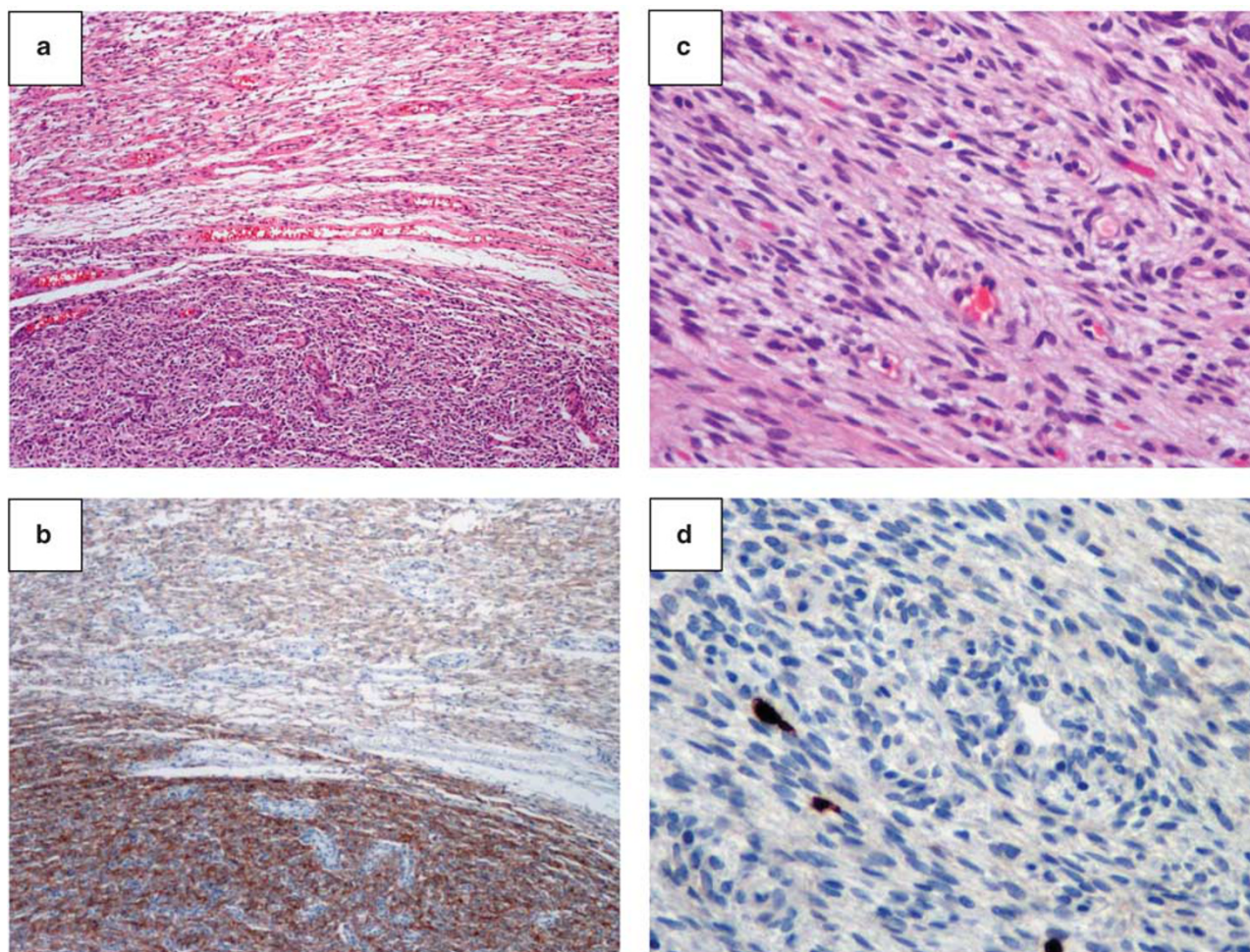
In the current study, we observed consistent and diffuse KIT positivity in the high-grade round/epithelioid cell component of *YWHAE-NUTM2A/B* endometrial stromal sarcomas. The intensity of staining was usually moderate, although strong staining intensity comparable to that of stromal mast cells (internal positive control) and typical KIT-positive gastrointestinal stromal tumors was encountered in a subset of cases as well. In contrast to the high-grade round/epithelioid cell component, the low-grade fibromyxoid areas displayed negative to weak KIT positivity. As *YWHAE-NUTM2A/B* endometrial stromal sarcoma frequently demonstrates



**Figure 1** KIT and ANO1 immunostaining of the high-grade round/epithelioid cell component of *YWHAE-NUTM2A/B* endometrial stromal sarcoma. Histologic features of the high-grade round cell component of an *YWHAE-NUTM2A/B* endometrial stromal sarcoma, with adjacent myometrium in the bottom left corner (a):  $\times 100$  magnification. The round cell component has KIT cytoplasmic/membranous immunostaining, with an intensity similar to that in mast cells in the adjacent myometrium (b):  $\times 100$  magnification and negative ANO1 immunostaining (c):  $\times 100$  magnification. Another *YWHAE-NUTM2A/B* endometrial stromal sarcoma with a high-grade epithelioid cell component (d):  $\times 400$  magnification showed diffuse cytoplasmic/membranous KIT immunostaining (e):  $\times 400$  magnification and negative ANO1 immunostaining (f):  $\times 400$  magnification.

extrauterine extension at the time of initial diagnosis with formation of pelvic/abdominal mass(es) and its uterine origin may not be apparent

by imaging, the finding of KIT positivity in the high-grade round/epithelioid cell component of *YWHAE-NUTM2A/B* endometrial stromal sarcoma



**Figure 2** KIT immunostaining of the low-grade ovoid/spindle cell component of *YWHAE-NUTM2A/B* endometrial stromal sarcoma. *YWHAE-NUTM2A/B* endometrial stromal sarcoma (a):  $\times 40$  magnification with admixed high-grade (lower half) and low-grade (upper half) components. The high-grade component showed moderate–strong KIT immunostaining, whereas the low-grade component showed weak KIT immunostaining (b):  $\times 40$  magnification. Another *YWHAE-NUTM2A/B* endometrial stromal sarcoma with low-grade spindle cell area (c):  $\times 200$  magnification shows negative KIT immunostaining, in contrast to the strong KIT immunopositivity of the stromal mast cells (d):  $\times 200$  magnification.

**Table 2** KIT and ANO1 immunostaining results in 14 *YWHAE-NUTM2A/B* endometrial stromal sarcomas

Histology	KIT positivity	ANO1 positivity
Pure high-grade (round/epithelioid cell)	6/6 <sup>a</sup>	0/6
Pure low-grade (ovoid/spindle cell)	0/2	0/2
Mixed high-grade and low-grade		
High-grade component	6/6 <sup>a</sup>	0/6
Low-grade component	3/6 <sup>b</sup>	0/6

<sup>a</sup>Moderate to strong cytoplasmic/membranous immunostaining.

<sup>b</sup>Weak and focal cytoplasmic immunostaining.

in a limited tissue sample (ie core biopsy) can result in its misdiagnosis as an epithelioid gastrointestinal stromal tumor. Our findings here substantiate the observation made by Amant *et al*<sup>7</sup> of a KIT-positive *YWHAE-NUTM2A/B* endometrial stromal sarcoma as well as Goh *et al*,<sup>26</sup> who also reported an

endometrial stromal sarcoma with epithelioid and low-grade spindle cell areas that was KIT positive in only the epithelioid component. The morphologic and immunophenotypic features described in that report are suggestive for being a *YWHAE-NUTM2A/B* endometrial stromal sarcoma. The finding of KIT positivity in *YWHAE-NUTM2A/B* endometrial stromal sarcoma is a potential diagnostic pitfall to be aware of, as it joins a growing list of tumors that can demonstrate KIT immunoreactivity, including dysgerminoma, renal cell carcinoma, mesothelioma, leiomyosarcoma, angiosarcoma, Ewing sarcoma, PEComa, angiomyolipoma, dedifferentiated liposarcoma, solitary fibrous tumor and melanoma,<sup>15,27–32</sup> all of which can occur as primary or metastatic tumor in the gynecologic tract and/or abdominal/pelvic soft tissue. It also underscores the importance of combining KIT with another immunomarker such as ANO1 in the evaluation of a suspected gastrointestinal stromal tumor in core biopsy samples.<sup>8</sup> Although KIT is consistently expressed in the

high-grade round/epithelioid cell component of YWHAE-NUTM2A/B endometrial stromal sarcomas, ANO1 is not expressed by these tumors. A KIT-positive and ANO1-negative immunoprofile in a suspected gastrointestinal stromal tumor should prompt a careful review of the radiologic (evaluating the uterus) and histologic features of the tumor, with possible reconsideration of the differential diagnosis and further molecular testing. More specifically, the findings of possible uterine origin based on radiologic correlation and/or a focal low-grade fibromyxoid component that is negative or weakly positive for KIT and positive for CD10, estrogen receptor and progesterone receptor would suggest the possibility of an YWHAE-NUTM2A/B endometrial stromal sarcoma. Cyclin D1 immunohistochemistry should be useful in these cases because YWHAE-NUTM2A/B endometrial stromal sarcoma consistently shows diffuse (>70%) and strong nuclear immunopositivity of the high-grade component.<sup>6</sup>

To further explore the potential of KIT as therapeutic target in YWHAE-NUTM2A/B endometrial stromal sarcomas, we interrogated KIT mutations in KIT-positive YWHAE-NUTM2A/B endometrial stromal sarcomas, and found no mutations involving KIT or other receptor tyrosine kinases including PDGFRA. In the absence of an activating mutation, the rationale for targeting YWHAE-NUTM2A/B endometrial stromal sarcomas with imatinib and/or other small-molecule inhibitors of receptor tyrosine kinases remains questionable. There was however an anecdotal KIT-positive high-grade endometrial stromal sarcoma (lacking demonstrable KIT/PDGRA mutation) that showed evidence of apparent response radiologically with tumor shrinkage and histologically with extensive tumor necrosis from adjuvant imatinib therapy.<sup>33</sup> It is unclear whether this tumor was in fact a YWHAE-NUTM2A/B endometrial stromal sarcoma or an undifferentiated endometrial sarcoma (lacking demonstrable genetic fusions). In addition to small-molecule inhibitors, treatment with anti-KIT antibody was recently shown to exhibit promising efficacy against gastrointestinal stromal tumor in *in vitro* and in xenograft model and it may also be considered as a potential therapy for other KIT-expressing tumors such as YWHAE-NUTM2A/B endometrial stromal sarcoma.<sup>34</sup> Interestingly, a known somatic missense TP53 was detected at very low frequency in an YWHAE-NUTM2A/B endometrial stromal sarcoma. The significance of this is unclear, although this may represent the development of a tumor subclone that has acquired a TP53 mutation.

In summary, we report consistent expression of KIT in the high-grade round/epithelioid cell component of YWHAE-NUTM2A/B endometrial stromal sarcoma, with negative to focally weak expression of KIT in the low-grade ovoid/spindle cell component. ANO1 expression was found to be absent immunohistochemically in both components and no

hotspot mutations involving KIT and PDGFRA were identified. This is a potential diagnostic pitfall that pathologists need to be aware of in the evaluation of pelvic/abdominal mass(s) in female patients. This pertains to both biopsy and surgical resection specimens, in which judicious application of a panel of diagnostic markers and thorough tumor samplings (of the resection specimen) are important to ensure the correct diagnosis.

## Disclosure/conflict of interest

The authors declare no conflict of interest.

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