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Endometrial/Endometrioid Stromal Tumors with Extensive Whorling and *CTNNB1* Translocation: A Report of Three Cases

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Abstract

Endometrial/endometrioid stromal tumors are rare and morphologically heterogenous, and their diagnosis may be challenging. We identified three endometrial/oid stromal tumors with identical and previously undescribed histologic features and herein report their morphologic, immunohistochemical, and molecular profiles.

Patients were 53-, 62-, and 79-year-old. Tumors were well-circumscribed, tan-yellow solid masses measuring 10.0, 11.0 and 18.7 cm, and were intramyometrial (n=2) or in the broad ligament (n=1). All showed small, tight whorls of epithelioid to slightly spindled tumor cells with minimal cytoplasm and negligible mitoses, multifocally associated with hyalinization and myxoid change set in a loose fibroblastic background with small, delicate vessels. This morphology was seen throughout in one tumor and in ~20% and 70% of the two others with the remaining areas showing sex cord-like differentiation.

Tumor cells expressed CD10 (3/3, 1 focal), calretinin (3/3 diffuse), WT1 (3/3 diffuse), ER (1/1, diffuse). RNA-sequencing was successful in one tumor and revealed a *GREB1-CTNNB1* in-frame fusion. All three tumors harbored a *CTNNB1* translocation by fluorescence *in situ* hybridization (FISH) correlating with nuclear β-catenin expression. Whole-genome DNA methylation analysis classified all three tumors within the low-grade endometrial stromal sarcoma reference class with flat copy number profiles.

One patient (79-year-old) died of unrelated causes two months after surgery and the other two were alive without disease after 13 and 75 months. We have described a rare subset of

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endometrial/oid stromal tumors with extensive whorling and *CTNNB1* translocation, expanding the morphologic and molecular spectrum of these neoplasms.

Keywords

Endometrial stromal tumor; *CTNNB1* ; Beta-catenin

Introduction

Endometrial/endometrioid stromal tumors are uncommon and morphologically heterogenous and their diagnosis may be challenging when they show variant morphology such, most commonly, as smooth muscle and sex cord-like differentiation [1-4] and less often fibromyxoid features [5] and pseudopapillae [6]. Herein, we describe three tumors, two endometrial stromal nodules, and one endometrioid stromal tumor within the broad ligament with features not previously reported, distinctive whorling of tumor cells set in a fibroblastic background and β-catenin pathway activation via *CTNNB1* translocation, with detailed characterization of their morphologic, immunohistochemical and molecular profiles.

Materials and Methods

Following approval by Massachusetts General Hospital institutional review board, three tumors were retrieved from the consultation files of the authors (R.H.Y. and E.O.). None of the cases had been previously reported. Clinical (patient age, symptoms at time of presentation, follow-up) and gross features were obtained from consultation correspondence.

An average of 16 H&E slides was examined (range 12-20). Pathologic features evaluated included location, size, borders, architectural patterns, presence of conventional endometrial stromal neoplasia, cytologic atypia, mitoses/10 high power fields (HPF) corresponding to 2.37 mm^2, vascularity, presence of necrosis or lymphovascular invasion.

One representative formalin-fixed and paraffin-embedded (FFPE) block of tumor was selected from each case and five-micron serial sections were obtained for immunohistochemical studies using β-catenin (Leica PA0083) antibody in three, CD10 (Leica PA0270), calretinin (Roche 790-4467), WT1 (Leica PA0562) smooth muscle actin (Leica PA0258) antibodies in two tumors. All studies were performed in accordance with the manufacturer's recommendations with appropriate controls.

All three tumors were subjected to RNA-sequencing at the Integrated Genomics Operation (IGO) at Memorial Sloan Kettering Cancer Center (MSK) and data analyzed using validated bioinformatics methods, as previously described [7]. Oncogenic/ fusion driver probability was defined using Oncofuse [8]. *CTNNB1* split-apart (5' orange, 3' green, Empiregenomics) fluorescence *in situ* hybridization (FISH) was performed using validated protocols at MSK's Molecular Cytogenetics Core [7]. At least 50 non-overlapping interphase nuclei with well delineated contours were analyzed for the presence of *CTNNB1* rearrangements.

Whole genome DNA methylation analysis was performed from FFPE extracted DNA using Illumina EPIC array using clinically validated protocols as described previously and data were analyzed by the DKFZ sarcoma classifier using Random Forest as previously described [9]. Calibrated score >0.9 is considered high confidence, while score between 0.3-0.9 is considered intermediate and may suggest low tumor cell content or other aberrations not included in the classifier. Copy number analysis was performed using the *conumee* package at New York University Langone Medical Center.

Results

The patients were 53, 62, and 79 years old. Two presented with postmenopausal bleeding and one with a pelvic mass. Both patients with uterine tumors underwent hysterectomy with bilateral salpingo-oophorectomy while the patient with the broad ligament tumor underwent complete excision of the mass. On gross examination, all three tumors were well-circumscribed, tan-yellow and solid measuring 10.0 (pelvic), 11.0 and 18.7 cm; the uterine tumors were intramural.

Microscopically, all tumors exhibited orderly arranged, small, tight, uniform whorls of epithelioid to slightly spindled bland small cells set in a loose fibroblastic background (Fig 1). The tumor cells had scant cytoplasm, round to oval nuclei with open chromatin, and variably visible tiny nucleoli (Fig 1c, 1d). Hyalinization and/or myxoid change were often noted within the whorls (Fig 1d). This morphology was present ranging from 20 to 100% of the sections examined. The background stroma was hypocellular with loose collagen, banal-appearing fibroblasts, and predominantly delicate small vessels (Fig 1b). Areas of hyalinization were focally present. This fibroblastic background differed in amount from tumor to tumor and also within the tumors, being less abundant if whorls were numerous and extensive when whorls were scant.

Sex cord-like differentiation was observed in the two uterine tumors comprising ~30% and 80%. In the former, a minor corded growth within the whorls transitioned to interanastomosing cords within a hyalinized background (Fig 2a). In the second tumor, sex cord-like differentiation was represented by cords, hollow tubules, nests, and trabeculae (in decreasing order of frequency) of epithelioid cells with round to irregularly shaped small nuclei, and variably prominent nucleoli set in a hyalinized stroma without a transition with the whorls (Fig 2b).

Mitotic activity was negligible in the whorls, sex cord elements, and background stroma. Ischemic but no tumor cell necrosis was present in two tumors and lymphovascular invasion was absent in all. Areas of conventional endometrial stromal neoplasia were not identified.

One patient with a uterine tumor (the 79-year-old) died of unrelated causes two months after surgery while the other two patients were alive and well 13 and 75 months following surgery.

All three tumors were CD10-positive; diffuse in both whorls and fibroblastic stroma in one (no sex cord elements in this tumor), extensive in whorls and focal in the background stroma in one, and only focal in both components in the third. Sex cord elements were present on

the block from only one of the tumors and were only minimally CD10 positive. Calretinin and WT1 showed positivity, predominantly in the whorls and to a lesser extent in the stroma. Sex cord-like areas showed extensive positivity for these two markers. Smooth muscle actin was positive in the stroma but negative in the whorls. Additional immunostains performed on one tumor without sex cord-like differentiation showed strong and diffuse ER and PR expression in the whorls and fibroblastic stroma and was negative for inhibin, HMB45, S100, BCOR, and CD34.

RNA-sequencing was successful in one tumor and revealed a *GREB1-CTNNB1* in-frame fusion with a driver probability of 99% (Fig 3a). The breakpoint was confirmed by RT-PCR (Fig. 3a). In this fusion, exons 1 – 23 of *GREB1* are fused to exons 4 – 16 of *CTNNB1.* FISH analysis using a *CTNNB1* break-apart probe confirmed the presence of the *CTNNB1* rearrangement and revealed *CTNNB1* translocation in all three neoplasms (Fig 3b). These findings correlated with diffuse nuclear β-catenin expression by immunohistochemistry (Fig 3c).

Using whole genome DNA methylation signatures and random forest classifier, all three tumors classified within the low-grade endometrial stromal sarcoma reference class by methylation analysis. The tumor with whorled architecture but without sex cord-like differentiation had a high calibrated score of 0.95 while the other two tumors showing whorls as well as sex cord-like differentiation had intermediate scores of 0.85 and 0.54, the latter showing whorled morphology in only 20% of the tumor. All tumors had flat copy number profiles.

Discussion

It has been appreciated largely in the past two decades that endometrial stromal tumors display many morphologic variations [2, 4] and may show smooth muscle, sex cord-like, glandular, myxoid/fibroblastic, papillary/pseudopapillary, bizarre cells, clear or oxyphilic cells, adipocytic, and rhabdomyoblastic differentiation [5, 6, 10-14]. Herein, we report three endometrial/oid stromal tumors with extensive whorling and fibromyxoid background, a novel subset of endometrial stromal tumors molecularly defined by *CTNNB1* translocation.

Despite the sporadic mention of myxoid and/or fibroblastic features in endometrial stromal tumors in multiple case series in the literature, the first large series was reported by Oliva et al. [5] describing 10 such examples. The tumors were remarkable for a prominent fibroblastic background (n=6, with 3 showing extensive hyalinization), myxoid matrix (n=2), or both (n=2). Despite all having small, arteriole-like vessels, only four showed focally conventional areas of endometrial stromal neoplasia and one tumor displayed extensive sex cord-like differentiation. They were classified as endometrial stromal tumors due to their location, growth pattern with tongue-like infiltration, presence of arterioles, and accompanying conventional stromal neoplasia.

Subsequently, Yilmaz et al. reported six primary and eight metastatic endometrial stromal sarcomas with fibromyxoid features representing 5 to 100% of the tumors at primary and 95% to 100% at metastatic sites [15]. Only two primary tumors showed a conventional

endometrial stromal component and one had sex cord-like differentiation. The authors also noted a shift in morphology between primary and metastatic tumors and between recurrences over time. Of note, none of the tumors in these two series showed the morphology reported in the cases reported herein.

The three tumors described herein, despite having a fibroblastic background similar to that described in prior studies, had a unique morphology with prominent and uniform whorling of tumor cells set in a fibroblastic background, a feature not previously reported to the best of our knowledge. The whorled morphology comprised 20, 70, and 100% of the slides examined while the remaining areas showed sex cord-like differentiation. Remarkably, these sex cord areas transitioned to cords within the whorls in one tumor, a finding that may suggest intermediate morphology sharing both fibroblastic and sex cord-like features.

Endometrial/oid stromal tumors are typically CD10 positive and all three tumors in this series were positive, two being diffuse and one focal although it has been reported that the fibroblastic variant of endometrial stromal tumors may be CD10-negative as noted in 2 of 12 tumors by Yilmaz et al [15]. WT1 and calretinin were positive in all three tumors in both whorled and sex cord-like foci, perhaps suggesting a shared differentiation. In addition to the morphologic and immunohistochemical findings, methylation studies provided further support for their classification as ESTs as they matched with low-grade endometrial stromal sarcoma reference class. Despite sharing unique morphologic features, they had different matching scores with the rate decreasing in tumors with less whorled component.

Many genetic alterations underlying ESTs have been reported to date. Rearrangements of *JAZF1, SUZ12, PHF1*, and *EPC1* have been recurrently identified, *JAZF1-SUZ12* fusion being the most common [1, 3, 11, 16]. In the largest study to date with 78 uterine ESTs exploring the frequency of known gene rearrangements in these tumors by FISH, they were identified in approximately 50-60% of ESTs, *JAZF1-SUZ12* fusion being present in 50% of ESNs and 33% of ESSs, followed by *PHF1, JAZF1* and *EPC1* fusions [16]. The study also included 3 endometrioid stromal tumors and all showed fusions, providing further evidence for a similar pathogenesis. Additionally, similar gene fusions have been detected in EST with variant morphology but to a lesser extent (67% vs 50%). Among tumors with variant morphology, 5/9 tumors with fibromyxoid features (all *JAZF1-SUZ12*) and 2/5 with sex cord-like differentiation (*JAZF1-SUZ12, EPC1-PHF1*) harbored known gene rearrangements. Overall, these findings suggest more studies are needed to identify additional genetic alterations in ESTs, especially those with variant morphology.

The tumors reported herein harbored a *CTNNB1* translocation confirmed with FISH and by RNA-sequencing in one tumor identifying *GREB1* as the fusion partner. The detected transcript consisted of the first 23 exons of *GREB1* and exons 4-16 of *CTNNB1*, leading to a truncated form of β-catenin without the 87 N-terminal amino acids that are involved in the protein degradation upon phosphorylation [17]. *CTNNB1* translocations or more specifically, *GREB1-CTNNB1* fusion, have not been previously reported in endometrial/oid stromal tumors. Furthermore, in our cases, tumor cells showed β-catenin nuclear expression, confirming the activation of this pathway. β-catenin expression has been previously evaluated in endometrial stromal tumors. In one study on β-catenin expression

in mesenchymal tumors, 4 of 10 ESSs showed high-nuclear positivity (>25% of tumor cells) among other tumor types including fibromatosis, solitary fibrous tumor, and synovial sarcoma [18]. Another study identified nuclear β-catenin expression in 2/2 of ESTs and 11/12 low-grade ESSs while endometrial stroma and leiomyomas were negative and only one of the 15 tumors tested showed a *CTNNB1* mutation (tumor not illustrated) [19]. These findings indicate that nuclear β-catenin expression may also be seen in ESTs independent of *CTNNB1* gene status. It is difficult to be certain whether the β-catenin pathway may play a role in the pathogenesis of endometrial stromal tumors, but our study provides evidence that β-catenin can be a driver in the pathogenesis of a very specific subset of these tumors.

A similar *GREB1-CTNNB1* transcript leading to the same truncated form affecting *CTNNB1* has been previously identified by Croce et al. in a tumor reported as a uterine tumor resembling an ovarian sex cord tumor (UTROSCT) [20]. A 70-year-old patient had a 10 cm, well-circumscribed, yellow, soft, fleshy uterine tumor, grossly, ruptured the ovarian serosa. Microscopically, the tumor was composed of epithelioid cells with negligible mitotic activity forming nests, trabeculae, and tubules in a fibroblastic/myxohyaline background. The tumor was diffusely positive for CD10, ER, PR and focally for WT-1, calretinin, Melan-A, desmin while it was negative for inhibin, caldesmon, and FOXL2. No areas of conventional endometrial stromal neoplasia were identified. The tumor recurred 17 months later with widespread pelvic spread and despite exenteration and aromatase inhibitors the patient developed lung metastases one year later. Figures from that case are reminiscent of the areas with sex cord-like differentiation in two of the cases in our series and it is possible that a minor endometrial stromal component with whorled morphology may not have been sampled for microscopic examination and, thus, we favor that these tumors may be related.

The major differential diagnosis includes UTROSCTs as they may also rarely show whorling as part of the sex cord architectural patterns [21]. UTROSCTs typically show an admixture of different sex cord patterns and often show admixed smooth muscle but lack the orderly and uniform arrangement of whorls and fibroblastic background seen in the tumors described herein. Molecularly, they are characterized by *ESR1, NCOA1/2/3* fusions and lack *CTNNB1* translocation. *GREB1*-rearranged uterine sarcomas may also be considered in the differential diagnosis, but they only show minimal sex cord-like differentiation, the overall morphology differs from the tumors described herein and additionally, the fusion partners do not include *CTNNB1* [22]. Endometrial stromal tumors with sex cord-like differentiation may enter in the differential diagnosis as the sex cord-like areas may closely overlap with the appearance seen in our tumors. However, the tumors herein lack conventional areas of endometrial stromal neoplasia which are the ones typically associated with sex cord-like differentiation [23]. Uterine plexiform tumorlets, in addition to epithelioid morphology, may rarely show whorl-like architecture; however, these tumors are very small and are extensively positive for smooth muscle markers [24]. As shown previously, DNA methylation can help to classify soft tissue tumors with overlapping morphological features, improve diagnostic accuracy and delineate novel entities [9].

Outside the uterus, the main differential diagnosis is dedifferentiated liposarcoma with meningothelial-like whorls [25, 26]. Whorled architecture may comprise up to 75% of these tumors and these areas may lack significant pleomorphism or increased mitosis.

The whorling in these tumors has been reported to be seen commonly with metaplastic bone or cartilage formation. Identification of these features in addition to finding well-differentiated liposarcoma and/or conventional dedifferentiated foci as well as performing MDM2 immunohistochemistry or FISH will be helpful.

Endometrial/oid stromal nodules are surgically treated and their prognosis is excellent. Evaluation of the tumor borders is critical as a diagnosis of low-grade endometrial stromal sarcoma portends different prognosis and treatment. All tumors in this series were classified as stromal nodules. Although this category is only used for uterine tumors, the broad ligament tumor was well-demarcated, extensively sampled and was classified similarly. One patient died of unrelated causes and the other two were alive and well 13 and 75 months after the surgery.

In conclusion, we report three endometrial/oid stromal tumors with unique morphological features with extensive whorling, fibroblastic background and variable sex cord-like differentiation. They epigenetically matched with endometrial stromal sarcomas using DNA methylation signatures and carried recurrent *CTNNB1* translocation.

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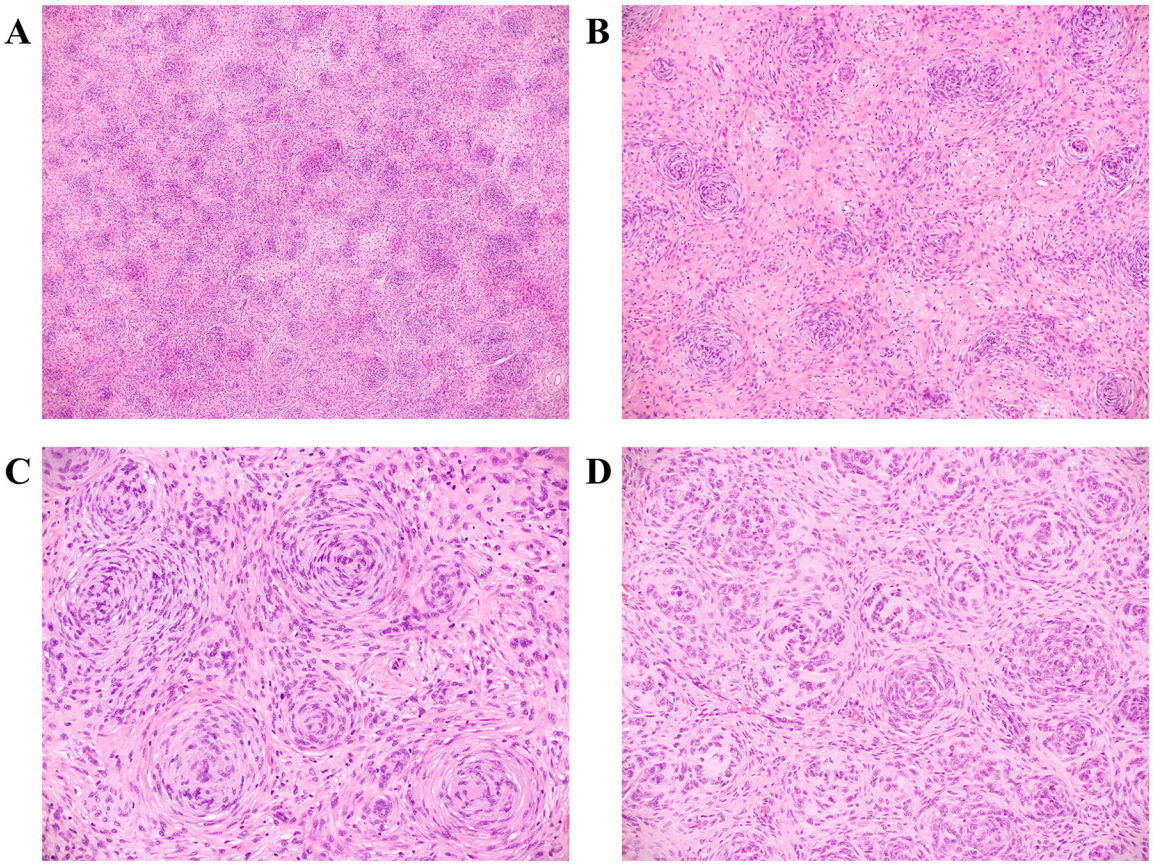

Figure 1:

Orderly arranged, uniform whorls of tumor cells (a) set in a loose fibroblastic background (b). Whorls composed of bland small, spindled cells (c). Whorls composed of short cords of epithelioid cells associated with hyalinization and myxoid change; notice one whorl with spindled cells in the center (d).

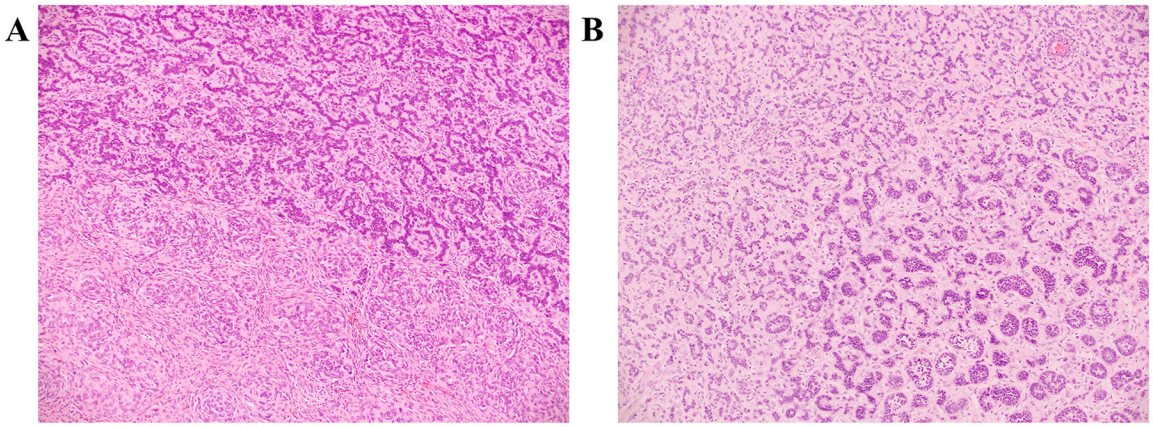

Figure 2:
Whorls transitioning to sex cord-like differentiation (a). Tubules and cords in areas with sex cord-like differentiation (b).

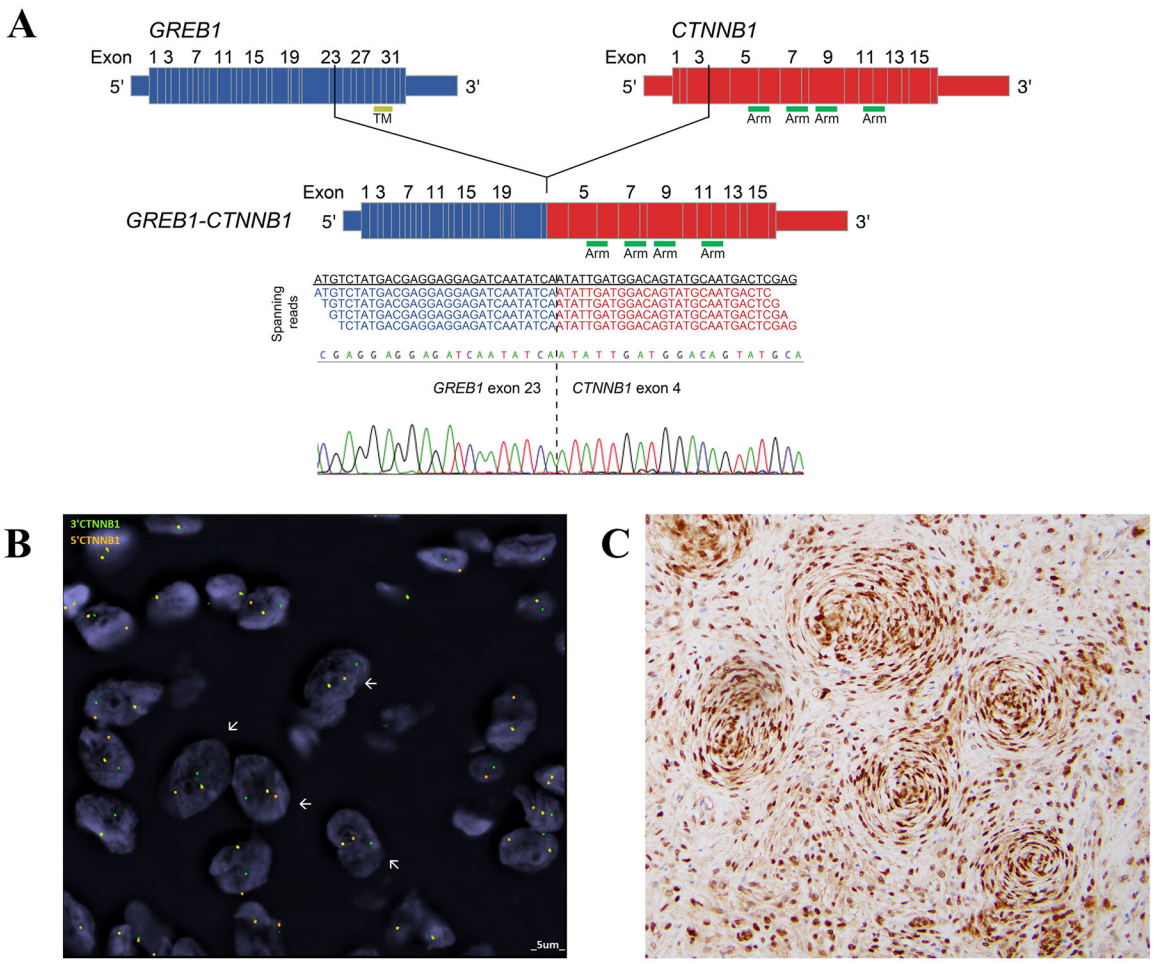

Figure 3:

Schematic representation of the *GREB1-CTNNB1* fusion transcript identified in one tumor, including the exons and domains involved (top). The breakpoint of the 5' and 3' partner genes are represented as black vertical lines. Spanning reads are depicted and aligned to the predicted junction sequence (middle). Representative Sanger sequencing electropherogram of the genomic *GREB1-CTNNB1* breakpoint (bottom) (a). Fluorescent *in situ* hybridization with *CTNNB1* split-apart probe showing translocation (b), correlating with beta-catenin pathway activation (nuclear beta-catenin positivity) (c).