Int J Clin Exp Pathol 2025;18(1):30-36
www.ijcep.com /ISSN:1936-2625/IJCEP0162120

Case Report

Female adnexal tumor of probable Wolffian origin (FATWO): a case report and literature review

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Received November 19, 2024; Accepted December 21, 2024; Epub January 15, 2025; Published January 30, 2025

Abstract: Female adnexal tumor of probable Wolffian origin (FATWO) is a rare gynecologic tumor. We describe a case of 53-year-old female patient in whom an adnexal mass was found. Microscopic examination revealed that the tumor arose in the adnexal soft tissue, composed of bland cells with an admixture of solid and sieve-like patterning, while presenting a high mitotic activity. Tumor cells were positive for Vimentin, CD10, and hormone receptors, while showing variable expression for sex cord-stromal markers, and was negative for GATA binding protein 3 (GATA-3), and thyroid transcription factor 1 (TTF1). The definitive diagnosis was FATWO. Subsequently, we conducted next-generation sequencing (NGS) in this case, and a CTNNB1 (c.98C>G, p.S33C) mutation was detected. The patient underwent tumor resection, hysterectomy, and bilateral adnexectomy, followed by annual computed tomography scans for monitoring. No evidence of recurrence or metastasis was observed at the 2-year postoperative follow-up. To the best of our knowledge, this is the fourth study having performed NGS on a FATWO. To further elucidate this rare neoplasm and improve the accuracy of diagnosis, we conducted a comparative analysis of the clinicopathological, immunohistochemical, and molecular features of our case with those previously reported in the literature, subsequently discussing the differential diagnosis.

Keywords: Female adnexal tumor of probable Wolffian origin, gynecologic pathology, ovary neoplasms, next-generation sequencing

Introduction

The female adnexal tumor of probable Wolffian origin (FATWO) is a rare gynecologic tumor of low malignant potential, which was initially described by Kariminejad and Scully in 1973 [1]. FATWO is postulated to be derived from mesonephric remnants, exhibiting the following characteristics: 1) occurrence in the adnexal area, 2) bland and uniform epithelial cells arranged in tree main primary patterns: solid, tubular and sieve-like, 3) an immunophenotype characterized by cytokeratin (CK)+, epithelial membrane antigen (EMA)-, paired box 8 (PAX8)-, Vimentin+, CD10+, GATA binding protein 3 (GATA3)-, thyroid transcription factor 1 (TTF1)-, variable sex cord markers and hormone receptors. Fewer than 140 cases of FATWO have been reported in the English literature, and to date, only three studies have utilized next-generation sequencing (NGS) to elucidate its molecular alterations. The diagnosis of FATWO remains challenging due to its rarity and overlap in both morphological features and immunophenotype with many common entities in the ovary. However, differentiating FATWO from its mimics is crucial in guiding subsequent clinical management. To further elucidate this challenging neoplasm and improve the accuracy of pathological diagnosis, we present a case of FATWO harboring a CTNNB1 (c.98C>G, p.S33C) mutation detected via next-generation sequencing, and conducted a comparative analysis of its clinicopathological, immunohistochemical and molecular features with those reported in previous literature, and subsequently discussed the differential diagnosis.

Case report

A 53-year-old female patient presented to a local hospital for the treatment of uterine pro-

https://doi.org/10.62347/JQLB5802

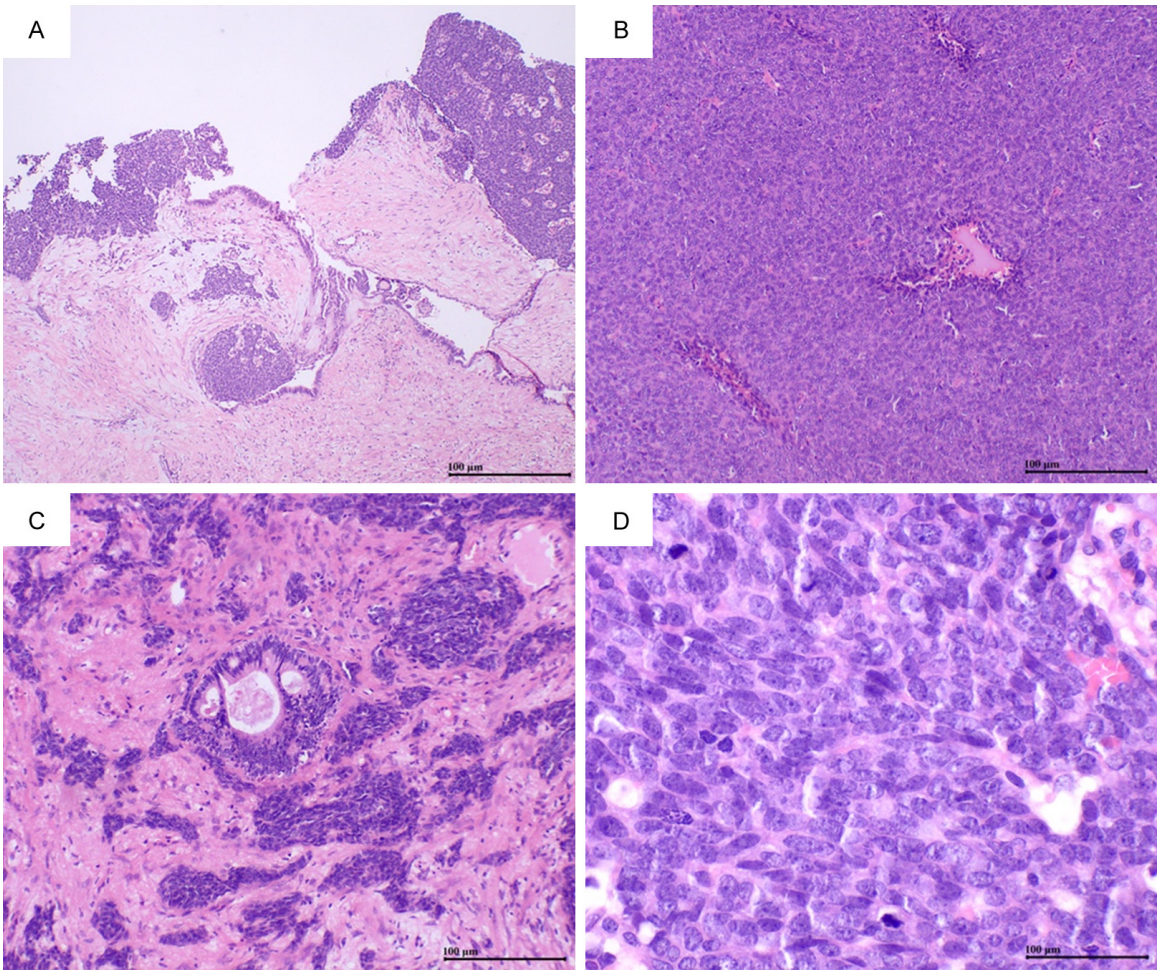

Figure 1. Microscopic features of our case. A. The tumor was juxtaposed to the fallopian tube serosa (Hematoxylin & Eosin stain, ×40). B. The cells exhibited mild atypia with a dominant solid growth pattern (Hematoxylin & Eosin stain, ×100). C. The sieve-like structure was detected as well (Hematoxylin & Eosin stain, ×100). D. In foci, tumor cells showed a high mitosis (Hematoxylin & Eosin stain, ×400).

lapse, during which an adnexal mass was incidentally discovered via pelvic computed tomography (CT). The patient remained asymptomatic and lacked any significant past medical or familial history. CT revealed a 2.8-centimeter, regular shaped, round mass on the right side of the uterus. Subsequently, surgical resection of the tumor, hysterectomy and bilateral adnexectomy were conducted at the local hospital. The local hospital's referring diagnosis was of a mesenchymal tumor, prompting referral to our institution for a definitive diagnosis. Subsequently, the patient came to our institution for pathological consultation, with the formalin-fixed, paraffin-embedded (FFPE) tumor tissue blocks.

Microscopic examination revealed the tumor arose in the adnexal soft tissue and was juxtaposed to the fallopian tube serosa (**Figure 1A**). The tumor presented a primarily solid growth pattern with hyalinized small vessels (**Figure 1B**). A focal sieve-like pattern was also observed (**Figure 1C**). Tumor cells were arranged in cords and irregularly shaped nests, surrounded by hyalinized stroma and myxoid matrix in scattered foci. The overall stromal component was minimal. The cells appeared bland and relatively uniform, exhibiting scant cytoplasm and ovoid to round nuclei. The mitotic index was approximately 15 per 10 high-power fields (**Figure 1D**). Colloid-like intraluminal eosinophilic secretion was observed in foci, while necrosis was absent.

Immunohistochemically, the tumor cells exhibited diffuse positivity for Vimentin, CD10, forkhead box protein L2 (FOXL2), steroidogenic fac-

tor-1 (SF-1), estrogen receptor (ER), progesterone receptor (PR) and androgen receptor (AR). EMA, PAX-8, epithelial cell adhesion molecule (Ep CAM), CyclinD1 and p16 were focally positive. No stanning was observed for α-inhibin, Calretinin, Wilms tumor protein 1 (WT-1), GATA-3, TTF-1, caldesmon, CD34, CD117 and BCL6 co-repressor (BCOR). p53 exhibited a wild-type pattern (**Figure 2**).

To exclude an adult granulosa cell tumor (AGCT), sanger sequencing was performed to investigate FOXL2 c.402C>G (p.C134W) mutation, and no FOXL2 (p.C134W) mutation was detected. Combining the morphological features, immunophenotype, and results of Sanger sequencing, we definitively diagnosed this case as a FATWO. Considering the scarcity of molecular studies on FATWO in the literature, we conducted NGS analysis on the tissue from our case. Genomic DNA was subjected to targeted sequencing utilizing the 1021-Gene Mutation Detection Kit (GenePlus, Beijing, CN), a panel targeting 1021 cancer-associated genes, on the Geneplus 2000 sequencer (GenePlus, Beijing, CN) according to standard techniques. NGS analysis detected an activating missense CTNNB1 mutation in exon 3 (c.98C>G, p.S33C) with a frequency of 67.1%. No FOXL2 mutation was detected via NGS. Furthermore, NGS indicated that our case exhibited microsatellite stability, and the tumor mutational burden (TMB) was determined to be 0.0 Mut/Mb.

No further treatment was performed on our patient. The patient underwent annual follow-up with CT scan of her abdomen and pelvis. There was no evidence of recurrence or metastasis 2 years after the surgery.

Discussion

FATWO was initially described by Kariminejad and Scully in 1973 [1]. They identified a series of tumors characterized by the following features: 1) arising in the leaves of the broad ligament, 2) bland and uniform epithelial cells, 3) growing in diffuse, trabecular, and tubular patterns, 4) an overall favorable prognosis. They designated this tumor as “female adnexal tumor of probable Wolffian origin”, because they considered the most possible origin to be Wolffian remnants. Subsequent studies have supported their findings, and further described the immunophenotype of FATWO (summarized in **Table 1**). FATWO is typically positive for CK, Vimentin, CD10, and negative for EMA, PAX8, GATA3, TTF1, and shows variable expression for variable sex cord markers and hormone receptors. The immunophenotype observed in our case is generally consistent with prior studies. However, PAX-8 was focally positive in our case, in contrast to a reported positivity rate of 7% in the literature. The positivity of PAX-8 does not invalidate the prior hypothesis that FATWO may originate from mesonephric remnants in the upper zone of the Wolffian system, as it has been reported that the rete ovarii exhibit positivity for PAX-8 [2].

The limited amount of molecular research conducted on FATWO has identified recurring KDR mutations in 3 cases and KMT2D mutations in 4 cases [3, 4]. However, neither of these mutations was detected in our study. Instead, we identified a CTNNB1 (p.S33C) mutation, which has also been identified in one case previously reported by Cossu et al. [3]. This mutation results in the loss of a phosphorylation site in the β-catenin, thereby contributing to the dysregulation of the Wnt signaling pathway. Based on the cancer database (https://cancer.sanger.ac.uk/cosmic), the CTNNB1 (p.S33C) mutation is a confirmed somatic mutation that has been observed in various tumors, including endometrioid adenocarcinoma (EC), microcystic stromal tumor (MCST), and ovarian solid pseudopapillary neoplasms (SPN) [2, 5]. Interestingly, FATWO shares some similar morphologic features and immunophenotype with MSCT and SPN, including monotonous tumor cells with round to ovoid nuclei, and diffuse positive expression for CD10 and Vimentin. In contrast to MSCT and SPN, FATWO are predominantly located in the broad ligament and mesosalpinx rather than ovary, and typically lack the microcystic, macrocystic and pseudopapillary structures observed in MSCT and SPN. Furthermore, the immunohistochemical nuclear expression of β-catenin, which resulted from nuclear β-catenin accumulation due to dysregulation of the Wnt signaling pathway, is a defining feature of MSCT and SPN [5]. However, FATWO exhibit β-catenin expression on cell-cell boundaries, rather than cytoplasmic or nuclear expression, although β-catenin immunostaining was only performed on two cases of FATWO in the literature [6]. A previous study has identified two APC mutations in one case [7], the tumor suppres-

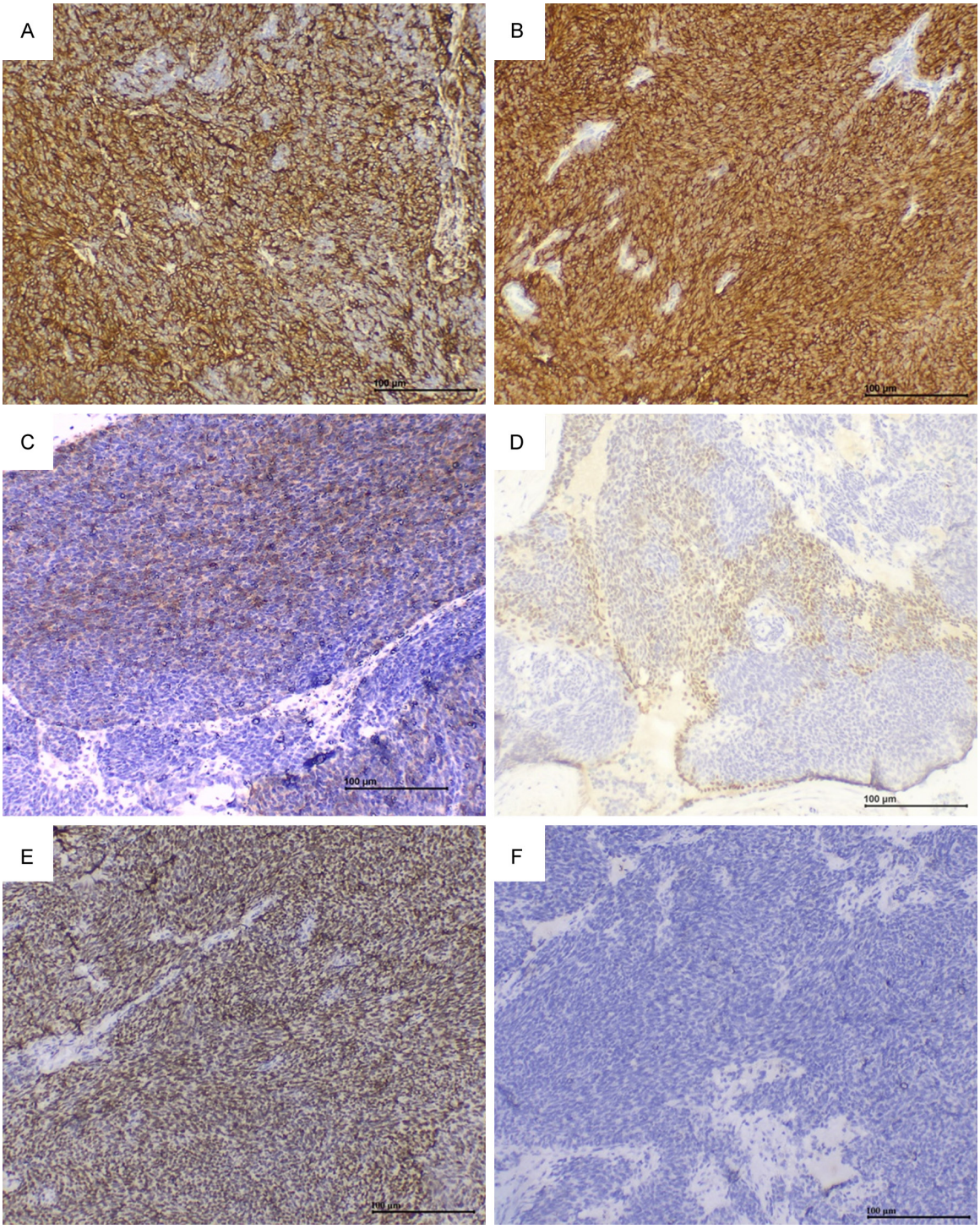

Figure 2. Immunophenotype of our case. The tumor cells exhibited diffuse and strong positivity for (A) Vimentin (×100) and (B) CD10 (×100), while focal positivity for (C) epithelial membrane antigen (EMA) (×100) and (D) paired box 8 (PAX-8) (×100). The tumor showed a variable expression for sex cord markers, (E) diffuse positivity for forkhead box protein L2 (FOXL2) (×100), (F) while no stanning for α-inhibin (×100).

sor protein that interacts with β-catenin in the Wnt signaling pathway. However, mutations involving the Wnt signaling pathway have been identified in only 3 of 22 cases, and their role in the pathogenesis of FATWO requires further investigation. Bennett et al. reported a recur-

Table 1. Summary of immunohistochemical profile of FATWO

Markers	In Literature (Positive Cases/Tested Cases)	Current Study	Total (Positive Rate)
Cytokeratin (CK)	82/83 (99%)	NP	82/83 (99%)
Vimentin	73/77 (95%)	+	74/78 (95%)
CD10	54/62 (87%)	+	55/63 (87%)
Cytokeratin 7 (CK7)	54/72 (75%)	+	55/73 (75%)
Calretinin	65/90 (72%)	-	65/91 (71%)
Forkhead Box Protein L2 (FOXL2)	6/9 (67%)	+	7/10 (70%)
Wilms tumor protein 1 (WT-1)	17/28 (61%)	-	17/29 (59%)
α-inhibin	61/99 (62%)	-	60/100 (61%)
Steroidogenic factor-1 (SF1)	17/32 (53%)	+	18/33 (55%)
Androgen receptor (AR)	11/27 (41%)	+	12/28 (43%)
CD117	6/15 (40%)	-	6/16 (38%)
Progesterone receptor (PR)	24/62 (39%)	+	25/63 (40%)
Estrogen receptor (ER)	25/71 (35%)	+	26/72 (36%)
Epithelial membrane antigen (EMA)	14/92 (15%)	+	15/93 (16%)
GATA binding protein 3 (GATA3)	5/36 (14%)	-	5/37 (14%)
Thyroid transcription factor 1 (TTF1)	1/9 (11%)	-	1/10 (10%)
Paired box 8 (PAX-8)	2/44 (5%)	+	3/45 (7%)

+, positive; -, negative; NP, not performed.

ring STK11 mutation in FATWO [7], however, after their further study, this group of tumors is now classified as STK11 adnexal tumor [8]. Compared with FATWO, STK11 adnexal tumors are frequently associated with Peutz-Jeghers syndrome and a worse prognosis, and are characterized by inter-anastomosing cords and trabeculae and an abundant myxoid matrix [2, 8]. Although the molecular heterogeneity of FATWO suggests that there seems to be no specific molecular mechanism underlying the pathogenesis, the absence of typical molecular alterations observed in its mimics facilitates the accurate diagnosis, including FOXL2 for adult granulosa cell tumor (AGCT), DICER1 for Sertoli-Leydig cell tumor (SLCT), KRAS for mesonephric-like adenocarcinoma (MLA), STK11 for STK11 adnexal tumors, BAP1 and CDKN2A/p16 for mesothelioma [2, 5, 8, 9].

The primary differential diagnosis of FATWO includes EC, MLA, AGCT, SLCT, MCST, and peritoneal mesothelioma. EC is more commonly located in the ovary rather than in adnexal soft tissue, and through extensive sampling and careful microscopic examination, typical EC components, squamous differentiation and related lesions (such as endometriosis, benign or borderline endometrioid tumors) can be observed. As for MLC, an immunophenotype of TTF-1+/GATA3+/ER-/PR- is valuable in differential diagnosis. Given that both FATWO and sex cord-stromal tumors express sex cord markers to varying degrees, the classic histologic features are more helpful in assisting diagnosis than immunohistochemistry alone, including nuclear grooving and Call-Exner bodies for AGCT, Leydig cell components and heterologous elements for SLCT, microcystic and macrocystic structures for MCST [2, 5, 8-10]. As for peritoneal mesothelioma, firstly, mesothelioma is more likely to involve multiple sites in the pelvis. Secondly, given that Calretinin and WT-1 function as both sex cord markers and mesothelioma markers, the inclusion of a broader panel of mesothelioma markers, particularly cytokeratin 5/6 (CK5/6) and D2-40, facilitates the distinction. In the literature, FATWO is negative or focally positive for CK5/6 and D2-40 [9]. Furthermore, the typical molecular alterations observed in mesothelioma, such as homozygous deletion or biallelic mutation of BRCA1-associated protein-1 (BAP1) gene and homozygous deletions of CDKN2A/p16, have not been reported in FATWO. The former results in loss expression of BAP1, and the later can be detected through fluorescence in situ hybridization [9].

The histopathologic characteristics definitive of malignant FATWO remain elusive, primarily due to its rarity. Predictive indicators reported previously include necrosis, capsular invasion, hypercellularity, cellular pleomorphism, and an increased number of mitoses [2, 11]. The cases with high mitotic activity in the literature exhibit an aggressive behavior, however, recurrence or metastasis have also been reported in cases with a low mitotic activity (<2/10HPF), and the recurrence tumors show a higher mitosis than primary tumors [11]. In our case, a high mitotic activity (15/10HPF) was observed, but no evidence of recurrence or metastasis was evident at 2 years post-surgery. Given that the reported time for recurrence in the literature ranges from 1.5 to 84 months, an association between high mitotic activity and aggressive behavior cannot be discounted. Therefore, long-term radiographic follow-up is essential for the FATWO cases with malignant morphological features. Due to its rarity, the optimal management of FATWO has not been established. Complete tumor resection is currently the preferred treatment, including total abdominal hysterectomy, bilateral salpingo-oophorectomy and debulking surgery [12]. To our knowledge, although adjuvant chemotherapy, radiotherapy, hormone therapy and target therapy have been used to treat recurrent and metastatic patients, the effects are controversial and still require further investigations.

In summary, although the diagnosis of FATWO is challenging, an accurate diagnosis can be established through a combination of tumor location, uniform and bland tumor cells with three main architectural patterns, a panel of antibodies for immunohistochemistry, and absence of specific molecular variants of its mimics. We identified a CTNNB1 mutation utilizing NGS technology, albeit the molecular heterogeneity that FATWO exhibits suggests there seems to be nonspecific molecular mechanisms underlying the pathogenesis, and further investigation is necessary.

Acknowledgements

This work was funded by Sichuan Science and Technology Program (No. 2022NSFSC0708).

Disclosure of conflict of interest

None.

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