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Everolimus plus anastrozole for female adnexal tumor of probable Wolffian origin (FATWO) with *STK11* mutation

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ABSTRACT

Female adnexal tumor of probable Wolffian origin (FATWO) are a rare type of cancer that originates from Wolffian duct remnants. Due to its rarity, no standard systemic treatment is established for cases of recurrent or metastatic disease. Previous literature reported the use of platinum-based chemotherapy and c-Kit tyrosine kinase inhibitors for FATWO cases with c-Kit positive expression. Currently, however, the broader availability of next-generation sequencing (NGS) tests allows a better molecular characterization of rare cancer such as FATWO and a possibility for the use of personalized, targeted therapy. Previous case series that performed NGS for FATWO patients described the presence of *STK11* mutations in a considerable number of cases, representing a potential target in this population. To our knowledge, we describe here the first case report of a patient with FATWO and *STK11* mutation exhibiting a considerable and durable response after treatment with an mTOR inhibitor plus endocrine therapy.

1. Introduction

The female adnexal tumor of probable Wolffian origin (FATWO) is a rare entity represented by tumors that originate from residual Wolffian tissue. The Wolffian ducts or mesonephric ducts are embryonic structures that give origin to the male internal genitalia. Otherwise, in females, they go through a regression, occasionally leaving small remnants located at *para*-adnexal soft tissues that can originate FATWO. Since its morphology and immunohistochemistry pattern may overlap with other pelvic neoplasia, FATWO diagnosis is frequently a challenge.

In the face of the disease rarity, studies evaluating treatment strategies for these patients are scarce. Surgical resection is the treatment of choice when feasible. However, 10–20% of the cases have a locoregional or distant recurrence (Hübner et al., 2019). No standard systemic treatment is established. For patients with metastatic or unresectable disease, the use of platinum-based therapies has been reported, but its efficacy seems to be limited (Kwon et al., 2016). Selected patients with c-Kit-positive FATWO may benefit from treatment with c-Kit tyrosine kinase inhibitors (Syriac et al., 2011). For instance, Steed et al. reported a c-Kit-positive FATWO case who presented a favorable response to imatinib after treatment with multiple chemotherapy lines (Steed et al., 2004).

In the last years, the expansion of next-generation sequencing (NGS) tests allowed an evaluation of FATWO molecular characteristics in a few case series (Cossu et al., 2017; Mirkovic et al., 2019; Bennett et al., 2020). Indeed, NGS represents a valuable tool for a better comprehension of rare tumors and the identification of potential targeted therapies for some diseases that have no standard treatment (Groisberg et al., 2018). An interesting finding from these studies was the occurrence of an *STK11* pathogenic mutation in some FATWO cases, identified by tumor sequencing (Mirkovic et al., 2019; Bennett et al., 2020). However, this genomic finding implication for the response to targeted therapies in FATWO has not been evaluated so far.

We report here a case of FATWO with an *STK11* (also called *LKB1*) mutation detected by somatic NGS, presenting with a sustained response to everolimus and anastrozole.

2. Case description

A 29-year-old female without comorbidities started presenting pelvic pain in December 2015. The patient had two pregnancies and two parities previous to the initiation of her symptoms. Regarding her family

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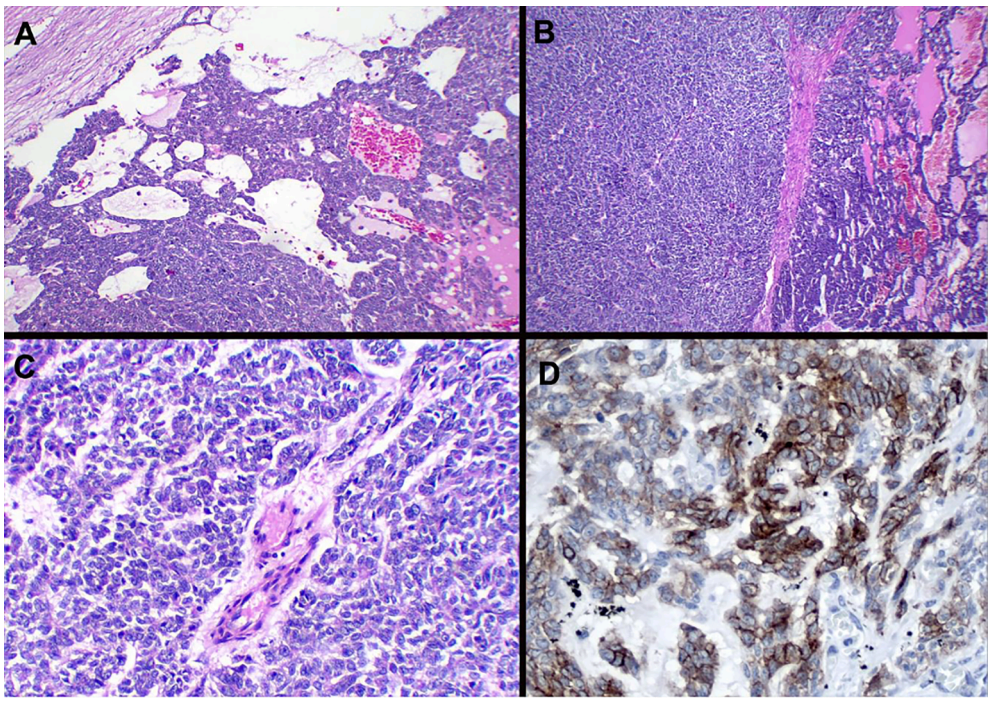


Fig. 1. Pathology from the *peri*-tubal lesion resection on May 2016, showing (A) circumscribed contour tumor, (B) high cellularity with solid, cystic, and trabecular architectural pattern, and (C) epithelioid and fusiform cell types. (D) c-kit positive tumor cells seen in the lesion on January 2021.

Table 1
Immunohistochemistry result from the *peri*-tubal lesion.

Positive	Negative
Estrogen receptor (20–80%)	GATA-3
Progesterone receptor (70%)	EMA
Vimentin	FOXL-2
CD10	CD117 (c-kit)
Inhibin	Synaptophysin
WT1	Chromogranin
Calretinin	PAX-8
Cytokeratin AE1/ AE3	
CD34	
Ki67 (40%)	

history, her maternal grandfather presented a prostate cancer at age 80 and paternal grandfather presented a cancer from unknown origin at age 75.

She was submitted to a pelvic ultrasound that showed a 2.6 cm cystic lesion in the left ovary. Her pelvic pain persisted despite the use of non-steroidal anti-inflammatory and contraceptive drugs. In May 2016, she went through a laparotomy with resection of the lesion and the left Fallopian tube. Her pathology review showed a *peri*-tubal neoplastic lesion measuring 9 cm at the largest diameter, predominantly circumscribed with minimally infiltrative foci, with solid, cystic, and trabecular architectural pattern, epithelioid and fusiform cell types, with high cellularity, and high mitotic count (Fig. 1). The immunohistochemistry results are shown in Table 1. The anatomopathological and immunohistochemical analyses defined as a female adnexal tumor of probable Wolffian origin.

After surgery, the patient was followed with radiological images, and a disease recurrence was diagnosed in December 2016. A magnetic resonance imaging (MRI) of the abdomen and pelvis showed multiple peritoneal nodules compatible with secondary implants, located mainly in the pelvis, the largest of them measuring 4.5 cm (Fig. 2). She was then submitted to a total radical hysterectomy, bilateral salpingo-oophorectomy, omentectomy, and resection of all peritoneal nodules, with no evidence of residual disease. Pathology confirmed a FATWO with a multifocal involvement of the peritoneum, parametrium and uterine serosa, and liver capsule.

After optimal cytoreduction, the patient received adjuvant chemotherapy with BEP (bleomycin, etoposide, and cisplatin) for four cycles from December 2016 until March 2017. In July 2018, an MRI showed a disease recurrence with a 1.9 cm lesion with a high T2 signal, close to the duodenum. A laparoscopy was performed with completed resection of the lesion, followed by chemotherapy with TIP (paclitaxel, ifosfamide, and cisplatin) for four cycles from July until October 2018.

The patient remained disease-free until August 2019, when a new disease recurrence was detected, with unresectable peritoneal disease. By that time, we performed a somatic next-generation sequencing, which showed microsatellite stability, intermediate tumor burden (8 mutations per megabase), and an STK11 (L55fs*108) mutation. The sample submitted to the next-generation sequencing was the one from the surgery for the first disease recurrence from December 2016. Considering the STK11 mutation, the patient started treatment with everolimus (10 mg per day orally) and anastrozole (1 mg per day orally).

With everolimus and anastrozole, she presented with a sustained partial response for more than one year (Fig. 3) until January 2021, when the disease progressed. Despite the progression, due to the considerable response previously presented, she could be submitted to a laparotomy with optimal cytoreduction in January 2021. In this last pathology, the immunohistochemistry showed a c-Kit-positive FATWO (Fig. 1**D**), and treatment with imatinib was initiated in February 2021. Until the current date, the patient has no evidence of disease and continues to receive imatinib. A timeline of her oncologic history is shown in Table 2.

3. Discussion

To the best of our knowledge, this is the first case report of a treatment with a mTOR inhibitor for a FATWO patient with *STK11* mutation. In the present case, treatment with everolimus and anastrozole showed a favorable activity. The patient presented with a partial response, which was sustained for over a year and allowed disease resectability.

A previous case series with 15 FATWO patients reported NGS from 9

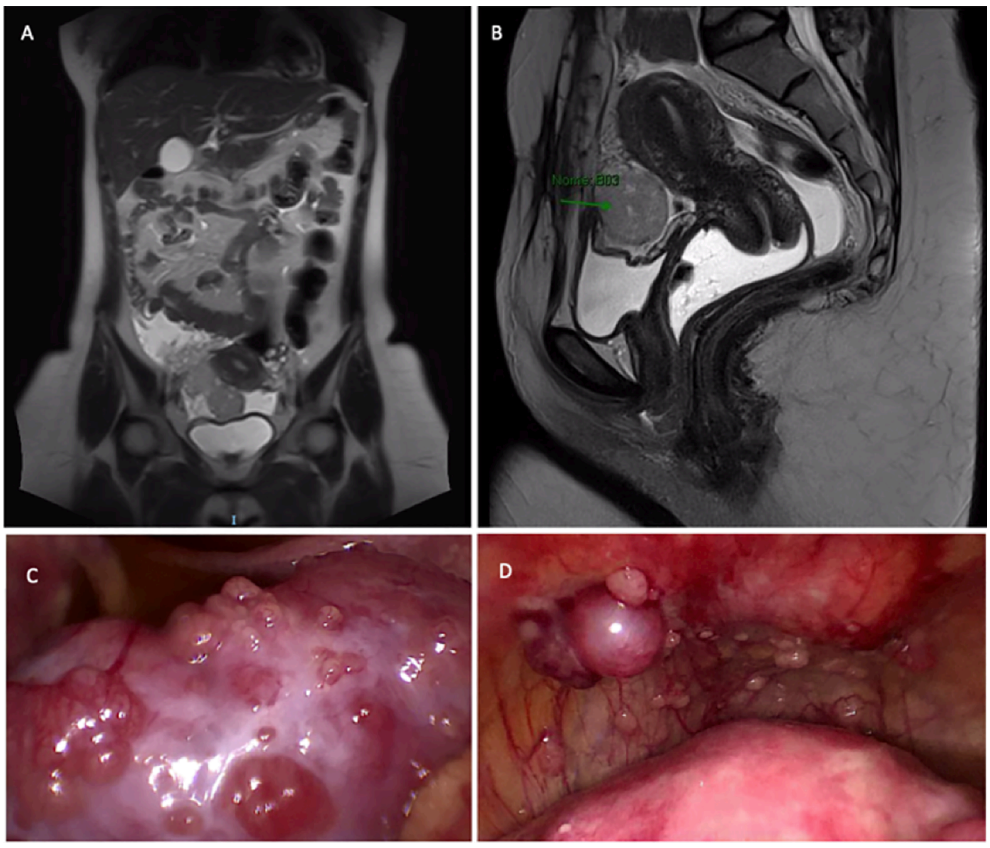


Fig. 2. Magnetic resonance imaging from the first disease recurrence and intra-operatory images from the surgery of December 2016 (A, coronal plane; B, sagittal plane; C and D, intra-operatory images).

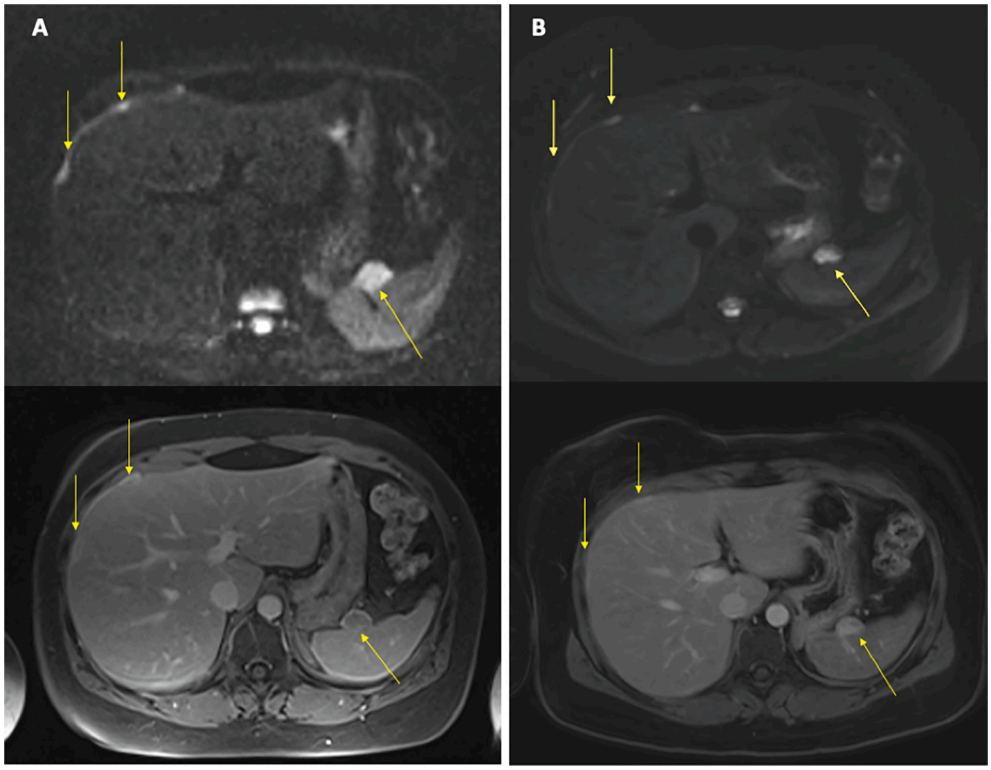
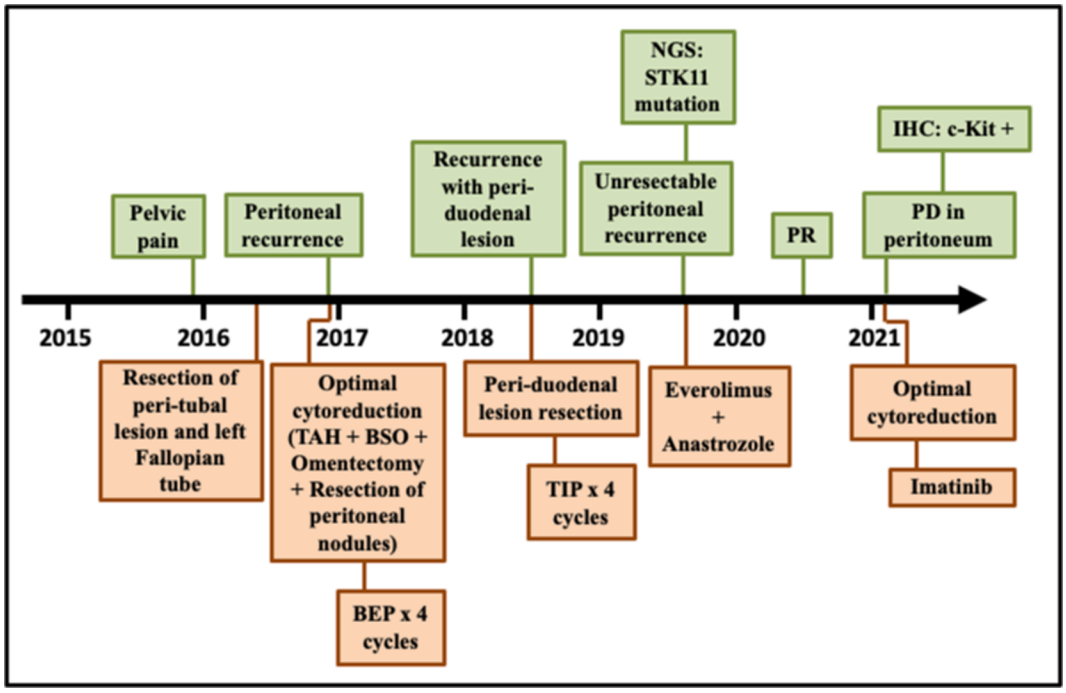


Fig. 3. Magnetic resonance imaging previous (A) and during (B) everolimus plus anastrozole treatment, showing partial response.

Table 2
Timeline of the oncologic history. Abbreviations: TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy; BEP, bleomycin, etoposide, and cisplatin; TIP, paclitaxel, ifosfamide, and cisplatin; NGS, next-generation sequencing; PR, partial response; PD, progressive disease; IHC, immunohistochemistry.



patients and found that 3 of them had an *STK11* mutation (Bennett et al., 2020). Despite the small number of patients, the results are remarkable since this was the most common pathogenic mutation, and it represents a proportion of 33% of the patients with FATWO harboring an *STK11* mutation. Similarly, another study that performed massively parallel sequencing of 7 FATWO cases identified *STK11* mutations in 2 of them (29%) (Mirkovic et al., 2019). Unfortunately, however, no information was provided on the treatments received by these patients.

STK11 is a tumor suppressor gene that regulates cell polarity, metabolism, and apoptosis. Germline *STK11* pathogenic variants imply in Peutz–Jeghers syndrome, characterized by mucocutaneous pigmentation, gastrointestinal hamartomatous polyps, and increased cancer risk. The cancer types involved in the syndrome include gastrointestinal, breast, uterus, and ovarian cancer. Regarding FATWO, despite the extreme rarity of this neoplasia, some FATWO cases have been reported in Peutz-Jeghers syndrome patients, raising the question if FATWO is also part of the syndrome tumors spectrum (Mirkovic et al., 2019; Beauchesne and King, 2021). Thus, a consideration of germline testing is relevant for FATWO patients with an *STK11* mutation detected by tumor sequencing.

STK11 also actuates as a negative regulator of the PI3K/ AKT/ mTOR pathway (Forcet et al., 2005). An impairment of *STK11* function due to loss-of-function mutations may lead to higher activation of mTOR, providing the rationale for using mTOR inhibitors in the scenario of an *STK11* mutation (Laderian et al., 2020; Korsse et al., 2013). A few cases have been described in other tumor types, suggesting mTOR inhibitors' efficacy in tumors harboring an *STK11* mutation (Parachoniak et al., 2017; Klümpen et al., 2011). Parachoniak et al. reported a heavily pretreated breast cancer case with an *STK11* mutation with a near-complete and durable response to everolimus and exemestane (Parachoniak et al., 2017). Klümpen et al. also observed a partial response in a patient with Peutz-Jeghers Syndrome and pancreatic cancer after treatment with everolimus (Klümpen et al., 2011). In the present case, everolimus was combined to endocrine therapy due to the estrogen and progesterone receptor expression in the tumor and the synergism of this combination in breast cancer (Baselga et al., 2012).

In conclusion, based on this case report and literature review, testing for *STK11* mutation should be considered in FATWO patients. The frequency of *STK11* mutations in the previous case series was substantial, and patients harboring these mutations may benefit from targeted therapy with mTOR inhibitors. However, additional studies are warranted to confirm these findings. Furthermore, the evaluation of *STK11* status and its impact on treatment response in future trials of mTOR inhibitors would provide valuable information.

Consent

The patient provided written informed consent for the publication of the present case report and its accompanying images.

Author contributions

All the authors contributed to this manuscript concept and design. All authors read and approved the final version of the manuscript.

Disclosures

RCB has received grant and financial support for educational programs from AstraZeneca, grant from Novartis, financial support for attending symposia from Roche and AstraZeneca, and personal fee for expert testimony from Ache, outside the submitted work. All other authors have no disclosure/ conflict of interest.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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