Case Report

Antitumor activity of everolimus in recurrent metastatic endometrial cancer with *PTEN* deletion: a case report

Xuhong Zhang[1], Junping Shi[2], Junying Li[2], Xiaoliang Shi[2], Xiaoliang Liu[2], Yingli Zhang[3], Yanzhi Cui[4]

[1]Gynecology Department, Tianjin Department Medical University General Hospital, Tianjin, China; [2]OrigiMed Co. Ltd, Shanghai, China; [3]Department of Gynecologic Oncology, Zhejiang Cancer Hospital, Hangzhou, China; [4]Department of Medical Oncology, the Fourth Hospital of Hebei Medical University, Shijiazhuang, China

Correspondence to: Yanzhi Cui. Department of Medical Oncology, The Fourth Hospital of Hebei Medical University, 12 Health Road, Shijiazhuang 050011, China. Email: cyz_2005@126.com.

Abstract: Endometrial cancer (EC) is one of the most common gynecological tumors. The first-line treatment for advanced EC is chemoradiotherapy. However, patients in poor health, such as those with intestinal obstruction, have limited tolerance for the side effects of chemoradiotherapy. Individualized precision treatment may bring new hope to these patients. Herein, we have reported on a 56-year-old female patient with metastatic EC combined with severe intestinal obstruction. Due to her inability to tolerate needle biopsy and standard treatment protocols, next-generation sequencing (NGS)-based circulating tumor DNA (ctDNA) testing was performed and *PTEN* deletion was found. Following, the patient commenced everolimus (10 mg, qd) treatment and partial shrinkage of metastases was observed one month later. Then, everolimus (10 mg, qd) plus carboplatin (100 mg d1, 8, 15, q28d) for 2 cycles, everolimus (10 mg, qd) plus carboplatin (200 mg d1, 8, q21d) for 2 cycles, and everolimus (10 mg, qd) plus carboplatin (200 mg d1, 2, q21d) for 2 cycles were performed, and the patient got partial response for 10 months. From June 2019, the patient continued to benefit from everolimus and subsequently experienced continued benefit for more than 12 months. This is the first reported case of an EC patient who benefited from everolimus as a first-line treatment based on *PTEN* deletion. This case provides important clinical experience for the precision treatment of patients with advanced EC.

Keywords: Endometrial cancer (EC); circulating tumor DNA (ctDNA); PTEN deletion; everolimus; case report

Submitted Jun 04, 2021. Accepted for publication Aug 19, 2021.
doi: 10.21037/gs-21-422
View this article at: https://dx.doi.org/10.21037/gs-21-422

Introduction

Endometrial carcinoma (EC) is the fourth most commonly diagnosed tumor and the fourth leading cause of death among females in the world (1). The incidence rate of the EC is about 20 to 30 per10 million people, and is increasing year by year (2). The poor prognosis of recurrence EC is partly due to the poor responses to salvage chemotherapy and limited treatment options (3). Alternative therapeutic options are desperately needed.

Mutation of the PI3K/AKT/mTOR pathway is common in EC, and most of them involve the loss of *PTEN* (4). PTEN regulates the activity of PI3K/AKT/mTOR pathway through phosphorylation, which plays an important role in the development and maintenance of endometrial cancer (5). A number of studies have evaluated the role of single-agent mTOR inhibition in recurrent EC as both primary and second-line therapy (6-8). Although the remission rate of single drug therapy is not ideal, blocking this biological pathway is a reasonable way to control the disease. Everolimus is an effective, selective and orally active mTOR inhibitor (9). In recent years, everolimus combined with hormonal therapy was reported to be effective in recurrent endometrioid EC patients (10,11). These studies suggest that mTOR inhibitors such as everolimus may effectively alleviate the resistance of endocrine therapy.

Molecular analysis of tumor tissue has been widely applied to the treatment of solid malignant tumor patients. However, whether there are enough samples is a concern for tumor tissue-based testing (12). Due to the heterogeneity of tumor cells, tissue obtained from primary surgical resection or biopsy may not reflect the current tumor molecular composition. While plasma-derived circulating tumor DNA (ctDNA) provides a more convenient and real-time option to detect the potentially actionable mutations of tumor. So far, the U.S Food and Drug Administration (FDA) has approved a number of ctDNA testing for many cancers in progression on or after endocrine therapy (13). In this case report, we present a case of recurrent metastatic EC with *PTEN* deletion. To our knowledge, this is the first report of *PTEN* deletion identified by ctDNA testing in an EC patient. The evaluation of everolimus in patients with *PTEN* deficiency will provide evidence for future precision treatment of ECs. We present the following article in accordance with the CARE reporting checklist (available at https://dx.doi.org/10.21037/gs-21-422).

Case presentation

A 56-year-old postmenopausal female presented with abnormal vaginal bleeding in November 2012. Magnetic resonance imaging (MRI) examination revealed uneven endometrial signals and abnormal signals in the left posterior wall of the uterus, suggesting uterine fibroids (*Figure 1A*). The patient received diagnostic curettage, and the pathology result indicated EC. She underwent complete surgical staging including hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic and para-aortic lymphadenectomy. The pathologic result showed a well-differentiated polypoid adenocarcinoma of the endometrium. The tumor was 2 cm × 1.6 cm, without any metastasis, indicating the International Federation of Gynecology and Obstetrics (FIGO) stage IA. At the conclusion of the case there was no evidence of gross residual disease. The immunohistochemistry (IHC) results were: estrogen receptor (ER) (++), progesterone receptor (PR) (+), human epidermal growth factor receptor 2 (HER-2) (–), Ki-67 (+), and p53 (–). The patient had been disease-free until October 2017, when she developed intestinal obstruction and epigastric distention with anorexia, nausea, constipation, and weight loss of 15 kg within 3 months. The computed tomography (CT) examination showed multiple metastatic lesions in the liver, abdominal, and pelvic cavity in January 2018 (*Figure 1B*). Abdominal pelvic fluid was also revealed by CT. The levels of cancer antigen 125 (CA125), CA199, and carcinoembryonic antigen (CEA) were 2,726 U/mL (reference value: 0–35 U/mL), 220.5 U/mL (reference value: 0–35 U/mL), and 10.33 ng/mL (reference value: 0–5 ng/mL), respectively. She was in a poor general condition with a performance status (PS) score of 3.

The patient vehemently refused to undergo puncture for further diagnosis after referral to our center. Due to severe intestinal obstruction and extreme gastrointestinal side effects, the patient was unable to receive a single-agent chemotherapeutic of paclitaxel or the combination of paclitaxel and carboplatin. The patient voluntarily accepted the next-generation sequencing (NGS) based ctDNA testing which was performed by OrigiMed (Shanghai, China), from where the laboratory was certified by the College of American Pathologists (CAP) and Clinical Laboratory Improvement Amendments (CLIA). Considering the detected *PTEN* deletion, the patient commenced everolimus (10 mg, qd) treatment on 15 January 2018. On 15 February 2018, the patient's symptoms were significantly relieved. The CT imaging showed partial shrinkage of metastases and indicated a stable disease (SD) (*Figure 1C*). The patient was then treated with everolimus (10 mg, qd) plus carboplatin (100 mg d1, 8, 15, q28d) for 2 cycles, everolimus (10 mg, qd) plus carboplatin (200 mg d1, 8, q21d) for 2 cycles, and everolimus (10 mg, qd) plus carboplatin (200 mg d1, 2, q21d) for 2 cycles. The clinical efficacy was evaluated as partial response (PR) by CT imaging in July 2018 (*Figure 1D*). From July 2018, the patient received everolimus (10 mg, qd) monotherapy, and the clinical efficacy was evaluated as SD by CT imaging in January 2019 (*Figure 1E*). From June 2019, the patient continued to benefit from everolimus. During the treatment, the patient had no special discomfort or side effects. The patient had a history of hypertension, and took oral nifedipine to control blood her pressure.

The *PTEN* c.36_79+4del deletion and *PIK3R1* c.1300-72_1426-301delinsCT mutation of this patient detected by NGS-based ctDNA detection are shown in *Figure 2*.

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this

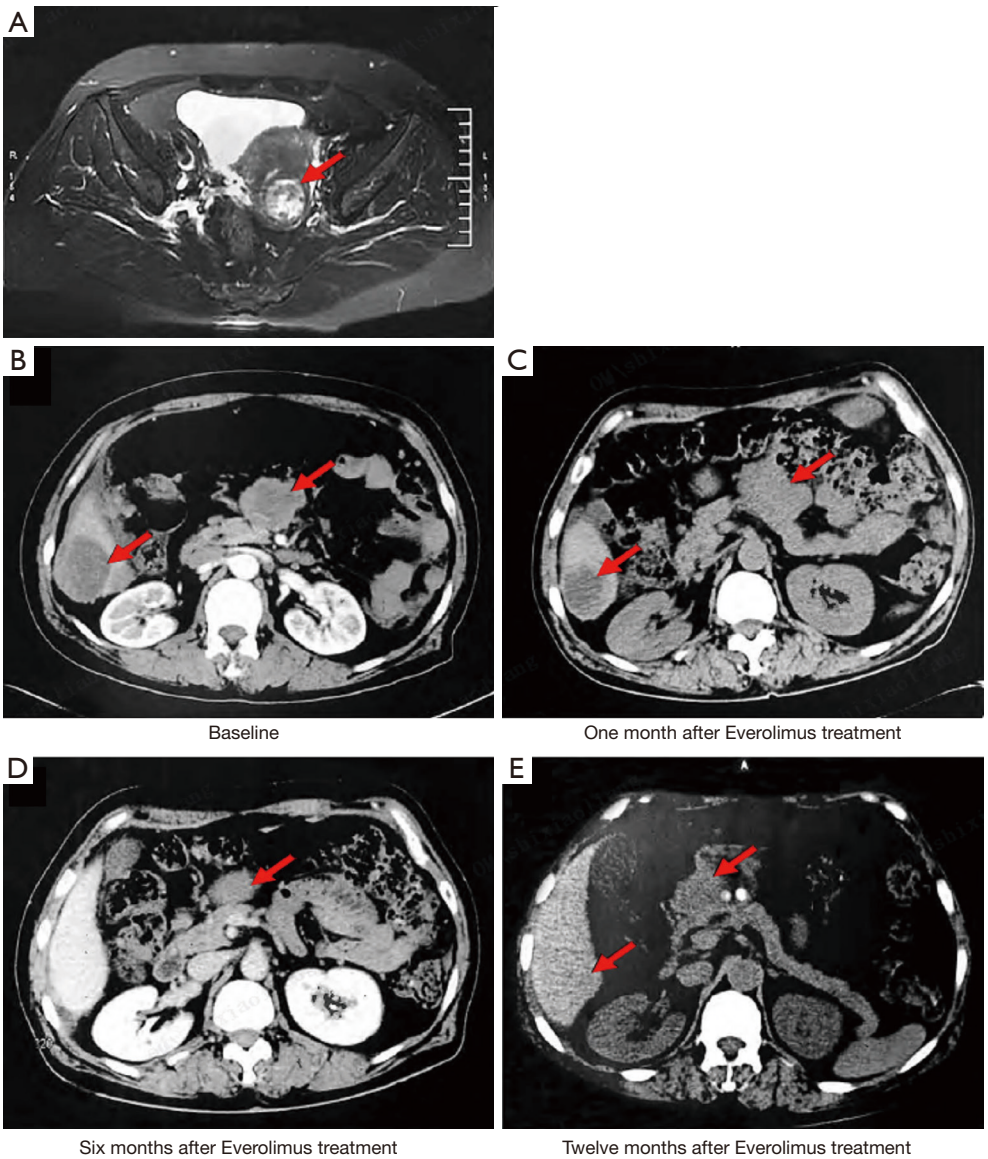

Figure 1 Image evaluation of the patient. (A) MRI examination in December 2012. CT scans, (B) baseline; (C) the patient received everolimus treatment for 1 month; the patient recieved everolimus plus carboplatin treatment for 6 months (D), and 12 months (E). The red arrow indicates the location of the tumor. MRI, magnetic resonance imaging; CT, computed tomography.

case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal. The study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University.

Discussion

Liquid biopsy, which include sampling of blood and other body fluids, is becoming to be effective for cancer diagnosis, routine monitoring, and prognosis. The ctDNA is a popular liquid biopsy biomarker that has been found to be easily detectable in the plasma of cancer patients (14). At present, an increasing number of studies have shown that ctDNA detection has outstanding clinical application value in monitoring tumor progression and precision therapy (13,15). CtDNA detection is a non-invasive and easily accessible way to determine prognosis and treatment methods (13). However, tissue biopsy is still the gold

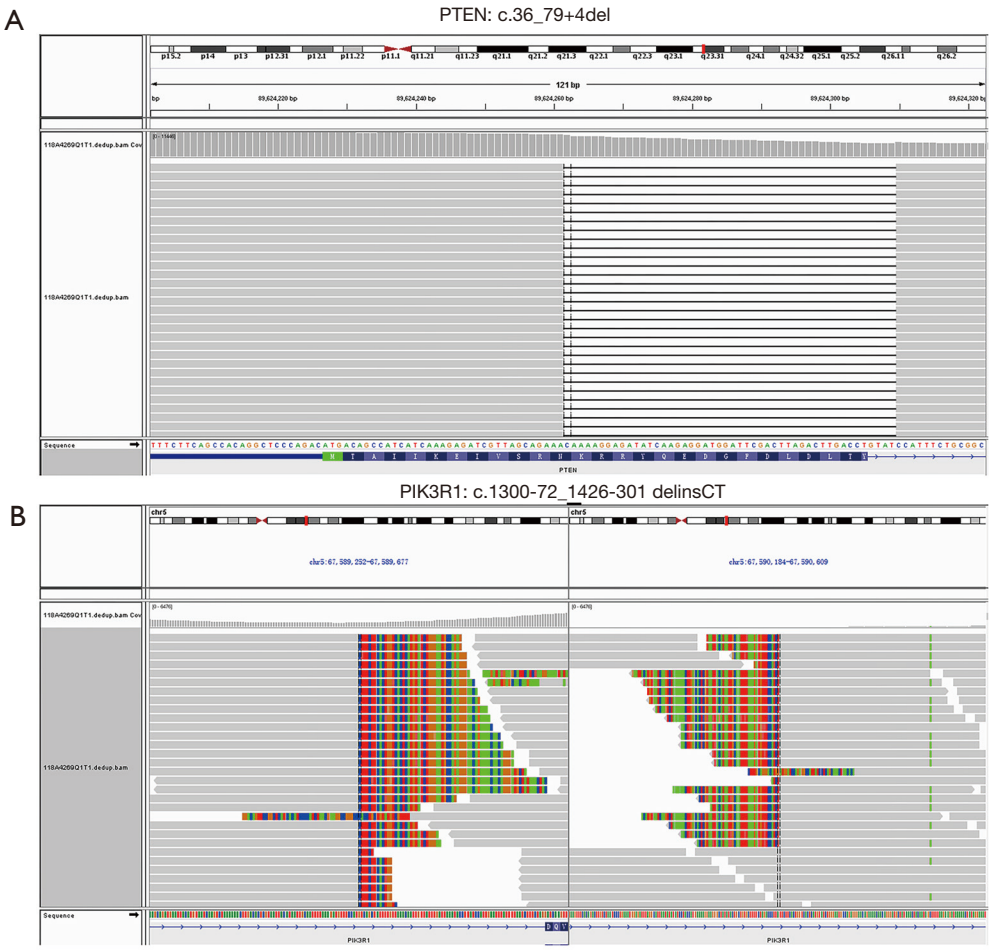

Figure 2 The integrative genomics viewer snapshot of mutations detected by NGS-based ctDNA detection. (A) *PTEN* c.36_79+4del deletion mutation; (B) *PIK3R1* c.1300-72_1426-301delinsCT mutation.

standard for gene detection, with higher accuracy and specificity. The use of ctDNA is a good alternative when tissue is not available. It can also provide some certain references for clinical diagnosis and treatment. In clinical practice, reference is much better and meaningful than no reference. The patient in our study had a poor physical condition with intestinal obstruction during tumor recurrence and had strongly opposed invasive diagnosis and traditional treatment, including needle biopsy, and traditional radiotherapy and chemotherapy. The use of ctDNA detection provided an option for diagnosis and treatment of this patient.

Through NGS-based ctDNA testing, *PTEN* deletion and *PIK3R1* mutation were identified in this patient. The *PTEN* gene is the most significantly altered gene (77%) and the mutation frequency of *PIK3R1* is about 15% in EC (16). However, there are no FDA approved anti-tumor drugs targeting *PTEN* or *PIK3R1*. The *PTEN* gene is a negative regulator of the PI3K-AKT-mTOR pathway, which plays an important role in regulating of cell growth and survival (17). Both *PTEN* deletion and *PIK3R1* mutations can activate PI3K activity and promote phosphorylation of AKT (17), suggesting that Akt inhibitors or mTOR inhibitors may be potential therapies for tumors harboring these gene mutations. Several studies have evaluated the effect of single-agent mTOR inhibitors in recurrent ECs as both first- and second-line therapy (6-8). Although the objective effective rate was 0–24%, the stable SD rates have reached as high as 90%.

Everolimus is a rapamycin (mTOR) inhibitor that has an antitumor effect on cancers (18,19). Everolimus effectively reduced endometrial proliferations progression of and thyroid hyperplasia in *PTEN*-deficient mouse models (20).

The phase II trial of GINECO demonstrated efficacy and acceptable tolerability of everolimus in advanced or metastatic EC patients with chemotherapy-refractory, which supported the further development of PI3K-targeted therapies in EC (21). In addition, everolimus combined with letrozole in patients with advanced and recurrent EC showed a clinical benefit rate of 40% and objective response rate of 32% among 35 evaluable patients, respectively (11). Epidermal growth factor receptor 2-positive breast cancer with *PIK3CA* mutations, *PTEN* loss, or hyperactive PI3K pathway may have opportunity to benefit from everolimus (22). The phase II trial (NCT02029001) of the mTOR inhibitor everolimus for the treatment of patients with advanced tumors carrying *PIK3R1* mutations is ongoing (23). In addition, it was reported that a patient with *PTEN*-deficient metastatic endometrioid endometrial adenocarcinoma displayed a profound sensitivity to platinum-containing regimens (24). In this study, the patient was treated with everolimus for first-line treatment and achieved a certain effect and her physical condition improved significantly. After the addition of carboplatin chemotherapy on the basis of everolimus, the mass was further reduced, and the therapeutic effect was evaluated as PR. The conventional treatment of endometrial cancer includes surgery, radiotherapy, chemotherapy, and hormone therapy. Slomovitz *et al.* shows that everolimus and letrozole may be a reasonable choice for second-line treatment of recurrent endometrioid EC (25). Combined with this case, especially for patients with advanced or recurrent EC, we suggest that NGS based genomic detection is necessary for the identification of potential drug targets. For patients with PETN, everolimus combine with carboplatin chemotherapy may be a potential choice.

Conclusions

We have presented a metastatic EC patient with *PTEN* deletion who achieved PR after receiving the mTOR inhibitor everolimus, and benefited from it for more than 12 months. To our knowledge, this was the first report of patients with advanced EC for targeted therapy through NGS-based ctDNA testing. This case supports the possibility of everolimus combined with carboplatin chemotherapy in the treatment of EC patients with *PTEN* mutation, and provides important clinical experience for the precision treatment of patients with advanced ECs.

Acknowledgments

Funding: This work was supported by National Natural Science Foundation of China (81602267).

Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://dx.doi.org/10.21037/gs-21-422

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://dx.doi.org/10.21037/gs-21-422). All authors have declared no conflicts of interest.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal. The study was approved by the Ethics Committee of the Fourth Hospital of Hebei Medical University.

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Cite this article as: Zhang X, Shi J, Li J, Shi X, Liu X, Zhang Y, Cui Y. Antitumor activity of everolimus in recurrent metastatic endometrial cancer with *PTEN* deletion: a case report. Gland Surg 2021;10(8):2585-2590. doi: 10.21037/gs-21-422