Combined anti-HER2 and hormonal treatment in a patient with HR$^+$HER2$^+$ clear-cell uterine carcinoma: A case report

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Abstract. Clear-cell carcinoma (CCC) of the uterus is an aggressive disease. Current international guidelines on the treatment of uterine carcinomas predominantly cover cancer with endometrioid histology, and clinicians tend to use the same approach for patients with non-endometrioid histology due to the absence of separate guidelines for these rare tumor types. At present, molecular analysis enables the assessment of novel and non-standard treatment options based on the individual characteristics of a tumor. The present report presents a clinical case of successful treatment of a patient with clear cell uterine carcinoma with HER2 and ER expression. Non-toxic targeted treatment was used based on immunohistochemistry (IHC) data. The patient received anti-HER2 and hormonal treatment and demonstrated an excellent response. The follow-up period was 47 months and the patient remained stable during treatment without significant toxicity. Therefore, this approach demonstrated the potential for selecting highly-specific therapy for rare tumors, which lack distinct recommendations for their treatment.

Introduction

Clear-cell carcinoma (CCC) is responsible for ≤5% of all uterine carcinomas (1), and 1/3 CCC cases are diagnosed when distant metastases are present. However, options for systemic therapy remain limited, and it has been reported that CCC has a low response rate to chemotherapy (2). Moreover, clinical recommendations do not offer distinct treatment plans for rare uterine histologies, including CCC, and their molecular mechanisms are different from endometroid cancer types.

CCC has one of the lowest expression levels of estrogen receptors (ER) and progesterone receptors (PR) among the uterine cancer types (1). Hormonal treatment usage is limited to endometrioid histologies, and has not been studied or used for other types (3).

It has been revealed that 3-40% of all the uterine cancer types express human epidermal growth factor receptor 2 (HER2) (4,5). Furthermore, upregulation of HER2 in uterine carcinomas is associated with poor characteristics of the tumor, such as serous or clear cell histology and high grade, as well as unfavorable prognosis. HER2 is upregulated in a 1/2 of all serous tumors and 1/3 of CCC (5). Trastuzumab has demonstrated efficacy in patients with serous histology, with progression-free survival being significantly improved in experimental groups (6). However, to the best of our knowledge, there are no reports on anti-HER2 treatment in patients with CCC.

Case report

A female patient (born 1954) was examined in January 2016 due to dysuria. Ultrasound results identified multiple enlarged paraaortic lymph nodes, which compressed both ureters. Ureteral stents were installed. Concurrently, multiple bone lesions were detected. The female patient was admitted in N.N. Blokhin National Medical Research Center of Oncology 1 month later, in February 2016, with severe back pain. ^{18}F-FDG-PET/CT was performed, which detected bone metastases, metastatic lesions in paraaortic lymph nodes and metastatic node on the uterus stump (the partial amputation of the uterus was performed in 1995 most likely due to leyomyoma).

Biopsy from left iliac bone revealed adenocarcinoma. Morphological examination from the metastatic site in the bone identified bone marrow tissue with three hematopoietic cell lines and a tumor, which had the appearance of adenocarcinoma, containing various patterns and cell types (Fig. 1A). A total of three major types of structures were observed: Tubule-cystic, papillary and solid, which were disorderly and intermixed on the fibrocollagenous,

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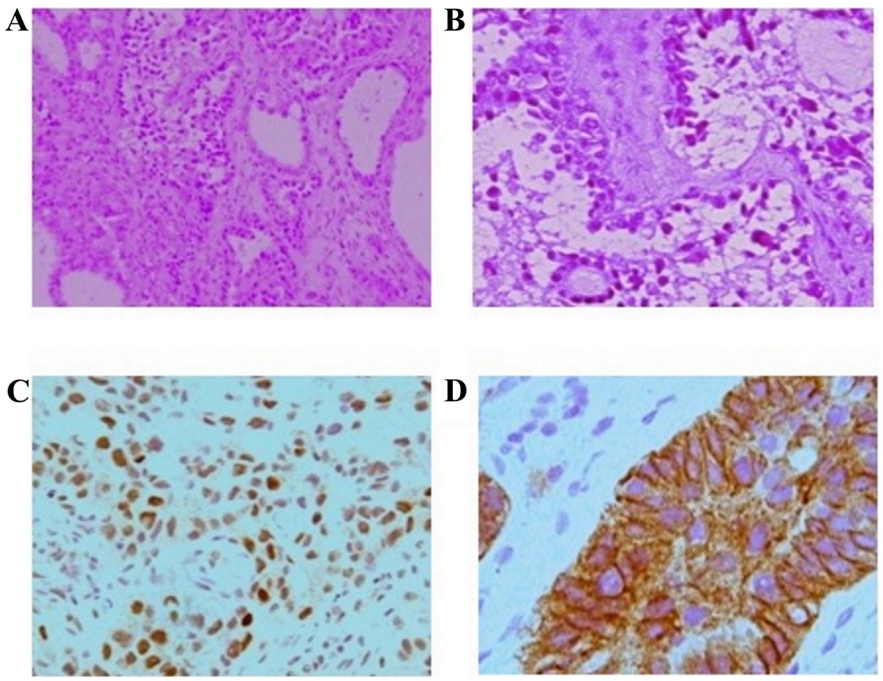

Figure 1. Pathology findings of bone metastasis. (A) Bone metastasis (magnification, x10). (B) Bone metastasis (magnification, x20). (C) High estrogen receptor expression (magnification, x10). (D) High human epidermal growth factor receptor 2 expression (magnification, x20).

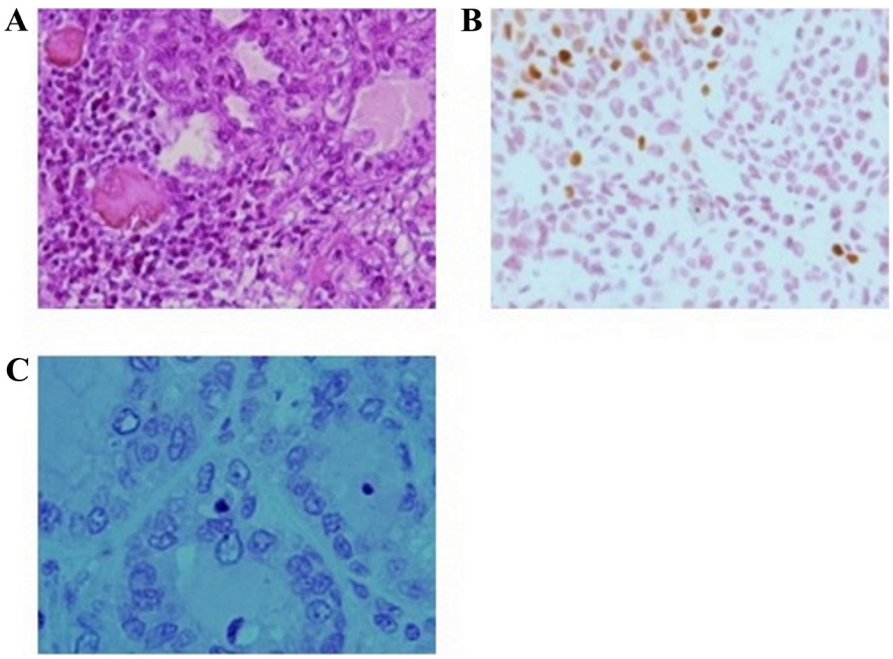

Figure 2. Pathology findings of brain metastasis. (A) Brain metastasis with dystrophy and lymphoplasmacytic infiltration. Magnification, x20. (B) Low estrogen receptor expression. Magnification, x20. (C) Absence of human epidermal growth factor receptor 2 expression. Magnification, x20.

partly hyalinized, background. The tumor cells in the solid structures were large with an eosinophilic granular or clear vacuolated cytoplasm, voluminous nuclei and occasional eosinophilic nucleoli. The lining of the tubule-cystic structures displayed a continuum of cells from flattened to cuboid, or highly prismatic cells. The large bulbous nuclei often protruded into lumen, acquiring the appearance of hobnail cells. The cellular covering of papillae with different complexity was analogous to that of cystic linings. The cystic cavities contained colloid type material and the cells with eosinophilic hyaline bodies (Fig. 1B). The PAS reaction was positive in the cell cytoplasm. The IHC results, using Springer antibodies, ER (SP1, Spring Bioscience 1:100), PR (SP2, Spring Bioscience 1:400), Her2 neu (SP3, Spring Bioscience 1:400), demonstrated that the tumor cells were positive for ER (Fig. 1C), Her2/neu (3+) (Fig. 1D), CK7, Pax8 and napsin. The diagnosis of clear cell carcinoma was considered.

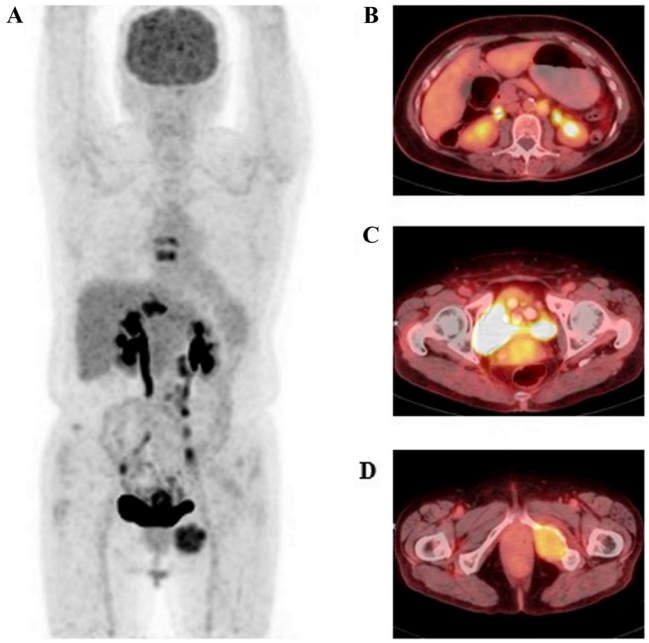

Figure 3. ^{18}F-FDG-PET/CT before treatment (January 2016). (A) PET scan depicting multiple bone lesions, metastases in paraaortic lymph nodes and metastatic node on the uterus stump. Co-registered PET/CT scan demonstrating increased FDG uptake in (B) paraaortic lymph node, (C) node on the vagina stump and (D) left ischium with soft-tissue mass. ^{18}F-FDG, 2-deoxy-2-[fluorine-18]fluoro-D-glucose; PET, positron emission tomography; CT, computed tomography.

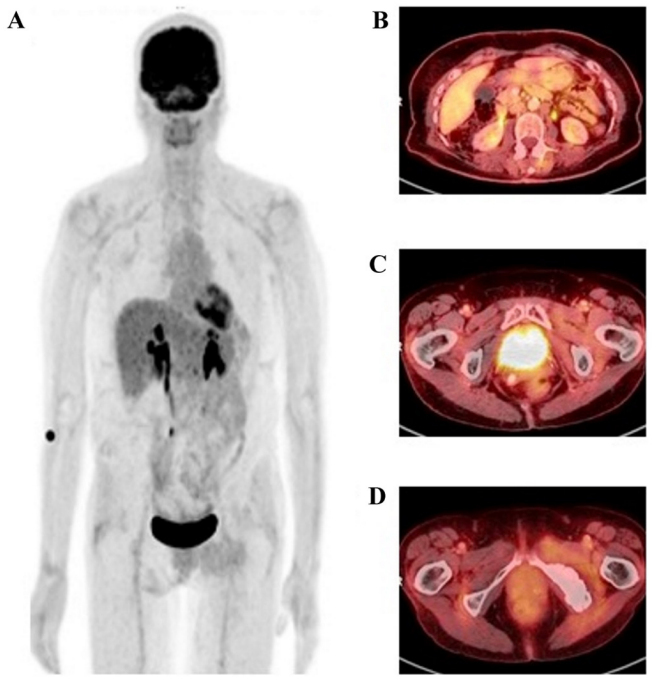

Figure 5. ^{18}F-FDG-PET/CT and efficacy of treatment (December 2019). (A) PET scan and co-registered PET/CT scan with low FDG uptake in (B) remaining paraaortic lymph node, and no evidence of pathologic FDG uptake in (C) uterus stump and (D) left ischium. F-FDG, 2-deoxy-2-[fluorine-18]fluoro-D-glucose; PET, positron emission tomography; CT, computed tomography.

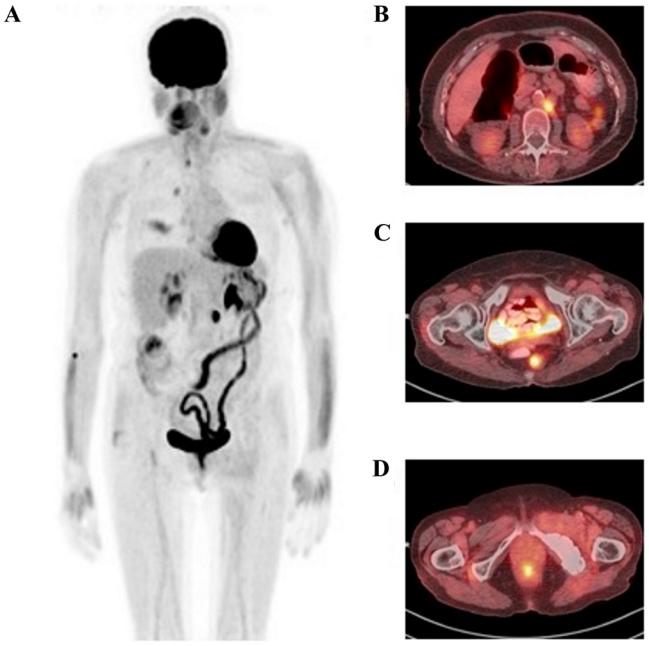

Figure 4. ^{18}F-FDG-PET/CT and efficacy of treatment (July 2018). (A) PET scan depicting metastasis in paraaortic lymph node with no evidence of any other lesions with pathologic FDG-uptake. Moderate FDG uptake was observed in the right lung due to inflammation. Co-registered PET/CT scan depicting (B) increased FDG uptake in paraaortic lymph node, and no evidence of FDG uptake in (C) node on the vagina stump and (D) left ischium. F-FDG, 2-deoxy-2-[fluorine-18]fluoro-D-glucose; PET, positron emission tomography; CT, computed tomography.

Based on the pathology findings, the presence of the node on uterus stump and the absence of other suspected primary tumors, the patient was diagnosed with metastatic CCC of the uterus.

Treatment started with radiotherapy: The first part of irradiation covered the soft-tissue mass at the Th7-12 spinal cord level (30 Gy in 10 fractions) and the second covered lesions in pelvis (30 Gy in 10 fractions). Radiotherapy resulted in a substantial decrease in pain. Due to requirement for systemic low-toxic treatment during radiotherapy and based on the pathology examination results, systemic therapy with aromatase inhibitors (letrozole in standard dose) and zoledronic acid was initiated in March 2016. The patient remained stable without chemotherapy, and thus in June 2016 hormonal therapy was continued and Herticad®, a Russian biosimilar of trastuzumab, was added (Biocad, loading dose 8 mg/kg, followed by 6 mg/kg every 3 weeks). This approach resulted in clinical improvement and a partial radiological response with a significant decrease in metastatic lesions, both in size and FDG-uptake.

A total of 27 months after initiation of the treatment, the patient began to complain of dizziness. Therefore, a brain MRI was performed, which revealed one lesion in cerebellum. PET/CT results did not demonstrated any sign of progression with respect to extracranial lesions. In July 2018 the lesion was surgically removed. The structure of brain metastasis (Fig. 2A) was principally identical to that of bone metastasis obtained previously during biopsy. The brain lesion differed in terms of high cellular density, elevated polymorphism and marked dystrophy in both the cytoplasm and nuclei. The clear cell component was obvious, together with extensive necrosis, hemorrhages and marked lymphoplasmocytic infiltration, which was not necessarily confined to necrotic foci. The significant finding was the negative HER2 reaction (Fig. 2C)

in the cancer cells in metastatic foci, as well as the notable reduction of reactivity to ERs both in number of positively stained cells and the intensity of the staining itself (Fig. 2B).

Due to the long-lasting clinical and radiological benefit and surgical removal of HER2 non-expressing tissue, it was decided to continue with anti-HER2 and endocrine therapy. Then, trastuzumab was switched to lapatinib, based on its ability to cross the blood-brain barrier. The patient started the new combination (letrozole + lapatinib in standard dose) in June 2018 and remains stable until December 2019, with the only sign of disease being in one paraaortic lymph node. Figs. 3-5 present the radiological response to treatment.

Discussion

CCC is a rare type of uterine carcinoma associated with an unfavorable prognosis. Current treatment options for this tumor type do not differ from endometroid tumors, and only include chemotherapy. However, an individual approach for every patient remains a milestone of cancer treatment. In the metastatic setting, the aim of treatment is to increase the survival of the patient, as well as improve the quality of life. Thus, the present study aimed to use hormonal and targeted agents whenever possible.

In the present clinical case pathologic report investigated not only the histological subtype and grade, but also multiple characteristics that had a significant influence on the treatment decision. Both the morphological findings and the observed benefit allowed the ability to prescribe non-toxic and long-lasting effective treatment.

The follow-up period for this patient was 47 months. Median overall survival for patients with metastases with the same condition is 12-15 months (7). The current patient complained of reduced clarity of speech after removal of metastasis from cerebellum, but was otherwise stable. The patient continues treatment with hormonal and anti-HER2 therapy without any signs of toxicity.

Thus, the present report demonstrated the efficacy of combined hormonal and anti-HER2 therapy (a biosimilar of trastuzumab, followed by lapatinib) in a patient with a rare and aggressive disease, which otherwise would be treated with chemotherapy due to current approaches.

In conclusion, standard approaches and guidelines on cancer treatment often do not cover treatment possibilities for rare tumors due to a lack of evidence. Current diagnostical opportunities allow the possibly to identify a molecular pattern of every tumor. Thus, the present report aimed to identify novel options and appropriate solutions for patients whose tumor is not mentioned in current guidelines. The present results demonstrated a benefit of using hormonal and anti-HER2 therapy in a patient with clear cell uterine carcinoma, as the treatment lead to prolonged survival without any significant toxicity.

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Availability of data and materials

Data sharing is not applicable to this article, as no datasets were generated or analyzed during the present study.

Authors' contributions

LAM, AAM and OOG were treating physicians. NAM was responsible for radiology diagnosis. AIK was responsible for pathology diagnosis. OOG, AAM and AIK drafted the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Competing interests

The authors declare that they have no competing interests.

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