Brain metastasis of ovarian cancer >20 years after initial diagnosis: A case report

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Abstract. Brain metastasis from ovarian cancer, particularly from clear cell ovarian cancer, is extremely rare and its pathology remains unclear. In the present study we treated a patient in whom this cancer was diagnosed after chemotherapy was administered for lung metastases. The patient, a 76-year-old woman, presented to Department of Obstetrics and Gynecology, Showa General Hospital (Tokyo, Japan) in February 2025 with sudden confusion and dizziness. The patient was surgically treated for ovarian cancer 20 years previously that displayed two clear histological types: Left clear cell and mucinous carcinomas and right endometrioid carcinoma. The patient was treated several times for recurrent metastases in the umbilicus and inguinal lymph nodes, of either clear cell or endometrioid carcinoma. The treatment administered varied from resection to radiotherapy. In 2016, lung metastasis was suspected, but the lesion size remained unchanged for several years. In 2019, the left inguinal lymph node again became swollen, and re-irradiation was performed for 2 weeks. In 2023, the right lung metastases grew larger and palliative radiotherapy was administered at another hospital. The right lung metastases continued to grow, and the patient returned to our hospital in May 2024 with a severe cough; metastasis from ovarian cancer was diagnosed. Paclitaxel-carboplatin chemotherapy was resumed for 6 months; the tumor grew slightly smaller, and the severe cough disappeared. The patient underwent maintenance olaparib therapy from January 2025 for platinum-sensitive recurrent ovarian cancer. After presenting to our department in February 2025, imaging studies revealed multiple substantial brain metastases and growth of the lung metastases. Palliative whole brain radiotherapy was administered, with the confusion improving slightly. The patient was transferred to a nursing home. Multiple pathological types coexisted in our patient, creating a complicated condition that, after various treatments were administered, was difficult to comprehend. Appropriate pathological diagnosis through biopsy, as well as comprehensive consideration of the treatment strategy based on the characteristics of the pathological type, is necessary.

Introduction

Globally, ovarian cancer is the eighth most common cancer among women and the second leading cause of death from gynecological cancer. In 2020, it accounted for an estimated 3.7% of cases and 4.7% of cancer deaths (1,2). Ovarian cancer is associated with a poor prognosis because 70% of cases are diagnosed at stage III or IV disease (3). Brain metastasis from ovarian cancer is extremely rare, accounting for less than 1% of all ovarian cancers (4). The most common histological type of such brain metastasis from ovarian cancer is serous carcinoma. Brain metastasis from clear cell ovarian cancer is particularly uncommon, and its pathology remains unclear (5).

Few cases of ovarian cancer metastasizing to the brain have been reported, with the average period from initial diagnosis to brain metastasis being approximately 19.6 months; the median survival time after diagnosis of brain metastasis is reported to be less than 6 months (6,7). Because the prognosis of this type of brain metastasis is poor, few reports regarding the course of the disease and its treatment exist, and no consistent consensus regarding treatment has been established. Given the uniqueness of metastasis of ovarian cancer to the brain and the difficulty in treating repeated metastases, the best treatment options for ovarian cancer and the various outcomes must be considered. Herein, we report a rare case of brain metastasis that occurred more than 20 years after ovarian cancer was initially diagnosed.

The patient provided written informed consent prior to receiving chemotherapy or radiotherapy in our hospital and consent to publish.

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Abbreviations: ADP, adenosine diphosphate; CT, computed tomography; MRI, magnetic resonance imaging

Key words: brain metastasis, case report, clear cell carcinoma, endometrioid carcinoma, mucinous carcinoma, ovarian cancer, recurrence

Case report

In February 2025, a 76-year-old woman, gravida 2 para 2, developed sudden confusion and dizziness caused by brain metastases of ovarian cancer after undergoing chemotherapy for lung metastases of ovarian cancer. When she was 57 years old, she presented to a clinic with abdominal swelling, which had been present for 6 months. The patient was first introduced to our hospital with suspected ovarian cancer in July 2005. She had a history of hypertension and diabetes, which were controlled with medication. Magnetic resonance imaging (MRI) and computed tomography (CT) scans showed a massive ovarian tumor without distant metastasis. In 2005, the patient underwent abdominal hysterectomy, bilateral salpingo-oophorectomy, partial omentectomy, pelvic lymphadenectomy, and para-aortic lymphadenectomy. Based on the pathological findings of the specimens obtained during the surgery, the final diagnosis was ovarian cancer, including clear cell and mucinous carcinomas in the left ovary and endometrioid carcinoma in the right ovary (Fig. 1). Six cycles of paclitaxel-carboplatin chemotherapy were administered as adjuvant therapy.

In 2007, the patient was diagnosed with an umbilical tumor and underwent umbilical tumor resection. The resulting diagnosis was recurrent umbilical clear cell carcinoma (Fig. 2).

In 2011, the patient developed swelling in her right inguinal lymph node. In February 2012, she underwent a resection and was diagnosed with recurrent endometrioid cancer. Postoperative radiotherapy (60 Gy in 30 fractions) was administered from March to April 2012. In March 2012, the patient presented with an enlarged lymph node in the left groin, and resection was performed in September 2013. The lesion was diagnosed as recurrent endometrioid carcinoma. Postoperative radiotherapy (50 Gy in 25 fractions) was administered from August to October 2013. In June 2016, CT revealed suspected lung metastasis; however, because the sizes of the lesions remained constant for several years, the patient was placed under observation (Fig. 3A).

In September 2019, recurrent metastasis was again noted in the left inguinal lymph node. Considering that the previous radiotherapy had enabled relatively long-term control of the disease, we performed radiotherapy at the same site to achieve local control. Intensity-modulated radiotherapy at 48 Gy in 12 fractions was administered with a 12 Gy boost in 4 fractions; the total dosage administered was 60 Gy in 16 fractions.

In August 2023, the metastases in the lung grew to a maximum diameter of 2 cm (Fig. 3B), and chemotherapy was initially planned. However, against the treatment guidelines of our institution, the patient requested and underwent palliative radiotherapy (35 Gy in 10 fractions) at another hospital.

The metastases in the lower lobe of the lung grew larger and spread further, and the patient returned to our hospital in May 2024 with a severe cough. Biopsy of the lung and regional subcarinal lymph nodes revealed a clear cell carcinoma, which was diagnosed as metastasis from ovarian cancer. To accurately determine the pathological condition, we attempted homologous recombination deficiency testing on ovarian surgical specimens; however, given that the pathological specimens were from 20 years ago, their processing was not sufficiently accurate to allow homologous recombination deficiency testing. Instead, BRCA analysis was performed on a blood sample collected in May 2024. The analysis was commissioned from Myriad Genetic Laboratories, Inc. Genomic DNA was extracted from whole blood, and polymerase chain reaction amplification and Sanger sequencing were subsequently performed to check for mutations in the *BRCA1/2* genes. No *BRCA1/2* mutations were detected.

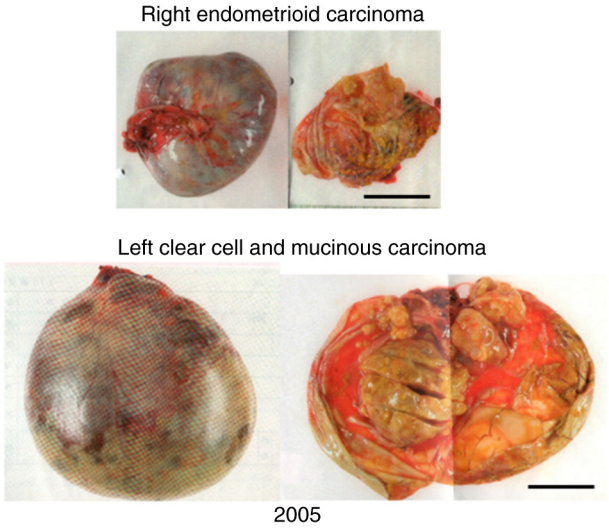

Figure 1. Image of the resected specimens obtained via abdominal bilateral salpingo-oophorectomy. Endometrioid carcinoma was diagnosed in the right ovary, and clear cell and mucinous carcinomas were diagnosed in the left ovary. Scale bar, 5 cm.

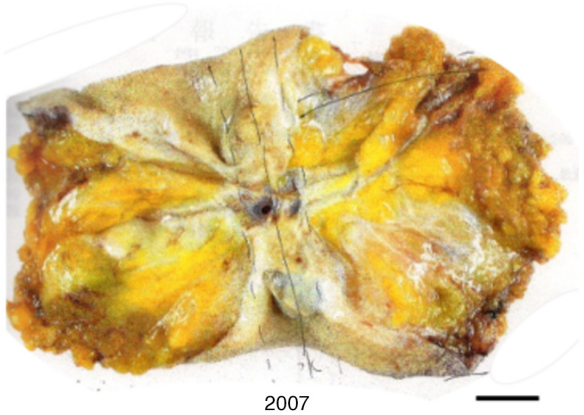

Figure 2. Image showing the resected specimen of the clear cell carcinoma in the umbilicus. Scale bar, 1 cm.

Paclitaxel-carboplatin chemotherapy was resumed from June to November 2024; the tumor size was partially reduced, and the severe cough disappeared (Fig. 3B). The patient underwent treatment with a poly adenosine diphosphate (ADP) ribose polymerase inhibitor (olaparib; 600 mg/day) from January 2025 as maintenance therapy for platinum-sensitive recurrent ovarian cancer. In February 2025, she developed sudden confusion and dizziness. CT and MRI scans showed significant multiple brain metastases and enlargement of the lung metastases (Fig. 4). The patient had impaired consciousness and difficulty moving; consequently, her ability to perform activities of daily living was significantly reduced. The patient's

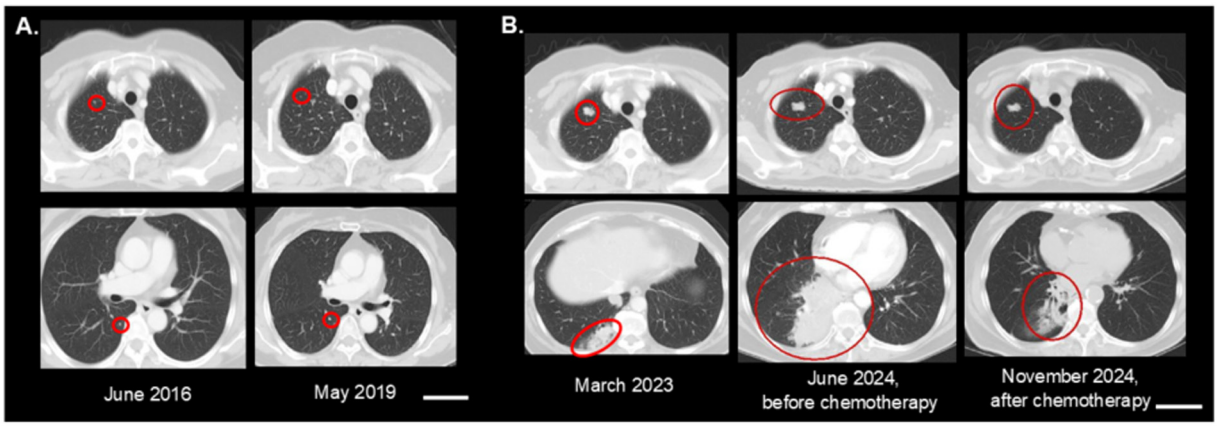

Figure 3. Computed tomography images of the lungs captured between June 2016 and November 2024. (A) The sizes of the right lung metastases were constant for several years. (B) The lung metastases in the right lung were significantly larger in March 2023 than they were in June 2016. After chemotherapy was administered, the right lung metastases were smaller (lung metastases encircled in red). Scale bar, 5 cm.

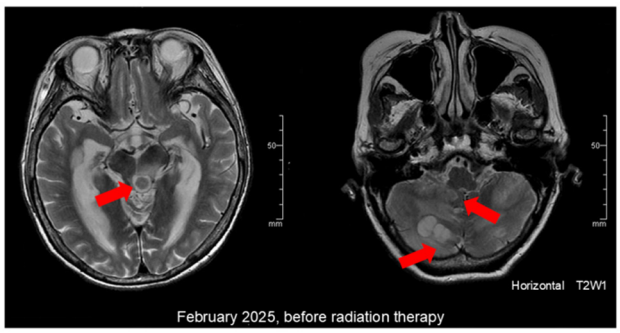

Figure 4. T2-weighted magnetic resonance images of the head, before radiation therapy. Multiple brain metastases are visible (arrowheads indicate metastatic brain lesions).

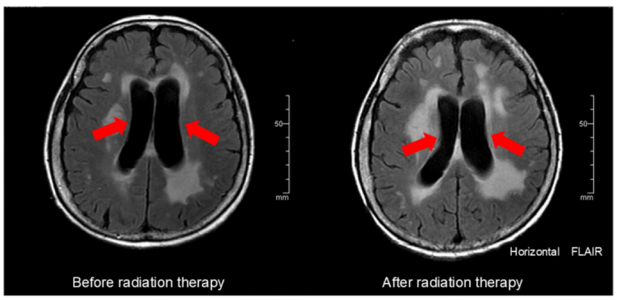

Figure 5. Fluid-attenuated inversion recovery magnetic resonance images of the head, before and after radiotherapy in February 2025. The images show slight narrowing of the lateral ventricles, with some improvement in the hydrocephalus (arrowhead indicates the lateral ventricles.). FLAIR, fluid-attenuated inversion recovery.

overall condition was poor, and she was unable to tolerate invasive tests such as biopsy of the brain tumor and collection of cerebrospinal fluid. MRI revealed multiple lesions in the cerebellum, cerebral parenchyma, basal ganglia, and brainstem, accompanied by extensive cerebral edema surrounding the lesions. The lesions demonstrated low to isointense signal on T1-weighted imaging and mildly hyperintense signal on T2-weighted imaging. The patient also presented with multiple pulmonary metastases, which were enlarging, consistent with ovarian cancer. Based on the imaging and clinical findings, a diagnosis of multiple cerebral metastases from ovarian cancer was made (8).

The invasiveness of standard therapies for brain metastasis, such as surgical resection or stereotactic radiosurgery, would have been intolerable in this patient. Consequently, palliative therapy was chosen, and palliative whole brain radiotherapy (30 Gy in 10 fractions) was administered. Although only slight improvement in the hydrocephalus was observed on MRI, the patient's clinical symptoms improved (Fig. 5). Her sense of orientation improved, enabling her to understand her circumstances. Additionally, her stability improved, allowing her to remain seated in bed or in a wheelchair, as well as to perform tasks such as holding a spoon to eat.

The patient was transferred to a nursing home. To date, 6 months after the transfer, the patient is still alive.

Discussion

Cases of metastasis to the brain of an ovarian cancer that was initially diagnosed 20 years earlier are extremely rare. The incidence of ovarian cancer metastasizing to the brain is estimated to be only 1 to 3% (4). In a Surveillance, Epidemiology, and End Results-based study involving 2,418 cases, 35 (1.6%) patients developed metastases in the brain, 13 (0.54%) developed combined metastases in the lung and brain, and only 3 (0.12%) developed metastases in the lung and/or brain only (9). One clinical report of eight cases indicated a median interval of 19.6 months (range, 0.1-61.6 months) from the initial diagnosis of ovarian cancer to the detection of brain metastases (6). A previous review of 38 clinical series comprising 521 patients with central nervous system metastases from ovarian carcinoma, and spanning the years 1978 to 2011, reported an average interval of 24.3 months (range, 11-46 months). The shortest recorded interval was 0 months and the longest 291 months (4,7,10-44). Considering the reports to date, an interval of 20 years from the initial diagnosis of ovarian cancer to brain metastasis is extremely long.

The histology of the ovarian cancer with brain metastases observed in the current case was also rare. In previous studies, the most common histological type associated with brain

metastases was high-grade serous carcinoma (77.6%), whereas clear cell carcinoma accounted for only 5.2% (5). In general, brain metastasis from ovarian cancer is associated with a poor prognosis (45). One study reported a median overall survival of 8.3 months (range, 1-28 months) following the diagnosis of brain metastasis (46). First-line chemotherapy drugs, such as paclitaxel and platinum, are reportedly unable to cross the blood-brain barrier, making the treatment of brain metastases difficult (47-49). Particularly, several studies have shown that conventional platinum-based chemotherapy regimens yield a poorer prognosis in patients with clear cell carcinoma than in patients with serous subtypes (50-53).

Clear cell carcinoma has a low sensitivity to platinum-based chemotherapy. The findings of an *in vitro* study suggest that the low proliferation of such carcinomas may contribute to cisplatin resistance (54,55). Indeed, the Ki-67 labeling index was found to be significantly lower in clear cell carcinoma than in serous adenocarcinoma (54,55). In the present case, the patient's return to the hospital likely coincided with increased tumor activity in a typically slow-growing clear cell carcinoma. The delayed resumption of chemotherapy for lung metastases may have enabled residual disease to progress and ultimately metastasize to the brain.

Although the use of poly ADP-ribose polymerase inhibitors has shown efficacy in overcoming the blood-brain barrier in animal models of brain metastasis from ovarian cancer (47,56,57), the use of these agents was ineffective in the present case. Among the poly ADP-ribose polymerase inhibitors, olaparib, used in the present case, has limited brain permeability, resulting in restricted exposure of brain tumors to the drug. Additionally, olaparib demonstrates minimal activity in the central nervous system (58-60). Therefore, the efficacy of poly ADP-ribose polymerase inhibitors for treating brain metastasis may be constrained, necessitating further research. The delayed initiation of chemotherapy may also have contributed to the inability of the inhibitor to control disease progression.

The current case showed an unusual course of brain metastasis 20 years after the initial diagnosis. The unusual course may have arisen because multiple histological subtypes coexisted, thereby complicating the clinical picture, especially after numerous lines of treatment were administered. Accurate pathological diagnosis via biopsy is essential for tailoring treatment strategies based on the tumor characteristics. The administration of radiotherapy was a second possible contributing factor. Radiotherapy was initiated at the patient's request, but outside the guidelines of the National Comprehensive Cancer Network (version 3, 2024) (61). Several reports have indicated that radiotherapy can alter the biology and microenvironment of the tumor, potentially exacerbating disease progression through mechanisms such as cytokine modulation and changes in cell division (62-64). Although palliative radiotherapy may be appropriate for symptomatic lung metastases when chemotherapy is contraindicated, our patient was asymptomatic at the time of radiotherapy. Thus, chemotherapy should have been considered as the initial approach. The limitation of this report is that the findings from a single case cannot be generalized. Nevertheless, the disease course reported in this case provides a foundation for the development of various treatment strategies and new treatment possibilities.

Currently, no standardized treatment strategy exists for ovarian cancer with brain metastasis. Some studies report a median survival time of 4.5 months (range, 1.1-28.7 months) following cranial radiation and dexamethasone treatment (6), whereas others report a median survival of 6.4 months (range, 1-28 months) (7). In cases of isolated, solitary brain metastasis, surgical resection followed by whole brain radiotherapy is often recommended. For multiple brain metastases, whole brain radiotherapy with or without systemic chemotherapy is typically administered. From initial treatment for ovarian tumors to recurrence in the umbilicus, lymph nodes, and lungs, we sought optimal curative therapy through surgery, radiation therapy, and chemotherapy, aiming to prevent recurrence. However, curative treatment was not an option for this multiple brain metastasis. Although curative treatment was not feasible, administering treatment that improved the patient's level of consciousness and provided her with more time to spend with her family may have offered some benefit to her quality of life.

With advances in treatment options and imaging techniques, the long-term prognosis for patients with ovarian cancer has improved; similarly, the capability of detecting brain metastasis has improved (65). Molecular profiling and next-generation sequencing have recently been proposed as tools for guiding the choice of personalized medical therapy for recurrent, heterogeneous ovarian cancers. Multi-gene panel testing is widely used in the field of gynecological cancer (66,67). Although testing for *BRCA* gene mutations is the mainstream method for determining sensitivity to poly ADP-ribose polymerase inhibitors in advanced ovarian cancer (68,69), multi-gene panel testing can expand treatment options by identifying rare cancers, cancers of unknown primary origin, recurrent ovarian cancer, and drug-resistant recurrent ovarian cancer (70-72). Therapeutic decisions regarding ovarian cancer need to be based on pathological findings, with the long-term and genetic perspectives carefully considered.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CI, KM, MT, KN and YK treated the patient. CI and AT contributed to the conception and design of the report. CI contributed to data acquisition and wrote the manuscript. KM, KN, and YK confirm the authenticity of all the raw data. AT supervised the report. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for publication, authorizing the use of their imaging, pathological and clinical data for publication.

Competing interests

The authors declare that they have no competing interests.

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