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Brain Metastasis of Ovarian Cancer: Report four Cases and Review the Literature

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Abstract: Objective: The objective of this manuscript is to present different cases of brain metastasis of ovarian cancer. These cases were managed by a multimodal treatment. Materials and methods: To present the clinical characteristics, the imaging, the anatomopathological and immunohistochemical data, and the multimodal treatment (surgery, chemotherapy, in toto brain radiotherapy, and stereotactic radiotherapy) of brain metastases of ovarian cancers. Results: Patients aged 48, 49, 57, and 62 years followed since 2018 and 2019 for clear cell carcinoma of the ovary, high-grade serous adenocarcinoma diagnosed by anatomy pathology and immunohistochemistry examination. They were treated with Paclitaxel carboplatin chemotherapy with the clinical, biological, and radiological response (evaluated according to RECIST criteria); then total surgery. Fifteen, thirty-seven, and nine months after the totalization surgery, the patients presented a confirmed cerebral metastatic relapse. This cerebral relapse was treated by surgical removal of the metastases and by either total brain radiotherapy or stereotactic radiotherapy followed by chemotherapy. Post-radiotherapy chemotherapy was performed with anti-VEGF (bevacizumab) at 14, 29, 31, and 17 months after the radiotherapy sessions. Conclusion: Brain metastases from ovarian cancer are rare. Of late onset, the management requires a multimodal treatment, with chemotherapy, surgery, and radiotherapy either total brain or by stereotaxis.

Keywords: Metastasis, Brain, Ovary, Adenocarcinoma, Cancer

1. Introduction

Ovarian cancer is currently the main cause of death from gynecologic cancer [1], and the fifth leading cause of cancer death in women [2]. It is characterized by a high frequency of locoregional recurrence [1]. Despite sensitivity to chemotherapy, most tumor recurrence occurs within three years of completion of adjuvant therapy [1, 3]. The most common metastatic sites are the peritoneum and omentum (86%) [1, 4]. Brain metastasis (BM) is considered a rare and late event in ovarian cancer [5]. Despite the available treatment options, there are no established recommendations for the medical management of this severe complication [1, 4, 6]. The aim of our study was to investigate the clinical characteristics, treatment modalities, and prognostic factors of patients with BM from ovarian cancers.

2. Observations

2.1. Observation 1

A 48-years-old Female patient was consulted in May 2018 for abdominal distension evolving for 3 months. The clinical examination of the patient noted a preserved general condition with a slightly enlarged abdomen. Thoracic abdominal pelvic CT revealed ascitic and nodular peritoneal carcinosis with an 85 x 49 mm right ovarian tissue mass. The patient underwent diagnostic laparoscopy and right adnexectomy. Anatomopathological and immunohistochemical studies concluded a high-grade serous adenocarcinoma of the ovary. Intravenous chemotherapy with Paclitaxel-Carboplatin for 4 cures was performed followed by totalization (total hysterectomy associated with omentectomy, bilateral lymph node dissection, appendectomy, and peritoneal fluid collection). The patient was then put under clinical, biological, and radiological observation. Fifteen months after the end of the surgery, she presented a letf ovarian local relapse with two pelvic masses measuring 30 x 25 mm on the right and 56 x 45 mm on the left on CT scan and brain metastases with a 40 x 40 mm right frontoparietal lesion on brain MRI in favor of secondary lesion. She underwent excision of the pelvic masses and surgical excision of the brain lesion followed by intracranial stereotactic radiotherapy on the tumor bed at a dose of 27 Gy (3 x 9 Gy). Anatomopathological study of the intracranial lesions confirmed the secondary nature of a previously treated serous adenocarcinoma of the ovary. Chemotherapy with Gemcitabine, Cisplatin, and Bevacizumab was performed with satisfactory tolerance. One year after the end of the stereotactic radiotherapy the patient presented a new left occipital brain lesion. Given the profound alteration of the general state, the patient was put under supportive care. A 14-month setback was noted.

2.2. Observation 2

A 49-year-old patient was consulted in June 2018 for neglected abdominal distension. The clinical examination noted an enlarged abdomen and pain on palpation. A thoracoabdominal-pelvic CT scan showed peritoneal carcinosis with ascites and peritoneal nodules with a tissue mass of the left ovary measuring 90 x 50 mm. She underwent diagnostic laparoscopy and left adnexectomy. Anatomical pathology and immunohistochemistry examination showed a high-grade serous adenocarcinoma of the ovary. Paclitaxel and Carboplatin chemotherapy was performed in 4 courses. Fifteen months after the end of the chemotherapy, in front of a right Hemi paresis associated with headaches and vomiting, a radiological assessment made of a magnetic resonance imaging and thoracic-abdominal-pelvic CT scan was performed. Magnetic resonance imaging revealed a left frontoparietal lesion of 40 x 40 mm and a right frontal lesion of 17 x 18 x 22 mm in favor of secondary localization. Thoracic-abdominal-pelvic CT scan showed two bilateral pelvic masses of 33 x 22 mm on the right and 50 x 50 mm on the left. She underwent surgery on the left frontoparietal and frontal lesions, and totalization surgery (total hysterectomy associated with omentectomy, bilateral lymph node dissection, appendectomy, and peritoneal fluid collection). Anatomopathological and immunohistochemical studies showed a secondary cerebral location of a serous adenocarcinoma compatible with an ovarian origin. Cerebral stereotactic radiotherapy with a dose of 27 Gy (3 x 9 Gy) was performed on the tumor bed. Twelve months after completion of stereotactic radiotherapy, she had a 10-mm occipital brain relapse revealed on magnetic resonance imaging. A positron emission tomography scan showed no hypermetabolism suspicious of local or distant recurrence. The patient received Paclitaxel – Carboplatin - Bevacizumab and is currently undergoing Bevacizumab maintenance with a hindsight of 29 months.

2.3. Observation 3

A 57-year-old female patient who consulted in December 2018 for abdominal pain localized more to the right and an increase in abdominal volume. The clinical examination noted a preserved general condition and a mass in the right flank. The radiological workup showed a pelvic mass with right iliac and lumbo-aortic adenopathies without secondary locations. The initial tumor marker was 153 U/ml. The patient underwent exploratory surgery and cyto reduction. The surgical exploration noted a predominantly pelvic peritoneal carcinosis with massive epiploic involvement and voluminous pelvic and lombo-aortic adenopathies. Excision of the left adnexal mass and an omentectomy were performed. Anatomopathological (Figure 1) and immunohistochemical (Figure 2) studies showed a serous cystadenocarcinoma of the ovary. The patient was treated with neoadjuvant chemotherapy such as Paclitaxel and Carboplatin for six cures. A good partial radiological tumor response of about 50% according to RECIST criteria and negativity of the tumor marker was noted. A Totalization surgery was performed, and the anatomy pathology noted a fibrous and necrotic remodeling with cytosteatonecrosis lesion and macrophagic reaction without a viable tumor. She was then followed regularly in consultation. Twenty-seven months after surgery, the patient presented a cerebral metastatic relapse revealed by headaches and hemiparesis. A cerebral CT scan noted occipital cerebral tissue parenchymal lesions of secondary appearance. She underwent surgery to remove two occipital brain processes that were threatening. The anatomopathological and immunohistochemical study showed a secondary localization of a carcinomatous proliferation compatible with an ovarian origin. Total cerebral radiotherapy with a dose of 30 Gy, 3 Gy per session, and 5 sessions per week was performed (Figure 3). The patient is currently undergoing palliative chemotherapy such as Gemcitabine, Carboplatin, and Bevacizumab. A 31-month setback was noted.

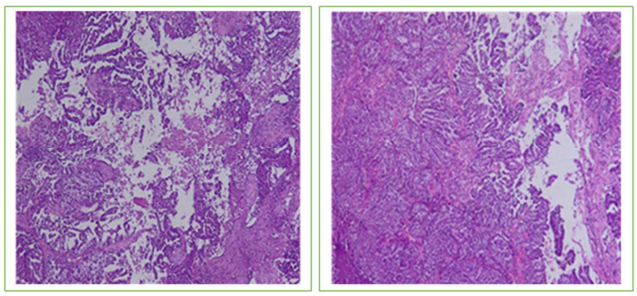

Figure 1. *Images of anatomy pathology.*

Focally necrotic carcinomatous proliferation, arranged in clusters, and sometimes in papillary, micro papillary structures. The tumor cells are pleomorphic, with marked atypia, anisokaryotic nuclei, nucleoli and abundant eosinophilic cytoplasm sometimes clarified.

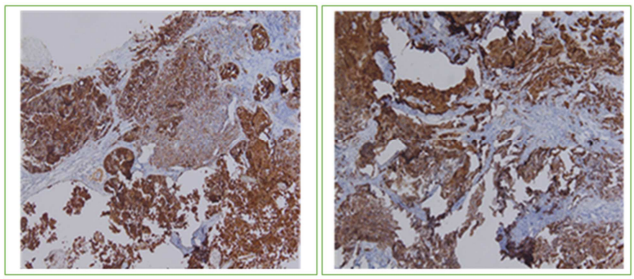

Figure 2. *Images of anatomy pathology and immunohistochemistry.*

The immunohistochemical study (performed on Dako Autostainer Link 48) shows that the tumor cells express cytokeratin AE1/AE3 (clone AE1/AE3).

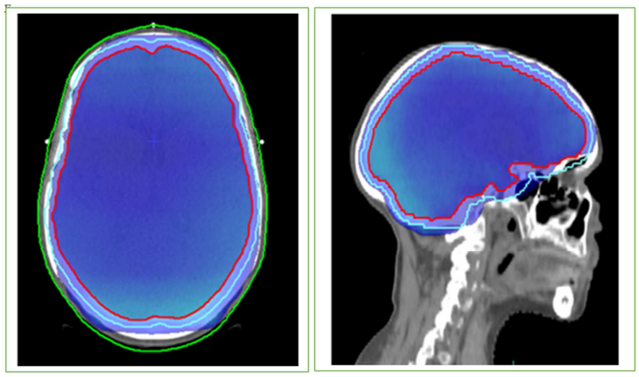

Figure 3. *Dosimetry images.*

Dose distribution representation for 95% over the PTV for brain metastasia at axial, coronal and sagittal plan.

2.4. Observation 4

A 62-year-old female patient who consulted in March 2019 for abdominal pain associated with bloating and increased abdominal volume. The clinical examination noted a general state rather preserved, an increase in the volume of the abdomen with a positive sign of flow objectifying an ascites of average abundance. The thoracic-abdominal-pelvic CT scan showed peritoneal carcinosis without pelvic mass syndrome or liver abnormality (Figures 4 and 5). The tumor marker CA 125 was 1325 U/ml. The patient underwent laparoscopy which revealed a peritoneal carcinosis extending to the diaphragmatic cupolas, with the presence of friable necrotic tumor formations on both ovaries. An ovarian and peritoneal biopsy was performed and the anatomopathological and immunohistochemical study showed a clear cell carcinoma. Intravenous chemotherapy with Paclitaxel-Carboplatin for six courses was performed with a good clinical, biological (Ca 125 at 8 U/ml), and radiological response (disappearance of peritoneal carcinosis and ovarian masses). Subsequently, a totalization surgery (Total hysterectomy without adnexal preservation, omentectomy, appendectomy, bilateral lymph node dissection and ascites collection) was performed, and the patient was regularly followed in consultation. Nine months after surgery, the patient presented a cerebral metastatic relapse revealed by headaches, vomiting, and a motor deficit of the left hemi-body. The radiological work-up made of cerebral CT and MRI noted secondary overlying parenchymal tissue lesions with overlying falcoral involvement and bone lytic lesions (Figure 6). The tumor marker Ca 125 was 19 U/ml. She underwent excision of two brain processes, temporal, and right frontal. Anatomopathological and immunohistochemical studies showed a secondary localization of a carcinomatous proliferation compatible with an ovarian origin. Total cerebral radiotherapy with a dose of 30 Gy, 3 Gy per session and 5 sessions per week was performed and then put under palliative chemotherapy such as Gemcitabine - Carboplatin - Bevacizumab. The patient is currently undergoing maintenance with bevacizumab monotherapy with a follow-up of more than 17 months. A setback of 17 months was noted. The last extension workup performed in December 2021 showed no evidence of local or distant progression.

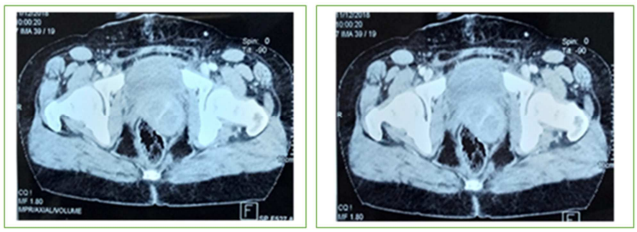

Figure 4. *Images of the scanner.*

Voluminous polylobed, heterodense, solid-cystic mass whose solid portions are moderately enhanced after injection of iodinated contrast medium. It measures 122 x 88 mm extended by 100 mm in height.

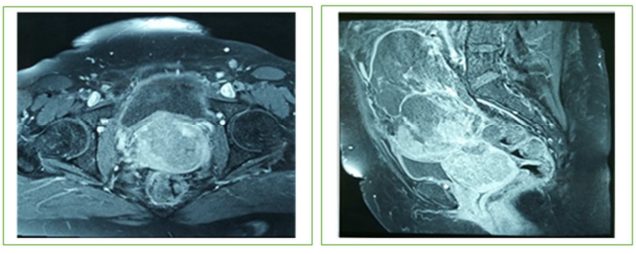

Figure 5. *Pelvic magnetic resonance imaging.*

Voluminous heterogeneous, solid-cystic, abdominal-pelvic tissue mass with a large vertical axis measuring 200 mm and an antero-posterior diameter of 90 mm.

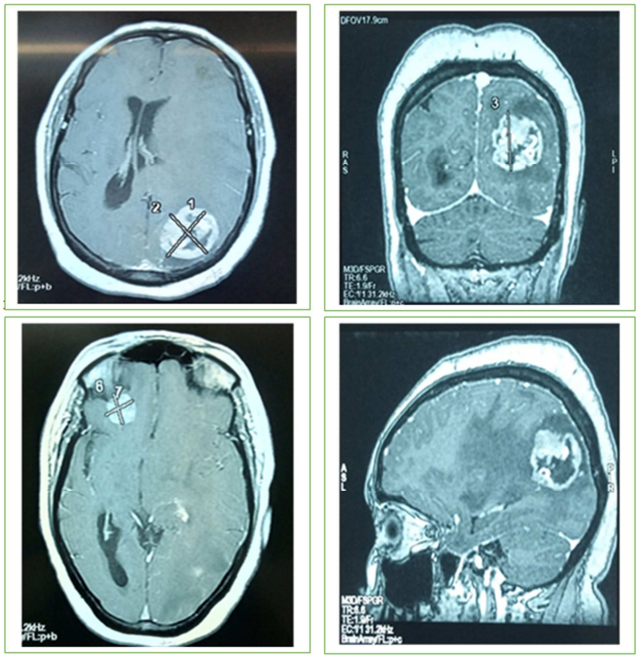

Figure 6. *Images of brain magnetic resonance imaging.*

MRI appearance of a left parieto-occipital process with T1 iso signal, T1 hypo signal, and discrete T2 hyper signal with central necrosis area that strongly enhances after injection of contrast medium. There is significant peri-lesional parietal edema. Presence of another right frontal lesion with hypo T1 signal and hyper T2 signal which is strongly.

3. Discussion

Brain metastases are rare in ovarian cancer and occur more often in patients with prolonged survival [7, 8]. A slight increase in frequency has been observed in recent years [7], reported in the literature to be 1 to 2.5% [9]. This increase is explained by improved imaging techniques, leading to an earlier and more sensitive diagnosis of brain lesions, prolonged patient survival due to improved therapeutic strategy, and biological mechanisms involving the blood-brain barrier that can either prevent water-soluble cisplatin from entering the central nervous system or lower its concentration, thereby increasing metastasis to the brain [10].

The median age of onset of brain metastases ranged from 52 to 58 years. The median interval between the diagnosis of ovarian cancer and the diagnosis of brain metastases varied from 14.5 to 46 months [7]. It is directly correlated with the initial stage of the tumor [9]. In the four reported cases, there were 18, 27, 28, and 30 months, respectively, between the diagnosis of cancer and the detection of brain metastases.

Pathologically, serous adenocarcinoma was the most common histological type [2, 9, 10] followed by other histologies such as mixed epithelial carcinoma, endometrioid carcinoma, mucinous carcinoma, and clear cell carcinoma [9]. One of our patients had a clear cell carcinoma.

The clinical manifestations of brain metastases depend on the location of the lesion. Headache is the most common symptom (40-50% of cases) mainly and vomiting [10] due to increased intracranial hypertension [7, 10]. Other common symptoms and signs included weakness of the extremities, hemiparesis, tremor, confusion, seizures, vertigo, speech disorders, and visual disturbances [7, 10].

The use of the CA 125 tumor marker in surveillance is controversial. Tay et al [10] pointed out that CA125 was not reliable for the diagnosis of brain metastases. Jia-Xin Yang et al [10] noted an apparent rise in CA125 (2.5 to 6 times normal) before the diagnosis of brain metastasis. None of our patients had increased cancer antigen 125.

The diagnosis of brain metastasis was mainly based on imaging examinations including CT and especially MRI. However, anatomical pathology examination confirms the diagnosis [10]. Radiologically, the brain involvement is often multiple and presents a mixed solid-cystic form. The frontal lobe is the most frequent location [9]. At the time of diagnosis, the extracranial disease is found in more than half of the patients [9].

As a rare disease, BM of ovarian carcinoma has no standard management. Different treatments should be used depending on the performance status, the location of the lesion, whether the lesion is single or multiple, and the absence or presence of extracranial metastases [10]. A multimodal therapy approach can improve patient outcomes and quality of life, and a significant prolongation of survival can be achieved [11]. Multimodal treatment includes surgery, total brain radiation therapy, stereotactic radiation therapy, chemotherapy, and supportive care [9].

Patients with single brain metastases are usually treated with surgery followed by radiation therapy, and this treatment modality appears to achieve longer survival compared with surgery or radiation therapy alone [7]. Total brain irradiation with or without sequential chemotherapy is the treatment of choice for multiple BM, with or without extracranial disease, but achieves a median survival of only 3 to 10 months [7]. A single brain metastasis may be associated with better outcomes and survival if treated with surgery, radiation, and chemotherapy [11]. The presence of multiple brain lesions showed a significantly reduced survival of 9.2 months for multiple lesions versus 21.4 months for single lesions [7].

After radiation therapy for single BM, median survival was 23.1 months for patients who received this integrated treatment (surgery plus total brain irradiation) versus 5.3 months for those who received total brain irradiation alone ($p < 0.01$) and versus 6.9 months for those who received surgery alone ($p < 0.01$) [7]. Other authors have reported a mean survival of 28 months in 11 patients with single brain metastases treated with surgical removal followed by radiation and chemotherapy [7].

However, approximately 50% of patients with solitary BM are not candidates for surgery due to extracranial disease or metastasis unresectability [7]. The recent introduction of radiosurgery and stereotactic radiotherapy has changed the treatment paradigm and improved the outcome of central nervous system metastatic tumors [11]. But there are data in the literature evaluating the role of stereotactic radiotherapy in the treatment of BM of gynecologic cancers. Johnston et al.

[12] reported that patients with ovarian cancer have a reduced risk of distant neurological complications after stereotactic radiotherapy [13]. Celejewska et al [14] reported improved survival after treatment with stereotactic radiotherapy. Combined multimodal treatment (stereotactic radiotherapy and surgery) was superior to any monotherapy in terms of survival [13]. For patients with limited BM, stereotactic radiotherapy can replace total brain irradiation or surgery [11]. It allows the delivery of high doses of focused radiation to a small intracranial target while sparing the surrounding brain parenchyma [7]. A prospective randomized trial demonstrated the beneficial effect of gamma knife in patients with one to four BM [11]. Among the cases presented, two patients received total brain radiation therapy and the other patients received stereotactic radiotherapy.

The importance of chemotherapy in the management of BM is still controversial. Some studies with chemotherapy have shown objective responses and promising survival rates for patients with BM from breast cancer and germ cell tumors, and recently even ovarian cancer [7]. Cooper et al. [15] reported a complete response and two partial responses in three patients with ovarian cancer and BM treated with carboplatin alone. One patient with multiple BMs achieved a complete response after total brain irradiation and sequential chemotherapy consisting of cisplatin and gemcitabine [16]. Three subsequent brain relapses were controlled with combination chemotherapy including 5-fluorouracil, cisplatin, and gemcitabine [7]. The combination of carboplatin and docetaxel achieved a complete response in a patient who developed multiple brains and meningeal metastases 10 months after completion of initial treatment with the same chemotherapy scheme [16]. Bevacizumab, a monoclonal antibody against vascular endothelial growth factor (VEGF), is the targeted therapy that has undergone the greatest clinical development in ovarian cancer, leading to its registration in combination with carboplatin-paclitaxel as first-line treatment [17]. The benefit of the addition of this antiangiogenic agent was demonstrated in two randomized phases III studies (GOG 218 and ICON 7) on the improvement of the primary endpoint, which was progression-free survival [17]. The combination of carboplatin-paclitaxel-bevacizumab followed by maintenance with bevacizumab is one of the standard treatments in the first-line management of cancers stage IIIB to IV [18]. The four patients reported receiving bevacizumab. No additional bleeding toxicity was observed. Larger prospective studies are needed to identify the optimal treatment strategy in patients with central nervous system metastases from ovarian cancers.

4. Conclusion

BM from ovarian cancer is a rare situation. They occur late in the course of the disease due to the prolongation of survival with the development of the proposed therapeutics. The treatment of BM requires a multimodal treatment combining a systemic treatment and a local treatment by surgery and/or radiotherapy. Despite this multimodal treatment, the prognosis remains poor.

Conflict of Interest

The authors declare that they have no competing interests.

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