Case 1 – Multiple brain metastases from ovarian cancer: a case report

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Abstract
58-year-old woman with a history of epithelial ovarian cancer, who manifested seizure disorder, characterized by sudden stiffening of her entire body with loss of consciousness. The imaging revealed the presence of multiple secondary lesions scattered throughout the brain parenchyma bilaterally in the supra and infratentorial areas; other evidences of disease were localized in the lung and abdominal cavity with signs of peritoneal carcinomatosis. She received a whole brain radiation therapy followed by adjuvant chemotherapy with carboplatin and paclitaxel. To date, after 11 months from initial diagnosis of brain metastasis, the patient is still well, without neurological symptoms, or local progression, in the brain or the abdomen.

Key words: brain metastases, case report, epithelial ovarian cancer, multimodal management, whole-brain radiation therapy

Introduction

Epithelial ovarian cancer (EOC) accounts for 3% of cancers among women, but is the fifth leading cause of cancer death in women and the leading cause of gynaecologic cancer death [1]. The predominant form of relapse after primary surgery and chemotherapy for EOC is in the abdomen and pelvis [2]. Central nervous system (CNS) and brain metastases (BM) in these patients are a rare occurrence, with reported incidence of 0.3–2.0% [3]. However, in recent years, the incidence has increased significantly up to 12% which could perhaps be attributable to increased survival and improvement in treatment options [4]. The therapeutic approach to patients with BM from EOC, due to the small numbers of cases and short follow-up periods available in other series, is challenging [4–6]. We report the case of a platinum-partially sensitive ovarian cancer patient who developed multiple BM after 30 months from primary treatment and was managed with whole-brain radiation therapy (WBRT) followed by platinum-based chemotherapy, achieving 41 months of survival.

Case presentation

A 58-year-old woman was admitted to our Institution in September 2010, with adnexal complex masses, ascites and carbohydrate antigen (CA) 125 values of 4431 U/mL. She underwent primary cytoreductive surgery, with residual tumour smaller than 0.5 cm. The histological examination documented a serous papillary ovarian carcinoma, moderately differentiated, stage IIIC according to FIGO (International Federation of Gynecology and Obstetrics) staging. She was also subjected to six cycles of adjuvant platinum-based chemotherapy according to the PT (carboplatin, paclitaxel) schedule, until April 2011. After primary treatment, a complete clinical remission (no apparent lesions at the second look surgery and CA 125 5.5 U/mL) was achieved. A first recurrence occurred 10 months after the last cycle of carboplatin-based chemotherapy (February 2012) at the lymph nodes in the perigastric, perihepatic and sub diaphragmatic seat with CA 125 values of 126 U/mL. A gastrectomy with anastomosis according to Billroth II and a cholecystectomy were performed. The histological examination revealed metastasis from poorly differentiated carcinoma with ovarian primitiveness. The patient underwent seven cycles of chemotherapy with pegylated liposomal doxorubicin 30 mg/m^2 plus trabectedin 1.1 mg/m^2 until September 2012

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with complete clinical and radiological response. Despite the good response, the treatment was discontinued due to the patient's decision. After 30 months from the initial diagnosis (March 2013), she complained of seizure disorder characterized by sudden stiffening of her entire body with loss of consciousness for a time estimated between 10 to 20 minutes. Blood tests were reported as essentially normal, except the CA 125 value, which was 476.7 U/mL. An electroencephalogram (EEG) was reported to be abnormal because of the presence of a slow-frequency discharge in the anterior half of the left hemisphere. Computed tomography (CT) scan of the head showed two focal lesions in the posterior temporal lobe and in the posterior frontal lobe, both 10 mm, with perilesional oedema in the temporal lobe. In the context of the white matter of the semi-oval centres and in the cortico-subcortical, there were some focal hyperdense <1cm of diameter areas of non-unique significance (possible repetitions or vascular alterations of paraneoplastic basis). After consultation with a neurologist, it was decided to perform a brain magnetic resonance imaging (MRI) and this revealed the presence of multiple secondary lesions, with diameters from a few mm to 1 cm, scattered throughout the brain parenchyma bilaterally in the supra and infratentorial areas. The larger lesions were located in the right side of the cerebellum, in the right parietal lobe and in the left side of the occipital lobe. The larger lesions had central necrosis and were surrounded by oedema (Figure 1 A-F). Levetiracetam, at a dosage of 500 mg twice a day was prescribed to prevent further crisis. The patient also underwent a positron emission tomography (PET)-CT scan; this showed other evidence of disease, localized at the upper lobe and the lower lobe of the right lung with diameters of between 2–5 mm; lymphadenopathy, with a maximum diameter of 17 × 23 mm in the right iliac artery, was also identified. Multiple lymphadenopathies were also seen in the inter-aorto-caval (diameter 10 mm) and lomboaortic (diameter 12 mm) area. Minimum inhomogeneity of the mesenteric adipose tissue without sure signs of peritoneal carcinomatosis was also described. Three hypodense formations with diameters of 2–5 mm were found in the liver parenchyma segment II and VI. After careful evaluation and discussion with the gynaecological oncological team and consideration of the multiple localization of disease, it was decided to treat the patient with WBRT, 30 Gy in 10 fractions over two weeks, together with steroids. After radiotherapy (April 2013), the patient's neurological symptoms disappeared. Considering her good performance status (ECOG 0) as appropriate, she received adjuvant chemotherapy with carboplatin and paclitaxel. First PET-CT imaging after 3 cycles of chemotherapy showed partial response of both brain and pelvic disease. She continued to receive systemic treatment but treatments were stopped after five more cycles because of adverse reactions and aggravation of general clinical condition. After 11 months from initial diagnosis of BM, the patient is still well, without neurological symptoms or local progression in the brain or abdomen.

Discussion

We report the case of a platinum-partially sensitive ovarian cancer patient who presented after 30 months from

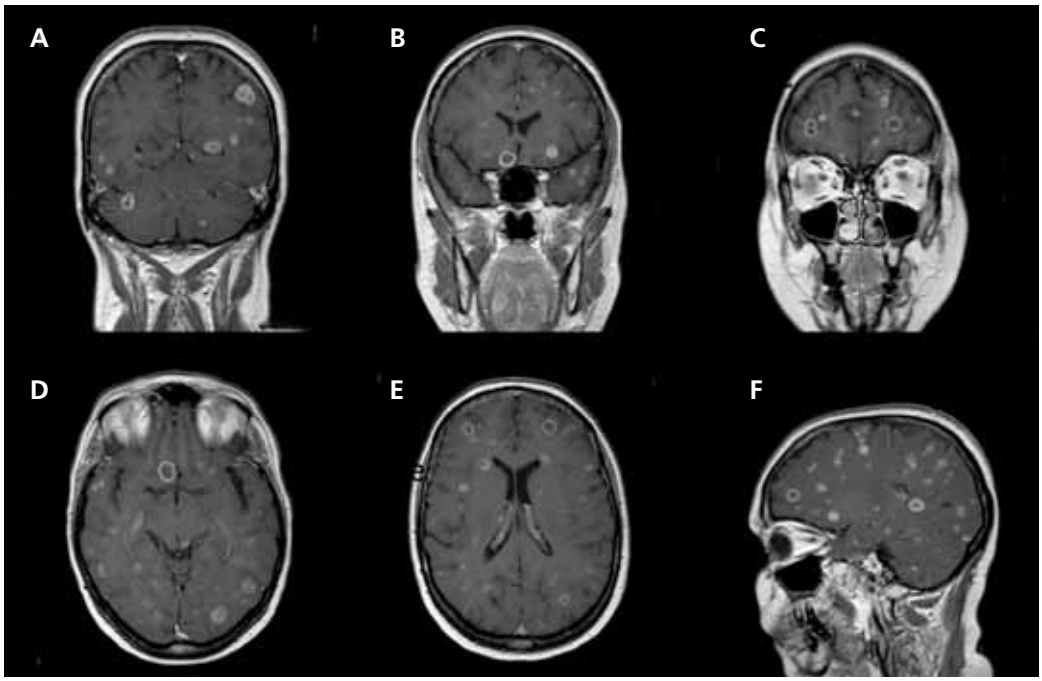

Fig. 1. Magnetic resonance imaging before whole-brain radiotherapy treatment for multiple brain metastases from ovarian cancer. Multiple secondary lesions, with a diameter between a few mm and 1 cm, scattered throughout the brain parenchyma bilaterally in the supra and infratentorial areas. The larger lesions were located in the right side of the cerebellum (A), in the right parietal lobe (A-C-D-E-F) and in the left side of the occipital lobe (A-B-D-E-F). The larger lesions had central necrosis and were surround by oedema.

initial diagnosis with multiple cerebral lesions and extracranial recurrent disease treated with radiotherapy followed by carboplatinum-based chemotherapy. In our patient, surgery was not recommended due to the multiplicity of lesions and the presence of extracranial disease, and a multi-treatment approach was preferred to improve her clinical condition, especially the neurological symptoms.

BM are the most common intracranial neoplasm in adults and represent an important cause of morbidity and mortality. It is thought that 50–60% of BM originate from lung cancer, 15–20% from breast cancer, and 5–10% from melanoma [7]. Ovarian cancer with BM remains a relatively uncommon clinical scenario (2% incidence), but their incidence is likely to increase due to better primary control of intra-abdominal disease with cytoreductive surgery and aggressive chemotherapy leading to a longer survival, which then allows neoplastic cells to seed and grow at distant sites [8]. It was suggested that BM from ovarian cancer occur via direct haematogenous seeding through Virchow-Robin perivascular spaces, via retrograde lymphatic spread for meningeal involvement, or via direct invasion into CNS after bony involvement [9]. Advanced tumour stage and high histological grade are risk factors for this complication [4–6]. The prognosis of patients with BM from gynaecologic malignancies is very poor. Previous studies reported the median survival after diagnosis of BM from ovarian cancer varied between 6 to 7 months, and only a few patients survive for more than 1 year [10, 11]. Cohen et al. [10] reported that the survival rates of patients at 1 and 5 years of follow-up were 31% and 5%, respectively; however, recently, a longer median survival time up to 23 months has been reported for patients with BM from ovarian cancer treated with multimodal treatment, including gamma-knife radiotherapy and surgical excision [10, 12, 13]. The therapeutic approach is different for an isolated, single metastasis compared to multiple metastases. Patients with isolated, single BM generally undergo neurosurgical resection followed by whole-brain irradiation (WBRT), and this treatment modality appears to achieve a longer survival when compared to either surgery or irradiation alone [14]. However, approximately 50% of patients with solitary BM are not candidates for surgery because of extracranial disease or tumour inaccessibility. Stereotactic radiosurgery, which allows the delivery of high doses of focused radiation, by either a linear accelerator or a gamma-knife, to a small intra-cranial target while sparing the surrounding normal brain, is also emerging as a valid option with lesions unsuitable for surgical resection. WBRT with or without 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 [14–16].

Conclusion

There is no consensus for the treatment of BM from ovarian cancer because the relatively small numbers of cases with BM from gynaecologic malignancies described in the literature precluded any conclusions being drawn about the optimal therapeutic management of these patients. In view of this, we decided to treat our patient with a multimodal approach. Our first aim was symptom palliation, which we achieved adequately after WBRT. In the majority of patients, treatment of BM is palliative because the primary disease is often advanced and the general condition of these patients often is poor.

Commentary

In the management of patients with newly diagnosed single or multiple BM, various treatment modalities exist, including WBRT, resection, stereotactic radiosurgery, and best supportive care with the use of dexamethasone. Treatment recommendations are based on patient factors (such as age, performance status), tumour factors (such as number and size of BM, tumour type and extracranial disease activity), and available treatment options (such as access to neurosurgery or stereotactic radiosurgery). The choice of treatment is performed according to the American Society for Radiation Oncology (ASTRO) guidelines.

Single BM and good prognosis (expected survival ≥3 months): *for a single BM larger than 3 to 4 cm and amenable to safe complete resection, WBRT and surgery (level 1) should be considered. Another alternative is surgery and radiosurgery/radiation boost to the resection cavity (level 3). For single metastasis less than 3 to 4 cm, radiosurgery alone or WBRT and radiosurgery or WBRT and surgery (all based on level 1 evidence) should be considered. Another alternative is surgery and radiosurgery or radiation boost to the resection cavity (level 3). For a single BM (less than 3 to 4 cm) that is not resectable or incompletely resected, WBRT and radiosurgery, or radiosurgery alone should*

be considered (level 1). For a non resectable single BM (larger than 3 to 4 cm), WBRT should be considered (level 3).

Multiple BM and good prognosis (expected survival ≥3 months): *for selected patients with multiple BM (all less than 3 to 4 cm), radiosurgery alone, WBRT and radiosurgery, or WBRT alone should be considered, based on level 1 evidence. Safe resection of a BM or metastasis causing significant mass effect and postoperative WBRT may also be considered (level 3).*

Patients with poor prognosis (expected survival <3 months): *patients with either single or multiple BM with poor prognosis should be considered for palliative care with or without WBRT (level 3).*

It should be recognized, however, that there are limitations in the ability of physicians to accurately predict patient survival. Prognostic systems such as recursive partitioning analysis, and diagnosis specific graded prognostic assessment may be helpful.

Radiotherapeutic intervention (WBRT or radiosurgery) is associated with improved brain control. In selected patients with a single BM, radiosurgery or surgery has been found to improve survival and locally treated metastasis control (compared with WBRT alone).

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