

CASE REPORT

Brain metastases in patients with epithelial ovarian cancer: report of two cases and literature review

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ABSTRACT

Brain metastasis from primary ovarian cancer is rare. We report two patients diagnosed with FIGO stage IIIc ovarian carcinoma. After primary diagnosis, the two patients underwent six cycles of neoadjuvant paclitaxel plus carboplatin chemotherapy, followed by optimum debulking surgery and three additional cycles of adjuvant chemotherapy. Patient 1 developed several supratentorial lesions twenty months after initial diagnosis and subsequently was treated with intrathecal chemotherapy, cranial radiotherapy and intravenous chemotherapy. Patient 2 developed an isolated cerebellar metastasis ten months after initial diagnosis and subsequently was treated with surgical resection, cranial radiotherapy and intravenous chemotherapy.

Keywords: brain neoplasm, chemotherapy, ovarian epithelial cancer, ovarian neoplasm, radiotherapy, review literature as topic.

INTRODUCTION

Ovarian cancer is one of the most challenging diseases in the field of gynecologic oncology and represents one of the major causes of mortality associated with genital tumors¹. The disease is associated with an elevated rate of recurrence and high mortality, even after performing optimal cytoreduction (debulking) surgery and adjuvant therapy. Recurrence is observed mainly in the abdomen with peritoneal or lymphatic spread and is rarely observed extra-abdominally by hematogenous dissemination¹⁻⁴.

Brain metastases develop in approximately 10 to 30% of patients with cancer and the prognosis is poor^{1,5,6-10}. The primary neoplasms originating these metastases are more frequently from the lung, breast and melanoma. With the exception of choriocarcinoma, brain metastases from gynecological cancers are rare, with incidence from 0.29 to 5%^{1,10}.

The mean survival after the development of central nervous system (CNS) metastases varies from 3 to 9 months^{2-4,6-8}, and should take into account the type of treatment. The therapeutic options involve radiotherapy and chemotherapy^{6-9,11-13}. Neurosurgical resection is limited

to patients with single metastasis and/or easy surgical access^{9,10,14}. Patients who receive no treatment have a mean survival of 0.5 months and those who receive some type of treatment survive an average of 9 months⁸. Tay et al.¹⁴ found a mean survival of 19.5 months in their study.

Our report is on two patients with serous papillary ovarian adenocarcinoma, stage IIIc of the International Federation of Gynecology and Obstetrics (FIGO), who had CNS metastases, with one patient presenting multiple supratentorial lesions and the other patient presenting a single cerebral metastasis.

This is an uncommon pattern of recurrence in ovarian cancer, as the largest series in the literature from a single institution is 72 cases. The other retrospective series are restricted to case reports or to numbers less than 20 patients each. Until now there are fewer than 200 cases reported in the literature. Therefore, this review aims to highlight two possible forms of presentation of metastases and assist in the treatment of cases similar to these.

CASE REPORTS

Case 1

The patient, a 44-year-old female, was diagnosed with epithelial ovarian cancer (metastatic serous papillary adenocarcinoma, FIGO stage IIIc) following laparoscopy from another medical service. CA-125 was 7787.6 U/ml. Due to the vast extension of the tumor, we chose to do six cycles of neoadjuvant chemotherapy with carboplatin (AUC 5) and paclitaxel (175mg/m²), at intervals of 21 days between each cycle, with a reduction in CA-125 to 9.2 U/ml. Subsequent optimal debulking surgery (total hysterectomy, bilateral salpingo-oophorectomy, supra- and infra-colic omentectomy, appendectomy, pelvic and para-

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-aortic lymph node dissection and peritoneal exudate) was performed at Hospital ASCOMCER (Juiz de Fora, Brazil). An additional three cycles of adjuvant chemotherapy with an interval of 21 days were carried out. After the primary treatment, the patient was disease free. Twenty months after initial diagnosis, the patient had cerebellar ataxia. MRI exam showed multiple nodular supratentorial parenchymatous lesions in the frontal, occipital, and parietal lobes and peritrigonal region, with no evidence of disease elsewhere. The cytopathological analysis of cerebrospinal fluid revealed the presence of neoplastic cells of epithelial ovarian origin. After the diagnosis of metastases, the patient received six cycles of intrathecal chemotherapy consisting of methotrexate (12.5 mg) and cytarabine (30 mg), six cycles of intravenous chemotherapy consisting of docetaxel (123 mg) and carboplatin (640 mg) and was subjected to radical cranial radiotherapy, with a total dose of 4000cGY and with photon beam energy in a 10 MV linear accelerator. We performed another MRI, revealing control of multiple parenchymatous lesions with sparse cortico-subcortical focus in the brain parenchyma with signs of significant regression of the same. However, lesions of the right superior frontal gyrus, ipsilateral supramarginal gyrus and cortex of the left lateral occipital gyrus persisted, indicating partial response to treatment according to RECIST criteria. Six months after the diagnosis of brain metastases, the patient was asymptomatic, with normal CTs of the chest, abdomen, pelvis and bone scintigraphy. The patient died from cancer eleven months after diagnosis of metastases.

Case 2

The patient, a 58-year-old female, had signs of ascites and severe abdominal discomfort. She underwent abdominal CT that showed signs of peritoneal carcinomatosis. Uterus and ovaries were not visualized because of voluminous ascites. CA-125 was elevated to 2800 U/ml. The ascitic fluid was submitted for oncotic cytology, which revealed a malignant epithelial tumor metastasis. The patient underwent six cycles of neoadjuvant chemotherapy with carboplatin and paclitaxel with intervals of 21 days between cycles. After the sixth cycle, the CA-125 was reduced to 21.7 U/ml. Optimal debulking surgery (total hysterectomy, bilateral salpingo-oophorectomy, supra- and infra-colic omentectomy, appendectomy, pelvic and para-aortic lymph node dissection and peritoneal exudate) was performed at Hospital ASCOMCER (Juiz de Fora, Brazil). The pathological examination revealed metastatic papillary serous adenocarcinomas, FIGO stage IIIc. An additional three cycles of adjuvant chemotherapy with an interval of 21 days were carried out. Ten months after the diagnosis of ovarian cancer, the patient had cerebellar ataxia. An MRI revealed an expansive solid-cystic lesion measuring 4.5 cm affecting the superior portion of the right cerebellar

hemisphere. The patient underwent surgical resection of the CNS lesion. Histopathology revealed cerebellum infiltrated by papillary adenocarcinoma consistent with primary ovarian carcinoma. After surgery, twenty cycles of cranial radiotherapy were performed with a total dose of 4000cGY, along with six cycles of intravenous chemotherapy with docetaxel and carboplatin. The patient died due to complications of cancer, seven months after the diagnosis of CNS metastasis.

DISCUSSION

Ovarian cancer is the fifth most common malignancy in women in industrialized countries, with most having the disease diagnosed in advanced stages (stages III and IV according to FIGO classification). The combination of debulking surgery followed by cisplatin or carboplatin with paclitaxel represents the front line treatment for patients with advanced disease after demonstration of increased life in randomized clinical trials^{1,2}.

After surgery and chemotherapy, only 20 to 30% have survival of five years or more^{1,11,12}. This type of cancer rarely progresses with brain metastases¹⁻³. The incidence reported in the literature is 0.29 to 5%. The two patients in this review showed papillary serous adenocarcinoma, FIGO stage IIIc.

The mean age of patients diagnosed with ovarian cancer reported in the literature are described in Table 1. The most common histological subtype of ovarian cancer of epithelial origin is serous¹⁻⁹. There is not a consensus among all studies in the literature as to staging of ovarian tumors in patients who developed brain metastases. Cohen et al.², Anupol et al.⁴, Geisler and Geisler⁸, and Porthuri et al.⁹, and noted that most patients had primary advanced disease (stage III and IV according to FIGO norms), which was not observed by Ogawa et al.¹ and Kolomainen et al.⁶.

In the first report, the development of brain metastases occurred 20 months after the diagnosis of ovarian cancer and in the second report, after 10 months. The mean time reported in the literature varies from 18.5 to 46 months^{2-4,6-8}.

The main neurological symptoms that patients experience are headache, hemiparesis, motor, sensory and visual disturbances, cerebellar dysfunction and seizures^{5,6,8,9,11,12}. The patients in question had the diagnosis of ataxic syndromes.

There is no consensus in the literature about the best treatment in the case of brain metastases^{2,3,10,13,14}. However, the choice of the most appropriate therapeutic regimen should consider the location and number of metastatic CNS neoplasms^{2,10,14-16}. Surgery is contraindicated in cases of multiple metastases and/or tumors located in areas of difficult surgical access⁹⁻¹². Accordingly, gamma knife ra-

Table 1. Review of the literature on brain metastases originating from primary ovarian cancer.

Reference	Number of patients with ovarian cancer	Period of the study	Mean age at diagnosis of ovarian cancer (years)	Number of patients with brain metastasis	Incidence of brain cancer in ovarian cancer (%)	Mean interval for brain metastasis (months)	Mean survival time after brain metastasis (months)
Cohen et al. ²	8225	1975-2001	50.4	72	0.9	22.08	6.2
Rodrigues et al. ⁷	795	1977-1990	54.5	15	1.9	18.5	9
Kolomainen et al. ⁶	3690	1980-2000	52	18	0.49	46	7
Anupol et al. ⁴	1042	1986-2000	58	15	1.4	22	6
Lee et al. ³	1413	1983-2005	55	15	1.3	28	6
Geisler e Geisler ⁸	479	1979-1992	56.6	16	3.3	19	3
Tay et al. ¹⁴	605	1993-2003	-----	4	0.66	16.5	19.5

diosurgery (GKS) would be an appropriate option. GKS at high doses induces tumor necrosis releasing minimal radiation to the healthy nerve tissue⁵. In the first case, the choice was made to combine cranial radiotherapy, intrathecal chemotherapy with methotrexate and cytarabine and intravenous chemotherapy with docetaxel and carboplatin. In the second case, surgical resection of cerebral metastasis, cranial radiotherapy and intravenous chemotherapy was performed.

According to Cohen et al.², patients treated only with steroids, radiotherapy alone, surgery alone or surgery combined with radiotherapy have a mean survival of 1.60, 5.33, 6.90 and 23.07 months, respectively. In their study, Ogawa et al.¹ observed a median survival of 9.3 months in patients treated with both radiotherapy and surgery and 2.9 months in patients treated only with radiotherapy. In our study, the median survival found was nine months after the finding of CNS metastases. The importance of radiotherapy as palliative treatment should be noted since studies have reported an improvement in neurological symptoms of patients, which was also observed in our patients.

CONCLUSION

Brain metastases from ovarian cancer represent an extremely rare situation and the prognosis is very poor. Neurosurgical resection is restricted to patients with a limited number of lesions in the CNS with easy surgical access¹⁻⁹. Radiotherapy combined with surgery appears to improve the survival of patients. Multiple metastases and difficult surgical access should not be approached surgically and should proceed with intravenous chemotherapy associated with cranial radiotherapy^{9,11,12}. Intrathecal chemotherapy is indicated in cases of the presence of neoplastic cells in cerebrospinal fluid^{1-4,12}.

REFERENCES

- Ogawa K, Yoshii Y, Aoki Y, Nagay Y, Tsuchida Y, Toita T, et al. Treatment and prognosis of brain metastases from gynecological cancers. *Neurol Med Chir (Tokyo)* 2008;48:57-62;discussion 62-3.
- Cohen ZR, Suki D, Wenberg JS, Marmor E, Lang FF, Gershenson DM, et al. Brain metastases in patients with ovarian carcinoma: prognostic factors and outcome. *J Neurooncol* 2004;66:313-25.
- Lee YK, Park NH, Kim JW, Song YS, Kang SB, Lee HP. Gamma-Knife radiosurgery as an optimal treatment modality for brain metastases from epithelial ovarian cancer. *Gynecol Oncol* 2008;108:505-9.
- Anupol N, Ghamande S, Odunsi K, Driscoll D, Lele S. Evaluation of prognostic factors and treatment modalities in ovarian cancer patients with brain metastases. *Gynecol Oncol* 2002;85:487-92.
- Melichar B, Urminská H, Kohlová T, Nová M, Cesak T. Brain metastases of epithelial ovarian carcinoma responding to cisplatin and gemcitabine combination chemotherapy: a case report and review of the literature. *Gynecol Oncol* 2004;94:267-76.
- Kolomainen DF, Larkin JM, Badran M, A'Hern RP, King DM, Fisher C, et al. Epithelial ovarian cancer metastasizing to the brain: a late manifestation of the disease with an increasing incidence. *J Clin Oncol* 2002;20:982-6.
- Rodriguez GC, Soper JT, Berchuck A, Oleson J, Dodge R, Montana G, et al. Improved palliation of cerebral metastases in epithelial ovarian cancer using a combined modality approach including radiation therapy, chemotherapy, and surgery. *J Clin Oncol* 1992;10:1553-60.
- Geisler JP, Geisler HE. Brain metastases in epithelial ovarian carcinoma. *Gynecol Oncol* 1995;57:246-9.
- Porthuri B, Chi DS, Reid T, Aghajanian C, Venkatraman E, Alektiar K, et al. Craniotomy for central nervous system metastases in epithelial ovarian carcinoma. *Gynecol Oncol* 2002;87:133-7.
- Largerwaard FJ, Levendag PC, Nowak PJ, Eijkenboom WM, Hanssens PE, Schmitz PI. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int J Radiation Oncol Biol Phys* 1999;43:795-803.
- Watanabe A, Shimada M, Kigawa J, Iba T, Oishi T, Kanamore Y, et al. The benefit of chemotherapy in a patient with multiple brain metastases and meningitis carcinomatosa from ovarian cancer. *Int J Clin Oncol* 2005;10:69-71.
- Decelle L, D'Hondt L, Andre M, Delree P, Calicis B, Lonchay C, et al. Ovarian cancer associated with carcinomatous meningitis: a case report and review of the literature. *Int J Gynecol Cancer* 2007;17:1136-40.
- Heckmann JG, Tilz C, Dutsch M, Blumcke I, Hildebrandt M, Schwab S. Intracerebral hemorrhage due to metastasis of ovarian granulose cell carcinoma 36 years after initial diagnosis. *Eur Neurol* 2007; 58:114-5.
- Tay SK, Rajesh H. Brain metastases from epithelial ovarian cancer. *Int J Gynecol Cancer* 2005;15:824-9.
- Sehouli J, Pietzner K, Harter P, Münstedt K, Mahner S, Hasenburg A, et al. Prognostic role of platinum sensitivity in patients with brain metastases from ovarian cancer: results of a German multicenter study. *Ann Oncol* 2010;21:2201-5.
- Monaco E 3rd, Kondziolka D, Mongia S, Niranjana A, Flickinger JC, Lunsford LD. Management of brain metastases from ovarian and endometrial carcinoma with stereotactic radiosurgery. *Cancer* 2008;113:2610-4.