Original Article

Current Opinion in Gynecology and Obstetrics Unusual Early Cerebral Metastasis of Ovarian Carcinoma as Initial Presentation

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Abstract

Background: Although systemic malignancies are frequently metastasizing to the central nervous system (CNS), ovarian carcinoma, which is a common malignancy in females, is rarely affecting brain. In general, the outcome for ovarian carcinoma with brain metastases is dismal as most of these patients usually present late with metastases elsewhere.

Materials and methods: A retrospective review of four cases with cerebral metastases as the initial presentation of ovarian carcinoma in patients ages 25 to 45 years. Three patients received hormonal therapy for infertility. All cases presented initially with symptoms and signs suggestive of increased intracranial pressure with unknown primary pathology. CT and MRI scans showed intracranial enhancing lesions in different locations. Full malignancy work up showed a primary lesion arising from the pelvis with no other lesions detected.

Results: Three patients underwent laparotomy for ovarian carcinoma resection once their neurological condition optimized, one case died early before she had laparotomy. All cases underwent Craniotomy for excision of the solitary metastatic lesion. In all cases, the histopathology demonstrated metastatic ovarian carcinoma. Subsequently, patients received chemo-radiotherapy. Although treatment all cases died within two years.

Conclusion: It is unusual for ovarian carcinoma to present initially with CNS involvement. Unlike other primary tumours, ovarian carcinoma does not have a predilection for the central nervous system. However, CNS involvement occurs at late stage of the disease. Although multimodal treatment the outcome still poor. Hormonal therapy for infertility may be a risk factor for ovarian carcinoma and its aggressive behavior with cerebral metastasis.

Keywords: Ovarian carcinoma, Cerebral metastases, Treatment modality, Chemoradiotherapy (CRT)

Introduction

Metastatic central nervous system lesions are one of the most devastating complications of malignancies and usually occur late; it is usually associated with involvement of other systems and determines the outcome; even small metastases can end with poor neurological symptoms. More recently, significant progresses have been made in diagnosis and management of brain metastases that

may lead to longer survival [1-3]. Conversely, outcomes with certain tumours remain poor regardless of multimodal treatment. This category includes metastatic ovarian carcinoma. The outcome of patients with ovarian carcinoma will be dramatically affected by cerebral involvement [4].

This communication documents the rarity of ovarian

carcinoma metastases to brain. However, ovarian carcinoma ranks fifth in mortality rate for cancers in females. The incidence of intracranial metastases from ovarian carcinoma during its natural course in most series is extremely low at a rate of 1.4 - 3.3% except for germ cell tumors; it usually occurs late and as a part of multiorgan involvement rather than as an isolated metastases. It is known that up to 38% of patients with this ovarian malignancy may develop distant metastases as initial presentation but mostly to liver, pleura, lung and bone with least involvements to intracranial spaces [5-8].

Clinical Materials and Methods

This study was approved by the Institutional Research Board at Jordan University of Science and Technology (JUST) and King Abdullah University Hospital, and then approved by the University Review Committee for Research on Humans at JUST.

The study group consisted of four patients who were treated for ovarian carcinoma with early presentation of intracranial metastasis at King Abdullah University Hospital from December 2005 to December 2016.

Inclusionary criteria included all cases attended only with ovarian metastatic intracranial lesions as an early presentation of ovarian carcinoma. Exclusionary criteria included late presentation of intracranial metastasis from ovarian carcinoma and other gynecological metastasis to brain.

Case Presentation

Case 1

A 25-year old female patient was admitted in 2007 with a three-week history of worsening headache, vomiting and blurred vision. She had a baby two months ago with a smooth normal vaginal delivery and she was breast feeding. On the day of admission she developed rapid progressive right sided weakness. Unenhanced CT scan of the brain showed left motor strip well defined hyper dense lesion compatible with hemorrhagic neoplasm, the urgent MRI of the brain demonstrated a left hemorrhagic cerebral lesion with surrounded edema. She started on antiepileptic medications and corticosteroid therapy, on the same day she underwent a left posterior parietal stereotactic craniotomy for excision of the lesion. Histopathology revealed metastatic Choriocarcinoma (Figure 1a,b). However, on postoperative CT scanning of the chest, abdomen and pelvis, confirmed a large mass lesion measuring 16 x 12 cm and displacing the

uterus to the right. B HCG was elevated. Bone scan was normal. When her neurological status optimized, she had ovarian biopsy under CT scan guidance, the histopathology was Choriocarcinoma compatible with the brain results. She commenced brain radiotherapy and planned for chemotherapy. However, the patient did not receive any hormonal therapy in the past. After three weeks of radiotherapy commencement she developed rapid deterioration in conscious level, a repeat CT scan revealed recurrence of hemorrhagic tumour with severe edema and midline shift required urgent craniotomy. Clinically, the patient did not improve although aggressive treatment. She continued to deteriorate and died after eight weeks of her first operation.

Figure 1 a, b: Metastatic brain and primary ovarian choriocarcinoma.

(high power Haematoxylin and Eosin) a view of choriocarcinoma from the cerebral excision of the tumour (1a) and ovarian biopsy (1b). Metastatic choriocarcinoma involving superficial cortex and extending into overlying subarachnoid space (arrowed). (Haematoxylin and Eosin stained section) (Original magnification $\times 100$).

Case 2

A previously healthy 45-year old woman was admitted in 2009 with a one-week history of headache, vomiting and blurred vision. On the day of admission she acutely developed acute confusion. Brain CT scan showed no abnormalities, MRI of the brain with gadolinium revealed multiple punctate enhancing lesions within the cerebral and cerebellar hemispheres with mild dilatation of ventricles. She started on antiepileptic medications and corticosteroid therapy, on the same day she had

an external ventricular drain inserted which confirmed raised intracranial pressure with no abnormal cells in the ventricular fluid. The CSF cytology was normal. She revealed some neurological improvement and after five days this was converted to a ventriculoperitoneal shunt. However, CT scanning of the chest, abdomen and pelvis revealed a large cystic mass measuring 13 x 12 cm and displacing the uterus to the right was present in the pelvis (Figure 2). CA-125 was also elevated. Bone scan was normal. She commenced whole brain radiotherapy followed by chemotherapy. In a retrograde manner, the patient received hormonal therapy for treatment of infertility. She then underwent laparotomy for hysterectomy, bilateral salpingo oophorectomy and omentectomy three months post craniotomy. Intraoperatively, a predominant mass of tumour was identified in the left ovary with small tumour foci within the right ovary, while the uterus and omentum appeared normal. Histopathology was reported as high grade papillary cystadenocarcinoma, with many atypical features consistent with the brain lesion. She then received chemotherapy postoperatively and had local radiotherapy within the pelvis. The patient remained stable for fourteen months until her disease progressed again and died one and a half year from her initial presentation.

Figure 2: Ovarian carcinoma. axial and sagittal CT scan. Sagittal and axial CT scanning of the pelvis reveals a large cystic ovarian mass measuring 13 x 12 cm and displacing the uterus to the right was present in the pelvis (arrowed).

Case 3

A 39-year old female patient, previously healthy, was admitted in 2014 with a four-week history of worsening headache, vomiting and blurred vision. CT scan and subsequent MRI of the brain demonstrated right

fronto-parietal two close mass lesions with surrounding edema and enhancement. She started on antiepileptic medications and corticosteroid therapy. She had stereotactic craniotomy for resection of the two lesions. Histopathology revealed metastatic adenocarcinoma. The CT scanning of the chest, abdomen and pelvis, confirmed a large cystic mass measuring 12 x 10 cm and displacing the uterus to the left was present in the pelvis. Serum CA-125 was elevated. Bone scan showed increased uptake of the right side of pelvis. She received whole brain radiotherapy followed by chemotherapy. In a retrograde manner, the patient received hormonal therapy for infertility. She then underwent laparotomy for bilateral salpingo-oophorectomy, omentectomy and hysterectomy two months post craniotomy. Intraoperatively, a predominant mass of tumour was identified in the right ovary, while the left ovary, uterus and omentum appeared normal. Histopathology was reported as high grade clear cell adenocarcinoma, morphologically consistent with mucinous cystadenocarcinoma of the ovary, with many atypical features similar to many features seen with the brain lesion (Figure 3a, b). The patient received a second cycle of chemotherapy postoperatively and had local radiotherapy to bone metastases within the pelvis. Regrettably, her disease continued to progress and she died after two years from her initial presentation.

Figure 3 a, b: Mucinous adenocarcinoma of the brain and ovary. (Haematoxylin and Eosin histopathology). Right ovarian carcinoma excised three months after craniotomy (3b). The tumour shows similar architectural features to those of the cerebral tissue (3a). (Intermediate magnification).

Case 4

A 37-year old female patient, previously healthy, was

admitted in 2016 with a four-week history of worsening headache, blurred vision and unsteady gait and right sided weakness. CT scan of the brain showed right cerebellar well defined mass with secondary hydrocephalus, the MRI of the brain demonstrated no other lesions. She started on antiepileptic medications and corticosteroid therapy. She had Ventriculo-Peritoneal shunt for hydrocephalus. The CSF cytology was normal. She then underwent suboccipital craniotomy for resection of the tumor. Histopathology revealed metastatic adenocarcinoma. However, on postoperative CT scanning of the chest, abdomen and pelvis, confirmed a large cystic mass measuring 12 x 9 cm and slightly displacing the uterus to the right was present in the pelvis. Bone scan was normal while CA-125 was high. She commenced whole brain radiotherapy followed by chemotherapy. In a retrograde manner, the patient received hormonal therapy for treatment of infertility . She underwent laparotomy for hysterectomy, salpingo oophorectomy and omentectomy three months post craniotomy. Intraoperatively, a large tumour was identified in the left ovary, while the right ovary, uterus and omentum appeared normal. Histopathology was reported as high grade serous cystadenocarcinoma, with many atypical features similar to many features seen in the brain lesion (Figure 4a,b). The patient, post operatively, was given another cycle of chemotherapy and had local radiotherapy to the pelvis. Unfortunately, her disease continued to progress and she died after a year from her initial presentation.

Figure 4 a, b: MRI axial and coronal with contrast, papillary cystadenocarcinoma. Coronal and axial gadolinium-enhanced MRI scan of the brain showing the cerebellar metastasis (arrowed) (4a). Serous cystadenocarcinoma of ovary (4b). (Intermediate magnification).

Analytical Review and Results

The study group consisted of four patients ages 25 to 45years (average age: 37.4 years). All cases underwent multimodal treatment for their primary ovarian carcinoma and cerebral metastases that included surgical resection, radiotherapy and chemotherapy.

The patient demographics were reviewed and analyzed in a retrospective manner (Table 1).

Table 1: Demonstrates the demographic distribution of cases with intracranial metastasis from the ovarian carcinoma.

	Case 1	Case 2	Case 3	Case 4
Age	25	45	39	37
Clinical presentation	high ICP	high ICP	high ICP and weakness	high ICP and unsteady gait
Hormonal therapy for Infertility	No	Yes	Yes	Yes
Treatment	Craniotomy	CSF shunt	Craniotomy	Craniotomy + shunt
Modality	Radiotherapy	Laparotomy, CRT	Laparotomy, CRT	Laparotomy, CRT
Histopathology of the Brain	Choriocarcinoma	Papillary CA	Mucinous CA	Serous CA
Histopathology of the ovary	Choriocarcinoma	Papillary CA	Mucinous CA	Serous CA
Tumor marker	BHCG	Ca-125	Ca-125	Ca-125
Survival per month	2	18	24	12

Abbreviations
ICP: intracranial pressure
CRT: ChemoRadioTherapy
RT: Radiotherapy
CA: Cystadenocarcinoma

All cases were treated initially for brain metastatic lesions that instigated from the ovarian carcinoma. The diagnosis was based on the clinical presentation of raised intracranial features and initially managed by neurosurgery; computed tomography CT and MRI scans of the brain were positive for intracranial lesions; pelvis CT scan revealed ovarian mass lesion; and finally the histopathology of both lesions demonstrated presence of similar highly malignant features, the tumour biomarkers were positive in all cases.

All cases underwent craniotomy or shunt diversion to reduce the high ICP and to optimize the neurological status. A full malignancy work up was then carried out on all patients and proved to have primary ovarian carcinoma. Initially, the origin of malignancy could only be identified in pelvis from the ovary and there were no evidence of metastasis to other organs. All cases received radiotherapy to the central nervous system. Only three cases underwent laparotomy for hysterectomy, bilateral salpingo oophorectomy and omentectomy followed by chemoradiotherapy. While one case had very aggressive choriocarcinoma and she continued to deteriorate until she passed away after 2 months of presentation.

Three patients received fertilizing hormonal therapy for infertility which may play a role in development of aggressive course of the ovarian carcinoma. Furthermore, there was no family history of malignancy.

On the regular assessment for 24 months the survival rate was variable, the shortest one was for 2 months and the longest was for 24 months with average at about one year (12.6 months).

Discussion

Ovarian carcinoma is a common and aggressive female malignancy, it ranks fifth in mortality rate for cancers in females. The predilection for intracranial metastases is rare and develops in late stage of the disease. The intracranial metastasis may be as a result of effective chemotherapy weakening the blood-brain barrier and making the brain a target for tumour emboli. Additionally, chemotherapy may improve the patient's survival which increases the potentiality of brain involvement in the late stages of the disease. However, early neural involvement is unusual. Only a few reported cases in the literature confirm early brain metastases as initial presentation and usually as a single lesion [9-11]. The ovarian metastases to brain have a predilection for the parenchyma rather than the leptomeninges [12-14]. As documented in this

study the initial clinical presentation of ovarian carcinoma was neurological features. Subsequently, investigations confirmed presence of brain lesions with histopathology and tumor markers indicating metastasis and the ovarian carcinoma was evident.

The literature review confirmed that once central nervous system metastasis has occurred with ovarian carcinoma, life expectancy is short even with multimodal treatment. With Median survival rate variable from five to seventeen months which is close to our results [2,6,15,16]. However, surgical resection of brain metastatic lesion may have longer survival rate and improve quality of life and outcome, largely, if followed by chemo-radiotherapy as recommended by many authors [3,17].

The reason why ovarian carcinoma doesn't have predilection to the brain and why it may present early as central nervous system involvement in scattered cases still unanswered. Some authors raised the potential use of infertility medications and the ovarian carcinoma with brain metastasis. Fundamentally, is there an association between infertility drug treatment and ovarian carcinoma that promote the cancer initiation or its aggressiveness and brain involvement [1,4,18].

The treatment of choice of metastatic brain lesion from ovarian carcinoma is still controversy. However, multi treatment modalities are the only available option to improve the patients' quality of life and to prolong the survival rate this may include stereotactic radiotherapy [19,20].

Having reviewed the literature it seems this is the largest review with early presentation of intracranial metastasis from ovarian carcinoma which again raise the concern of hormonal therapy for infertility as a risk factor for ovarian carcinoma and its aggressive behavior and cerebral metastasis [4]. Yet, further evaluation will be needed to correlate between hormonal therapy and ovarian carcinoma with intracranial metastases.

Conclusion

Ovarian carcinoma is a common malignancy encountered in females and rarely affecting central nervous system. It is usually seen in late stages of the disease and after receiving treatment for the ovarian carcinoma and as a part of multiorgan involvement. The early presentation of ovarian carcinoma with brain metastases is exceptionally uncommon with low survival rate even with multimodal treatment. Although it is

uncommon, metastases from ovarian carcinoma should be again considered in young females mainly, in patients received hormonal therapy for infertility as hormonal therapy may be implicated.

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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