



Case report

Clinical presentation of brain metastases from endometrial carcinoma: A case series

Marisa R. Moroney*, Lindsay J. Wheeler, Bradley R. Corr

University of Colorado Denver, Department of Obstetrics and Gynecology, Aurora, CO, United States

ARTICLE INFO

Keywords:

Endometrial cancer
brain metastases

ABSTRACT

Brain metastases from endometrial carcinoma are rare, however they do occur, and they are associated with an especially poor prognosis. There is evidence demonstrating improved outcomes with early diagnosis and subsequent multimodal treatment. This study therefore aims to review cases of brain metastases from endometrial carcinoma with specific focus on clinical presentation and disease history. This retrospective case series evaluated all cases of brain metastases from endometrial carcinoma at a single institution over a seven-year period. A medical records search was performed using ICD codes for endometrial cancer, brain lesions and brain imaging. Analysis of patient and disease characteristics was performed with descriptive statistics. Twelve cases were identified. The majority of cases had intermediate or high-grade histology (97.7%), advanced stage disease (58.3%), and at least one prior disease recurrence (66.7%). Eleven of 12 cases (91.7%) had lung metastases diagnosed prior to brain metastases. All 12 cases had neurologic signs and symptoms present at time of brain metastases diagnosis; 14 different types of neurologic deficits were noted. Headache was the most common neurologic symptom (5/12, 41.7%), followed by focal weakness (3/12, 25.0%) and aphasia (3/12, 25.0%). In conclusion, clinical presentation at time of diagnosis of brain metastases consistently includes neurologic signs and symptoms with persistent headache being the most common. Endometrial cancer patients that present with new neurologic complaints or exam findings should be evaluated for brain metastases.

1. Introduction

Endometrial cancer is the most common gynecologic cancer among women in the United States, with an estimated 61,180 new cases in 2019. Both incidence and mortality rates for endometrial cancer are increasing annually. (Siegel et al., 2019) > 70% of endometrial cancer cases present as stage I tumors and recurrence rates are low. (American College of Obstetricians and Gynecologists, 2015; Wright et al., 2012) When metastases do occur in endometrial cancer, the most common sites include local metastases to the pelvic or para-aortic lymph nodes or, less frequently, distant metastases to the liver, lung and bone. (Martínez-Mañas et al., 1998; Orru et al., 2007) The brain is not a common site for endometrial cancer metastases; in fact, endometrial cancer is considered to be “neurophobic,” with brain metastases only occurring in approximately 0.3–1.16% of cases. (Martínez-Mañas et al., 1998; Piura and Piura, 2012; Divine et al., 2016; Uccella et al., 2016)

Although cases of brain metastases from endometrial cancer are rare, when they do occur, they confer an especially poor prognosis with median survival of approximately 3.5–6.5 months from the time of

brain metastases diagnosis. (Uccella et al., 2016; Gien et al., 2004) Limited data evaluating brain metastases from endometrial cancer demonstrate that early diagnosis and treatment of brain lesions with surgical resection and whole brain radiation can extend prognosis to > 24 months survival. (Divine et al., 2016; Uccella et al., 2016; Gien et al., 2004; Nasu and Satoh, 2013; Cormio et al., 1996; Gressel et al., 2015) In this case series, we review recent cases at our institution, as well as the relevant literature, in order to further elucidate and better identify the clinical presentation of brain metastases in endometrial cancer patients.

2. Materials and methods

Medical records at our institution from January 1, 2012 to January 1, 2018 were reviewed for cases of endometrial cancer with metastases to the brain. Cases were found by searching for patients with ICD codes indicating endometrial cancer (ICD-9179.0, 182.0, 182.1, 182.8 or ICD-10 C54.1 and C55) who also had ICD codes indicating brain metastases (CD-9191.0-191.8 or ICD-10 C79.31, C71.9, D49.6) or brain imaging

* Corresponding author at: University of Colorado, Anschutz Medical Campus, School of Medicine, 12631 East 17th Avenue, B198-6, Aurora, CO 80045, United States.

E-mail address: marisa.moroney@ucdenver.edu (M.R. Moroney).

<https://doi.org/10.1016/j.gore.2019.03.004>

Received 4 January 2019; Received in revised form 4 March 2019; Accepted 5 March 2019

Available online 20 March 2019

2352-5789/ © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Table 1
Patient and disease characteristics (N = 12).

Characteristics	Value
Age in years, median (range)	52.5 (33–82)
BMI, median (range)	28.0 (17.3–61.6)
Time from cancer diagnosis to brain metastases in months, median (range)	33 (7–199)
Histology, n (%)	
Endometrioid	9 (75.0%)
Papillary serous	2 (16.7%)
Adenosquamous	1 (8.3%)
Histologic Grade, n (%)	
1	1 (8.3%)
2	3 (25.0%)
3	8 (66.7%)
Stage, n (%)	
IA	3 (25.0%)
IB	1 (8.3%)
II	1 (8.3%)
IIIB	1 (8.3%)
IIIC1	1 (8.3%)
IIIC2	1 (8.3%)
IVB	4 (33.3%)
Recurrences prior to brain metastases, n (%)	
0	4 (33.3%)
1	5 (41.7%)
2	3 (25.0%)
Location of other metastases, n (%)	
Pelvis	6 (50.0%)
Abdomen	6 (50.0%)
Lung	11 (91.7%)
Bone	3 (25.0%)
Neurologic Symptoms present, n (%)	
Yes	12 (100.0%)
No	0 (0.0%)

via computed tomography (CT) or magnetic resonance imaging (MRI). The resulting cases from this search were then reviewed to identify cases of endometrial cancer that did have brain metastases. Cases were excluded if they had any additional cancer diagnoses or if their uterine cancer was a sarcoma or carcinosarcoma. Patient charts were then abstracted for information regarding patient, disease and treatment characteristics. Analysis was performed with descriptive statistics.

3. Results

Brain metastases from endometrial carcinoma were identified in 12 cases. The patient and disease characteristics are listed in Table 1, and the history of each case is detailed in Table 2. Median age at time of diagnosis of cancer was 52.5 years (range 33–82 years). Median BMI at time of diagnosis was 28.0 (range 17.3–61.6). Median time from endometrial carcinoma diagnosis to diagnosis of brain metastases was 33 months (range 7–199 months).

Of the 12 identified cases, 9 (75.0%) were endometrioid adenocarcinomas, 2 (16.7%) were serous carcinomas, and 1 (8.3%) was an adenosquamous carcinoma. The majority of cases (8/12, 66.7%) had Grade 3 histology while 1 case (8.3%) was Grade 1 and 3 cases (25.0%) were Grade 2. Of the 9 cases whose lymphovascular space invasion (LVSI) status was known, 4 cases (44.4%) were LVSI positive, 3 cases (33.3%) were LVSI negative, and 2 cases (22.2%) were LVSI indeterminate. Of the 10 cases with available information on myometrial invasion, 4 cases (40.0%) had invasion in only the inner third of the myometrium, 3 cases (30.0%) into the middle third of the myometrium, and 3 cases (30.0%) into the outer third of the myometrium. FIGO stage at presentation varied from Stage IA to IVB; the majority of cases (7/12, 58.3%) were advanced stage (Stage III – IV).

All 12 cases had extra-cerebral metastases at time of diagnosis of brain metastases. All but one case (11/12, 91.7%) had metastases to the lung present. Metastases were also present in the pelvis in 6 cases

(50.0%), the abdomen in 6 cases (50.0%), and bony structures in 3 cases (25.0%). Brain metastases were present at the first disease recurrence in only 4 cases (33.3%), whereas 8 cases (66.6%) had at least one recurrence prior to the diagnosis of brain metastases. No cases had brain metastases present at time of cancer diagnosis.

All 12 cases (100.0%) had neurologic signs and symptoms present at the time of diagnosis of brain metastases: headache was the presenting symptom in 5 cases (41.7%); focal weakness and aphasia in 3 cases each (25.0%); seizures, vision changes, word finding difficulty, and hyponatremia were presenting neurologic symptoms in 2 cases each (16.7%); altered mental status (AMS), localized extremity numbness, dizziness, confusion, balance issues, gait disturbance and memory loss were each present in 1 case (8.3%) (Table 3). The brain lesions in all 12 cases (100%) were visualized on MR Brain imaging. Six of the cases (50%) had CT brain imaging performed prior to MR imaging, and, in all six of these cases, the CT imaging diagnosed the brain lesions before the MRI further elucidated the lesions.

Following diagnoses of brain metastases, 11 of the 12 patients (91.7%) died. Time to death from diagnosis of brain metastases was < 6 months in 7 of 12 patients (58.3%) and 6 to 12 months in 5 of 12 patients (33.3%). One patient (8.3%) is still alive at 12 months from disease.

4. Discussion

Brain metastases from endometrial carcinoma are atypical in that they are extremely rare; however, this case series demonstrates that there is some consistency in clinical presentation and disease history of brain metastases from endometrial carcinoma. The cases in our study were mostly high grade, advanced stage, recurrent endometrial carcinoma, which is the anticipated pathology for disease that progresses to such a distant and anomalous metastatic site as the brain. In addition, every one of the cases presented with neurologic symptoms that are known to be signs of brain lesions.

Among the 12 cases in our study, there were three different types of histology (endometrioid, serous and adenosquamous). The majority of cases were of endometrioid histology. Previous studies support the finding that brain metastases can occur from endometrial carcinoma of any histologic type, but these studies also demonstrate that the most common histology seen in brain metastases is endometrioid. (Martínez-Mañas et al., 1998; Piura and Piura, 2012; Uccella et al., 2016; Gien et al., 2004) For example, in a case series of 18 patients with brain metastases from endometrial carcinoma, Uccella et al. found that 66.7% had endometrioid histology, but also found cases of serous, adenosquamous and undifferentiated carcinomas. This plurality of endometrioid histology among cases of brain metastases is expected, not because endometrioid histology is a risk factor or has an affinity for metastasizing to the brain, but because it is the most common histologic type of endometrial carcinoma.

In our study, there were also cases of all histologic grades, but 91.7% of cases were intermediate or high grade and the only case of Grade 1 histology was advanced stage (Stage IIIC). Our series had the full gamut of disease stages with cases ranging from Stage IA to IVB, but the majority of cases were advanced stage (Stage III or IV). There were no cases of Stage I, Grade 1 disease. These findings of a predominance of higher histologic grade and surgical stage among cases of brain metastases from endometrial carcinoma is anticipatable as tumors with higher risk histologic features and more advanced disease are known to behave more aggressively. (Gien et al., 2004)

Hematogenous spread is thought to be the main mechanism of spread of endometrial carcinoma to the brain, whereas the more common local spread of endometrial carcinoma occurs through the lymphatic system. The path of this hematogenous spread is thought to go from the pelvis to the lungs, then the carotids arteries and then the brain. (Martínez-Mañas et al., 1998; Nasu and Satoh, 2013) The findings in our study support this consensus, as 11 of our 12 cases (91.7%)

Table 2
Characteristics of cases of brain metastases from endometrial cancer.

Patient no.	Age	Stage	Histology	Primary treatment	Recurrence no. prior to brain mets	Other sites of metastatic disease	Time to brain mets (months)	Brain lesion no.	Location of brain lesions	Brain imaging	Neurologic symptoms	Treatment for brain mets	Survival following brain met diagnosis
1	61	IB	Endometrioid Grade 3 M3	Robotic-TLH, BSO, LND Carbo/Taxol	1	Pelvic Pulmonary	20	1	R cerebellum	CT MRI	Headache AMS	Resection RT	7 months
2	66	II	LVSI positive Serous Grade 3 M1	Robotic-TLH, BSO, LND Carbo/Taxol	1	Pulmonary	32	1	R occipital	MRI	Headache Vision changes Aphasia Seizures	RT Topotecan	3 months
3	50	IA	LVSI positive Endometrioid Grade 2 M1	Pelvic RT TAH, BSO, LND Megace	1	Pelvic Abdominal	34	2	L parietal R occipital	CT MRI	Seizure	None, Transitioned to Hospice	3 months
4	55	IVB	LVSI indeterminate Endometrioid Grade 3	Carbo/Taxol Pelvic RT	0	Pelvic Abdominal Pulmonary Bone	7	1	Right parietal	MRI	Focal weakness	RT	3 months
5	71	IVB	Endometrioid Grade 3 M1	Robotic-TLH, BSO Carbo/Taxol	2	Pulmonary Bone	20	2	Right frontal	MRI	Confusion Hyponatremia	RT Carbo/Taxol	10 months
6	49	IIIC1	Endometrioid Grade 3 M1	Robotic-TLH, BSO, LND Carbo/Taxol	0	Pelvic Pulmonary	57	> 5	Multifocal and bilateral	CT MRI	Focal weakness	RT	2 months
7	45	IVB	LVSI indeterminate Adenosquamous Grade 3	Pelvic RT TAH, BSO Carbo/Taxol	1	Pulmonary Bone	9	5	R frontal L temporal R dentate nucleus R cerebellum R parietal-occipital junction	MRI	Hyponatremia	None, Transitioned to Hospice	1 month
8	54	IVB	Serous Grade 3 M3	LAVH, BSO by generalist Staging surgery with LND Carbo/Taxol	0	Pulmonary Pelvic Abdominal	12	4	L parietal R frontal R occipital R occipital	CT MRI	Headache Focal weakness Focal numbness	Resection RT Bevacizumab	AWD, 12 months from diagnosis
9	82	IIIC2	Endometrioid Grade 3 M3	Robotic-TLH, BSO, LND Carbo/Taxol	1	Abdominal Pulmonary	82	1	L orbital	CT MRI	Headache Balance issues Vision changes	RT	7 months
10	51	IA	LVSI Positive Endometrioid Grade 2 M2	Pelvic RT TAH, BSO, LND	2	Pelvic Abdominal Pulmonary	199	1	L temporal	MRI	Memory Loss Aphasia	RT	1 month
11	51	IA (at least)	Endometrioid Grade 2 M2	Pelvic RT BSO Pelvic RT	0	Pulmonary Abdominal Pulmonary	37	3	R parietal R occipital R corpus collusum	CT MRI	Headache Confusion Gait disturbance	Resection RT Carbo/Taxol	9 months

(continued on next page)

Table 2 (continued)

Patient no.	Age	Stage	Histology	Primary treatment	Recurrence no. prior to brain mets	Other sites of metastatic disease	Time to brain mets (months)	Brain lesion no.	Location of brain lesions	Brain imaging	Neurologic symptoms	Treatment for brain mets	Survival following brain met diagnosis
12	33	IIIB	Endometrioid Grade 1 M2 LVSI negative	TAH, BSO, LND Carbo/Taxol	2	Pulmonary	110	1	L temporal	MRI	Dizziness Aphasia	Resection RT	5 months

Abbreviations: M, myometrial invasion (M1 inner third, M2 middle third, M3 deep third); LVSI, lymphovascular space invasion; Robotic-TLH, robotic-assisted total laparoscopic hysterectomy; BSO, bilateral salpingo-oophorectomy; LND, lymph node dissection; Carbo, carboplatin; RT, radiation therapy; R, right; L, left; CT, computed tomography; MRI, magnetic resonance imaging; AMS, altered mental status; SIADH, syndrome of inappropriate antidiuretic hormone secretion; AWD, alive with disease.

Table 3
Neurologic signs and symptoms present at the time of diagnosis of brain metastases.

Symptom	Value
Headache	5 (41.7%)
Focal Weakness	3 (25.0%)
Aphasia	3 (25.0%)
Seizures	2 (16.7%)
Vision Changes	2 (16.7%)
Aphasia	2 (16.7%)
Hyponatremia	2 (16.7%)
Altered Mental Status	1 (8.3%)
Localized Extremity Numbness	1 (8.3%)
Dizziness	1 (8.3%)
Confusion	1 (8.3%)
Balance Issues	1 (8.3%)
Gait Disturbance	1 (8.3%)
Memory Loss	1 (8.3%)

had metastatic pulmonary nodules. Other extra-cranial metastases present in our series occurred at sites in the pelvis, abdomen and bones. The majority of cases had a recurrence at one of these other extra-cranial sites prior to diagnosis of brain metastases, and no cases had brain metastases present at time of diagnosis of endometrial carcinoma. This is consistent with prior evidence that only approximately 0.12% of endometrial carcinoma cases have brain metastases present at time of cancer diagnosis.(Uccella et al., 2016)

Clinical presentation with neurologic signs and symptoms was a consistent finding in all 12 cases of brain metastases from endometrial carcinoma in our study. The most common presenting symptom was headache. The patients who presented with headache all reported a persistent headache that lasted at least a week with the acute addition of other neurologic symptoms like focal weakness, vision changes, aphasia, and AMS. Prior neurologic studies have demonstrated that brain metastases from all types of primary cancers most commonly present with headache (up to 57% of cases).(Noh and Walbert, n.d.) As headache is a non-specific symptom, it can be difficult to clinically extrapolate the presence of a brain lesion in a cancer patient with a headache. Neurologic literature describes headaches caused by brain metastases as dull, bilateral and similar to tension-headaches. It is important to consider central nervous system involvement in any cancer patient with a new, persistent headache, especially with concomitant neurologic deficits.(Klos and O'Neill, 2004; Noh and Walbert, n.d.) Other common presenting neurologic symptoms include focal symptoms, altered mental status, seizures, gait abnormalities, speech and visual changes, and persistent nausea/vomiting.(Noh and Walbert, n.d.) In this study, the other common presenting neurologic symptoms were focal weakness and aphasia, occurring in 3 patients each (25.0%). Both of these were not only reported as symptoms by the patients but were also noted as neurologic findings on physical exam. In total, there were 14 different neurologic signs and symptoms noted in these 12 cases, and the majority of cases (8/12, 66.6%) presented with more than one neurologic deficit.

Our focus on the clinical presentation of brain metastases from endometrial carcinoma differentiates our case series from others, which have mainly focused on treatment and survival. There are case reports that demonstrate improved survival following treatment of brain metastases with combined surgery and radiation therapy (RT) versus single modality treatment,(Orru et al., 2007; Cormio et al., 1996) and in a large meta-analysis, Uccella et al. found that cases of brain metastases treated with combined surgery and RT had an overall survival of 27 months compared to only 3.5 months in cases that did not receive this multimodal treatment ($p < .001$). (Uccella et al., 2016) Overall, the available literature is consistent in reporting prolonged survival in patients with early diagnosis of brain metastases and subsequent treatment with both surgery and RT.(Cormio et al., 1996) We

recognized from this literature review that early detection of brain metastases is essential for improving prognosis, and we therefore chose to evaluate and describe the clinical presentation of brain metastases in order to promote early identification. The main weaknesses of this case series are sample size and retrospective design, both of which are due to the low incidence of brain metastases from endometrial carcinoma.

In conclusion, patients with brain metastases from endometrial carcinoma consistently present with neurologic symptoms. These patients also usually have a history of high grade or advanced stage disease, prior disease recurrence, and lung metastases but disease characteristics can vary. Due to the consistency of neurologic symptoms at presentation, the abysmal prognosis associated with brain metastases and the prolonged survival with early detection and treatment of brain metastases, we recommend that all endometrial carcinoma patients that present with new neurologic complaints or exam findings be evaluated for brain metastases.

Conflict of interest statement

There were no financial or other forms of outside support provided for this study. There are no potential conflicts of interest to disclose.

Author contribution

Marisa R Moroney, MD contributed in project development, IRB proposal, literature review, data abstraction and analysis, abstract and manuscript writing, highlights.

Lindsay J Wheeler, MD contributed in literature review and abstract and manuscript editing, highlights.

Bradley R Corr, MD contributed in project development, IRB proposal, abstract and manuscript editing.

References

- American College of Obstetricians and Gynecologists, 2015. Endometrial Cancer. In: ACOG Practice Bulletin. vol. 149 American College of Obstetricians and Gynecologists, Washington.
- Cormio, G., Lissoni, A., Losa, G., et al., 1996. Brain metastases from endometrial carcinoma. *Gynecol. Oncol.* 61, 40–43.
- Divine, L.M., Kizer, N.T., Hagemann, A.R., et al., 2016. Clinicopathologic characteristics and survival of patient with gynecologic malignancies metastatic to the brain. *Gynecol. Oncol.* 142, 76–82.
- Gien, L.T., Kwon, J.S., D'Souza, D.P., et al., 2004. Brain metastases from endometrial carcinoma: a retrospective study. *Gynecol. Oncol.* 93, 524–528.
- Gressel, G.M., Lundsberg, L.S., Altwerger, G., et al., 2015. Factors predictive of improved survival in patients with brain metastases from gynecologic cancer: a single institution retrospective study of 47 cases. *Int. J. Gynecol. Cancer* 25 (9), 1711–1716.
- Klos, K.J., O'Neill, B.P., 2004. Brain metastases. *Neurologist* 10 (1), 31–46.
- Martínez-Mañas, R.M., Brell, M., Rumià, J., et al., 1998. Brain metastases in endometrial cancer. *Gynecol. Oncol.* 70, 282–284.
- Nasu, K., Satoh, T., 2013. Nishio, et al. Clinicopathologic features of brain metastases from gynecologic malignancies: a retrospective study of 139 cases (KCOG-G1001s trial). *Gynecol. Oncol.* 128, 198–203.
- Noh, T., Walbert, T., 2018. Brain metastasis: clinical manifestations, symptom management and palliative care. In: Schiff, D., Van den Bent, M.J. (Eds.), *Handbook of Clinical Neurology, Metastatic Disease of the Nervous System* 149 <https://doi.org/10.1016/B978-0-12-811161-1.00006-2>.
- Orru, S., Lay, G., Dessi, M., et al., 2007. Brain metastases from endometrial carcinoma: report of three cases and review of literature. *Tumori* 93, 112–117.
- Piura, E., Piura, Benjamin, 2012. Brain metastases from endometrial carcinoma. *ISRN Oncol* 2012, 1–13.
- Siegel, R.L., Miller, K.D., Jemal, A., 2019. Cancer statistics, 2019. *Ca Cancer J* 69 (1), 7–34.
- Uccella, S., Morris, J.M., Multinu, F., et al., 2016. Primary brain metastases of endometrial cancer: a report of 18 cases and review of the literature. *Gynecol. Oncol.* 142, 70–75.
- Wright, J.D., Barrera Medel, N.I., Sehoul, J., et al., 2012. Contemporary management of endometrial cancer. *Lancet* 379, 1352–1360.