Case report

Clinical characteristics of CNS metastases from primary gynecologic cancers☆

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ABSTRACT

The development of brain and central nervous system (CNS) metastases from primary gynecologic cancers is an extremely uncommon but deadly process. Through this retrospective case series of patients treated at a single institution from 2004 to 2018, we aim to explore potential clinical patterns of this phenomenon with respect to primary tumor type, histology, and symptomatology.

A total of 42 patients were identified with CNS metastases, with 24 patients having endometrial cancer, 9 patients with ovarian cancer, 5 patients with cervical cancer, and 4 patients with gestational trophoblastic neoplasia (GTN). The two most common presenting complaints were headache and ataxia. Most patients (67%) presented with more than one lesion on imaging and the frontal lobe was most likely to be involved. The median age of diagnosis for both primary cancer and CNS metastasis were significantly younger in the GTN group when compared to other cancers. Meningeal involvement was more prevalent in patients with cervical cancer. Over 83% of endometrial cancer patients in this cohort had type II histologies, a significantly higher percentage than that in the general population.

While the rarity of CNS metastases in primary gynecologic malignancies precludes routine screening, patients diagnosed with more aggressive histologic subtypes of endometrial and uterine cancers may benefit from a lowered threshold of brain imaging in the context of new onset neurological symptoms.

1. Introduction

Primary central nervous system (CNS) metastases from gynecologic malignancies are extremely rare, occurring in around 1% of all tumors of uterine, cervical or ovarian origin (Hacker and Rao, 2016). Typically, tumors of the breast, lung, and skin are considered the most likely to metastasize to the brain with these three primary sites accounting for more than 75% of all brain metastasis (Nussbaum et al., 1996). Apart from gestational trophoblastic neoplasia (GTN), particularly choriocarcinoma, most gynecologic malignancies are described as "neurophobic" due their infrequent spread to the brain in the clinical literature (Hacker and Rao, 2016; Piura and Piura, 2012). Consequently, few studies have examined in detail the clinical presentation or histological subgroups most commonly accounting for these rare events. There are currently also no known genetic factors or biomarkers that accurately and consistently predict CNS metastasis of gynecologic tumors. Further, early identification can be difficult due to the rarity of this presentation and unpredictable clinical progression patterns. Through this study, we sought to add to the present literature a case series describing the clinical progression, symptomatology, and characteristics of brain metastases in patients with primary gynecologic cancers at a single tertiary care center.

2. Materials and methods

Following institutional review board approval (IRB #17-2368), we conducted a retrospective review of all patients diagnosed with new brain metastases from primary gynecologic cancer at a single tertiary care institution from 2004 to 2018 within two institutional databases. Subjects with diagnoses of gynecologic cancers who underwent brain imaging were identified using CPT (Current Procedural Terminology) codes in association with the EMERSE (Electronic Medical Record Search Engine) tool in EPIC. Patient demographics, clinical outcomes, and tumor characteristics were abstracted from the electronic medical

Table 1
Patient and tumor characteristics.

Total patients	N = 42
Median age at diagnosis, gynecologic	58.1
Median age at diagnosis, brain	61.2
Median time between diagnoses	1.7
Type of gynecologic cancer	
Uterine	24 (57%)
Ovarian	9 (21%)
Cervical	5 (12%)
Gestational trophoblastic neoplasia	4 (10%)
Stage	
I	3 (7%)
II	4 (10%)
III	22 (52%)
IV	13 (31%)
Grade	
1	2 (5%)
2	4 (10%)
3	36 (85%)
Brain imaging indication	
Headaches	12 (29%)
Ataxia	10 (24%)
Weakness	8 (19%)
Altered mental status	7 (17%)
New seizures	7 (15%)
Dizziness	5 (12%)
Syncope	4 (10%)
Numbness	3 (7%)
Aphasia	2 (5%)
Vision	0 (0%)
Asymptomatic, incidental finding	3 (7%)
Location of metastases	
Frontal lobe	28 (67%)
Parietal lobe	20 (47%)
Temporal lobe	16 (38%)
Occipital lobe	11 (26%)
Insular lobe	3 (7%)
Midbrain	4 (10%)
Cerebellum	15 (36%)
Brainstem	5 (12%)
Meninges	3 (7%)
No. of CNS/brain metastases	
1	14 (33%)
2–10	24 (57%)
> 10	4 (10%)
Tumor characteristics	
Vasogenic edema	37 (88%)
Enhancement	36 (86%)
Midline shift	7 (17%)
Hemorrhagic	15 (36%)
Cystic	4 (10%)
Bilateral	20 (48%)
Gray-white junction	5 (12%)
Median size of brain metastasis (cm)	2.7
Lung metastasis at time of brain diagnosis	22 (52%)

record. Radiology and surgical pathology reports were individually reviewed to ensure inclusion accuracy. Descriptive and comparative statistics were performed using the software Prism 8 (GraphPad). Statistical significance between experimental groups were computed using Kruskal-Wallis one-way analysis of variance with Dunn's test for multiple variable comparison correction. A p-value of < 0.05 was considered significant.

3. Results

During the study period, 67 patients with primary gynecologic malignancy who had brain imaging concerning for metastasis were identified. Of these, 25 patients were excluded for non-gynecologic primary tumor (e.g. second primary) or benign CNS tumor on final

pathology. This left a total of 42 patients with CNS metastases from gynecologic primaries to comprise our study cohort (Table 1). The majority of this cohort had primary endometrial cancer (57%, n = 24). Most patients were stage III or IV at time of initial diagnosis of gynecologic malignancy (83%, n = 35), Most tumors were high grade (85%, n = 36). Median time from initial diagnosis of gynecologic cancer to diagnosis of CNS metastasis was 20.7 months (standard deviation 29.9 months, range 0.0–107.8 months, IQR 8.7–45.2 months). All patients received diagnostic brain MRI or confirmatory MRI after positive CT head, with the most common indication being new neurological symptoms (93%, n = 39). Only 3 patients (7%) were asymptomatic at time of imaging. The most common presenting symptoms were headaches (29%, n = 12) and ataxia (24%, n = 10). The majority of tumors were found in the frontal lobe (67%, n = 28), followed by the parietal lobe (47%, n = 20) and temporal lobe (38%, n = 16). Most lesions presented with vasogenic edema (88%, n = 37) and enhancement (86%, n = 36) on initial MRI. The majority of patients had more than one brain lesion (67%, n = 28) with 4 patients (10%) presenting with more than 10 metastatic sites in the brain appreciated on imaging. Approximately half of the cohort had measurable lung metastases (52%, n = 22), confirmed either radiologically or by biopsy at the time of brain diagnosis.

Patients were also analyzed by sites of primary cancer including uterine, ovarian, cervical, and GTN (Table 2). Patients with GTN were significantly younger at both time of original primary cancer diagnosis as well as diagnosis of brain metastases. Median time between cancer diagnoses and CNS metastasis diagnosis, however, did not differ between primary sites of disease. There were no differences between initial stage or grade with regards to primary tumor site. When evaluating the location of CNS metastatic disease, cervical cancer patients exhibited a higher percentage of meningeal involvement (40%, n = 2) than other primary sites (uterine: 3%, n = 1; ovarian: 0%; GTN: 0%). There was no difference in the percentage of patients with lung metastasis when comparing by primary site of disease. There was no difference in median tumor size, total number of CNS lesions, or symptomatology triggering brain imaging between primary disease sites.

The histologies associated with brain metastases within each primary gynecologic cancer disease site were also reviewed (Table 3). In patients with uterine cancer, the endometrial subtypes were the most likely to present with brain metastasis (92%, n = 22) with only two sarcoma patients with CNS spread (1 leiomyosarcoma, 1 pleomorphic sarcoma). Of the 22 cases of endometrial cancers, only 4 (17%) were grade 1 or 2 endometrioid subtype. The majority of brain metastasis (59%, n = 25) in uterine cancers were seen from grade 3 endometrioid tumors (29%, n = 7), serous carcinomas (17%, n = 4), and carcinosarcomas (13%, n = 3). For tumors originating from the ovary (n = 9), serous epithelial carcinoma was the most likely histology (89%, n = 8). For cervical cancer patients (n = 5), squamous cell carcinoma comprised of 80% (n = 4) of brain metastasis; no CNS spread was seen in adenocarcinomas in this cohort. In patients with GTN (n = 4), choriocarcinoma was the most common histology (75%, n = 3).

4. Discussion

This study sought to add to the literature on CNS metastasis from gynecologic malignancies by reviewing the presentation and histologic subtype associated with CNS metastasis from gynecologic cancers. Currently, there is minimal data describing the clinical presentation of patients with brain metastasis in tumors of gynecologic origin. We found that most patients identified with a brain metastasis from gynecologic primary were symptomatic with a new neurologic complaint.

Several mechanisms of spread have been postulated regarding CNS and brain metastases, including direct hematogenous seeding, retrograde lymphatic spread, and direct invasion secondary to bony involvement (Kumar et al., 2003). Neoplasms of gynecologic origin rarely involve the CNS as most tumors spread or recur via direct extension,

Table 2
Characteristics by primary tumor origin.

	Uterine (N = 24)	Ovary (N = 9)	Cervix (N = 5)	GTN (N = 4)	P-value
Median age at diagnosis, gynecologic	61.2	61.8	47.6	31.3	0.006
Median age at diagnosis, brain	63.0	64.6	52.8	33.0	0.004
Median years between diagnoses	1.9	1.9	1.2	0.4	0.22
Stage					0.98
I	3 (13%)	0 (0%)	1 (20%)	0 (0%)	
II	2 (8%)	1 (11%)	1 (20%)	0 (0%)	
III	12 (50%)	6 (67%)	2 (40%)	2 (50%)	
IV	7 (29%)	2 (22%)	1 (20%)	2 (50%)	
Grade					0.99
1	2 (8%)	0 (0%)	0 (0%)	0 (0%)	
2	2 (8%)	1 (11%)	1 (20%)	0 (0%)	
3	20 (83%)	8 (89%)	4 (80%)	4 (100%)	
Location of metastases					
Frontal lobe	16 (67%)	7 (78%)	3 (60%)	2 (50%)	0.78
Parietal lobe	12 (50%)	4 (44%)	2 (40%)	2 (50%)	0.98
Temporal lobe	9 (38%)	3 (33%)	3 (60%)	1 (25%)	0.71
Occipital lobe	6 (25%)	3 (33%)	0 (0%)	2 (50%)	0.37
Insular lobe	2 (8%)	1 (11%)	0 (0%)	0 (0%)	0.82
Midbrain	2 (8%)	1 (11%)	0 (0%)	1 (25%)	0.65
Cerebellum	8 (33%)	5 (56%)	2 (40%)	0 (0%)	0.29
Brainstem	2 (8%)	2 (22%)	1 (20%)	0 (0%)	0.57
Meninges	**1 (4%)**	**0 (0%)**	**2 (40%)**	**0 (0%)**	**0.03**
No. of CNS/brain metastases					
1	8 (33%)	1 (11%)	2 (40%)	3 (75%)	0.16
2–10	15 (63%)	5 (56%)	3 (60%)	1 (25%)	0.58
> 10	1 (4%)	3 (33%)	0 (0%)	0 (0%)	0.06
Brain metastasis characteristics					
Vasogenic edema	21 (88%)	7 (78%)	5 (100%)	4 (100%)	0.55
Enhancement	18 (75%)	9 (100%)	5 (100%)	4 (100%)	0.16
Midline shift	4 (17%)	0 (0%)	2 (40%)	1 (25%)	0.28
Hemorrhagic	8 (33%)	5 (56%)	0 (0%)	2 (50%)	0.20
Cystic	2 (8%)	1 (11%)	0 (0%)	1 (25%)	0.65
Bilateral	12 (50%)	6 (67%)	2 (40%)	0 (0%)	0.17
Gray-white junction	4 (17%)	1 (11%)	0 (0%)	0 (0%)	0.64
Brain imaging indication					
Headaches	5 (21%)	2 (22%)	2 (40%)	3 (75%)	0.15
Ataxia	5 (21%)	4 (44%)	1 (20%)	0 (0%)	0.33
Weakness	6 (25%)	2 (22%)	0 (0%)	0 (0%)	0.45
Altered mental status	4 (17%)	1 (11%)	2 (40%)	0 (0%)	0.41
New seizures	5 (21%)	0 (0%)	2 (40%)	0 (0%)	0.19
Dizziness	3 (13%)	2 (22%)	0 (0%)	0 (0%)	0.55
Syncope	2 (8%)	1 (11%)	1 (20%)	0 (0%)	0.78
Numbness	2 (8%)	1 (11%)	0 (0%)	0 (0%)	0.82
Aphasia	1 (4%)	1 (11%)	0 (0%)	0 (0%)	0.75
Asymptomatic, incidental finding	2 (8%)	0 (0%)	0 (0%)	1 (25%)	0.39
Median size of brain metastasis	2.3 cm	1.9 cm	2.9 cm	3.8 cm	0.37
Lung metastasis at time of brain diagnosis	12 (50%)	5 (55%)	2 (40%)	3 (75%)	0.76

Statistical significance was determined by Kruskal-Wallis one-way analysis of variance with Dunn's test for multiple variable comparison correction. For median age of gynecologic diagnosis, the GTN subgroup was significantly less than the Uterus subgroup (adjusted p = 0.009) and Ovary subgroup (adjusted p = 0.02). For median age of brain diagnosis, the GTN subgroup was again significantly less than the Uterus subgroup (adjusted p = 0.006) and the Ovary subgroup (adjusted p = 0.01). For meningeal metastases, the Cervix subgroup had significantly more events than the Uterus subgroup (adjusted p = 0.03) and the Ovary subgroup (adjusted p = 0.04). Abbreviations: CNS – central nervous system; GTN – gestational trophoblastic neoplasia.

Table 3
Histologic subtypes of gynecologic cancers.

	No. of patients
Uterus (N = 24)	
Endometrioid adenocarcinoma (grade 1/2)	4 (17%)
Endometrioid adenocarcinoma (grade 3)	7 (29%)
Papillary serous carcinoma	4 (17%)
Carcinosarcoma	3 (13%)
Adenosquamous	1 (4%)
Clear cell carcinoma	1 (4%)
Leiomyosarcoma	1 (4%)
Pleomorphic sarcoma	1 (4%)
Small cell neuroendocrine carcinoma	1 (4%)
Mixed adenocarcinoma	1 (4%)
Ovary (N = 9)	
Serous carcinoma	8 (89%)
Malignant Brenner tumor	1 (11%)
Cervix (N = 5)	
Squamous cell carcinoma	4 (80%)
Small cell neuroendocrine carcinoma	1 (20%)
Gestational trophoblastic neoplasia (N = 4)	
Choriocarcinoma	3 (75%)
Endodermal sinus tumor	1 (25%)

transcoelomic dissemination, or by locoregional lymphatic channels, with incidence rates reported at 0.5–1% for uterine, ovarian, and cervical cancers (Ratner et al. 2019; Moroney et al., 2019; Kim et al., 2018). Typically, gynecologic cancers exhibiting hematogenous spread are associated with advanced stage or widely disseminated disease, particularly to the lungs. In line with existing literature, the majority of patients in our cohort was found to have existing pulmonary metastases at or before the time of diagnosis of brain or CNS involvement. Choriocarcinoma, an aggressive form of GTN, classically involves the lungs and brain relatively early in its course, and is considered unique in its preferential hematogenous spread by malignant derivatives of trophoblastic cell types (Seckl et al., 2010). Additionally, GTNs classically affect younger and pre-menopausal women, as the majority of these neoplasms arise from cell types present only during gestation.

Our cohort demonstrated recurrent headaches as the primary presenting complaint, similar to other primary tumors with brain metastasis, including tumors of the lung, breast and skin (Rostami et al., 2016; Forsyth and Posner, 1993). In non-gynecologic cancers, headaches alone in patients have been shown to be a poor predictor for the presence of brain lesions unless concurrent neurological issues (e.g. papilledema, ataxia, or other focal deficits) exist (Argyriou et al., 2006). However, gynecologic tumors with cerebral involvement may have an altered presentation from those of other origins. From our cohort, 11 patients (Table 2) were found to have metastatic disease to their occipital lobes, but without initial visual symptoms. A previous study noted that up to 40% of patients have visual field defects when these metastatic lesions involve the occipital lobe (Kaal et al., 2005). For these 11 patients, the most common presenting symptom was headache, though almost all were found to have concurrent involvement of other lobes on initial MRI. Interestingly, the single patient with a solitary occipital lobe tumor initially presented with new-onset aphasia. These findings may illustrate a possible need for brain imaging in the setting of new singular neurological symptoms, such as unexplained headaches, especially in patients with high-risk tumors (advanced stage, high grade, or choriocarcinoma). However, due to the rare nature of CNS metastases in gynecologic cancers, routine brain imaging for headache would likely result in overuse of imaging.

The frontal lobe was the most common site of involvement in our cohort, consistent to metastatic patterns displayed by other primaries

(Nussbaum et al., 1996). Other common sites include the parietal lobe, the temporal lobe, and cerebellum. When compared to other primaries, patients with cervical cancer were found to have a significantly higher percentage of leptomeningeal involvement. Metastatic spread to parts of the meninges have been postulated to occur via retrograde lymphatic flow, though cervical cancers are not proven to exhibit this characteristic more than ovarian, uterine, or GTNs. This finding may be due to our small sample size. Notably, at time of this report, there are less than 30 cases of carcinomatous meningitis secondary to cervical cancer reported in the English literature, with an incidence of less than 0.05% (Yust-Katz et al., 2013).

A total of 22 patients in our cohort had endometrial primaries with only 4 patients (17%) displaying the usual grade 1 or 2 endometrioid histologies. The disproportionately high percentage of type II endometrial cancers in the population with brain metastasis (83% in this cohort vs 20–30% in general population) is not unexpected due to the known aggressiveness of these histologies, and is consistent with existing literature (Moroney et al., 2019; Uccella et al., 2016). Furthermore, on a molecular level, there are marked differences in surface protein expression, such as mutation load of cadherin proteins, which increases the risk of intercellular cohesion loss and potentially downstream hematogenous spread (Liu, 2007). Consequently, increased suspicion should be maintained in women with type II endometrial cancer who present with symptoms that could represent CNS metastasis.

5. Conclusion

This study described patterns in clinical presentation, symptomatology, and diagnosis of metastatic brain metastases in the context of gynecologic cancer. Given the highly variability of presentation of neurological symptoms and lack of correlation to patterns of CNS spread, early identification remains difficult, especially in asymptomatic patients. However, our data infers a possible increased risk of brain metastases for patients with type II endometrial cancers, which may support lowering the threshold for brain imaging in this patient population, though effects on patient outcomes remain uncertain and will need further investigation. There are a number of major limitations to this study, as it is retrospective in nature, and includes a relatively small sample of patients. Consequently, statistically significant results and the analyses described should be interpreted in this context. Nevertheless, this project may help serve as a foundation for furthering our understanding of the clinical presentation of this phenomenon. Further studies survival indices stratified by treatment will be needed, though may be challenging given the rarity of these cases.

Author contributions

Y.Z. performed the chart review and data collection with support from M.S. and W.S. Statistical analysis was performed by Y.Z. and verified by all authors. All authors discussed the results and provided critical feedback. Y.Z. and W.S. wrote the manuscript and tables in consultation with M.S. and L.C. L.C. designed and supervised the project.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

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