Is Endometrial Cancer Really a Neurophobic Tumor? A Case Report and Review of the Literature

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Abstract. *Brain metastases due to endometrial cancer are rare and usually occur in the context of widespread disease. We present a rare case of a 74-year-old woman with recurrent endometrial cancer in terms of a solitary brain lesion two years after initial diagnosis. She was treated with local resection of the brain metastasis and subsequent whole-brain radiotherapy. She then experienced relapse twice, presenting two solitary metastases at two different time points at the same location as at initial diagnosis, but never showed any signs of extracranial widespread disease. The patient has been alive for 13 months after detection of her initial brain metastasis. Despite the identification of some risk factors, there is still very limited knowledge why some patients develop brain metastases as the only sign of distant spread. Our review of the literature revealed that the combination of two treatment modalities yields higher survival rates than single treatment-alone, as was the case in the presented patient. Further case reports, as well as large and prospective studies, may contribute to a better understanding of the etiology and dynamics of this disease and allow better evaluation of treatment options.*

Endometrial cancer is one of the most common gynecological malignancies in postmenopausal women (1). It usually metastasizes by local invasion or lymphatic spread (2). Brain metastases occur in about 10-30% of all patients with cancer and are usually associated with a poor prognosis (3). While lung cancer, breast cancer and melanoma, as well as cancer of unknown primary site, are the most common causes of brain metastases, gynecological malignancies rarely metastasize to the brain, with the exception of choriocarcinoma (3).

In case of hematogenous spread, pulmonary lesions are the most common site, followed by liver, bones and brain (4). The brain is a rare site of cancer recurrence from primary endometrial cancer with an incidence of 0.3-1.4% in clinical settings (5, 6) and 1-3% in autopsy series (5, 7, 8). When brain metastases occur, they usually represent widespread disease (3, 9). Although the mode of spread to the brain is traditionally considered to be *via* the lungs first and then to the brain *via* the pulmonary vessels (3), this theory has not yet been proven.

In this case report, we present a patient that developed a solitary brain metastasis almost two years after treatment of endometrial cancer. To the best of our knowledge, there have been 127 cases of patients reported suffering from brain metastases due to endometrial cancer to date, with the first case published in 1972 (10).

Our purpose was to approach this rare condition through research of the literature to gain insight into clinical features and causes of distant spread to the brain in patients with a history of endometrial cancer. Furthermore, our aim was to gather tangible information regarding survival rates in this particular group of patients, and to compare them with our patient's data.

For our literature review, we searched the PubMed database for relevant articles, especially case reports, using the terms: "brain metastasis", "endometrial cancer", "endometrial carcinoma", "CNS metastasis" and "biology of brain metastasis". No date or language restriction was employed.

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Case Report

In spring 2010, a 72-year-old German patient was seen by her gynecologist for a regular gynecological check-up. The gynecological history revealed beginning of menarche at the age of 14 and cessation of menstruation at the age of 57. She had had two deliveries and one abortion. Except for a fibroplastic mastopathy, no other gynecological diseases, including breast cancer, or other malignancies were known at the time of presentation. The family history revealed the patient's mother had had breast cancer. The patient has hypertonia, coronary disease, hypothyroidism, and asymptomatic stenosis of the right carotid artery. The present history, however, did not reveal any abnormalities. She had a body-mass index of 24.6 kg/m^2 and was in good general condition. However, on routine examination, a positive Pap smear (Pap 3) was detected. Repeated tests revealed Pap 5, and subsequently the patient underwent a conization and fractional curettage. The removed tissue was considered as adenocarcinoma, with the main manifestation in the uterine corpus and small lesions in the superficial stromal parts of the cervical transformation zone. Finally, the patient underwent surgery with total resection of the uterus, bilateral removal of the adnexa, and pelvic and para-aortic lymphonodectomy. The histopathological examination revealed a moderately-differentiated endometrial cancer of endometrioid type, with infiltration to the outmost muscular layer, and involvement of the mucosa of the isthmus. The initial staging was as follows: pT2, pN0 (0/36), G2, L0, V0, R0. No expression of estrogen (ER) or progesterone (PR) steroid hormone receptors was found. The patient's characteristics are summarized in Table I.

Table I. *Patient characteristics*.

Age	74 years
Karnofsky performance status (prior to gynecological operation)	90%
FIGO stage	II
Pathohistology	
Histological type	Endometrioid
Grade	II
Deep myometrial invasion	+
Cervical invasion	+
Lmphovascular space invasion	–
Lymph node involvement	–
Expression of steroid hormone receptors	
ER/PR	–/–
Other primary malignancies	No

FIGO Fédération Internationale de Gynécologie et d'Obstétrique; *ER* estrogen receptor; *PR* progesterone receptor.

Since a complete resection (R0) of the tumor was achieved, the surgical situation was considered to be low-risk. In addition, chest x-ray, abdominal computed tomographic (CT) scans and mammography revealed no signs of malignancy. The decision not to treat the patient with chemotherapeutics nor with hormone therapy was supported by an interdisciplinary tumor conference. Therefore, the patient received an adjuvant after-loading contact therapy four times with 6.5 Gy to the vaginal stump one and a half months after the initial surgery. According to guidelines (11), the patient was seen by her local gynecologist every three months for two years, with no evidence of recurrence at any visit.

In summer 2012, the patient was referred to hospital after experiencing general convulsive seizures. Apart from post-ictal somnolence and drowsiness, the patient did not present any acute symptoms. On gross clinical examination, nothing abnormal was detected. Except for discrete ataxia seen in the finger-to-nose test, no abnormal findings were found on further neurological examination. A cranial CT was carried out and a suspicious lesion on the left temporal side was noticed. Magnetic resonance imaging (MRI) was performed one day later and confirmed a cerebral mass between the inferior temporal gyrus and the middle temporal gyrus with perifocal edema. A cranial MRI was repeated three days later and revealed discrete progress of the lesion (Figure 1).

An osteoplastic trepanation was performed and a soft, beige-colored mass of 1.8×1.2×0.4 cm with a weight of 0.89 g was removed. It had extensive areas of necrosis and portions of papillary adenocarcinoma with increased mitotic activity. Almost no periodic acid-Schiff (PAS) positivity was found within tumor cells. Expression of cytokeratin-7 (CK-7) and cytokeratin-20 (CK-20) was found on immunohistochemical staining, but there was no expression of ER or PR receptors. The removed lesion was considered to be a metastasis of the previous endometrial cancer.

Almost two months after surgical removal of the cerebral metastasis, MRI scans revealed a recurrent lesion in the resection cavity on the left temporal side (Figure 2). Thereupon, another operation with removal of the intracerebral mass was performed. The histopathological examination showed the mass to be beige to grey-brown-colored, moderately solid of 2.4×1.8×0.5 cm and a weight of 0.97 g. Apart from necrotic areas, portions of pleomorphic papillary carcinoma with strong expression of CK-7, partially of vimentin, and expression of CK-20 were seen (Figure 3). The removed metastasis was considered to derive from the previous endometrial cancer.

The patient received whole-brain radiotherapy and boost radiation. MRI scans were performed according to guidelines (12) and did not show any evidence of relapse. However, another lesion of 8 mm was found in the left frontal gyrus at regular MRI examination in summer 2013. Prior to this examination, the patient did not present any symptoms or signs of recurrent disease. Stereotactic radiosurgery (Gamma Knife) was then performed in the beginning of August 2013.

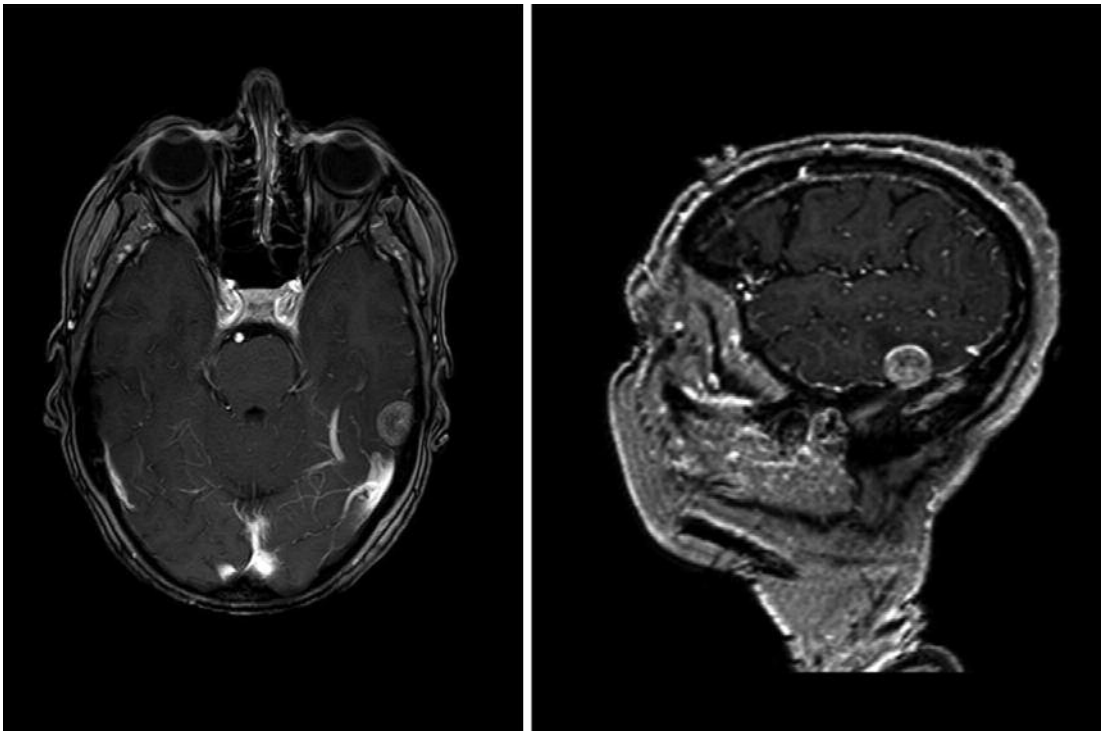

Figure 1. *Cranial magnetic resonance imaging (MRI) revealed a left temporal mass with slight perifocal edema on transverse (left) and sagittal (right) section.*

Discussion

In comparison to other gynecological malignancies, such as ovarian or cervical cancer, endometrial cancer often has a very good prognosis, but its volatile metastatic potential remains "the intrinsic treachery of the disease" (13).

Metastases to the brain arising from endometrial cancer represent a rare event (5, 6), and if found, they usually occur in the context of widespread disease (14, 15), which is in contrast to the findings in our patient, where only one solitary brain metastasis was present with no evidence of spread to other distant sites. Studies on applied approaches to incidence, treatment and survival rates of patients suffering from brain involvement due to endometrial cancer remain few, and are mainly limited to case reports and small retrospective case series (14).

In order to provide a better comparison, we list the 59 documented cases of the past 10 years (2003-2013) in Table II.

Our patient presented a series of three solitary brain metastases throughout a time period of one year. In their review article, Piura and Piura showed that in approximately 60% of cases, the brain metastasis was solitary (15). Amongst others, in complete contrast, in a small cohort, Mahmoud-Ahmed *et al*. recorded 7 out of 10 cases presenting multiple brain lesions (16). The cerebrum is described as the most frequent site of metastases from endometrial carcinoma, which is in line with the observed localization of metastatic lesions in our patient and in cancer patients with brain metastases in general (17).

As is well-known, the most common mechanism of metastasis to the brain is hematogenous spread, usually by the way of the lungs (18, 19). Since our patient showed neither evidence of pulmonary involvement nor other signs of widespread disease, we were specifically interested in identifying other risk factors that might further the development of distant spread to the brain. High tumor grade, advanced stage of disease and the presence of lymphovascular space invasion have been validated as correlating with the future development of brain metastases (14). In one study assessing predictors of hematogenous dissemination in endometrial cancer, deep myometrial invasion was the strongest predictor together with an advanced stage IV according to the Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) (20). This finding was supported by a retrospective analysis and a review of the literature by Chura *et al*. who revealed that 16 out of 20 patients with brain metastases and concurrent endometrial cancer who underwent hysterectomy had a median depth of myometrial invasion of 69% (21). Hence, they pondered its importance as surrogate marker for the risk of distant spread

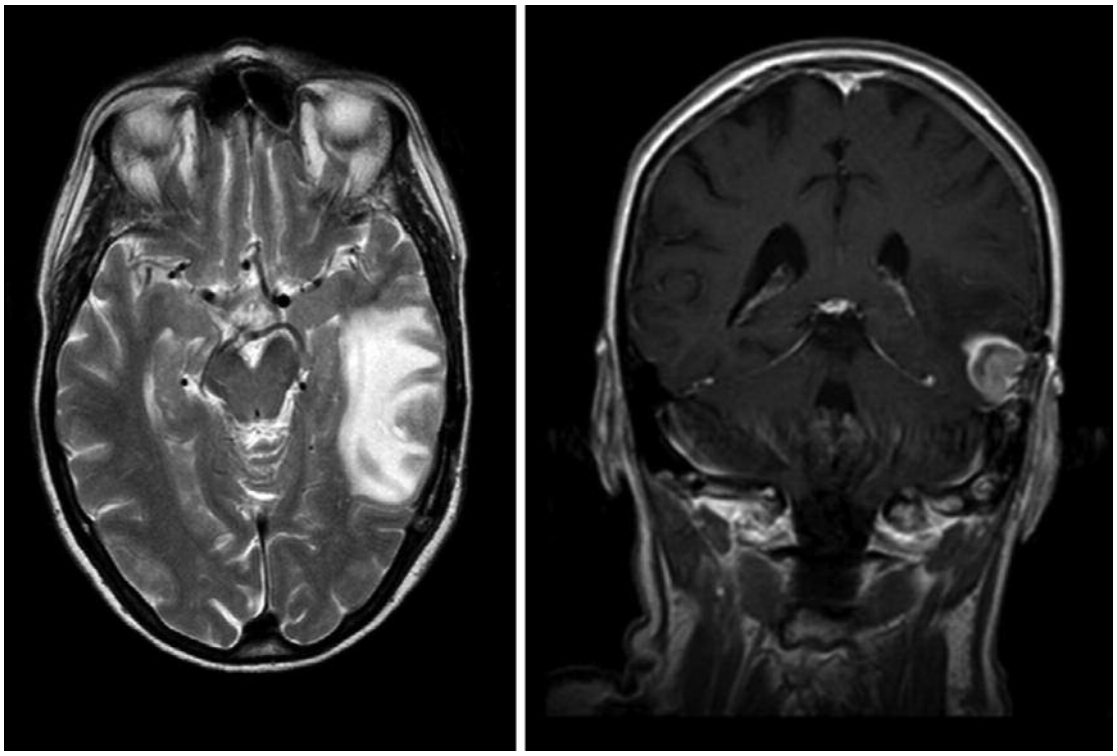

Figure 2. *MRI scans revealed a recurrent lesion in the resection cavity on the left temporal side on transversal (left) and frontal (right) sections.*

(21). In addition, histological grade 3 (5, 8) and cervical invasion (18) were also noted as risk factors for the development of future cerebral metastases. In detailed studies about the establishment of other risk and prognostic factors in endometrial cancer, individuals with poor survival can be identified depending on the presence of ER and PR, whereupon ER and PR negativity was correlated with poor survival, high tumor grade, advanced stage and extrauterine spread in patients with endometrial cancer (22-24). Regarding the histological type as risk factor for distant spread, amongst others Rosenberg *et al.* found that it did not significantly affect survival (25). Bearing in mind that our patient presented with FIGO stage II disease – including deep myometrial invasion, involvement of the cervix and ER and PR negativity – it can be stated that apart from lymphovascular involvement and histological grade 3, all the aforesaid risk factors were present. However, the fact that no widespread disease was present might out-weigh all such risk factors and further represents a highly rare situation, since female genital tract carcinomas are considered to be 'neurophobic' (15).

Regarding the patient's exceptional course of disease, one of our objectives was to identify relevant prognostic factors in the context of metastatic involvement of the brain due to endometrial cancer. Several studies showed that patients with solitary brain metastases from endometrial cancer who underwent neurosurgical procedures and radiotherapy lived longer than those who were treated with radiotherapy or surgery alone (5, 9, 16). Chura *et al.* underlined the importance of multimodal therapy in contrast to no treatment or whole-brain radiotherapy alone, resulting in improved median survival times (9.2 months *vs.* 0.2 months and 0.9 months, respectively) (21); among the 20 patients that were investigated, those with no systemic disease had higher median survival compared to those where a systemic course of disease was noticed (26.5 months *vs.* 5.0 months) (21). A study by Zimm *et al.* that was published in 1981 revealed that among 191 patients with *ante mortem* diagnosis of intracerebral metastases from various types of cancer investigated throughout a period of four years, solitary brain metastases were revealed to be a favorable prognostic factor, leading to a median survival time of 3.7 months for the entire series after diagnosis of intracerebral metastasis (26). They also found that the type of treatment has an impact on survival, with those cases treated with surgery and radiotherapy having a median survival time of 9.7 months *vs.* 3.7 months for those treated with radiotherapy alone, and that patients who presented with brain involvement as initial site of distant spread were considered to be at higher risk of dying (26). In their review article, *Piura and Piura* reported

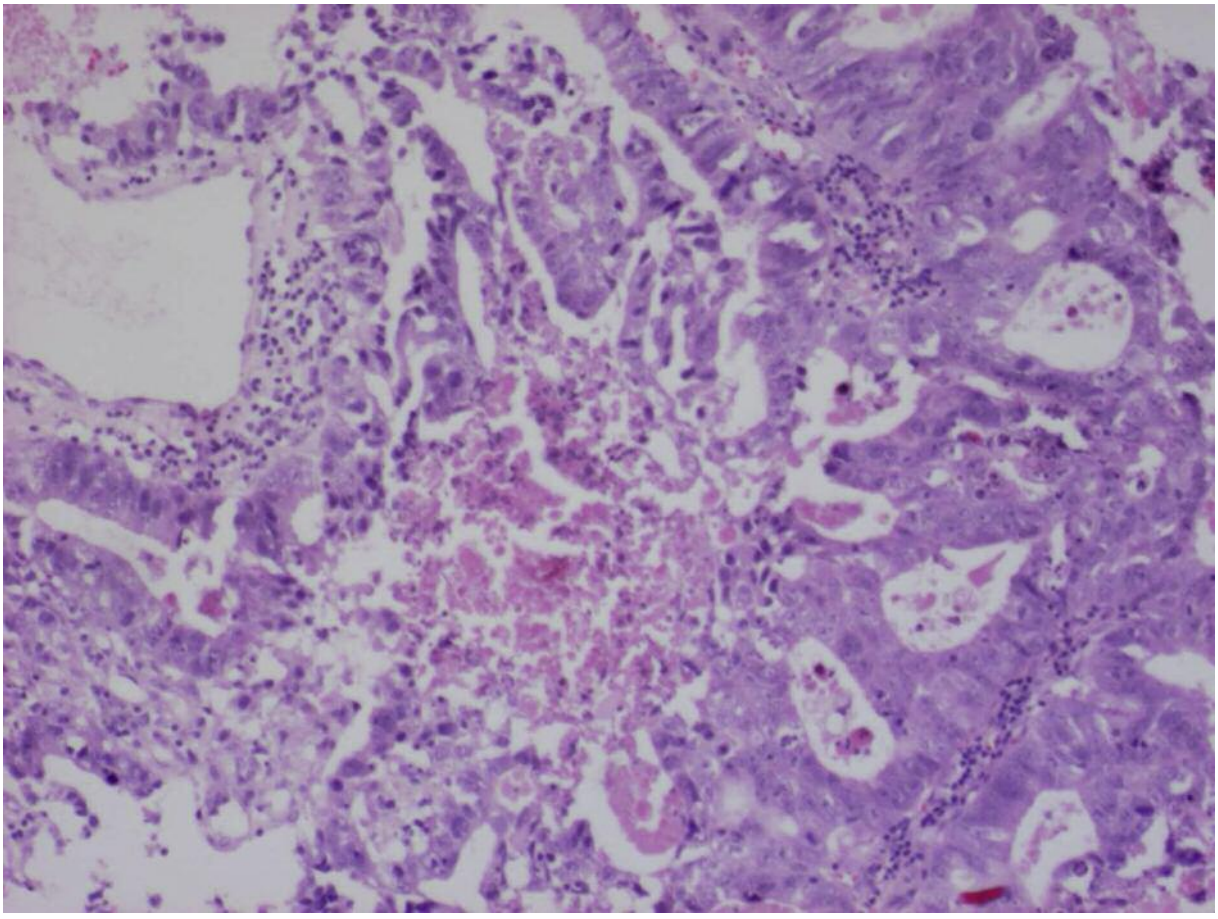

Figure 3. *On hematoxylin and eosin staining, a partially necrotic papillary carcinoma with high mitotic activity and lymphocytic infiltration in the stroma of the brain metastasis is seen (×100).*

that in the vast majority of cases, brain involvement was detected after diagnosis of endometrial cancer, with a median survival rate of 17 months between diagnosis of endometrial cancer and spread to the brain (15). These findings are in line with the observed survival rate of 13 months in our patient. However, in patients with controlled systemic cancer, in whom a solitary brain metastasis develops, the treatment of the brain involvement is the factor that will determine the length of survival (27). Sawada *et al*. reported a single case of a 43-year-old patient in 1990 who was diagnosed with a solitary brain metastasis in the left occipital lobe approximately 1.5 months after radical hysterectomy due to poorly-differentiated endometrial cancer, but had a disease-free interval of seven years after hysterectomy, and six years and 10 months after surgical removal of her brain metastasis (27). Since the aforementioned findings are somewhat old, they have to be considered carefully as treatments and their reporting change over time, and concise information regarding type and extent of the applied treatments cannot always be adequately provided. In addition, the above cited studies and case reports investigated only very small numbers of patients, potentially resulting in lower study power and bias to external validity.

Ogawa *et al*. reviewed a total of 556 patients with endometrial cancer and found that metastatic spread to the brain was present only in four cases (3). The median survival was 4.3 (range 3.1-4.9) months (3). They also identified five factors that had significant impact for survival: treatment modality, extracranial disease, total radiation dose, number of brain metastases and Karnofsky performance status (3). Two patients survived for more than two years and had each a single brain metastasis, inactive extracranial disease, 90-100% Karnofsky performance status, and were treated with surgery plus radiotherapy (3). One patient died of recurrent brain metastasis after 48.2 months, and the other patient died of recurrent extracranial metastasis after 28.4 months (3).

Central to the current discussion is the fact that our patient's survival did not show any deviations from that we found in our review of the literature. Most of the described risk factors for distant spread were also present in this case.

Table II. *Review of the literature of endometrial cancer patients with brain involvement of the last 10 years (2003-2013).*

Publication (year)	Number of cases	Age at detection of brain involvement (years)	*FIGO* stage	Histology			Solitary *vs.* multiple lesions	Widespread disease (extracranial)	Localization	Primary treatment	Time of occurrence after primary treatment (months)	Adjuvant treatment	Treatment of brain involvement	Median survival after detection of brain involvement (months)
				Type (subtype), N status, lymphovascular space invasion, Grade	Invasion of									
					deep myometrium	cervical stroma								
Shiohhara *et al.*, 2003 (37)	1	48	IIIA	AC (endometrioid), Nx, Lx, G3	NA	NA	Solitary	No	NA	HSOL	0	No	S + SRS + CHT	>38
Elliott *et al.*, 2004 (34)	1	51	IIB	AC (endometrioid), N1, L1, G3	+	+	Solitary	No	Left temporal lobe	HSOL	2	RT	S + WBRT + CHT	>30
Lee *et al.*, 2004 (38)	1	54	IB	AC (endometrioid), N0, L0, G3	–	–	Multiple	No	Frontal lobe	HSOL	108	RT	WBRT	0.25
Salvati *et al.*, 2004 (39)	2	62	IA	AC (NA), Nx, Lx, G2	–	–	Solitary	No	NA	HSO	48	RT	S + WBRT	>9
Llaneza-Coto *et al.*, 2006 (40)	1	43	IIA	AC (NA), Nx, Lx, G3	+	–	Solitary	No	NA	No	0	No	S	1
Orru *et al.*, 2007 (6)	3	61	IIIC	AC (endometrioid), N1, Lx, G3	+	+	Multiple	No	Frontal and temporal lobe	HSOL	17	CHT + RT + BT	S + WBRT	>64
		60	IIIA	AC (NA), N0, Lx, G3	NA	NA	Solitary		Frontal lobe	HSOL	6	No treatment	WBRT	4
		49	IIIB	AC (NA), N0, Lx, G3	NA	NA	Solitary		Parieto-occipital lobe	HSOL	10	RT + RT	S + WBRT	>16
Sohaib *et al.* 2007, (41)	1/86 *	NA	NA	AC (NA), Nx, Lx, Gx	NA	NA	Solitary	No	NA	HSO	NA	NA	NA	NA
Ramirez *et al.* 2008 (42)	1	61	IIB	AC (NA), Nx, Lx, G3	+	+	Multiple	No	Thalamus (bilateral)	HSO	12	RT	WBRT	17
Monaco *et al.* 2008 (14)	6	60.4	NA	NA, Nx, Lx, Gx	NA	NA	NA	NA	NA	NA	NA	NA	SRS	7
Al Mujaini *et al.* 2008 (43)	1	69	NA	AC (NA), Nx, Lx, Gx	NA	NA	Multiple	Yes	Occipital lobe (bilateral)	HSO	84	RT	NA	NA
Forster *et al.* 2011 (44)	1	58	I	AC (endometrioid), Nx, Lx, G2-3	NA	–	Multiple	Yes	Left temporal lobe and parietal lobes	HSO	108	RT	PARP 1 inhibitor	18
Cabuk Cömert *et al.* 2012 (45)	2/247	NA	IB	AC (endometrioid), N0, Lx, G2	–	–	Multiple	Yes	Cerebellum	NA	29	CHT	SRS	>30
		NA	IIIA	AC (serous-papillary), N0, Lx, G3	NA	NA	Solitary	Yes	Cerebellum	NA	2	CHT	NA	5

AC: Adenocarcinoma; NA: not available or not specified; HSO: total abdominal hysterectomy and bilateral salpingo-oophorectomy; HSOL: total abdominal hysterectomy and bilateral salpingo-oophorectomy and lymph node dissection; RT: radiotherapy; S:,surgical resection; WBRT: whole-brain radiotherapy; SRS: stereotactic radiosurgery; CHT: chemotherapy; HT: hormonal treatment; *patients with recurrent endometrial cancer following primary surgery; **this information refers to the whole investigated cohort.

Nevertheless, it still remains unclear why our patient did not show any evidence of distant organ involvement, but only one (recurrent) brain metastasis almost two years after initial treatment.

Sir James Paget, however, was the first one to posit that "the seeds of a plant are carried in all directions; but they can only live and grow if they fall on congenial soil" (28), indicating that cancer cells (the seed) metastasize to locations that are biochemically and physiologically favorable for implantation and growth (the soil). Nowadays, there is evidence that the interplay of circulating tumor cells, cancer stem cells, a series of implicated genes, the epithelial-mesenchymal transition, as well as mesenchymal–epithelial transition is of paramount importance for tumors to successfully metastasize (29). Our aim was not to delve into the detailed molecular concepts of distant spread, since that would exceed the scope of our present work. However, the brain indeed remains a challenging destination for metastatic cells, basically for two reasons: its lack of lymphatic drainage and the presence of the robust blood–brain barrier (29). Nevertheless, metastatic cells may circumvent these constraints by rupturing the endothelium to gain access (29, 30). After sufficient growth of the metastatic tumor, the leakage of the brain–barrier is furthered by tumor-associated necrosis, probably mediated by vascular endothelial growth factor, which leads to damage of the endothelium itself (29, 31).

Others assume a more radical way of metastatic attack, where astrocytes are considered to be protective for metastatic cells, helping to avoid their apoptosis (29, 32). There is also some suggestion that endometrial carcinoma belongs to the neurophobic group of carcinomas because of the lack of specific tumor cell receptors in the central nervous system (33). Elliott *et al*. presented an explanation for solitary brain lesions without lung involvement by the Batson's spinal venous plexus that might promote direct access to the central nervous system in the presence of increased intra-abdominal pressure and small spinal and brain lesions (34). In addition, they also considered the spread of tumor cells through an aberrant circulation that bypasses the pulmonary vasculature as another reasonable explanation for the development of brain metastases without lung involvement (34). An undiagnosed lesion of small volume in the lung that is cleared by the endogenous immune system might also be a source of metastatic spread to the brain (34). Despite these promising explanatory approaches, it still remains ambiguous why certain malignancies tend to metastasize to the brain while others do not. Furthermore, the exact pattern of invasion to the brain in the absence of widespread disease remains unclear. The further understanding of the process of distant spread to the brain is crucial, since patients often die of their brain disease even in the course of controlled systemic cancer (35). It is indeed provocative to doubt the neurophobic character of endometrial cancer since such cases are very rare. However, they do occur, but unless the means of the spread to the brain is entirely elucidated, the neurophobic character of endometrial cancer will continue to prompt discussions among experts in the field. Although a multimodal approach to treatment is advisable whenever possible (36), the paucity of pre-existing studies and case reports in the realm of gynecological cancer with brain involvement demands further large and prospective studies to strengthen evidence-based decision making.

Conclusion

Although endometrial cancer is considered to be a neurophobic tumor, cases of brain involvement occur even in the absence of extracranial systemic spread. The combination of more than one treatment modality, namely surgery and radiotherapy, yields higher survival rates than either alone, and therefore should be applied in patients with brain involvement due to endometrial cancer. The aim of the current case report was to elucidate features, factors and causes of brain metastases in patients with endometrial cancer. We also wish to encourage other researchers and clinicians to report on similar cases in order to consecutively highlight similarities and differences in the disease course of each patient. We raise the idea of establishing a national, or even global, interdisciplinary registry where patients with gynecological malignancies with brain involvement are registered and their course of disease documented comprehensively. To further the understanding of the molecular implications of metastatic spread and growth, we claim stronger support of translational research, with the aim of better evidence from bench to bedside.

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Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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