



Case report

Pineal gland metastasis from uterine serous carcinoma: A case report and review of the literature

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A B S T R A C T

Uterine papillary serous carcinoma (UPSC) is a highly aggressive endometrial cancer histology with a propensity for distant metastasis. Despite the aggressive nature of UPSC, central nervous system metastasis is a rare occurrence with few cases reported in the literature. We present a case of a 58-year-old woman with a history of Stage IIIA UPSC who was diagnosed with recurrent, metastatic disease in the pineal gland more than 6 years after her initial diagnosis.

1. Introduction

Endometrial carcinoma is the most common gynecologic malignancy in the United States. It typically presents in early stages and carries a favorable prognosis. Historically, endometrial cancer was classified as Type I or Type II based on hormonal and clinical features, however, recent advances in tumor molecular profiling, such as next-generation sequencing, have translated into better identifying the molecular alterations driving these tumors and subsequently, potential targeted therapies. Though molecular profiling has provided greater insight into the landscape of endometrial tumorigenesis, efforts are underway to best incorporate molecular classification with traditional pathologic classification in guiding clinical management. The histological subtype of uterine papillary serous carcinoma is considered an aggressive subtype of endometrial carcinoma which tends to present more often as advanced stage, and molecular profiling studies have demonstrated these tumors harbor alterations in TP53, CCNE1, and HER2, compared to other histologies. While UPSC represents less than 10% of endometrial cancer cases, it accounts for up to 50% of endometrial cancer related relapses and deaths.

Despite the common finding of extrauterine spread seen in UPSC, metastasis to the central nervous system remains a rare occurrence with endometrial cancer. When brain metastasis occurs, it is often in the context of widespread disease. Primary brain metastasis is seen in less than 1% of endometrial cancer cases, has been reported most commonly with endometriosis histology, and confers a poor prognosis with median survivals ranging from 1 to 6.5 months (Gien et al., 2004; Chura et al., 2007) There are only twelve published cases of UPSC metastatic to the

brain, to our knowledge (Gien, et al., 2004; Dietrich et al., 2005; Chura, et al., 2007; Çabuk Cömert et al., 2012; Talwar and Cohen, 2012; Gulsen and Terzi, 2013; Sierra et al., 2015; Eulálio Filho et al., 2019; Moroney et al., 2019) (Table 1) and this is the first documented case of metastasis to the pineal gland. Our patient is alive and disease-free 13 months after detection of central nervous system recurrence.

2. Case report

A 57-year-old woman with a history of FIGO Stage IIIA uterine papillary serous carcinoma diagnosed in December 2012, underwent an abdominal hysterectomy, bilateral salpingo-oophorectomy, lymph node dissection and omentectomy at that time. Her CA-125 at the time of surgery was elevated at 747 U/mL. She completed six cycles of adjuvant chemotherapy with carboplatin and paclitaxel. For the next 6 years, the patient was followed for surveillance with imaging without any findings concerning for recurrent disease, and serial CA-125 levels which remained within normal limits and less than 20 U/mL.

In June 2019, the patient presented to her ophthalmologist with complaints of diplopia. She was noted to have weakness of the right inferior rectus muscle on exam and was recommended to undergo workup for possible myasthenia gravis. The patient also underwent magnetic resonance imaging of the brain which noted a heterogeneously T2 and FLAIR hyperintense extra-axial lesion within the supracerebellar cistern favoring an atypical epidermoid cyst (Fig. 1). There were no suspicious radiographic features to suggest a neoplastic etiology. Laboratory evaluation including CA-125 was within normal limits.

The patient continued to have diplopia and also developed

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Table 1
Summary of reported cases of metastatic UPSC to the brain.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13
	Petru 2001	Gien 2004	Gien 2004	Dietrich 2005	Chura 2007	Cömert 2012	Talwar 2012	Gulsen 2013	Sierra 2015	Filho 2019	Moroney 2019	Moroney 2019	Carson 2021
Age (years)	60	72	82	71	63	NR	68	71	55	56	66	54	57
Stage (FIGO)	NR	IIIC	IIB	IC	IA	IB	IA	NR	IIIC2	IB	II	IVB	IIIA
LVS1	Yes	Yes	No	NR	NR	NR	No	NR	Yes	Yes	Yes	Yes	No
Depth myometrial invasion	M2	M2	M2	M2	M1	M2	M1	NR	M2	M2	M1	M2	M1
Treatment primary tumor	TAH, BSO, XRT, CT	TAH, BSO, XRT	TAH, BSO, CT	Surgical staging, CT	NR	NR	TAH, BSO, LND, CT, VBT	TAH, BSO, CT	TAH, BSO, LND, CT, XRT	TAH, BSO, LND, XRT, CT	TAH, BSO, LND, CT, XRT	TAH, BSO, LND, CT, XRT	TAH, BSO, LND, CT
Interval (months) between initial diagnosis and brain metastases	Unknown	40	24	22	0.6	2	62	27	11	15	32	12	80
Number of brain metastases	1	Multiple	Multiple	NR	NR	1	NR	Multiple	1	1	1	Multiple	1
Other sites of disease ^a	None	Lung	Vaginal vault	Lung	None	Abdomen	Lung	NR	None	None	Lung	Lung/Abdomen	None
Treatment CNS disease	Surgery, CT, progesterone	WBRT	Steroids	NR	Surgery, WBRT, CT	NR	WBRT, CT	Surgery, WBRT, CT	Surgery, WBRT, CT	Surgery, WBRT	RT, CT	Surgery, RT, CT	Surgery, WBRT
Survival with brain metastases (months)	15	5	0.25	2	9	5	NR	9 ^b	12 ^b	12	3	12 ^b	18 ^b

NR – Not reported; M1 – inner half; M2 – outer half; TAH abdominal hysterectomy; TLH – laparoscopic hysterectomy; BSO – bilateral salpingo-oophorectomy; LND – lymph node dissection; CT – chemotherapy; VBT – vaginal brachytherapy; XRT – external beam pelvic radiotherapy; WBRT – whole brain radiotherapy.

^a When brain metastases diagnosed.

^b Alive at last follow-up/publication of report.

worsening headaches, prompting referral to Neurosurgery for management. Neurosurgical evaluation recommended surgical resection of a likely atypical congenital epidermoid cyst due to symptomatic mass effect. The patient underwent a suboccipital craniotomy for supracerebellar infratentorial approach in August of 2019. Intraoperatively the lesion was noted to be localized to the pineal region with both solid and cystic components. Frozen sections sent to pathology were reported consistent with a papillary tumor. Neurosurgery successfully removed the tumor, however, a small portion of residual tumor capsule was left in place due to involvement of a branch of the posterior cerebral artery.

Postoperative magnetic resonance imaging of the brain noted a septated cystic lesion predominantly centered in the superior cerebellar cistern and left ambient cistern with leptomeningeal enhancement consistent with residual neoplasm. Final pathology of the pineal tumor was consistent with her uterine serous carcinoma. Positron emission tomography was negative for disease elsewhere and magnetic resonance imaging of the spine was also negative for metastatic lesions. The patient's case was reviewed at a multidisciplinary tumor board and adjuvant radiation for treatment of residual disease was recommended. She was referred to Radiation Oncology and received a total dose of 21 Gy stereotactic radiotherapy in three fractions. Recent magnetic resonance imaging of the brain confirmed post-surgical and post-radiation treatment changes, however, no new masses or findings suspicious for recurrent disease were present. The patient was asymptomatic and without evidence of recurrent disease 18 months following treatment.

3. Discussion

Endometrial cancer is the most common gynecologic malignancy in the United States and rates of new cases annually continue to rise. The most commonly reported uterine cancer histology reported in CNS metastasis is endometriosis. Only twelve cases of UPSC brain metastases have been published and this is the first documented case of endometrial cancer metastasizing to the pineal gland. The incidence of brain metastasis from uterine carcinoma is approximately 1%, but is a devastating event with a median survival of 9 months in our literature review. For patients who received multimodal treatment, the median survival was 12 months. Potential neurosurgical complications from tumor resection include infarction, hemorrhage or hematoma, infection, and edema. Complications of cranial radiation include acute complications which occur up to six weeks following treatment, and long-term complications which can develop six months or more after treatment. Acute complications are diverse and include fatigue, headaches, and radiation dermatitis and alopecia, among others. Conversely, long-term complications include neurocognitive impairment, radiation necrosis, and neuroendocrine dysfunction. Previously, these patients were often treated with supportive or palliative care, however, therapeutic and surgical advances have led to greater treatment options.

Risk factors for cranial metastasis include advanced stage, high grade, and presence of lymphovascular space invasion (Gien et al., 2004). Brain metastasis has most commonly been associated with widespread dissemination. While there is no standard or uniform treatment for patients with metastatic endometrial carcinoma to the CNS, multimodal therapy to include surgery and radiation is



Fig. 1. Magnetic resonance imaging of the brain with a heterogeneously T2 and FLAIR hyperintense extra-axial lesion within the supracerebellar cistern.

recommended. In a retrospective cohort study in gynecologic cancer patients with brain metastasis, only isolated brain metastasis was significantly associated with survival on multivariate analysis (Divine et al., 2016). Randomized clinical trials have also compared multimodal treatment including surgical resection and whole brain radiation to whole brain radiation alone in patient with solitary lesions and a survival advantage is seen with dual therapy. In addition to surgical treatment, factors that correlate significantly with increased survival include the absence of extracranial disease or presence of stable extracranial disease, longer time to the development of the brain metastasis, and younger age, which was consistent with our findings (Divine et al., 2016).

Our case report is unique in the following ways: 1) Compared to the other reported cases of serous endometrial carcinoma metastatic to the brain which occurred most commonly within 2 years of diagnosis, our patient was diagnosed with brain metastasis more than 6 years after initial diagnosis, and 2) the reported median survival after brain metastasis is approximately 9 months and our patient remains alive and well 18 months after brain metastasis detection. Given the low incidence of CNS metastasis with endometrial carcinoma, routine brain imaging is not commonly performed or recommended by NCCN guidelines. However, in a patient with a history of a high-grade endometrial carcinoma, new neurologic symptoms or visual changes should prompt early evaluation for potential metastatic disease to the CNS.

4. Conclusion

This is the thirteenth case report of brain metastasis from UPSC and the first report of UPSC metastatic to the pineal gland, with the longest post-treatment survival of CNS disease reported to date. Given its rarity, there is no standardized treatment for metastatic UPSC to the CNS. For oligometastatic brain lesions, the highest likelihood of curability, and survival is with multimodal treatment including surgical resection followed by radiotherapy. In patients with a history of UPSC with neurologic or ophthalmologic symptoms, prompt evaluation for potential CNS metastasis should be performed.

Patient consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review upon request.

Author contribution

All authors contributed to the literature search. SC and KB drafted the manuscript. KH and KB provided review of figures and revised the manuscript. All authors critically reviewed, edited, and approved the final manuscript for publication.

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Declaration of Competing Interest

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