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Case Series

Brain metastasis in two patients with stage IA papillary serous carcinoma of the uterus

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ABSTRACT

We report two cases of brain metastasis in patients initially diagnosed with extremely early stage UPSC after extensive staging surgery. They did not receive either adjuvant chemotherapy or adjuvant pelvic or vaginal cuff radiation. At the same time that these patients were diagnosed with systemic metastasis, they both had a local "drop" metastasis in the vulva or the vaginal cuff. After the initial response to palliative chemotherapy, they both developed brain metastasis. The pattern of recurrence with the lack of adjuvant treatment underscores the urgent need in further evaluation of the potential benefits of adjuvant treatment, including chemotherapy and possibly in combination with radiation in this highly aggressive disease.

1. Introduction

Papillary serous carcinoma of the uterus (UPSC) is a rare entity among the endometrial malignancies. In contrast to endometrioid adenocarcinoma of the endometrium, UPSC has a higher chance of abdominal and systemic recurrence, which is independent of myometrial invasion (Fader et al., 2009). In early stage UPSC cases with myometrial invasion, adjuvant chemotherapy and/or radiation are recommended (National Comprehensive Cancer Network, 2015). Here we report two patients with stage IA uterine papillary serous cancer who did not receive any adjuvant radiation or chemotherapy, who then developed vaginal, or vulvar recurrence and brain metastasis.

2. Case 1

An 81 year old female was diagnosed with stage IA G3 uterine papillary serous cancer after comprehensive surgery including total abdominal hysterectomy (TAH), bilateral salphingo–oophorectomy (BSO), pelvic lymph node dissection and omentectomy. The pathology showed superficial myometrial invasion (2 mm out of 11 mm) and lymphovascular space invasion, and none of the 13 lymph nodes from the pelvic and para-aortic area were involved. It was staged T1aN0M0. She was advised to take adjuvant chemotherapy and pelvic radiation but the patient decided against it. At the same time, the patient was also diagnosed with a noninvasive papillary urothelial cancer of the bladder which was resected by a transurethral approach. Past history was significant for a stable small meningioma and hypothyroidism. Family history was significant for breast cancer in her sister. Twenty four months later, a vulvar lesion was noted at routine follow-up which on biopsy showed metastatic papillary serous cancer. On further workup, several scattered new nodular opacities were found in the lungs which on biopsy also showed metastasis from the serous uterine cancer. Patient received palliative chemotherapy with gemcitabine and carboplatin for 3 months with radiographic regression of the lung nodules. This regimen was chosen due to her lifelong history of allergies to numerous allergens and her extreme concern regarding a possible allergic reaction to paclitaxel, as well as the known efficacy of gemcitabine and carboplatin combination (Gordon et al., 2011). Patient then opted for observation. Eight months after stopping chemotherapy and 3 years after initial surgery, she developed mental status changes and was found to have cerebral metastases (3 × 4cm right temporoparietal lesion, 2 cm left parietal lesion) for which she received palliative whole brain radiation (Fig. 1). After completion of radiation, there was a small decrease in size of the temporoparietal lesion (Fig. 1) but there were two new metastatic lesions (4 mm, left frontal and 6 mm, right occipital) (Fig. 2). Patient died of the disease 4 months after diagnosis of cerebral metastasis.

3. Case 2

A 62 year old woman who presented with post-menopausal bleeding was diagnosed initially with poorly differentiated endometrial

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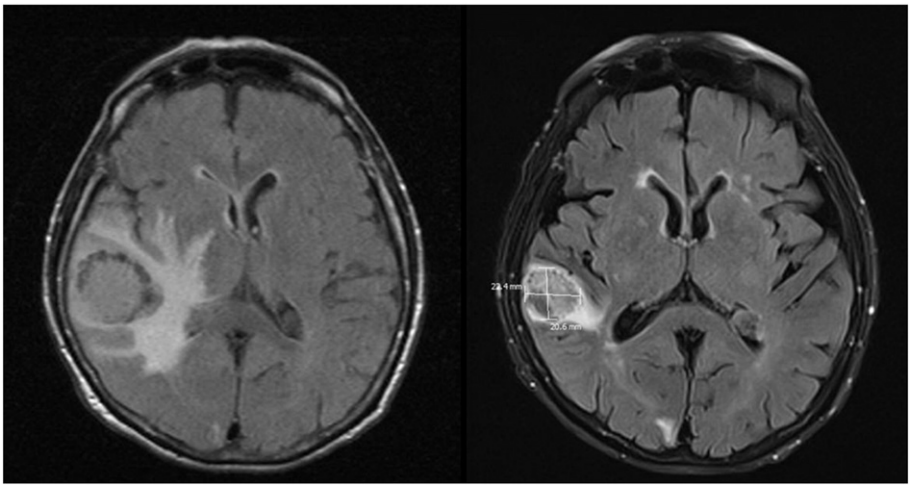

Fig. 1. MRI: Before radiotherapy. A. 3 × 4 cm right temporo-parietal metastatic lesion with surrounding vasogenic edema, mass effect and midline shift, approximately 0.5 cm shift to the left. B. Post radiotherapy image showing interval decrease in size in the right temporo-parietal lesion now measuring 2.2 × 2.0 cm with marked decrease in the surrounding vasogenic edema, resolution of the mass-effect on the lateral ventricles and the midline shift.

cancer in an endometrial polyp. She underwent TAH, BSO, pelvic lymph node dissection and omentectomy. Final pathology showed necrotic endometrium with no residual cancer in the specimen, and 5 pelvic lymph nodes were sampled and were negative. It was staged as T1aG3N0M0. Immunohistochemistry staining for mismatch repair (MMR) protein was performed on the endometrial biopsy specimen, all four genes produced proteins, indicating MMR proficient status, therefore it was unlikely that the patient had hereditary nonpolyposis colon cancer syndrome (HNPCC). Her past medical history includes aortic and mitral valve replacements (metallic) due to rheumatic heart disease, atrial fibrillation, hypertension, hyperlipidemia and adenocarcinoma in situ in a colonic tubulovillous adenoma. Family history was significant for lung cancer in the father and uterine cancer in her paternal grandmother at the age of 40. The patient was advised to take vaginal brachytherapy due to poorly differentiated cancer histology, however it was not done as her postoperative course was complicated by two episodes of small bowel obstruction related to adhesions. One year later, she developed vaginal bleeding, and was found to have recurrence in her vaginal vault, as well as in the pelvic and para-aortic lymph nodes. A CT guided biopsy of the pelvic lymph node showed features of serous adenocarcinoma. She was sent for a second opinion at an outside academic institution and all slides were reviewed by a gynecological pathologist there. Serous uterine cancer was found in the initial biopsy specimen as well as in the pelvic lymph node biopsy specimen. In addition, a small focus of serous carcinoma was found in the hysterectomy specimen. Patient received salvage treatment with concurrent weekly cisplatin with pelvic radiation followed by vaginal brachytherapy, which was complicated with thrombocytopenia and spontaneous subdural hematoma. She also developed gastrointestinal bleeding from extensive arterio–venous malformations. Six months after completion of chemotherapy and pelvic radiation she developed weakness in her right hand and was found to have a 2 cm solitary metastatic lesion in the left frontal area. Stereotactic resection of the brain metastasis was performed and the pathology was consistent with papillary serous carcinoma. Her postoperative course was complicated by bleeding into the surgical site resulting in right hemiparesis. She did not receive brain radiation or chemotherapy due to poor performance status. She was enrolled to hospice thereafter and passed away 34 months after initial diagnosis.

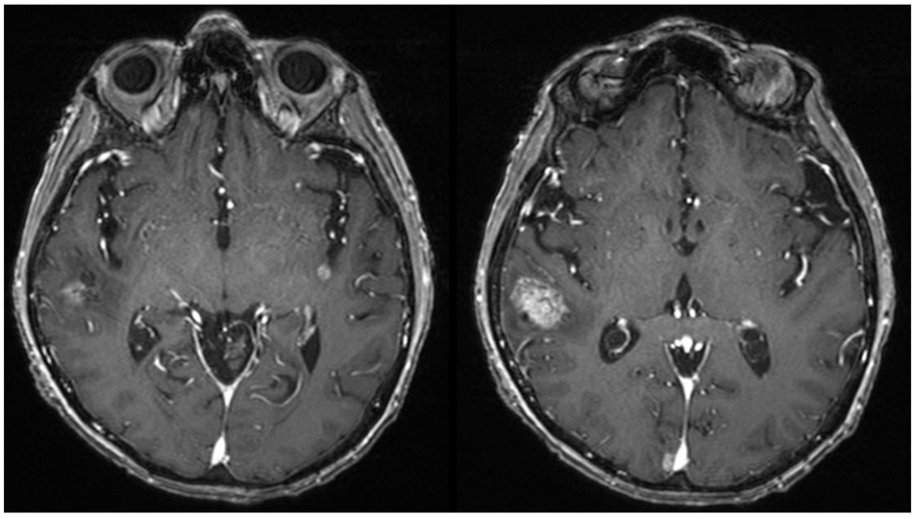

Fig. 2. MRI: Postradiotherapy images with new metastatic lesions. A. 4 mm metastatic lesion in Left frontal lobe abutting the sylvian fissure. B. 6 mm metastatic lesion in the right occipital lobe.

4. Discussion

Papillary serous carcinoma of the uterus (UPSC) is a rare tumor of the uterus comprising about 5–10% of all kinds of histology, and carries a worse prognosis in comparison with the endometrioid endometrial carcinomas (EEC) (Fader et al., 2009). Even in stage I, UPSC portends poor survival. Particularly, Hui et al. noted extra-uterine disease in 38% of comprehensively staged women whose uterine disease was solely present within a polyp (Hui et al., 2005). The 5 year survival for stage I UPSC is about 50–80% (Fader et al., 2009), while that for stage I EEC is above 80% (Creutzberg et al., 2000).

UPSC is known to behave like papillary serous carcinoma of the ovary. While the most common site of recurrence in patients with stage I endometrial cancer is the vagina and pelvis (Creutzberg et al., 2000), the majority of UPSC patients relapse outside of the pelvis, often in multiple sites (Fader et al., 2009). The usual features for predicting recurrence in EEC, such as myometrial invasion or lymphovascular space invasion, are not reliable in assessing for recurrence or metastatic disease in UPSC (Hui et al., 2005). Stage I UPSC, particularly 1A, is a disease which has not been well studied in randomized clinical trials; papillary serous histology is the excluding factor for both PORTEC-1 and PORTEC-2 trials (Creutzberg et al., 2000). Multiple large retrospective studies have shown benefit for adjuvant chemotherapy, or chemotherapy in combination of radiation in improving survival (Fader et al., 2009; Kelly et al., 2005). In one of the largest series of stage I UPSC patients, Fader et al. showed that the 5 year progression free survival and cancer specific survival was 81.5% and 87.6% in patients who received chemotherapy and radiation, 64.1% and 59.5% in patients who received radiation alone and 64.7% and 70.2% in patients who received no adjuvant therapy (Fader et al., 2009). An approach of "sandwich" treatment was tested in a prospective phase II trial where 45 (58%) stage 1A and 11 (14%) stage 1B patients were included (Einstein et al., 2012). The 3 year probability of survival for stage I and II patients were 84% (Einstein et al., 2012). In addition, Kiess et al. reported impressive outcome after adjuvant concurrent chemotherapy and radiation in stage I and II UPSC, with the 5-year disease free survival and overall survival in stage I patients to be 88% and 93% respectively (Kiess et al., 2012). Of note, none of those patients had vaginal recurrence. In the current NCCN guideline, version 1.2015, adjuvant chemotherapy +/− tumor directed RT is recommended for UPSC 1A with myometrial invasion, while observation, or chemotherapy +/− vaginal brachytherapy, or tumor directed RT can be considered for UPSC 1A without myometrial invasion (National Comprehensive Cancer Network, 2015).

The common features of our two cases, case 1 stage IA with myometrial invasion and case 2 stage IA without myometrial invasion are: (a) neither of the two patients received adjuvant chemotherapy or radiation treatment; and (b) both patients presented at recurrence with a local or "drop" metastasis in the vulvar or vagina, and systemic recurrence was discovered at the same time. This pattern of recurrence suggests that local recurrence in UPSC can still occur, following the same pattern of recurrence as in endometroid endometrial cancer. It was also found in a previous study that 19% of the patient who did not receive vaginal radiation recurred in the vaginal cuff; while none recurred in those who received vaginal radiation (Kelly et al., 2005). However, at the same time of local recurrence, our UPSC patients were not salvageable due to the concurrent systemic recurrence, while 85% of endometrial cancer patients with vaginal recurrence can still go into long term remission after treatment with curative intent (Creutzberg et al., 2000). This pattern of loco-regional recurrence supports the recommendation of adjuvant vaginal brachytherapy, probably also adjuvant chemotherapy. In addition, the pelvic lymph node dissection in case 2 may be suboptimal which could be an increased risk factor for her pelvic recurrence (Mahdi et al., 2013).

The two cases we report here are among the very rare cases reported of brain metastasis from endometrial cancer, and most of the cases exist only in case reports or case series (Petru et al., 2001; Wroński et al., 1993; Sewak et al., 2002; Shiohara et al., 2003). It has been perplexing why some cancers, such as lung cancer, have a high chance of brain metastasis while endometrial cancer has a very low incidence. Two theories have been proposed. The 'seed and soil' theory hypothesizes that there might be a lack of specific endometrial tumor-cell receptors in the brain and a lack of brain specific vascular endothelial receptors on endometrial cancer cells (Pauli et al., 1990). Another theory proposed by James Ewing hypothesizes that the circulatory patterns between a primary tumor and the specific secondary organs are the sufficient basis to account for organ-specific metastasis (Ewing, 1928). Our cases appear to be consistent with the second theory. The presence of cancer cells in the vaginal cuff or vulva at the time of recurrence allows them to enter systemic circulation to seed the brain directly or via the pulmonary circulation. In both cases, the brain metastasis occurred after an initial resection of the vulvar or vaginal recurrence, and a response to chemotherapy, indicating failure of chemotherapy in preventing brain metastasis or progression. The patient in case 2 developed brain metastasis even after salvage chemoradiation to the pelvis as well as vaginal brachytherapy, suggesting that the brain seeding might have happened at the time of vulvar or vaginal recurrence. The patient in case 1 had lung metastasis and did not have radiation to the vulvar recurrent site. Although microscopic disease in the vulvar may continue to supply seeding to the brain, it is also well known that metastasis in the lungs has a high tendency to develop brain metastasis.

We performed an analysis of all of the original case reports of brain metastasis from endometrioid endometrial cancer (Petru et al., 2001; Wroński et al., 1993; Sewak et al., 2002; Shiohara et al., 2003) and found following factors that appeared to be high risk factors: advanced stage, deep myometrial invasion, lymphovascular invasion, poorly differentiated tumors and extrauterine disease or recurrent disease. Our report of these two cases is the first report on stage I UPSC with metastasis to the brain. We found only one other report of brain metastasis from UPSC where the brain metastasis was found at initial presentation and therefore was stage IV disease (Petru et al., 2001).

UPSC appears to be an entity with aggressive nature for recurrence and metastasis. Randomized trials are urgently needed to evaluate the benefit of adjuvant treatment. In that regard, there is an ongoing phase III randomized study, the PORTEC-3 trial comparing adjuvant pelvic external beam radiation (EBRT) and adjuvant concurrent chemoradiation in the experiment arm (Creutzberg, 2006). Additionally, there is an ongoing GOG 258 trial in which patients (stages I and II with serous or clear cell type and positive cytology, stage III–IVA) are randomized to receive carboplatin and paclitaxel for six courses or concurrent chemoradiotherapy (EBRT ± vaginal brachytherapy (VBT) and two courses of cisplatin) followed by four courses of carboplatin and paclitaxel (Matei, 2001).

5. Conclusion

We report two cases of brain metastasis in patients initially diagnosed with extremely early stage UPSC after extensive staging surgery but did not get either adjuvant chemotherapy or adjuvant pelvic or vaginal cuff radiation. At the same time when these patients were diagnosed with systemic metastasis, they both had a local "drop" metastasis in the vulva or the vaginal cuff. After initial response to palliative chemotherapy or salvage chemoradiation treatment, they both developed brain metastasis. Those two cases demonstrate that local recurrences following the pattern of recurrence from endometrioid endometrial cancer can occur in UPSC, but they may not be salvageable due to concurrent presentation of pelvic and systemic recurrence. The sites of local recurrence in those two cases, the vagina and vulvar, may be the site of seeding to the systemic circulation and to brain metastasis. The pattern of recurrence with the lack of adjuvant treatment underscores the urgent need in further evaluation of the potential benefits of

adjuvant treatment, including chemotherapy and possibly in combination with radiation in this highly aggressive disease.

Conflict of interest statement

The authors report no conflict of interest.

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