Brain metastases from early stage endometrial carcinoma: a challenging issue

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Abstract
Brain involvement in endometrial carcinoma is a rare event and is usually associated with advanced stage, poorly differentiated tumors, widespread disease and a very poor prognosis. In high-grade endometrial carcinoma with vascular invasion, the median time to metastasis development appears to be reduced. We present two cases of endometrial carcinoma, both peculiar due to the early stage of the primary tumour. In these two patients, the short time between primary treatment and brain involvement, the presence of a single symptomatic metastasis and prompt diagnosis lead to subsequent successful treatment. These cases suggest that brain metastasis in endometrial cancer can be associated with low-risk disease. The usually poor prognosis may be improved in cases of single brain metastases. Given the rarity of this condition, it is difficult to identify the best treatment option and so further research is needed in order to better understand the dynamics of disease spread and improve survival rates in these patients.

Key words: brain metastases, case report, endometrial carcinoma

Introduction

Brain involvement from endometrial carcinoma is a rare event, reported in about 150 patients in the literature. It is usually associated with advanced stage, poorly differentiated tumours and mostly with widespread disease, and thus has a very poor prognosis. Patients affected by endometrial cancer mainly develop brain metastasis late in the course of the disease [1-7]. Presence of high-grade endometrial carcinoma and vascular invasion may reduce the median time of metastasis development [2]. Interestingly, in half of the patients with brain metastases from endometrial carcinoma, no other extracranial sites of disease were detected, and in most of them, brain lesions were solitary. Prognosis of these women is usually poor, with a limited therapeutic margin median survival of 5 months. We present two cases of brain involvement in women with endometrial carcinoma, both peculiar due to the early stage of the primary tumour, the short time between primary treatment and brain involvement and the presence of a single symptomatic metastasis. In both cases, prompt diagnosis led to subsequent successful treatment.

Case descriptions

Case report 1

The first patient was a 46-year-old woman who underwent a total abdominal hysterectomy for uterine fibroids. An incidental diagnosis of IA G2 endometrial cancer was made, characterised by diffuse intravascular and lymphatic invasion and 6/16 mm myometrial invasion. Two weeks after primary surgery, she underwent pelvic lymphadenectomy. Ten days later, even before any adjuvant treatment was administered, the patient developed gait difficulties. An MRI scan was immediately performed, detecting a 2 cm cerebellar lesion, which was then resected (Figure 1). Pathological examination revealed a metastasis of the endometrial carcinoma. Postoperatively the patient received cranial irradiation (total dose 60 Gy). Forty months after diagnosis, the patient is alive and without evidence of disease.

Case report 2

The second patient was a 56-year-old woman, complaining of vaginal bleeding. An US scan detected a uterine polyp. Afterwards, diagnostic hysteroscopy revealed an endometrioid adenocarcinoma and the patient then underwent surgery, comprising a total abdominal hysterectomy, bilateral oophorectomy and bilateral pelvic lymphad-

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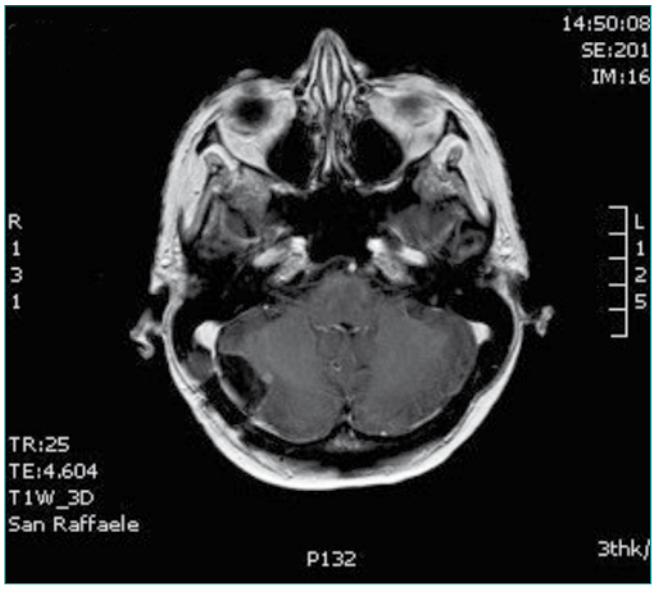

Fig. 1. Brain magnetic resonance imaging (MRI) scan performed after surgical resection of the 2 cm right cerebellar metastasis.

enectomy. Final pathologic examination revealed an endometrioid adenocarcinoma of the endometrium, IA G3 without vascular and lymphatic invasion. Myometrium was involved in 10/21 mm. No adjuvant treatment was planned. Two months after surgery the patient complained of severe headache. A MRI scan showed a 3 cm cerebellar mass and the patient was treated with craniotomy, metastasis resection and radiotherapy (for a comprehensive dose of 60 Gy in 2 Gy fractions). Her second remission lasted only 5 months, since she then developed diffuse brain metastases and died of disease.

Discussion

Brain metastases are a rare finding in women with endometrial carcinoma and only about 150 cases have been extensively reported in the literature. Endometrial carcinoma usually follows a pattern of local spreading. Less frequently it spreads through the haematogenous pathway; in this case, the most frequent sites involved are the lungs, liver and bones [1]. The two cases presented are even more peculiar and raise important issues in this setting.

Brain metastases are usually associated with advanced stage cancer. Among 75 cases described in the literature for which initial staging was available, only 18 (24%) were stage I. Poor tumour differentiation, lymphovascular and deep myometrial invasion have been traditionally identified as additional risk factors for distant metastases [2, 4]. Both of our patients were stage IA and neither of them showed vascular invasion.

Moreover, central nervous system (CNS) involvement in endometrial carcinoma is most often detected late in the course of the disease, with a median time between primary diagnosis and metastasis detection of 17 months (range 2–108 months). In our two cases, the diagnosis of the isolated solitary brain metastasis was made shortly after the primary diagnosis, without any pulmonary involvement. Actually, in 10% of the cases reported in the literature, brain metastases are detected simultaneously or even before the primary tumour, revealing a possible process of early dissemination, even with the so called "skip metastases". Interestingly, in half of patients with brain metastases from endometrial carcinoma reported in the literature, no other extracranial sites of disease were detected and, in most of them, the metastases were solitary, as in our cases. The prognosis of patients with CNS metastasis is poor, since most often the disease is already spread and palliative care is the only possible approach. The median survival rate described in the literature is 5 months (range 0.1–171 months); however, this data should be interpreted carefully, considering both the rarity of the disease and the consequent long-term accrual of patients, during which different treatment approaches have been followed. Nowadays, in cases of single CNS metastasis, surgery combined with radiotherapy, in particular stereotactic radiosurgery, which usefully reduces the neurotoxicity derived from whole-brain radiotherapy, is considered the best therapeutic option [8]. In such cases, careful selection of patients is always warranted in order to identify those who may have a survival benefit. Both of our patients were diagnosed with early-stage endometrial carcinoma and they presented with neurological symptoms 2 months after primary diagnosis. The prompt diagnosis of single brain metastasis allowed us to offer them curative treatment instead of simple palliative care. Even if brain involvement is a rare event during the course of this disease, signs and symptoms suggestive of CNS disease spread should always be carefully evaluated.

Conclusions

Brain metastasis in endometrial cancer may sometimes be unpredictable and sometimes associated with low-risk disease. Prognosis, usually poor even with prompt diagnosis, surgical resection and stereotactic surgery, may lead to a better outcomes in cases of single brain metastases. It is difficult to identify the best treatment option, given the rarity of this condition. Further case reports and possibly prospective clinical trials are needed in order to better understand the dynamics of disease spread and thus improve the survival rates in these patients.

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