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Uterine leiomyosarcoma metastatic to the brain: case report

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ABSTRACT

Background. We report a leiomyosarcoma of the uterus, an uncommon tumor with a very aggressive course and poor prognosis due to the fact that, despite complete resection, it recurs with micrometastases. The most common metastatic sites are the lung, intraperitoneal, pelvic and paraaortic lymph nodes, and liver. Brain and skull metastases are very rare.

Case. A 57-year-old woman underwent a hysterectomy and bilateral salpingo-oophorectomy for a grade T2N0M0 uterine leiomyosarcoma. There was no evidence of other lesions. Three months later a total-body PET scan demonstrated the presence of metastases in both lungs, and the patient was started on chemotherapy. One year later a cranial MRI demonstrated a brain metastasis to the temporal lobe. Emergency complete resection of the recurrence was performed, followed by whole-brain radiation and adjuvant chemotherapy.

Conclusions. Given the limited treatment options, the gold standard for uterine leiomyosarcoma brain metastasis is total surgical removal. Chemotherapy and radiation therapy may provide only palliative benefit.

Introduction

Uterine malignancies account for 4.7% of all female cancer. Five percent of uterine cancers are sarcomas, and about 1% of these are leiomyosarcomas[1-5]. Uterine leiomyosarcomas typically occur in women who are at least 50 years old. They invade and spread locally, but they may also have an aggressive growth pattern with lymphatic and hematogenous spread. At the time of diagnosis micrometastases are already present, and the most common sites of recurrence are the peritoneal cavity (30-50% of cases), lung (30-40%), and liver (about 10%)[6-8]. Only rarely do they involve the brain and skull (<1%)[1,5,9] owing to pulmonary arterial circulation[7,10-13]. Most brain metastases arise from lung, kidney, breast or skin primary sites[10,14-17]. Brain metastases are usually isolated and located supratentorially[17,18]. They are also typically a late manifestation of the disease and occur more than 1 year after the initial diagnosis and almost always after lung metastasis. Fewer than 40 cases have been described in the literature as small series or case reports[6].

Key words: *brain metastasis, leiomyosarcoma, uterine metastasis.*

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Case report

A 57-year-old woman was admitted after an episode of intense headache. One year earlier she had been diagnosed and treated for uterine leiomyosarcoma at stage II according to FIGO[8] or stage T2N0M0 according to the international TNM system. Treatment consisted of a hysterectomy and bilateral salpingo-oophorectomy, with complete resection of the disease. Cytological examination showed severely anaplastic tissue, but because the patient had no metastatic lymph nodes she received no further adjuvant

treatment. Three months after the first operation, a metastatic lesion was discovered in the right lung, and the patient was given anthracycline-based chemotherapy consisting of adriamycin 75 mg/m^2 of body surface every 4 weeks for 6 cycles. This resulted in stabilization of the lung disease. When the patient came to our observation, neurological examination revealed mild consciousness impairment. A contrast-enhanced CT scan showed a brain lesion with a mean diameter of 3 cm and marked surrounding edema. Presurgical post-contrast MRI documented the right temporopolar location of the mass (Figure 1). A right temporal craniotomy was performed. The lesion was reached via the T1-T2 gyrus, and it showed a good, cleavable interface with the surrounding parenchyma, allowing its complete removal. The surgical cavity and final appearance and consistency of the lesion are shown in Figure 2. After an uneventful recovery, the patient was discharged with intact neurological function. An early MRI examination 24 hours after surgery showed total removal of the lesion (Figure 3). Histological examination demonstrated that the lesion was a metastatic leiomyosarcoma (Figure 4). Postsurgical whole-brain irradiation (30 Gy in 2 weeks) was performed as adjuvant therapy. The patient was referred to the medical oncology department for a new adjuvant chemotherapy regimen: given the previous results obtained with adriamycin, this anthracycline was employed again at a dose of 50 mg/m^2 every 3 weeks, in combination with parenteral cyclophosphamide at a dose of 1 g/m^2.

Discussion

Uterine leiomyosarcoma is a rare malignancy of mesenchymal origin. It usually develops in the second half of life, without any specific clinical signs. Distant metastases to the central nervous system are usually associated with widespread dissemination of the disease. In fact, between 20% and 40% of patients with systemic cancer develop brain metastases[6]. Only a few cases with brain metastases preceding the diagnosis of uterine tumor have been reported in the literature[7,10,19,20]. On the other hand, intracranial metastases are the most common malignancies affecting the brain[21-23]. Their incidence is increasing, probably due to the use of improved imaging techniques (magnetic resonance imaging) and as a result of cancer patients' prolonged life expectancy[6,23,24]. The use of chemotherapy for treating systemic cancer is thought to increase the incidence of brain metastases secondary to improving systemic control of the disease and the failure of many chemotherapeutic agents to cross the blood-brain barrier (the brain as "sanctuary")[25-28]. For these reasons, even though sarcomas rarely metastasize to the brain, a recent increased incidence has been described[6].

The annual incidence of uterine sarcoma is approximately 1.7 per 100,000 women and uterine leiomyosar-

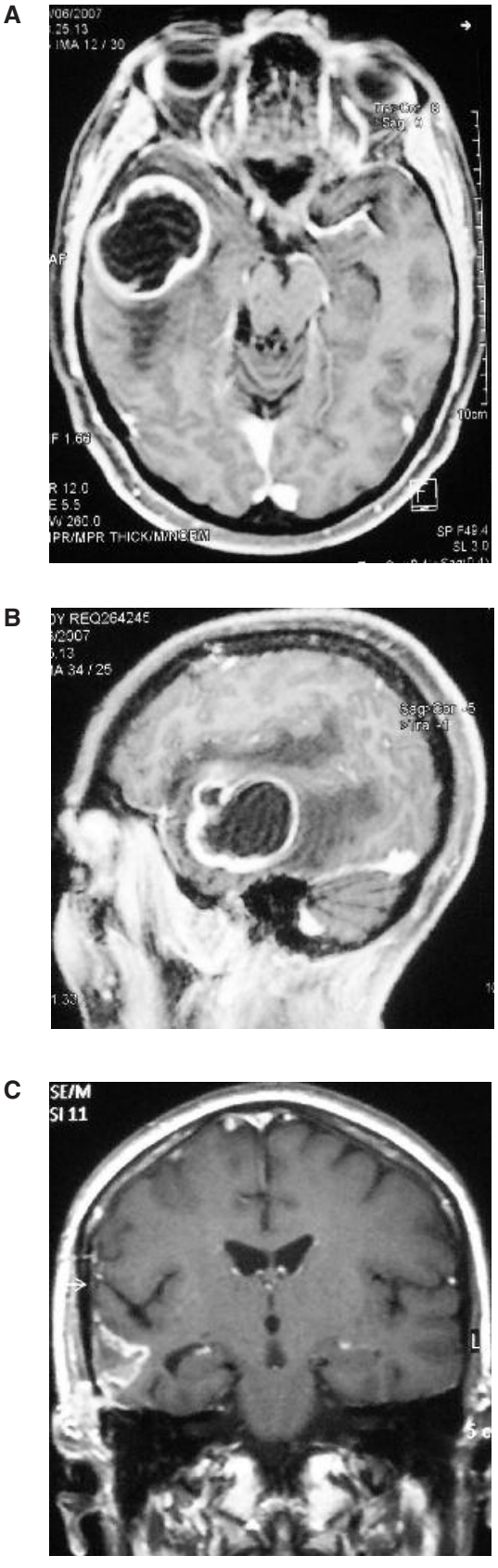

Figure 1 - Preoperative contrast-enhanced MRI scan showing the metastatic lesion and its anatomical landmarks.

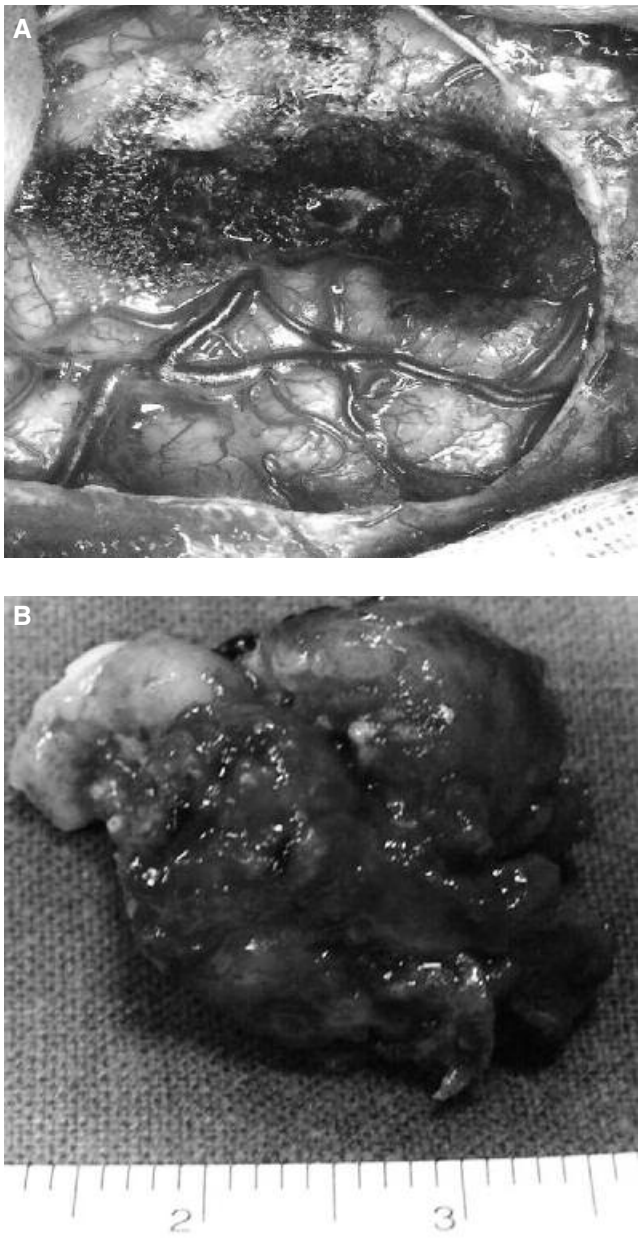

Figure 2 - Surgical cavity (A) after the excision of the lesion, and macroscopic appearance and consistency of the lesion (B).

comas have an incidence of 0.64 per 100,000 women[5,29], with 5-year survival rates of 20-30% overall and 50% in patients with stage I disease[30]. Median survival was estimated to be 20.6 months[2]. The aggressiveness and poor prognosis of these tumors are demonstrated by the high recurrence rate with early presence and spread of micrometastases, since the uterus as the primary disease site is usually completely resected[9]. The most common sites of metastasis are the lung, intraperitoneal, pelvic and paraaortic lymph nodes[31], and liver, while the brain

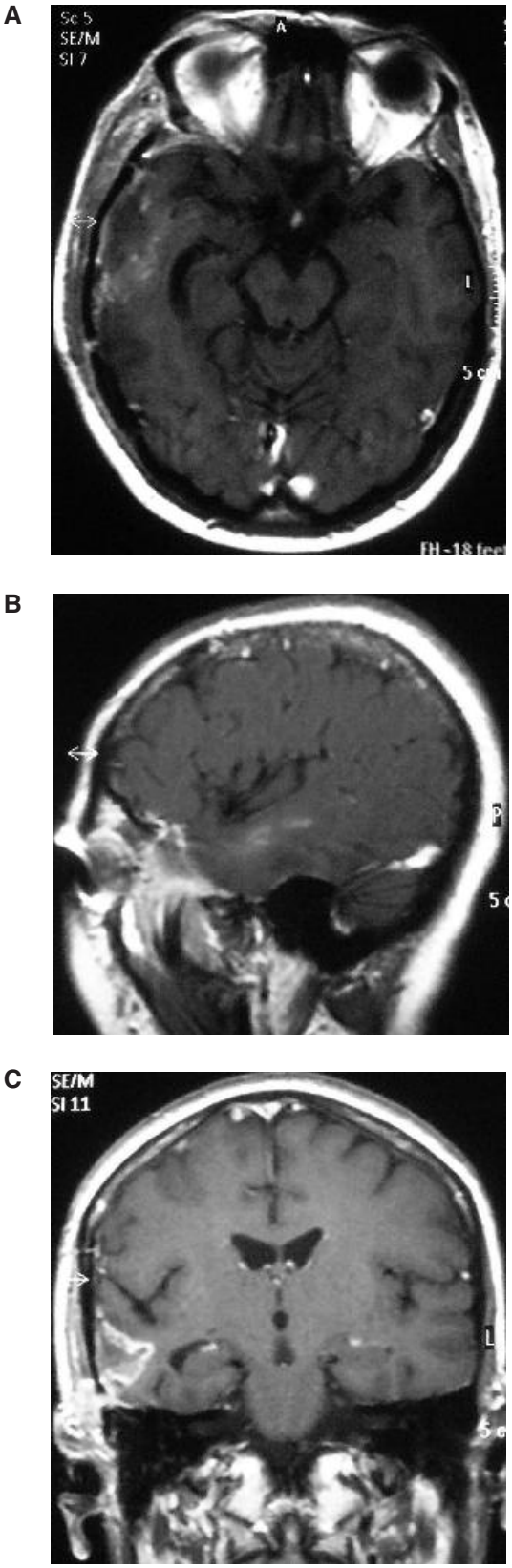

Figure 3 - Early MRI (24 hours after the operation) after injection of contrast medium showing total removal of the lesion. Marginal edema is absent.

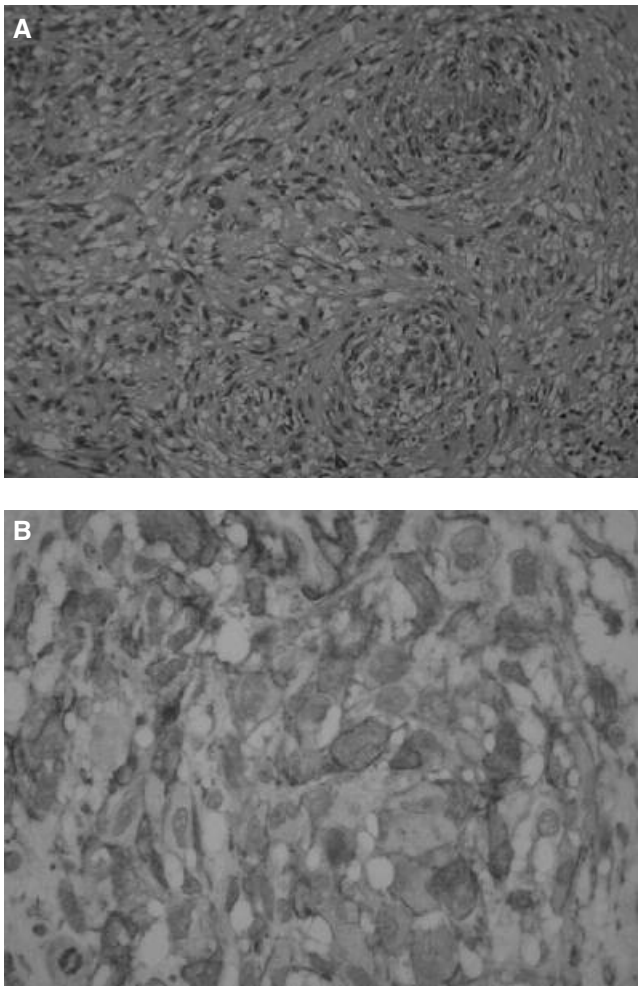

Figure 4 - Histological specimens. Hematoxylin-eosin staining shows fascicles of spindle-shaped cells (A, original magnification ×200). Evident pleomorphic nuclei with eosinophilic cytoplasm (B, original magnification ×350).

is rarely involved. When brain metastasis does occur, the preferred localization seems to be supratentorial, frequently involving the frontal and parietal lobes, especially the subcortical white matter[9,32-34]. This is strongly associated with the presence of lung metastases as a late event in the course of the disease[1,31]. It has been reported that brain metastases may develop as late as 16 years after diagnosis of the primary tumor.

Symptoms of brain metastases are correlated with the site or with spontaneous hemorrhage within the tumor and can develop even before clinical symptoms related to the primary neoplasm become evident[10-12,35,36]. The appearance of this kind of brain metastases on CT or MRI scan is not peculiar, the only constant feature being central necrosis of the mass due to the high proliferation rate of the tumor cells. Histological criteria for the distinction of leiomyosarcoma from benign leiomyoma are the presence of cellular atypia and mitotic figures exceeding 4 per 10 high-power fields[2,9].

The literature suggests that the treatment of choice for brain metastases from uterine leiomyosarcomas is neurosurgical resection of all known lesions[6,9], single or multiple, followed by postoperative whole-brain irradiation as adjuvant therapy, even if radiation therapy appears to improve local control without any significant impact on survival because most recurrences involve distant sites. The presence of concurrent lung metastases is not a contraindication to surgery[6,17,24]. Alternative choices in the treatment for brain metastases include whole-brain radiotherapy and gamma-knife radiosurgery for single small lesions[6,24,37,38]. The factors favoring surgical resection are preoperative KPS >70, age <65 years, symptomatic lesions, life expectancy >6 months, presence of mass effect or perilesional edema, and metastatic lesions larger than 3 cm[6,38], and all these conditions were present in the case described here.

The outcome of patients with brain metastasis from leiomyosarcoma still remains poor, with a median survival time of about 4 months or less after conservative management in the few cases reported[6]. Surgery followed by adjuvant radiotherapy resulted in improved outcome in 12 cases reported in the literature, and this combination should be recommended[6,37]. Regarding adjuvant chemotherapy, different regimens were used by different authors, and it is difficult for us to extrapolate a clear indication. What seems clear is that combined chemotherapy may result in a significant improvement in outcome, and that the most commonly used regimens are based on anthracyclines in combination with other drugs. There has been a 45% overall response with this combination, but the effect on the overall survival remains unclear[7,39]. In our case, radical tumor removal was performed and this should be the treatment of choice, in combination with adjuvant radiotherapy and chemotherapy using two different agents. Adriamycin was given again because it was well tolerated previously and showed some efficacy in the control of the lung metastases. It still seems very difficult to define a standard therapeutic protocol for this kind of aggressive tumor.

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