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Late Recurrence of Metastatic Meningioma in the Lung in a Patient with Endometrial Cancer: A Case Report

Authors' Contribution:

Study Design A
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Manuscript Preparation E
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Funds Collection G

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Conflict of interest: None declared

Patient: Female, 58-year-old
Final Diagnosis: Meningioma
Symptoms: Abdominal pain • bleeding • headache
Medication: —
Clinical Procedure: —
Specialty: Oncology

Objective: Unusual clinical course

Background: Meningiomas are the most frequently diagnosed of all primary brain tumors, including glioblastomas, and of all other central nervous system tumors. While non-malignant meningiomas account for 36.7% of all primary brain tumors, malignant meningioma is much less common, accounting for just 0.6%. The annual incidence of meningiomas in the United States is 5.3 per 100 000 people. The median age of diagnosis is 64, and incidence rises steadily with advancing age. Furthermore, extracranial metastatic meningioma remains extremely rare (0.1%), with the most common location for metastasis being the lung.

Case Report: We report a case of a patient with biopsy-proven endometrial adenocarcinoma with suspicious lung nodule, Stage IVB. She was managed with chemotherapy followed by surgery and radiation. During her course of management, she was found to have progressive pulmonary nodules. Later, biopsy from the pulmonary nodules showed a metastatic meningioma.

Conclusions: Our case highlights the importance of early recognition of metastatic meningioma, especially when treating patients with a history of intracranial meningioma.

Keywords: Carcinoma, Endometrioid • Meningioma • Neoplasm Metastasis

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Background

The current WHO classification of meningiomas is based on histological grading. The 3 grades of meningiomas are Grade I, which is the most common grade; Grade II or atypical meningioma, which accounts for 5-15% of all meningiomas; and Grade III or anaplastic meningioma, which accounts for 1-2% of all meningiomas [1]. Most meningiomas are associated with a benign clinical pattern; however, some show a malignant behavior that can lead to metastatic disease [2]. Incidence varies depending on age and sex, with incidence rising in the sixth and seventh decade, and with a higher risk in women than in men (female: male ratio of 3: 2 to 2: 1) [3].

It was previously believed that most metastatic meningiomas are Grade III. However, 56.2% of reported metastatic meningiomas originated from benign (Grade I) and intermediary (Grade II) tumors, as in our case [2]. In most cases of metastatic meningiomas, surgical resection of the original tumor was followed by progression within 5 years of diagnosis [4], leading to the hypothesis that surgical resection might initiate metastatic spread [2]. Our case emphasizes the need for early recognition of metastatic meningioma, especially when treating patients with a prior history of intracranial meningioma.

Case Report

Our patient is a 58-year-old post-menopausal woman with a history of hypertension and brain meningioma, status post-surgical resection 26 years ago. She presented to our institution with a history of vaginal bleeding for the past 10 months, associated with lower abdominal pain and weight loss of around 7 kg. A physical exam showed a soft and lax abdomen with no palpable mass. She was vitally stable, not pale or jaundiced;

her Eastern Cooperative Oncology Group (ECOG) performance status was 1 [5].

Laboratory investigations showed complete blood count (CBC) within normal values with no drop in hemoglobin (Hb). Both renal and hepatic coagulation profiles were normal. Tumor markers were significant for elevated cancer antigen 12-5 (CA 12-5; 201.6 U/ml).

Computed tomography (CT) of the chest, abdomen, and pelvis, done in March 2013, showed endometrial cancer with suspicious lung nodules, the largest of which was located at the lingula and measured 3.1×1.5 cm. Positron emission tomography (PET) scan showed extensive endometrial uptake extending to the cervix, associated with mild uptake in multiple bilateral pulmonary nodules (Figure 1). The patient then underwent endometrial biopsy, which showed an International Federation of Gynecology and Obstetrics (FIGO) Grade 2 endometrioid adenocarcinoma, with focal squamous differentiation.

On the bases of the investigations above, the patient was diagnosed with Stage IVB uterine endometrioid adenocarcinoma with lung metastasis. She was started on paclitaxel and carboplatin. The patient completed 6 cycles in November of 2013. She responded clinically with a cessation of vaginal bleeding and serologically with CA 12-5 decreasing to 30 U/ml but with stable pulmonary nodules. Her case was discussed at the tumor board and she underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy in January 2014. Histopathology revealed an endometrioid adenocarcinoma, Grade 2. The tumor extended to the inner half of the myometrium (<50%), but there was no lymphovascular invasion. The cervix, ovaries, and fallopian tubes were negative for malignancy. Later, she received pelvic radiation therapy (Image-Guided Radiation

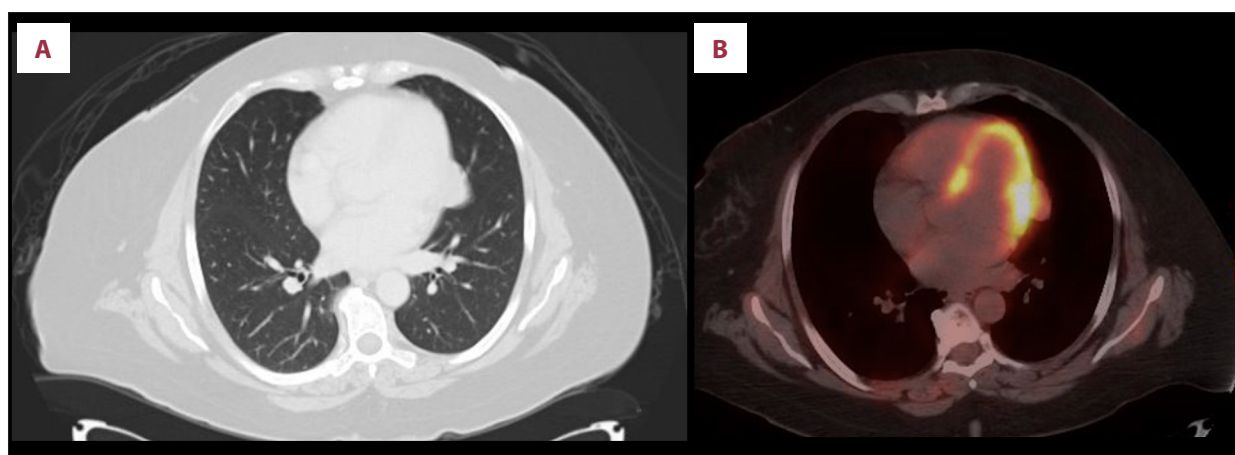


Figure 1. (A) CT scan of the lung showing suspicious nodule at the lingula abutting the heart border. (B) PET scan showing lung nodule at the lingula in a paracardiac position, measuring 1.5×3.4 cm and showing increased fluorodeoxyglucose accumulation (maximum standardized uptake value, 1.5).

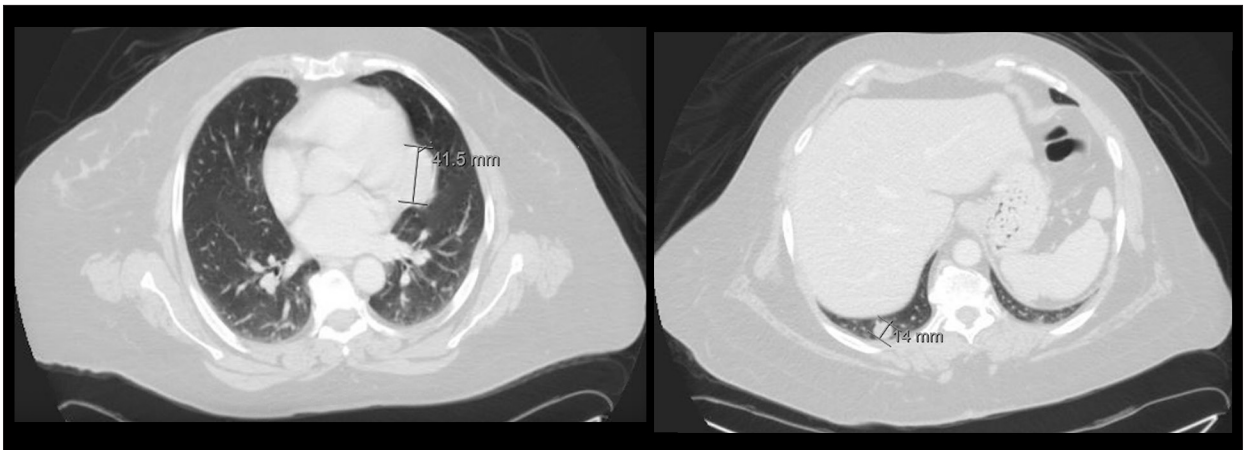


Figure 2. CT scan of the chest showing the increase in size of the metastatic lung nodules, with the lingula nodule showing a mass size of 4.1 cm.

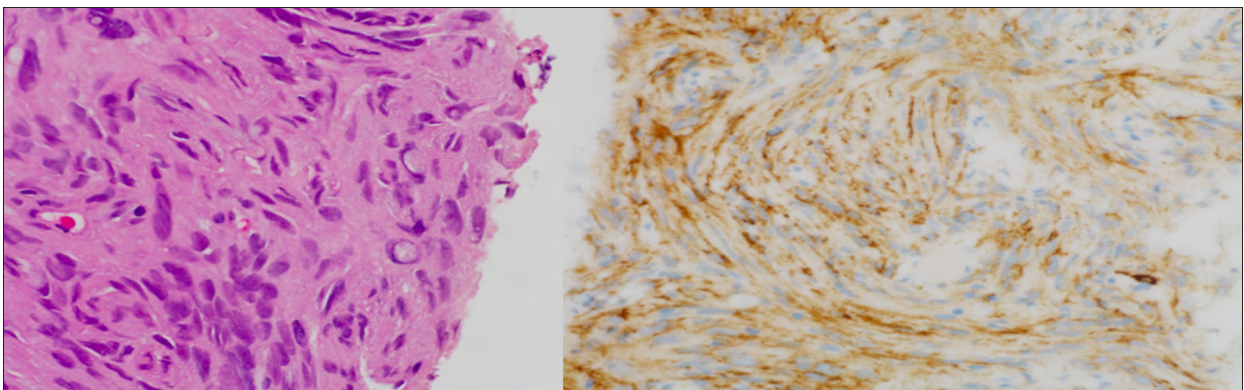


Figure 3. Lung biopsy showing meningioma with intranuclear inclusion; immunostaining for epithelial membrane antigen was positive.

Therapy, 45 Gy in 25 fractions) and high-dose brachytherapy (5 Gy in 2 fractions), which ended in May 2014.

Repeated CT of the chest in April 2014 showed a stable pulmonary nodule. However, chest CT in April 2017 showed progression in the metastatic lung nodules, the largest of which, at the left upper lobe adjacent to the pericardium, measured 4.1 cm (**Figure 2**). The right lung base nodule adjacent to the right pulmonary vein measured 1.2 cm; this same nodule had previously measured 0.7 cm. The right lung base nodule posteriorly measured 1.4 cm; it had previously measured 1.1 cm. The patient underwent fluoroscopic guidance lung biopsy in October 2017 from the right lower lobe lesion. Histological examination of the tumor was compatible with low-grade spindle cell neoplasm. The immunohistochemical studies showed that the tumor cells were positive for epithelial membrane antigen (EMA) and S100 protein with weak and focal positivity for progesterone receptor and low Ki67 (MIB1) proliferation index. The overall findings were compatible with metastatic meningioma (**Figure 3**). The case was discussed in the tumor board, and a decision was made to follow the metastatic nodules.

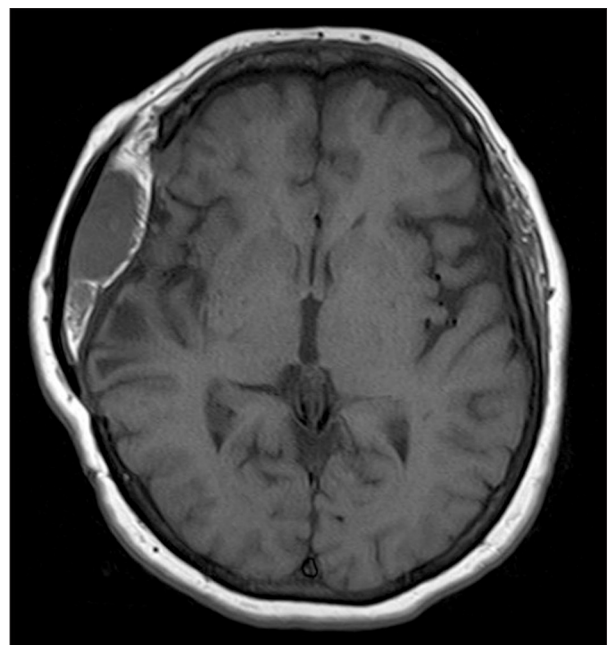


Figure 4. MRI of the brain, axial plane, revealing new brain lesion.

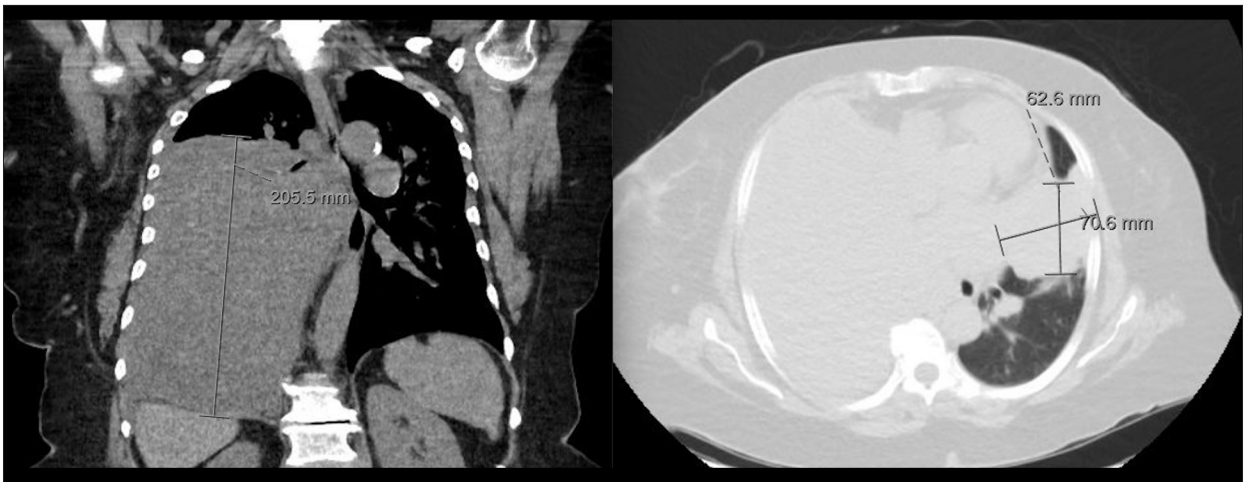


Figure 5. Chest CT, coronal and axial plane, showing progression of lung nodules.

In January 2019, magnetic resonance imaging (MRI) of the brain demonstrated new enhancing lesions at the operative site suggestive of recurrence of meningioma. The largest lesion measured 26×33 mm in maximum dimension on the sagittal plane (Figure 4). Her case was reviewed by the neurosurgery team, and they decided to consider surgical resection of the brain lesion if the lung metastasis could be resected. However, when her case was reviewed by the thoracic team, they deemed her not a candidate for surgical intervention. She was seen in the radiation oncology clinic and their impression was that she would not benefit from treatment. The patient underwent a CT-guided biopsy of the right lower lobe lesion in June 2019, which showed a low-grade spindle cell neoplasm consistent with meningioma. Later on, the patient started on a course of a single agent, hydroxyurea 500 mg daily, but the dose was then reduced as the patient had renal impairment. On follow-up chest CT and PET, the radiology revealed progression of lung metastasis with newly developed right pleural effusion. She was started on palliative vincristine and cyclophosphamide. After completing 3 cycles, follow-up imaging showed interval progression of lung masses; the right lung mass had increased in size to measure 20×10×18 centimeters, occupying approximately 75% of the right hemithorax, which caused a mass effect with a leftward shift of the mediastinum, also causing compression of the liver dome. The left lung mass had also increased in size, with interval invasion of the adjacent pleural layer, measuring 7×6.2×8.5 cm, compared with the previous 7×5×7.3 cm. The other small pulmonary nodules had also slightly increased in size (Figure 5). As the patient did not respond to chemotherapy, her code status was reviewed and a “do not resuscitate” (DNR) order was added to her chart after explaining the current condition to the patient and family members. Arrangements for transfer to palliative care were made.

Discussion

Meningiomas are the most frequently diagnosed tumor of all central nervous system tumors, including other primary brain tumors such as glioblastomas. Non-malignant meningiomas account for 36.7% of all brain tumors, while malignant meningiomas are much less common, accounting for 0.6% of all brain tumors [6], with a yearly incidence of 5.3 per 100 000 people in the United States. The tumors affect patients in advanced age, with a median age of diagnosis of 64. Furthermore, extracranial metastatic meningioma remains extremely rare (0.1%), with the most common location for metastasis being the lung.

One of the important predictors of the likelihood of recurrence after surgery is histology, with 7-20%, 40%, and 50-80% risk of recurrence after surgical intervention for benign meningiomas, atypical meningiomas, and malignant meningiomas, respectively [7]. High mitotic index and brain or bone involvement is another predictor of treatment failure [8].

As metastasis of meningioma is relatively rare, with few reported cases, there are no clear general guidelines regarding staging or treatment approach in such cases. The mainstay curative management for such cases is pulmonary metastasectomies of meningiomas [2,9]. The benign meningioma tumor must be resected entirely, including bone and dural attachment, to increase the chance of cure [10]. Some tumors are difficult to remove completely, especially in problematic locations, including parasagittal tumors (tumors that invade the sagittal sinus, olfactory groove, or lateral ventricle, making complete resection unattainable) [11]. For such cases, in which gross total resection cannot be carried out, or in tumors with pathology indicating a high risk for recurrence, radiation therapy is an attractive option [12]. In some reports, benign meningiomas that are treated with incomplete surgical resection with additional radiation therapy are associated with a

5-year progression-free survival rate of at least 80% and may be higher than 95% [13]. In one report, 5-year overall survival was 90% with surgery plus external beam radiation therapy (EBRT), compared with 45% after surgery alone [14].

Cytotoxic chemotherapy has not been demonstrated to be effective in the treatment of meningioma, with few published studies. It is mainly used in the treatment of recurrent tumors after surgical resection after radiotherapy options. In a case series, 14 patients with malignant meningioma each received 3 to 6 cycles of cyclophosphamide, adriamycin, and vincristine after surgical and radiotherapy intervention. The median survival was 5.3 years and was associated with considerable toxicity [15]. Hydroxyurea is a promising therapy and has been investigated in a study that involved 135 patients. Results included a statistically significant increase in median time to progression, ranging from 44 to 176 weeks, with 51% of patients achieving stable disease and 6% achieving minor or partial radiographic responses [16].

Inhibitors of angiogenesis have become an integral part of treatment for many malignancies. Targeted therapies, mainly acting on tyrosine kinase receptors, have been studied for such cases; for example, receptor kinases like VEGF, EGF, IGF, bFGF, and PDGF. One trial involving 25 patients evaluated the efficacy of vatalanib in recurrent or progressive meningioma. The atypical meningioma patients had a median progression-free survival (PFS) of 6.5 months, and an overall survival (OS) of 26.0 months; malignant meningioma patients had a median PFS of 3.6 months, and OS of 23 months [17]. Another trial, a prospective, multicenter, phase II trial, evaluated sunitinib. Thirty-six patients with atypical or anaplastic meningioma were enrolled. The results showed a median PFS of 5.2 months and a median OS of 24.6 months, leading to the conclusion that sunitinib is effective in treatment of such tumors [18].

The role of sex hormones in meningioma growth has long been investigated. Mifepristone, which is an oral progesterone receptor antagonist, was studied in a phase III trial. The trial involved 164 patients with unresectable meningioma and showed no PFS or OS benefits [19]. Another prospective trial involved long-acting sustained-release somatostatin injection (Sandostatin LAR). The trial involved 16 patients with recurrent meningiomas and confirmed presence of somatostatin receptors in their tumors. Of these 16 patients, 5 (31%) demonstrated a partial radiographic response, and 7 (44%) achieved PFS at 6 months. The median time to tumor progression was 5.0 months, and toxicity was minimal [20]. Pasireotide is a novel somatostatin analog, with a high affinity for somatotropin release inhibiting factor receptor subtypes sst1, sst2, sst3, and sst5. In a phase II trial for patients with recurrent or progressive meningioma, pasireotide showed limited activity in recurrent meningiomas. It was also associated with favorable outcomes [21,22].

Conclusions

Extracranial metastatic meningioma remains extremely rare. Metastasectomies can improve the prognosis or cure the disease. External beam radiation can be used for non-surgically resectable lesions, and for painful or symptomatic lesions. No established systemic therapy has been shown to treat recurrent meningioma effectively or to increase survival.

Our case highlights the importance of early recognition of metastatic meningioma, especially when treating patients with a history of intracranial meningioma. While thoracic intervention was not carried out in our case, surgery still remains the mainstay of treatment [23]; further studies are needed to assess the chemotherapy and radiotherapy response in such cases.

Conflict of Interest

None.

Declaration of Figures Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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