Case Report
Tumor-to-tumor metastasis: lung adenocarcinoma metastasizing to intracranial benign meningioma as a first clinical manifestation, with literature review

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Abstract: We report a case of lung adenocarcinoma metastasizing to intracranial meningioma as a first clinical manifestation. Surgeons should be aware of this rare lesion. A 70-year-old Chinese woman was admitted to our hospital with a complaint of progressive left hemiparesis, predominantly of the upper extremity, for 20 days. Computed tomography (CT) revealed a mass on the right side of the right occipital cerebral falx. The subsequent magnetic resonance imaging (MRI) showed an oval mass with equal intensity on T1 weighted imaging (WI) and heterogeneous equal intensity on T2 WI. Within the tumor, a low T1 signal lesion was moderately enhanced after enhanced scanning with a relative boundary. Neuroimaging indicated a meningioma and the patient underwent a total mass resection. Formalin-embedded sections demonstrated two histologically distinct tumors (meningioma and adenocarcinoma) simultaneously in the same lesion without an intermediate transitional zone. Meanwhile, immunohistochemical (IHC) staining showed two distinctly different immunophenotypes in these two tumors and indicated that the component of adenocarcinoma might be a metastasis from a primary lung cancer. Therefore, a subsequent pulmonary CT scan was performed and found a mass at the tip of the upper lobe of the right lung. Fine-needle aspiration biopsy demonstrated an adenocarcinoma. The primary lung adenocarcinoma shared similar histologic morphology with that of the intracranial metastatic site. The final diagnosis waslung adenocarcinoma metastasizing to intracranial benign meningioma. The patient died of heart failure 2 weeks after surgery.

Keywords: Tumor-to-tumor metastasis, lung adenocarcinoma, meningioma, clinical manifestation, immunohistochemistry

Introduction

Tumor-to-tumor metastasis is an uncommon phenomenon in which one tumor metastasizes to another tumor and was first reported by Pried *et al.* in 1930 [1]. Four criteria were proposed for the diagnosis of a tumor-to-tumor metastasis: (1) two or more distinct neoplasms coexist in the same tumor and a proven primary carcinoma must be histologically compatible with the metastasis, (2) the metastatic focus must be encased by a rim of histologically different tumor tissue without an intermediate transitional zone in order to exclude a "collision tumor", (3) the presence of extravascular metastasis, and (4) the recipient tumor should exclude generalized lymphatic or hematologic malignancy [2-6]. Scattered reports and an autopsy series indicated that the most common donor tumor was breast cancer and lung cancer, followed by kidney, prostate, thyroid, endometrial, gall bladder, esophagus, and colon cancer. On the other hand, the most common recipient malignant tumors were renal cell and thyroid carcinoma, while the benign counterparts were adrenocortical adenoma and meningioma [3, 4, 7-12].

Meningioma is the most common recipient tumor in the central nervous system. Clinically, a variety of signs and symptoms may occur, such as epileptic seizures, headaches, nausea and dizziness, cognitive and mood deteriorations, sensory and motor disturbances. With
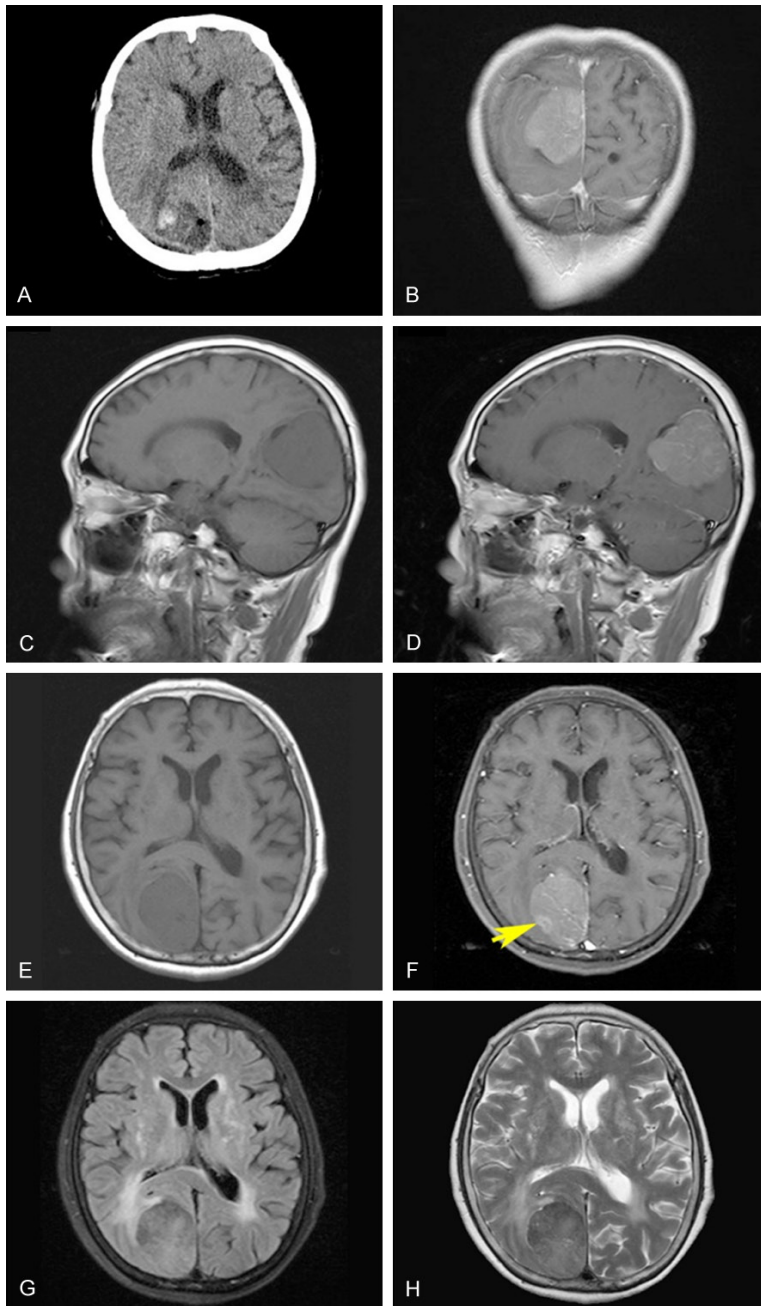
Figure 1. CT and MRI results of intracranial lesion. (A) CT revealed a mass on the right side of the right occipital cerebral falx. (B-H) The subsequent magnetic resonance imaging showed an oval mass (4.5 × 3.6 × 4.7 cm) with equal intensity on T1 WI and heterogeneous equal intensity on T2 WI. Within the tumor, a low T1 signal lesion was moderately enhanced after enhanced scanning with a relative boundary (The yellow arrow indicated the lesion which was suspicious for metastatic foci). (B: Post-contrast T1-weighted, coronal view; C: T1-weighted, sagittal view; D: Post-contrast T1-weighted, sagittal view; E: T1-weighted, horizontal view; F: Post-T1-weighted, horizontal view; G: FLAIR, horizontal view; H: T2-weighted, horizontal view).

greatly improved [2, 13-25]. On CT scan, metastasis within a meningioma usually exhibits a hyperdense mass invaginating into the typical meningioma with a relative clear boundary. Meanwhile, lung adenocarcinoma metastasizing to intracranial benign meningioma usually has an unfavorable prognosis compared with typical meningioma. Complete excision is a reasonable mode of treatment. In addition, complete sampling may improve the detection for this tumor, and correct recognition of the malignant component is important for subsequent treatment, as the therapy is different from that of typical meningioma.

Case presentation

Clinical history

A 70-year-old Chinese woman was admitted to our hospital with a complaint of progressive left hemiparesis, predominantly of the upper extremity, for 20 days. The patient also felt recent, progressive pain of the waist and hip. She had no headache, vertigo, nausea or vomiting since the illness began. CT revealed a mass on the right side of the right occipital cerebral falx (**Figure 1A**). The subsequent MRI showed an oval mass (4.5 × 3.6 × 4.7 cm) with equal intensity on T1 weighted imaging (WI) and heterogeneous equal intensity on T2 WI (**Figure 1B-H**). Within the tumor, a low T1 signal lesion was moderately enhanced after enhanced scanning with a relative boundary (**Figure 1F**). The tiny blood vessels from the sickle of the cerebrum formed a radical pattern. The adjacent meninges were thickened

recent advances in medical imaging, the detection rate for lung adenocarcinoma metastasizing to intracranial benign meningioma has been
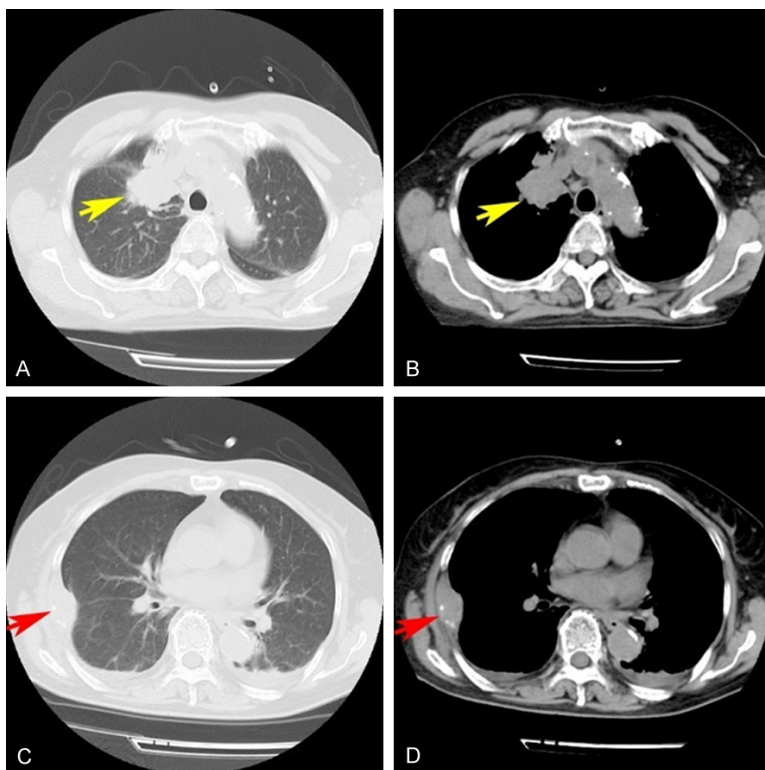
Figure 2. Pulmonary CT imaging results. A, B: CT scan was performed and found a mass (3.6 × 3.3 cm; CT value: 27 HU) on the tip of the upper lobe of the right lung (the yellow arrows indicated the tumor). C, D: A soft tissue shadow was observed in the chest wall which was suspicious for metastasis (the red arrows indicated the lesion).

block/cm of tumor. All specimens and samples of FNA biopsy were fixed in 10% formalin and embedded in paraffin. A series of 4-μm-thick sections was cut from each paraffin-embedded block. Commercially available prediluted monoclonal antibodies directed against epithelial membrane antigen (EMA), AE1/AE3, GFAP, S-100, Oligo2, CK7, TTF-1, Vimentin, PR, and Ki-67 were purchased from Mai Xin Inc., Fuzhou, China. IHC staining was performed using the streptavidin-peroxidase system (Ultrasensitive; Mai Xin Inc., Fuzhou, China) according to the manufacturer's instructions. The primary antibody was replaced with phosphate-buffered saline for negative controls. Alcian blue-PAS was performed according to the manufacturer's instructions.

Microscopic features and immunohistochemistry patterns of intracranial lesion

and showed enhancement after enhanced scanning. The posterior horn of the right lateral ventricle was compressed and narrow. Neuroimaging indicated a meningioma and the patient underwent a total mass resection. After complete sampling, we rendered a diagnosis of lung adenocarcinoma metastasizing to intracranial benign meningioma. Therefore, a subsequent pulmonary CT scanning was performed and found a mass (3.6 × 3.3 cm; CT value: 27 HU) at the tip of the upper lobe of the right lung (**Figure 2A** and **2B**). Also, a soft tissue shadow was observed in chest wall (**Figure 2C** and **2D**). FNA biopsy demonstrated an adenocarcinoma. The primary lung adenocarcinoma shared similar histological morphologies with those of intracranial metastatic sites. The patient died of heart failure 2 weeks after surgery.

Materials and methods

The intracranial mass was completely sampled following the routine guideline of sampling 1

At low magnification, the main body of the tumor was composed of transitional meningioma with foci of invaginated adenocarcinoma. The adenocarcinoma was surrounded by transitional meningioma without an intermediate transitional zone. The meningioma component combined features of both meningothelial and fibrous subtypes of meningioma and presented with extensive whorl formation, wherein tumor cells wrap around each other forming concentric layers (**Figure 3A** and **3B**). However, most of these hyalinized whorl structures did not have calcifications forming psammoma bodies. On the other hand, the investigated adenocarcinoma cells formed poorly differentiated glands or cribriform structures (**Figure 3C** and **3D**). The nuclei of tumor cells were characterized by chromatin condensation or occasional prominent eosinophilic nucleoli. Atypical mitotic figures were easy to observe in this case (**Figure 3D**). Intraductal secretions could also be focally observed in the poorly differentiated or cribriform glands.
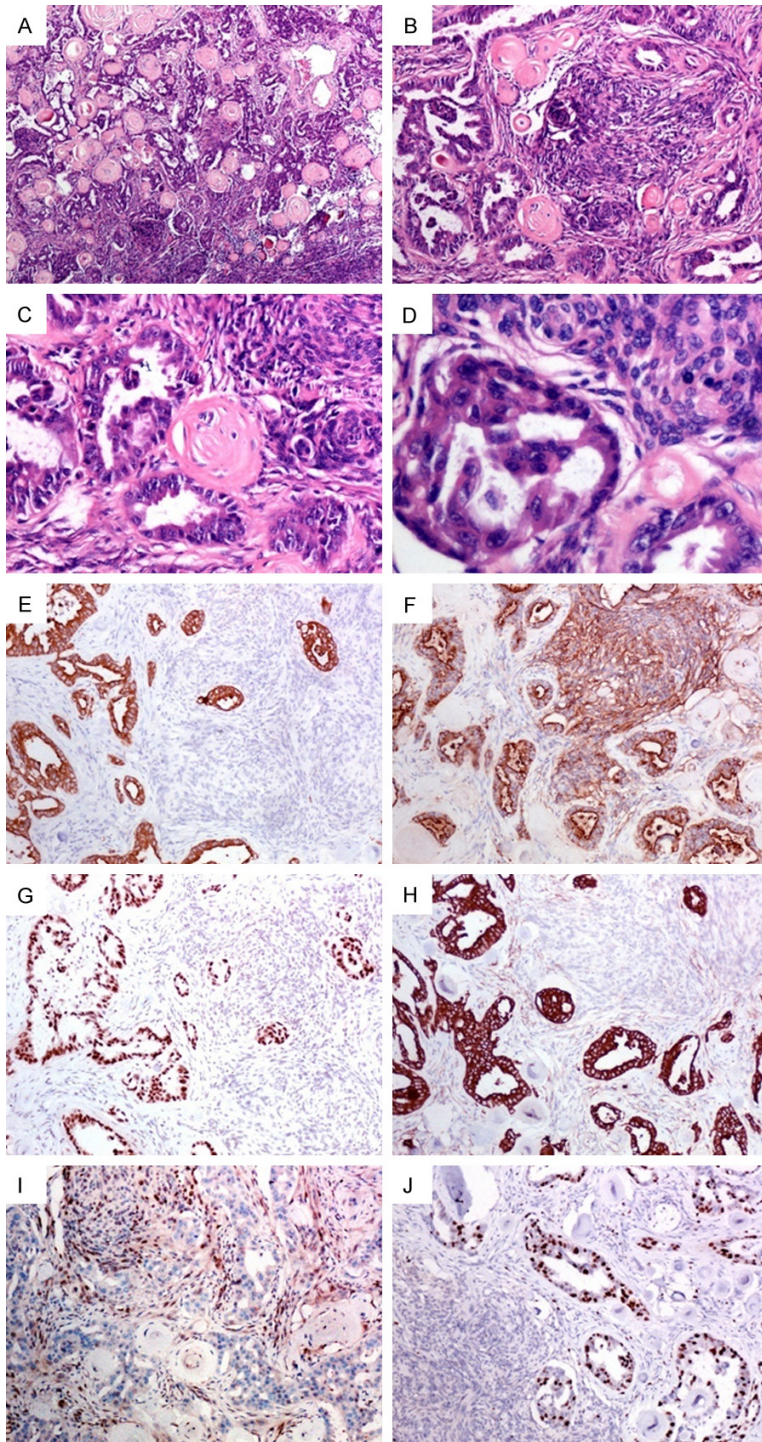
Figure 3. Histologic features and immunohistochemical staining results of intracranial lesion. (A) The adenocarcinoma was surrounded by transitional meningioma without an intermediate transitional zone. (B) The transitional meningioma showed extensive whorl formation, wherein tumor cells wrap around each other forming concentric layers. (C) The investigated adenocarcinoma cells formed poorly differentiated gland or cribriform structures. (D) The nuclei of tumor cells were characterized by chromatin condensation or occasional prominent eosinophilic nucleoli. Atypical mitoses were easily observed in this case. (E-H) The adenocarcinoma component was diffusely positive for AE1/AE3 (E), EMA (F), TTF-1 (G) and CK7 (H). (I) The meningioma component was diffusely positive for PR. (J) The Ki-67 labeling index was approximately 30%.

The adenocarcinoma component was diffusely positive for AE1/AE3 (**Figure 3E**), EMA (**Figure 3F**), TTF-1 (**Figure 3G**) and CK7 (**Figure 3H**), but negative for GFAP, S-100, Oligo2, vimentin and PR. On the other hand, the meningioma component was diffusely positive for EMA, vimentin, and PR (**Figure 3I**), and focally positive for AE1/AE3 and S-100, but negative for GFAP, oligo2, CK7 and TTF-1. The Ki-67 labeling index was approximately 30% (**Figure 3J**).

Microscopic features and immunohistochemical patterns of pulmonary lesions

The FNAB slide shared similar histologic features (abundant amphophilic cytoplasm, chromatin condensation and high N/C ratio) with those of the metastatic foci in the meningioma, although the gland structure was more obvious in the former (**Figure 4A-C**). The tumor cells in FNAB were also diffusely positive for CK7 (**Figure 4D**) and TTF-1 (**Figure 4E**). The Ki-67 labeling index was approximately 10%. The intracellular mucus in the adenocarcinoma cells stained positively for Alcian blue-PAS (**Figure 4F**).

Discussion

Tumor to tumor metastasis is a unique phenomenon and its diagnosis has strict criteria. Tumor to tumor metastasis is characterized by two or more histologically distinct tumors coexisting in the same lesion, which also occurs in a collision tumor. Therefore, inexperienced physicians may confuse these 2 concepts. The four criteria described in the introduction may help to distinguish between them and
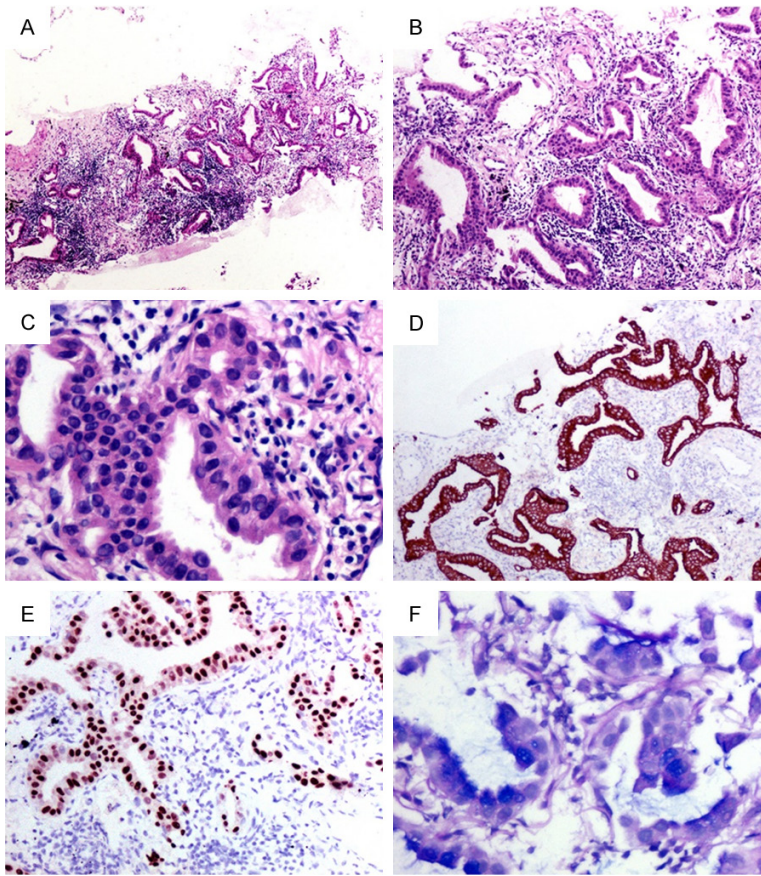
Figure 4. Histologic features and immunohistochemical staining results of pulmonary tumor. (A-C) The tumor cells formed irregular structures and were characterized by abundant amphophilic cytoplasm, chromatin condensation, and high N/C ratio (Magnification A: × 40; B: × 100; C: × 400). (D, E) The tumor cells were diffusely positive for CK7 (D) and TTF-1 (E). (F) The intracellular mucin in the adenocarcinoma cells stained positively for Alcian blue-PAS.

also demonstrated by FNA biopsy, which was in accordance with diagnostic criteria. In addition, upon review of the imaging, we found that it differed from that from that of the traditional meningioma. The typical meningioma is characterized by uniform enhancement on CT or MRI studies, while in this case, an abnormal enhanced nodule on T1 enhanced scanning was found within the mass and well-demarcated from the surrounding tumor tissues (**Figure 1F**). This lesion is fairly small and did not attract the attention of the doctor, but it is exactly where the metastatic focus was located.

The frequency of tumor-to-tumor metastasis is underestimated. A series of autopsies indicated that the most common donor tumor was breast cancer and lung cancer, followed by kidney, prostate, thyroid, endometrial, gall bladder, esophagus, and colon cancer [6]. On the other hand, the most common recipient malignant tumors were renal cell and thyroid carcinoma, while the benign counterparts were adrenocortical adenoma and meningioma [13].

make a definite diagnosis of a tumor-to-tumor metastasis [3-6]. The second criterion is that two or more histologically different tumor tissues coexist without an intermediate transitional zone in order to exclude a "collision" tumor. Considering the difficulty of acquiring samples from the primary lesion or uncertainty because of multiple system metastasis, a definite diagnosis of tumor to tumor metastasis is hard to achieve in clinical practice. Often, the occult primary lesion may be found only by autopsy. To our knowledge, only 15 cases of lung adenocarcinoma metastasizing to intracranial meningioma reported in the English literature fully meet the criteria of tumor-to-tumor metastasis (**Table 1**).

In the current case, the component of metastatic adenocarcinoma was encased by transitional meningioma without an intermediate transitional zone and the primary lesion was

Based on the reported cases, meningioma is the most common recipient tumor in the central nervous system [19, 21, 26, 27]. Tumor-to-tumor metastasis seems to favor a specific organ. Various factors were suggested to explain this interesting phenomenon, such as hypervascularity, low metabolic rate, tumor microenvironment (so called seed and soil theory), cell-cell adhesion, and complex interactions involving hormonal factors. However, the details of the mechanism remain unclear.

Matsukuma *et al*. investigated 9 cases of tumor-to-tumor metastasis (all primary tumors were lung cancer) by autopsy. In five (55.6%) of nine cases, metastases to nonneoplastic vasculature-rich tissues were not found [6].

Table 1. Clinical data of reported lung adenocarcinoma metastasizing to intracranial meningioma

Case	Authors	A/G	Onset symptom	Other me-tastases	Follow-up
1	Fried 1930 [1]	57/F	Left hemiparesis	Yes	2 months, DOD
2	Wolintz 1970 [23]	64/M	Epilepsy	Yes	ND
3	Weems 1977 [22]	68/F	Hemoptysis	Yes	40 days, DOD
4	Hope 1978 [18]	61/F	Left hemiparesis	Yes	30 days, DOD
5	Pamphlett 1984 [20]	79/M	Cough shortness of breath	Yes	2 weeks, DOD
6	Conzen 1986 [16]	69/M	Progressive right hemiparesis	ND	ND
7	Arnold 1995 [13]	71/F	"Dim" vision in the right eye	Yes	1 year, Recurrence 9 months since recurrence, DOD
8	Gardiman 1996 [17]	74/M	ND	ND	ND
9	Bhargava 1999 [14]	52/M	Progressive hemiparesis	Yes	5 weeks, Recurrence
10	Cserni 2002 [24]	48/F	Severe headaches	No	ND
11	Takei 2009 [25]	69/F	Headache and with altered mental status	Yes	1 year, Recurrence
12	Chatani 2014 [15]	74/F	Amnesia and abnormal gait	No	ND
13	Talukdar 2014 [2]	65/M	Episode of focal seizure	Yes	Lost to follow-up
14	Ravnik 2015 [21]	77/F	Acutely deteriorating hemiparesis	ND	ND
15	Nadeem 2016 [19]	68/F	Progressive right hemiparesis	Yes	6 months, DOD radiotherapy and chemotherapy
16	Current case	70/F	Progressive left hemiparesis	Yes	2 weeks, died of heart failure

A/G: Age/gender; M: male; F: female; ND: not described; NED: no evidence of disease; DOD: died of disease.

Therefore, hypervascularity in itself is insufficient to explain why tumor-to-tumor metastasis favors a specific organ. Tumor microenvironment (so called seed and soil theory) is a sound explanation. Brain, kidney, and adrenal gland are all lipid-rich organs favorable for implantation of metastatic cancer. We have reviewed cases of lung adenocarcinoma metastasizing to intracranial meningioma and summarized the clinical factors in **Table 1**. It is noteworthy that 10/16 cases (69%) had widespread other metastases, including our case which had chest metastasis. Therefore, metastasis to a lipid-rich organ may be only the local manifestation of generalized metastases.

It is worth mentioning that for a patient with tumor-to-tumor metastasis, the onset of symptoms is not always associated with primary tumor. 12 of 15 cases presented with central nervous system symptoms as the first clinical manifestation (**Table 1**). In addition, the prognosis of these patients was unfavorable. In 9/16 cases, the clinical course was shorter than 1 year, and seven patients survived no more than 6 months. For tumor-to-tumor metastasis, the most malignant componentdetermines prognosis, so the clinical course is usually shorter than for those with typical meningioma.

Conclusion

Here, we reported a rare case of lung adenocarcinoma metastasizing to intracranial benign meningioma as a first clinical manifestation. Surgeons should be aware of this rare metastatic phenomenon, as the prognosis and therapy are different from those of the typical meningioma.

Acknowledgements

Disclosure of conflict of interest

None.

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