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Case Report

Metastasis of lung adenosquamous carcinoma to meningioma: case report with literature review

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Abstract: The occurrence of metastasis of a systemic neoplasm to an intracranial tumor is a rare phenomenon. Meningiomas have been reported as the most common intracranial tumor to harbor a systemic metastasis, with breast and lung carcinomas being the most common sites of origination. Here, we report a case of an adenocarcinoma metastasis of an adenosquamous lung carcinoma found within a meningioma, resulting in the patient's first clinical manifestations. We also review the literature for other cases of adenocarcinoma metastatic to a meningioma and suggest mechanisms that make meningiomas likely to harbor systemic metastases including increased vascularity, slow growth rate, increased hyaline content and expression of cell-cell adhesion molecules.

Keywords: Tumor-to-tumor, meningioma, adenosquamous carcinoma

Introduction

Tumor to tumor metastasis, particularly to an intracranial neoplasm, remains rare. Two criteria have been proposed for the diagnosis of a tumor to tumor metastasis: 1) The metastatic focus must be encased by a rim of histologically distinct tumor tissue and 2) a proven primary carcinoma that is compatible with the metastasis [1, 2]. Meningiomas are the most common neoplasms to harbor metastases. The most common primary to spread to a meningioma is breast, followed by lung. Here, we report a case of an adenocarcinoma metastasis found within a meningioma.

Case report

A 57 year old male smoker presented with mental status changes, ataxia and a 20 pound weight loss. MRI revealed an extraaxial mass measuring 5.1 cm in its maximum diameter with a focal hemorrhagic component, and a chest CT revealed a 2.5 x 1.4 cm right suprahilar mass. Bronchoscopic biopsy of the lung mass revealed a poorly differentiated squamous cell carcinoma, and the brain mass was presumed to be a metastasis.

Patient underwent whole brain radiation for the extraaxial mass. As the mass did not decrease in size after completion, this was followed by resection. An intraoperative diagnosis of meningioma was made. However, microscopic evaluation demonstrated foci of metastatic adenocarcinoma within this meningioma. Patient was evaluated for resection of the lung mass, but was found to be a poor surgical candidate. He was treated with radiation therapy and concurrent Carboplatin/paclitaxel, and continues to receive treatment.

The surgical specimenconsisted of two oval pieces of tan-brown, firm tissue measuring 1.6 x 1.5 x 0.8 cm and 4 x 2.7 x 2 cm. One surface of the larger piece had an attached portion of dura measuring 4 x 1.6 x 0.2 cm. Sectioning of each piece revealed pale tan-pink and yellow cut surfaces.

The initial lung biopsy revealed a poorly differentiated squamous cell carcinoma (**Figure 1A**

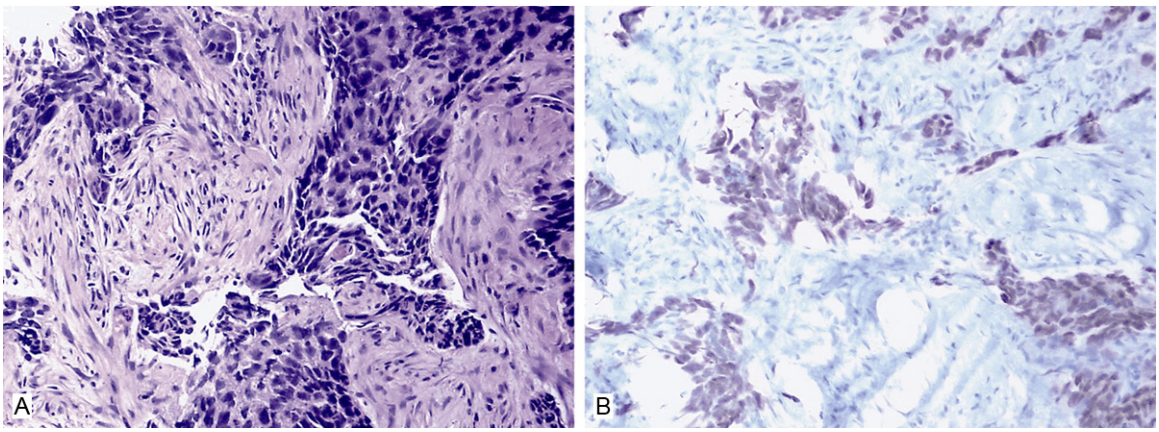

Figure 1. Bronchoscopic biopsy of primary lung carcinoma. A: Intercellular bridges and spindle cells can be observed. B: Tumor cells staining positive for p63. (Hematoxylin-eosin [A], original magnifications x 20 [A and B]).

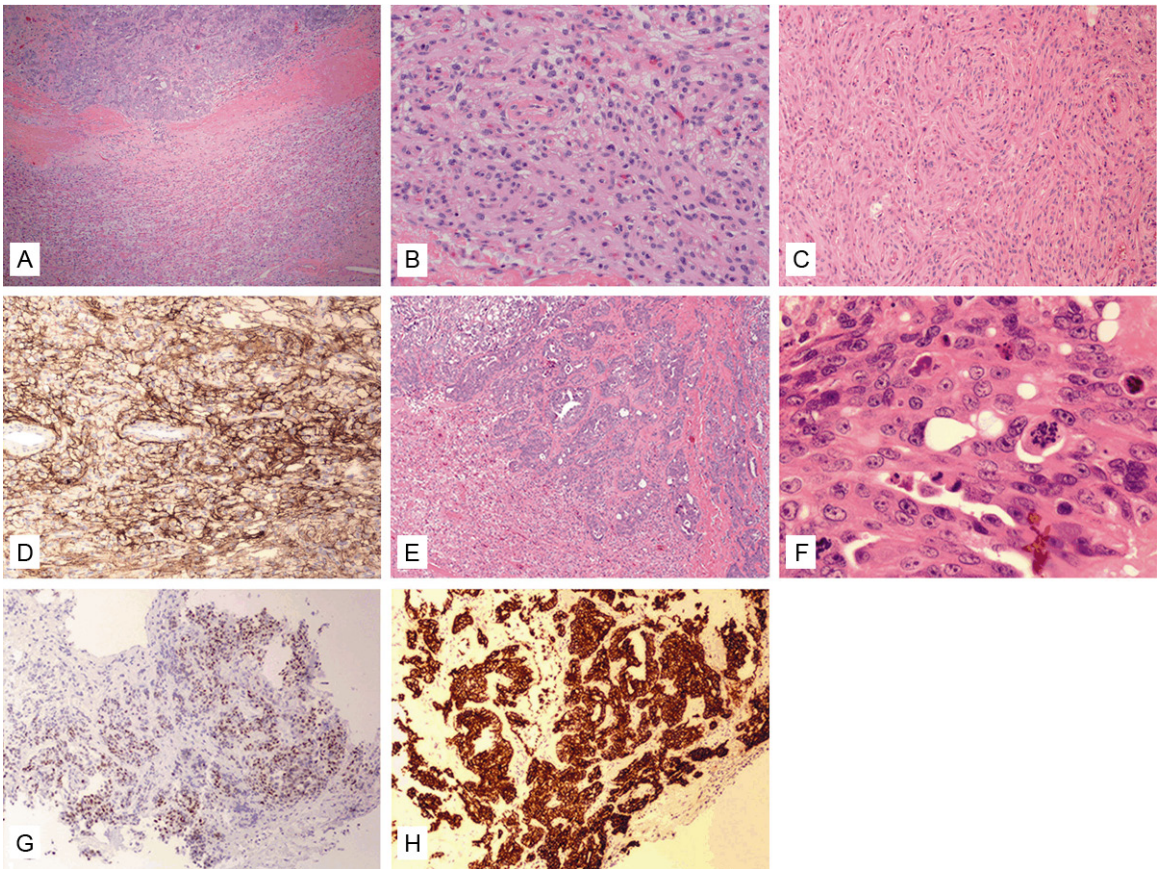

Figure 2. Surgical specimen of a meningioma encasing an adenocarcinoma metastasis. A: A focus of adenocarcinoma adjacent to a meningioma can be observed. The meningioma demonstrates a (B) Syncytial pattern with hyalinized vessels, as well as (C) Scattered whorl formation and (D) Membranous EMA positivity. E: Gland forming groups of cells separated by stroma can be observed. F: On higher power, pleomorphic nuclei with high N/C ratio, prominent nucleoli, nuclear clearing and several mitotic bodies can be observed. F: These cells stain positive for cytoplasmic CK7 (G) as well as nuclear TTF-1. (Hematoxylin-eosin [A-C, E, F], original magnifications x 4 [A] x 20 [B-E, G-H], x 40 [F]).

and **1B**). Histologic analysis of the brain mass demonstrated metastatic adenocarcinoma within a meningioma (**Figure 2A**). The bulk of the tumor was composed of lobules of relative-

Table 1. Reported Cases of Lung Adenocarcinoma Metastatic to Meningioma

Case No.	Reference	Age/Sex	Type of Meningioma
1	Fried, [20] 1930	57/F	Meningothelial
2	Wilson et al, [21] 1967	39/M	Meningothelial
3	Gyori, [22] 1976	69/F	Mixed
4	Hope et al, [23] 1978	61/F	Meningothelial
5	Pamphlett, [4] 1984	79/M	Angioblastic
6	Conzen et al, [24] 1986	?	Mixed
7	Arnold et al, [25] 1995	71/M	Meningothelial
8	Gardiman et al, [26] 1996	62/F	Transitional
9	Bhargava et al, [27] 1998	52/M	Transitional
10	Cserni et al, [28] 2002	48/F	Secretory
11	Kim et al, [29] 2013	71/F	Fibrous
12	Our Case	57/M	Meningothelial

ly uniform cells with oval nuclei, delicate chromatin, and indistinct cytoplasmic borders imparting a syncytial pattern (**Figure 2B**). Focal whorl formation was seen (**Figure 2C**). The tumor demonstrated focal necrosis, as well as a very low mitotic activity of less than 1 mitotic body per 10 high power fields. No brain invasion or small cell was seen. The metastatic carcinoma demonstrated gland formation (**Figure 2A** and **2E**). High power microscopy revealed nuclear pleomorphism with prominent nucleoli, nuclear clearing and several mitotic bodies per high power field (**Figure 2F**).

The initial lung biopsy showed a poorly differentiated carcinoma expressing CK5/6 and p63 (**Figure 1B**), and negative for CK7, Synaptophysin, TTF-1 or chromogranin, consistent with a poorly differentiated squamous cell carcinoma. In addition, EGFR was wild-type and ALK/FISH was not detected.

The primary brain tumor stained positive for EMA (**Figure 2D**), vimentin and progesterone receptor, and negative for Cytokeratin AE1/AE3, GFAP and S-100. Ki-67 labeled less than 2% of the nuclei, consistent with meningothelial meningioma (WHO grade I). The focus within the meningioma stained positive for CK7 and TTF-1, and negative for CK5/6, CK20 and p63 (**Figure 2G** and **2H**), consistent with metastatic lung adenocarcinoma.

Discussion

Tumor to tumor metastasis is a rare phenomenon defined by: 1) The metastatic focus must be encased by a rim of histologically distinct tumor tissue and 2) a proven primary carcinoma that is compatible with the metastasis [1, 2]. While our case fulfills the first criteria, it is interesting to note that the diagnosis made from initial biopsy was squamous cell carcinoma, whereas an adenocarcinoma metastasis was identified within the meningioma. As the lung biopsy provided a small sample and the patient was not a surgical candidate, making it impossible to obtain a more representative sample, it is likely that the patient's primary tumor was in fact a mixed adenosquamous carcinoma. This is consistent with findings from Kanazawa's group suggesting that these tumors transition from Squamous Cell Carcinoma to Adenocarcinoma, and also identifying Adenocarcinoma alone within metastases [3].

The most common malignancies to spread to a meningioma is breast primary, followed by lung, although a number of other malignancies have been reported within a meningioma including genitourinary tumors, renal cell carcinoma, prostate carcinoma and melanoma [4]. A literature search revealed 11 previously reported cases of pulmonary adenocarcinomas within meningiomas (**Table 1**).

A number of factors have been proposed to explain why meningiomas may provide a favorable environment for tumor seeding. Meningiomas are known to be highly vascular, making them susceptible to seeding from systemic tumors. They are known to exhibit a slow growth rate with low metabolic activity, which provides these metastases with prolonged exposure and a noncompetitive environment. In addition, the high collagen and lipid content of these tumors has been suggested to provide a "fertile soil" for seeding of malignant cells [5].

It has also been proposed that cell-cell adhesion may be responsible for tumor seeding to meningiomas. In the case of breast carcinoma, it has been suggested that progesterone expression by meningiomas may provide a favorable environment. It has also been demonstrated that meningiomas express epithelial cadherin (E-cadherin) and neural cell-adhesion

molecule (NCAM) [6]. There is considerable evidence suggesting E-cadherin has a role in the seeding of tumors to meningiomas [4], including the observation that malignant cells lose E-cadherin expression, but resuming it is necessary for growth at the target site [7]. In addition, the connective tissues and individual cells of meningiomas have also been shown to express versican [33], an extracellular proteoglycan capable to binding to CD44, mediating mesenchymal to epithelial reversion and inducing E-cadherin expression in metastatic cells [34].

The CD44 adhesion molecule may also play a role in tumor seeding. CD44 is a hyaluronic acid (HA) binding protein, and this binding has been shown to promote activation and localization of matrix metalloproteases 2 and 9 to plasma membranes [10, 11]. Lewy and Figarella's groups demonstrated that CD44 is strongly expressed in atypical meningiomas, as well as meningothelial and transitional meningiomas [8, 9]. It is well established that meningiomas contain high collagen content and hyalinized vessels, with pericellular hyaluronic acid staining observed in these tumors as well [19]. This interaction is known to play a role in leukocyte adhesion to endothelial cells, and has been shown to be critical to the metastasis and adhesion of prostate and colon adenocarcinomas [12-14]. In addition, several studies have shown elevations in hyaluronic acid content in metastatic lung and breast cancers [15, 16] as well as increased expression of CD44, particularly the v6 variant [17, 18] which has an extended capacity to bind glycosaminoglycans [30]. It is also worth noting that an inhibitor of the CD44-HA interaction is E-cadherin [31]. However, E-cadherin expression within a meningioma has been localized primarily to the cell surfaces and not within the fibrous or perivascular areas [32]. This would likely promote growth of the metastasis while having little effect on tumor seeding. Consequently, it is possible that binding between CD44 and HA with eventual binding of E-cadherin could 1) promote adhesion of circulating tumor cells; 2) stimulate the release of matrix metalloproteases; and 3) contribute to the increased propensity of meningiomas to harbor systemic metastases.

The diagnosis of tumor-to-tumor metastasis is difficult to make, as it is a rare and usually unanticipated finding. As meningiomas may normally contain areas of cysts, hemorrhage or necrosis, it is difficult to confirm a focus of metastasis using radiographic evidence alone. Previous reports have suggested that a meningioma may show more aggressive growth when housing another carcinoma, which translates to a rapid clinical deterioration [4, 29]. If the patient is known to have an additional tumor when an intraoperative diagnosis of meningioma is made, additional sections should be taken to ensure metastatic foci are not missed as this diagnosis can significantly impact care. In our case, the patient's initial brain mass did not respond as expected to radiation therapy, and the patient was even evaluated for hospice care. It is therefore important to distinguish between a single tumor and a tumor-in-tumor to ensure that the proper treatment can be established.

Disclosure of conflict of interest

None.

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