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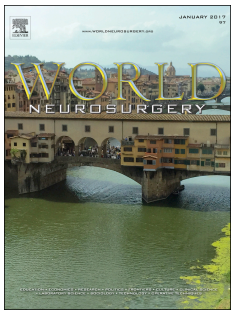

Rare Tumor-to-Tumor Metastases involving Lung Adenocarcinoma to Petroclival Meningiomas

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Abstract

Background and Importance: Lung carcinoma metastasizing to a skull base meningioma remains an extremely rare phenomenon with only 3 total reports in the literature. Furthermore, no documented cases have ever occurred in the petroclival region. Thus, we present the first two cases of tumor-to-tumor metastasis (TTM) in which a petroclival lesion, initially thought to be purely a meningioma, was also found to contain metastatic lung adenocarcinoma.

Cases Reported: We present two cases of patients with a known history of lung adenocarcinoma and stable petro-clival meningioma who then presented with new-onset neurologic deficits. Repeat imaging in both cases found increased lesion size and peritumoral enhancement, and thus both patients underwent emergent craniotomy for complete lesion resection. Intraoperatively, both lesions had zones of markedly different tumoral texture, and, upon histologic analysis, both lesions showed metastatic lung adenocarcinoma contained within the primary petroclival meningioma.

Conclusion: Skull base TTM is a rare entity for which no specific management guidelines have been created. Therefore, even if imaging characteristics suggest a more benign process, it should remain high on the differential in patients with a known primary cancer and new onset, rapidly progressive neurologic deficits. Close clinical follow-up with short interval repeat imaging in this subset of patients may prevent misdiagnosis and facilitate prompt treatment.

Background and Importance

Tumor-to-tumor metastasis (TTM) is a rare oncologic entity in which a donor tumor focus metastasizes to a recipient tumor of a different cell line.[1, 2] A limited number of intracranial TTM have been documented in the literature with the most common recipient lesions being meningiomas and the most common donors being lung and breast carcinomas.[1, 3, 4] Given the relative infrequency of intracranial TTM, no specific management guidelines exist. Furthermore, TTM involving skull base meningiomas remain exceedingly rare and present unique surgical and diagnostic challenges. Only three cases of lung carcinoma to skull base meningiomas have ever been reported and all were located in the sphenoid wing.[1, 5-8] Thus, we discuss the presentation and management of the first TTMs involving lung carcinoma to petroclival meningiomas.

Case Descriptions

A retrospective chart review was performed after Institutional Review Board approval was obtained. The consent process was waived because all patient information was deidentified.

Case 1

A 62-year-old female presented with axial back pain but was otherwise neurologically intact. She underwent thoracic computed tomography (CT) which demonstrated multiple pulmonary masses and a pathologic thoracic fracture suggestive of spinal metastasis. During additional workup, a brain magnetic resonance image (MRI) was performed which showed a 2.6 x 2.5 x 1.5 centimeter (cm) extra-axial, heterogeneously enhancing dural-based lesion within the right cerebellopontine angle (CPA) (Figure 1). T2 weighted MRI confirmed the lesion's petroclival location, showing the tumor's position medial to the ipsilateral trigeminal nerve (**Figure 2**).

Given these findings, the lesion was favored to be a meningioma and surgical resection was recommended on an elective basis once her cancer workup was completed. She subsequently underwent biopsy and immunohistochemical (IHC) staining of the thoracic lesion which confirmed the diagnosis of metastatic lung adenocarcinoma. However, over a six-week period she developed a right partial abducens palsy and repeat MRI demonstrated increased size of the CPA mass with worsening perilesional edema in the right pons and cerebellum (**Figure 3**). As a result, she underwent urgent surgical resection.

Intraoperatively, the texture and consistency of the tumor changed drastically along the medial aspect of the lesion as the capsule was attempted to be separated from the pons. Along the petrous face, hyperemia of the dura was noted and the tumor was gray with a consistency typical of meningiomas. Frozen section from this area was also consistent with a benign meningioma. However, upon medial dissection of the tumor capsule, the lesion became avascular, amorphous, and extremely adherent to the brainstem surrounding the pia at the trigeminal exit zone and engulfing branches of the right anterior inferior cerebellar artery (AICA). A separate sample was sent for frozen section from this portion of the lesion and was confirmed to be adenocarcinoma. Given the adherent nature of the lesion along the brainstem, a subtotal resection was achieved. Final pathology demonstrated a metastatic focus of lung adenocarcinoma within a World Health Organization (WHO) grade 1 meningioma **(Figure 4).**

Post-operatively, she developed a right facial nerve palsy (House-Brackmann 3/6) which improved over time however her abducens palsy remained. She subsequently underwent multiple

rounds of chemotherapy and radiation but was found to have worsening systemic disease 6 months after her surgery and eventually succumbed to her disease.

Case 2

The second case of TTM involving lung adenocarcinoma in the petroclival region involved a 64-year-old female with known metastatic lung adenocarcinoma. This patient had a brain MRI completed during her initial lung cancer work-up that demonstrated a small left petroclival dural-based mass with no significant mass effect on the underlying brain parenchyma **(Figure 5)**. T2 weighted MRI confirmed the lesion's petroclival location, showing the tumor appears medial to the left trigeminal nerve **(Figure 6)**. Initially, this was thought to be a meningioma and no intervention was performed at that time. After 6 months passed, the patient developed sudden onset right sided hemiparesis, dysarthria, left sided facial droop, left abducens palsy, with associated decreased hearing in the left ear and decreased sensation to the left side of the face. Repeat MRI demonstrated significant growth of the lesion with now severe compression of the brainstem and associated edema **(Figure 7)**. She was admitted emergently and subsequently rapidly deteriorated, becoming comatose and quadriplegic. An external ventricular drain was placed and the patient was taken emergently for a left far lateral craniotomy for resection of the lesion in question. Intraoperatively, the lesion appeared to be two different consistencies and was much more firm near the jugular foramen. Specimens were sent from both aspects of the lesion and final pathology demonstrated a metastatic focus of lung adenocarcinoma, confirmed with IHC staining, within a World Health Organization (WHO) grade 1 meningioma (**Figures 8 and 9**). Unfortunately, this patient had a protracted hospital course secondary to respiratory failure

from a pneumonia and when she was eventually extubated she requested to be placed in hospice care and subsequently expired.

Discussion

Literature Search

In performing the systematic literature review, articles were primarily sourced via the NCBI PubMed archive. To locate the specific articles analyzed within this review, the search terminology entered into the PubMed archive included “lung adenocarcinoma or lung carcinoma to meningioma and tumor to tumor metastasis” with no search filters. Only articles published after 1970 detailing lung carcinomas that had evidence of intracranial metastasis to an existing meningioma were included. Articles regarding cases that did not originate in the lungs were excluded, as were studies that included metastatic lung lesions that were not carcinomatous. Articles outlining collision lesions and articles without patient data were excluded, as were abstracts. No exclusions were made based on patient age. 86 articles were retrieved from several journals via a search of the PubMed Archive using the aforementioned search terms, and 14 met inclusion criteria for this review. An additional 3 articles were sourced from the reference section of two included articles. The 17 articles identified were compiled into a single database. The included data points were: study size, lesion type/size/locations, radiologic appearance, histopathologic analysis, treatment strategies and complications. The available studies, patient demographic information, lung carcinoma type and meningioma grade/location are listed in **table 1**. Treatment strategies, complications and follow-up are outlined in **table 2**.

Intracranial Tumor-to-Tumor Metastases

Intracranial TTM remains a rare phenomenon with only 100 cases ever described in the literature. The proposed pathophysiologic mechanisms leading to TTM suggest that increased local vascularity, secretion of chemokines, and upregulation of cell adhesion molecules by

recipient lesions create an environment favorable for the deposition of metastatic cells especially when they are located in anatomic locations typical of metastases.[3] Tumor collision, which occurs when a tumor of one distinct cell lineage grows adjacent to a separate tumor focus of a different lineage, can be distinguished from TTM because the latter must have a metastatic donor focus that is within, rather than adjacent to, the recipient lesion.[2, 24, 25] Additionally, to confirm TTM, there must be a rim of recipient cells at least partly surrounding the donor lesion on histopathology.[19]

The most commonly implicated recipient tumor in intracranial TTM are meningiomas and the first and second most common donor lesions are breast and lung carcinomas, respectively.[1] The majority of intracranial TTMs are located on the cerebral convexity, where the majority of meningiomas arise, with very few occurring along the skull base.[26] Furthermore, the large majority of those along the skull base occur at the sphenoid wing with very few isolated reports demonstrating TTM in other skull base locations.

Lung Carcinoma Metastases to Intracranial Meningiomas: Our Findings

In our review, we found the average age of patients diagnosed with TTM from lung carcinoma to be 64.3 years, with 73.3% of patients being female. Tumors located in the falx cerebri or over a cerebral convexity (defined as frontal, parietal, temporal or occipital lobes) accounted for the majority of these lesions (95.2%). This can be explained by the fact that meningiomas most often develop in these regions, making metastasis to these foci more likely. These regions are also very well vascularized, which is one proposed mechanism by which TTM is thought to occur. The remaining lesions were located near the sphenoid wing (n=3) or along the optic sheath (n=1).

With regards to carcinoma subtype, 85.7% (n=18) of lesions were adenocarcinomas and 14.3% (n=3) were unreported. On histology, the majority of meningiomas were typical meningiomas (n=12, 57.1%) or meningoepithelial (n=4, 19.0%). The remaining meningioma histologic profiles included one of each of the following: fibrous, microcystic, transitional, angiomatous and endotheliomatose. These findings are summarized in **table 1.**

Management of these TTMs involved either complete or partial resection in 76.1% (n=16) cases, medical management and observation in 14.3% (n=3), with no treatment documented in two studies. Mortality rate was 19.0% (n=4) and 3 deaths were due to extracranial disease. The remaining patient passed from a subdural hematoma several weeks post-operatively. 3 patients that succumbed to metastatic disease died in the first 6 months, however one patient died from metastatic burden 14 years after surgery. The median follow-up duration for all patients was 37.5 days. Only one complication was noted across all studies, which was neoplasm recurrence at the surgical site, and was treated with surgical resection and subsequent radiotherapy. These findings are summarized in **table 2.**

Other than our patients, only two other patients in our review presented with new onset neurologic deficits in the setting of a known meningioma being followed with serial imaging. Most patients (57.1%, n = 12) were treated with surgery at presentation, generally due to the severity of their presenting symptoms. However, 4 patients in this review were managed expectantly with serial neurologic examinations and imaging. 3 of these patients experienced new onset neurologic deficits, which then prompted further intervention. The onset of new neurologic deficits in these patients varied from 4 days to over 1 year. However, given these

findings, new onset neurologic deficits in the setting of an existing intracranial mass should raise suspicion for TTM. These findings are summarized in **table 3.**

When specifically evaluating TTM from a lung carcinoma to a meningioma, only 3 cases located at the skull base have ever been documented and all occurred along the sphenoid wing. Thus, we present the first case ever reported involving metastasis from a lung adenocarcinoma to a petroclival meningioma. Lesions in this location present unique operative challenges given their close proximity to the brainstem and cranial nerves. This can be exaggerated when overall prognosis is dependent on extent of resection as is the case for most intracranial malignancies.[27, 28]

Conclusion

We present the first two cases of a tumor-to-tumor metastasis from a lung adenocarcinoma to a petroclival meningioma. Due to the inherent difficulty in identifying tumor-to-tumor metastasis, patients with known metastatic disease and new onset neurologic deficits who are found to have a meningioma with intratumoral heterogeneity on imaging should warrant increased suspicion for intratumoral metastasis even if other imaging characteristics suggest a more benign process. Furthermore, when these lesions involve the skull base they can lead to rapid neurological decline secondary to compression of the brainstem or cranial nerves thus we recommend short interval follow-up to facilitate early detection and prompt treatment. Further studies are warranted to develop specific management guidelines for these lesions.

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Figures

Figure 1. MRI brain of patient 1 at initial presentation. (A) Heterogeneously enhancing, dural-based mass within the right cerebellopontine angle causing compression of the pons. (B) Initial FLAIR images demonstrating mild edema within the brainstem and cerebellum.

Figure 2. T2 weighted MRI brain of patient 1 showing petroclival location of meningioma.

Figure 3. MRI brain of patient 1 following onset of right abducens palsy. (A) Previously identified mass in the right cerebellopontine angle has increased in size. (B) Edema within the brainstem and cerebellum has increased significantly.

Figure 4. Hematoxylin and eosin (H&E) stain demonstrating interface of the meningioma and adenocarcinoma from patient 1. (A) Low power view demonstrating both the meningioma (left)

and the mucinous adenocarcinoma (right). (B) High power view demonstrating meningothelial proliferation with bland, round nuclei and pseudonuclear inclusions characteristic of a meningioma (top) and mucinous glands characteristic of an adenocarcinoma (bottom).

Figure 5. MRI brain of patient 2 at initial presentation (A) T1 with gadolinium contrast showing left petroclival dural-based mass without significant mass effect (B) FLAIR showing left petroclival dural-based mass

Figure 6. T2 weighted MRI brain of patient 2 showing petroclival location of meningioma.

Figure 7. MRI brain of patient 2 after new onset neurologic symptoms (A) T1 with gadolinium contrast showing left petroclival dural-based mass with mass effect (B) FLAIR showing left petroclival dural-based mass

Figure 8. Hematoxylin and eosin (H&E) stain demonstrating the interface of the meningioma and adenocarcinoma from patient 2. (A) Low-power H&E showing the adenocarcinoma at the bottom and meningioma surrounding the adenocarcinoma (B) High power H&E showing adenocarcinoma (yellow arrows), and meningioma (blue arrowheads) (C) Adenocarcinoma component of the lesion in question. (D) Meningioma component of the lesion in question,

Figure 9. Immunohistochemical (IHC) analysis of the lesion from patient 2. (A) IHC study for Cytokeratin 7 labeling adenocarcinoma component only (B) IHC study for SSRT2 labeling meningioma component only.

Table 2. Treatment strategies, complications, and follow-up across reported cases.

Article	Treatment	Complication	Follow-up Duration
Wolintz[6]	-	-	-
Weems[7]	Resection of lung mass Tumor identified on autopsy	-	40 days post-lobectomy until death from subdural hematoma from a fall
Hamperl[8]	Complete resection followed by radiotherapy and Gefitinib	-	3 weeks post-op (2 weeks from discharge)
Gyori[9]	Glucocorticoids Supportive care	-	Death on 6th day of admission Tumor discovered on autopsy
Ravnik[10]	Complete resection with frozen section	-	-
Conzen[11]	Complete resection	-	Well at 3 weeks
Talukdar[12]	Partial resection	-	Lost to follow-up, length not specified
Bhargava[13]	Total resection	Recurrent mass at surgical site	Well at 5-weeks
Takei[14]	Tumor resection followed by chemoradiation	-	1 year post-operatively, at which point bone metastasis was found
Arnold[15]	Observation of intracranial metastasis, and medical treatment of primary tumor	-	14 years until death from progression of metastatic disease
Jomin[16]	None documented	-	-
Chatani[17]	Total resection	-	-
Basaran[18]	Total resection in all cases	-	-
Liu[19]	Total resection	-	Death attributed to heart failure 2 weeks post-operatively
Glass[20]	Whole brain radiation followed by tumor resection Lung mass unresectable, and treated with radiotherapy, Carboplatin and Paclitaxel	-	-
Nadeem[21]	Complete resection followed by radiotherapy and chemotherapy	-	Death at 6 months

Cserni[22]	Near total resection followed by radiotherapy	-	Well at 5 months post-operatively
Kim[23]	Complete resection followed by chemotherapy	-	-

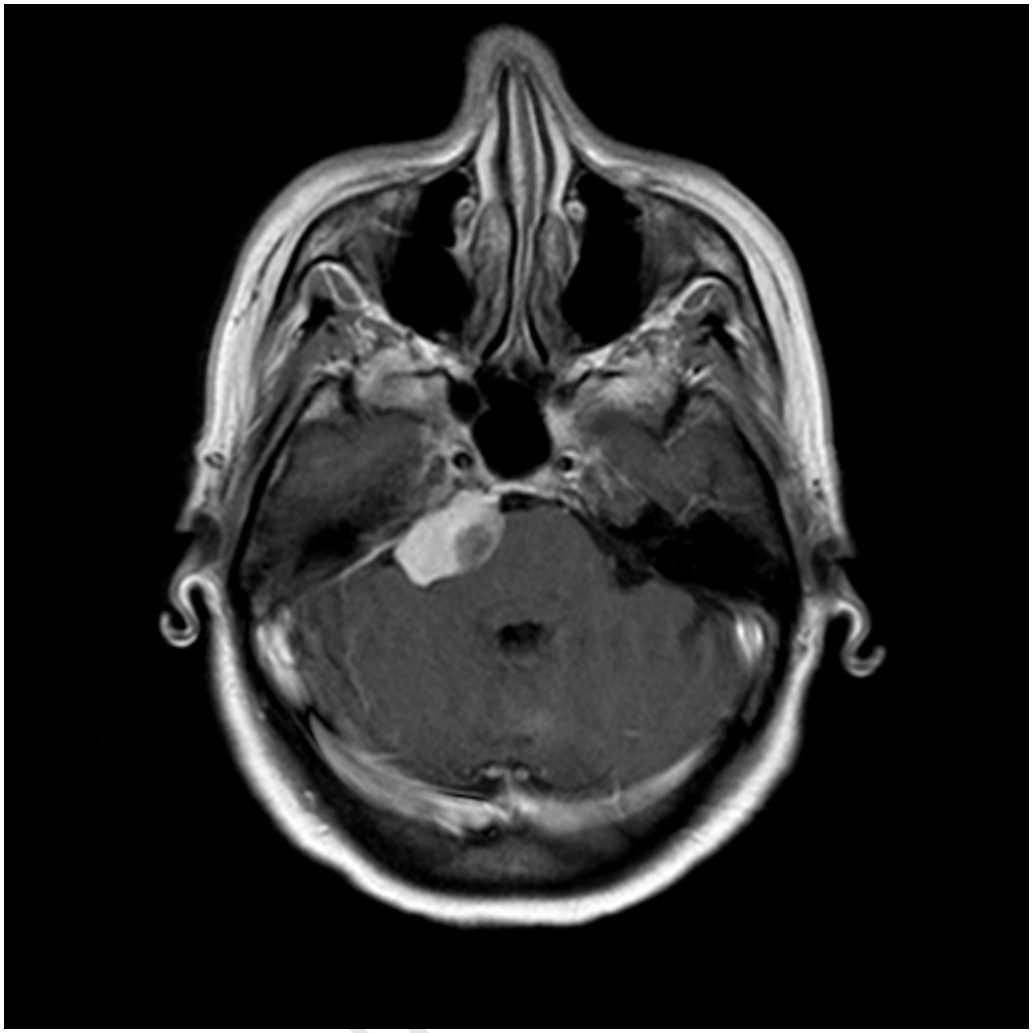
Table 3. Time course of symptoms in reported cases

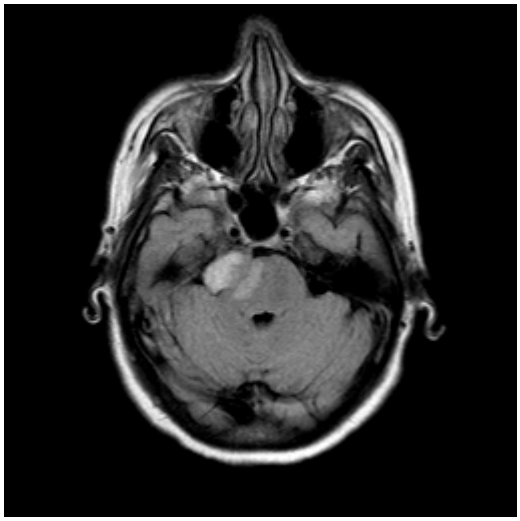
Article	Initial Presenting Symptom	Time until new symptoms emerged	New symptoms
Wolintz[6]	-	-	-
Weems[7]	Lethargy from subdural secondary to fall	Family deferred intervention	-
Hamperl[8]	Fatigue & weight loss at follow up for partially resected meningioma	Surgery performed on initial presentation	-
Gyori[9]	Ataxia and dizziness	4-5 days	Coma
Ravnik[10]	None. Asymptomatic meningioma for many years	> 1 year	Progressive, sudden onset, left hemiparesis
Conzen[11]	Progressive right hemiparesis	Surgery performed on initial presentation	
Talukdar[12]	Seizure	Surgery performed on initial presentation	
Bhargava[13]	Symptoms consistent with enlarging meningioma	1 year	-
Takei[14]	Headache and altered mental status	Surgery performed on initial presentation	
Arnold[15]	Visual loss that remained stable for 14 years	1 year	-
Jomin[16]	-	-	-
Chatani[17]	Amnesia and abnormal gait	Surgery performed on initial presentation	
Basaran[18]	Headache, nausea, dizziness and hemiparesis (individual patient symptoms not listed)	Surgery performed on initial presentation	
Liu[19]	Progressive hemiparesis	Surgery performed on initial presentation	
Glass[20]	Altered mental status, ataxia and weight loss	No new symptoms. Surgery was performed shortly after radiotherapy failed	
Nadeem[21]	Headaches, mood and behavior changes followed by hemiparesis and seizure	Surgery performed on initial presentation	
Cserni[22]	Headaches	No change	None
Kim[23]	Left arm weakness	10 months	Left hemiparesis

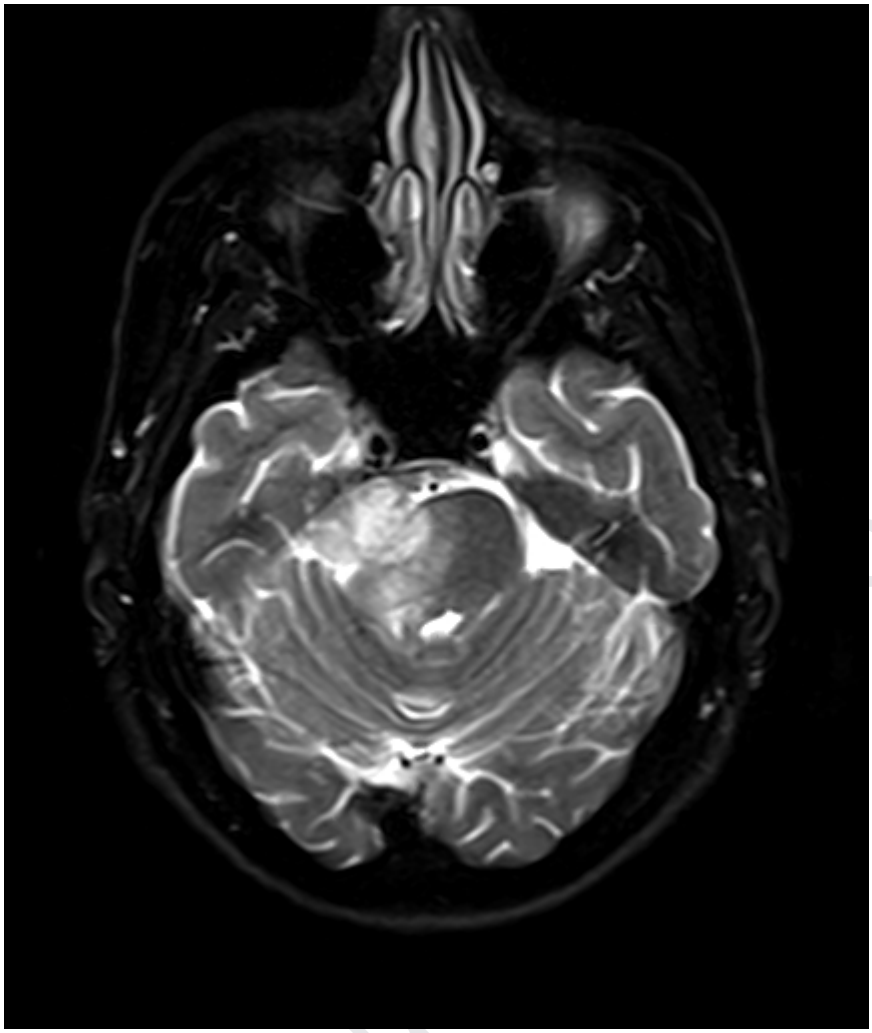
Table 1. Summary of lung carcinoma to meningioma tumor-to-tumor metastases.

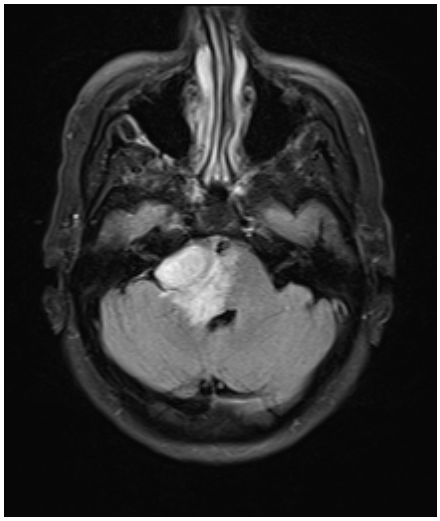
Article	n	Gender	Age	Donor	Meningioma Location	Meningioma Histology/WHO Grade
Wolintz[6]	(n=1)	n/a	n/a	Carcinoma (unspecified type)	Sphenoid ridge	WHO Grade N/A
Weems[7]	(n=1)	F	68	Bronchiolar carcinoma	Right sphenoid wing	WHO Grade N/A Typical Meningioma
Hamperl[8]	(n=1)	F	69	Adenocarcinoma	Medial sphenoid wing	Endotheliomatose meningioma WHO Grade I
Gyori[9]	(n=1)	F	69	Adenocarcinoma	Parasagittal	WHO Grade N/A
Ravnik[10]	(n=1)	F	77	Adenocarcinoma	Parasagittal, R Frontal	Angiomatous meningioma WHO Grade N/A
Conzen[11]	(n=1)	M	69	Adenocarcinoma	Falx	WHO Grade I Meningothelial, angiomatous meningioma
Talukdar[12]	(n=1)	M	65	Adenocarcinoma	Left parietal parafalcine	WHO Grade N/A Typical meningioma
Bhargava[13]	(n=1)	M	52	Adenocarcinoma	Right parasagittal	WHO Grade N/A
Takei[14]	(n=1)	F	69	Adenocarcinoma	Left temporal	Microcystic meningioma WHO Grade N/A
Arnold[15]	(n=1)	F	71	Adenocarcinoma	Right optic nerve sheath	Meningoepithelial meningioma WHO Grade N/A
Jomin[16]	(n=1)	M	52	Adenocarcinoma	Left frontoparietal	WHO Grade N/A
Chatani[17]	(n=1)	F	74	Adenocarcinoma	Falcotentorial	WHO Grade N/A
Basaran[18]	(n=4)	n/a	61.8	Adenocarcinoma	Right Temporal	WHO Grade N/A

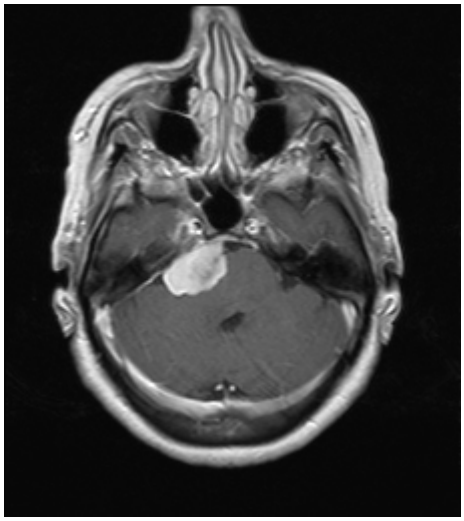
			(61-63)	(all lesions)	(2), Left & Right Frontal (2)	
Liu[19]	(n=1)	F	70	Adenocarcinoma	Right parafalcine occipital	Transitional meningioma WHO Grade N/A
Glass[20]	(n=1)	M	57	Adenocarcinoma	N/A	Meningoepithelial meningioma WHO Grade I
Nadeem[21]	(n=1)	F	68	Adenocarcinoma	Left frontal	Typical meningioma WHO Grade N/A
Cserni[22]	(n=1)	F	48	Adenocarcinoma	Right temporal	Meningoepithelial secretory meningioma WHO Grade N/A
Kim[23]	(n=1)	F	71	Non-small cell carcinoma	Right frontal	Fibrous meningioma WHO Grade N/A

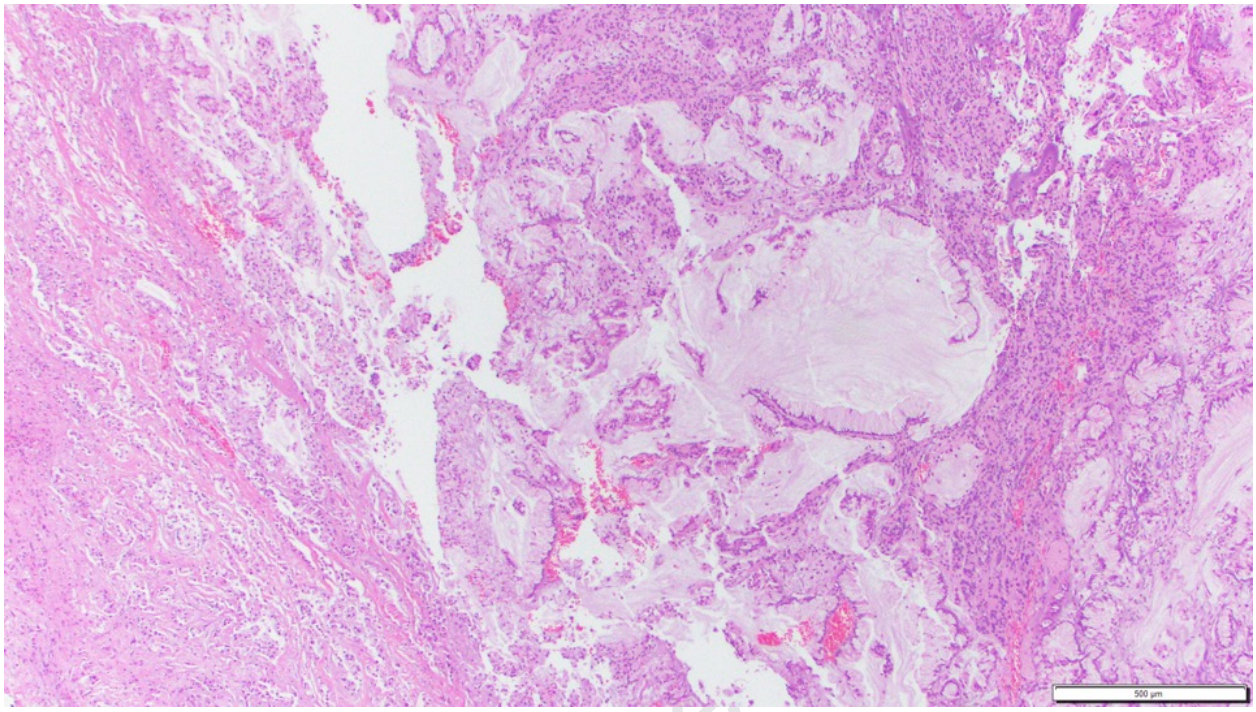


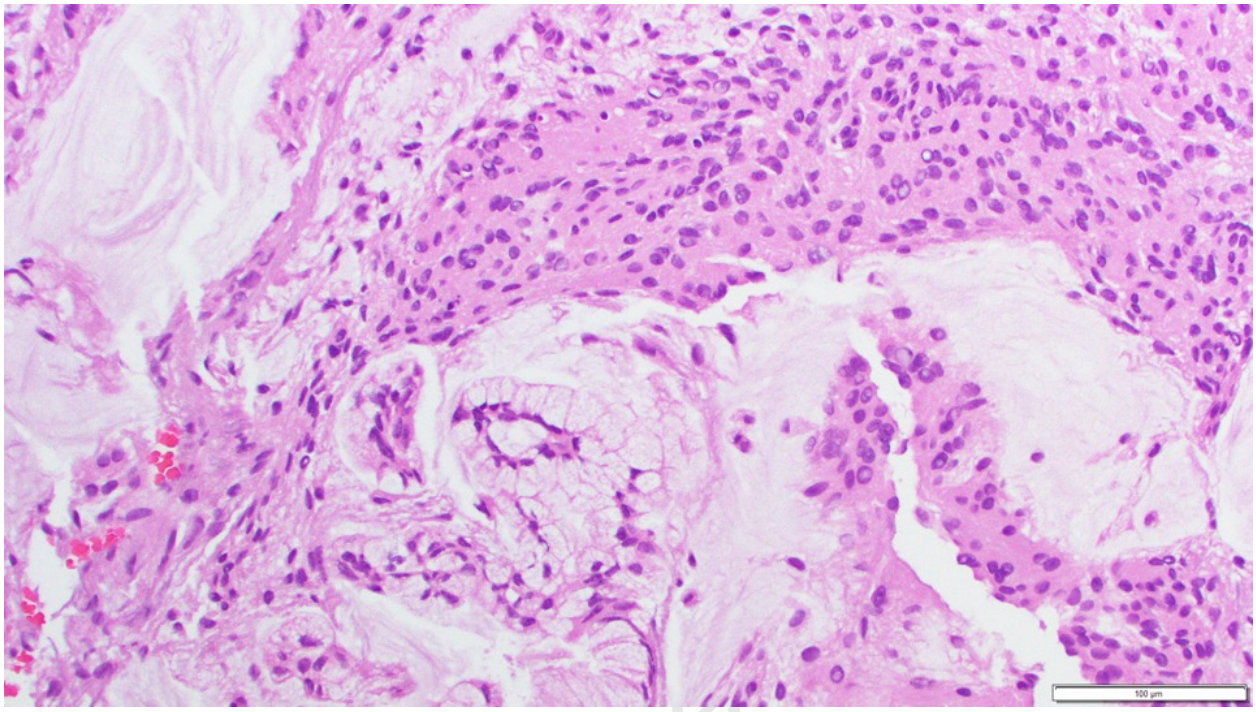


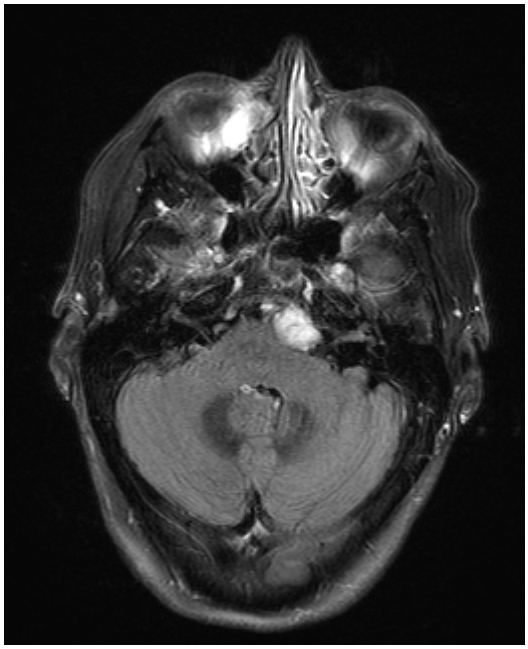


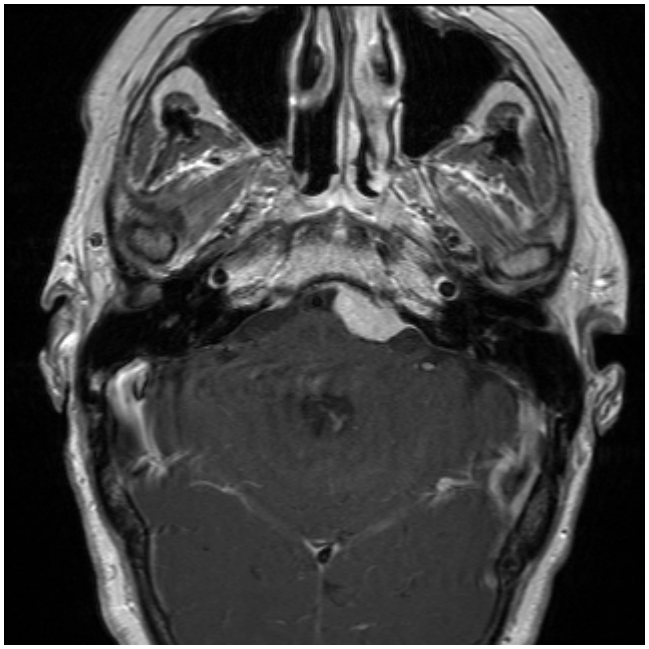


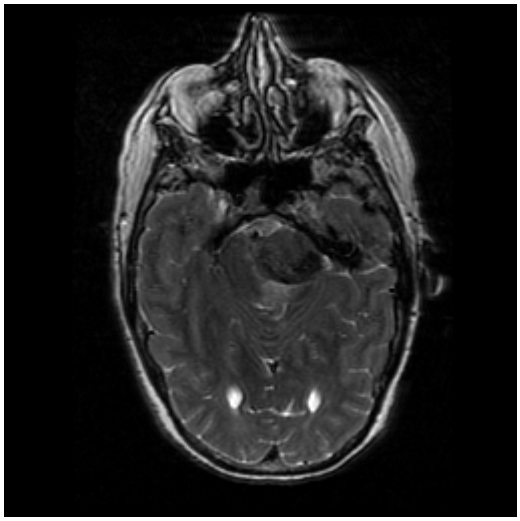


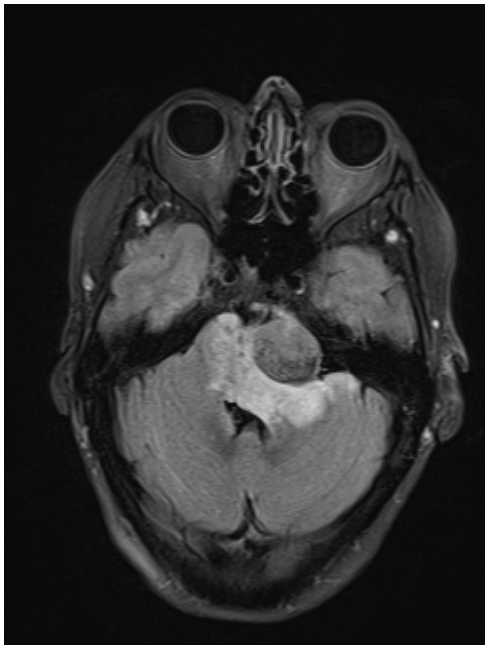


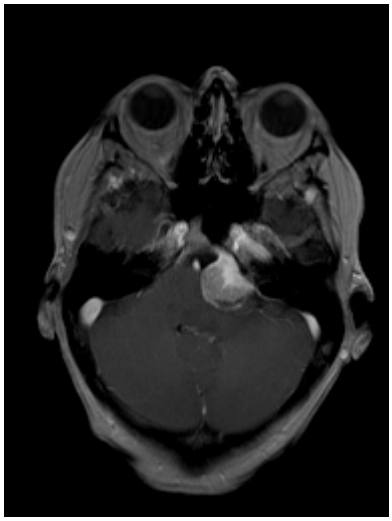


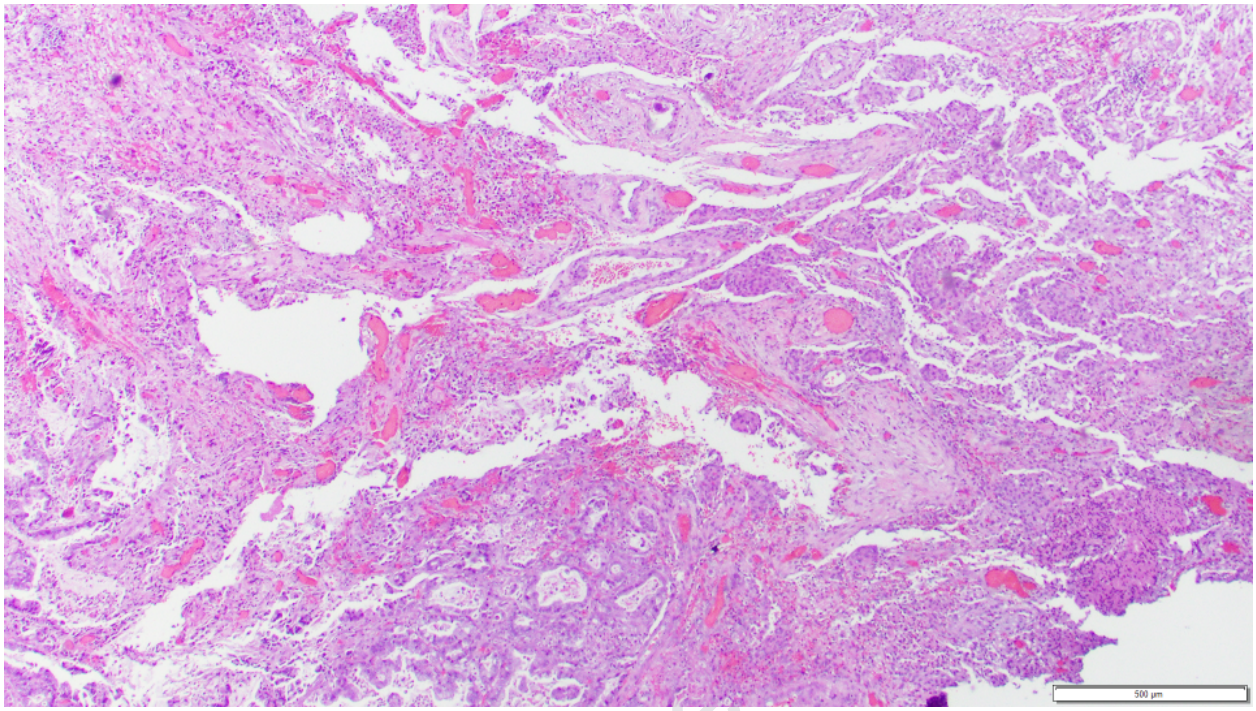


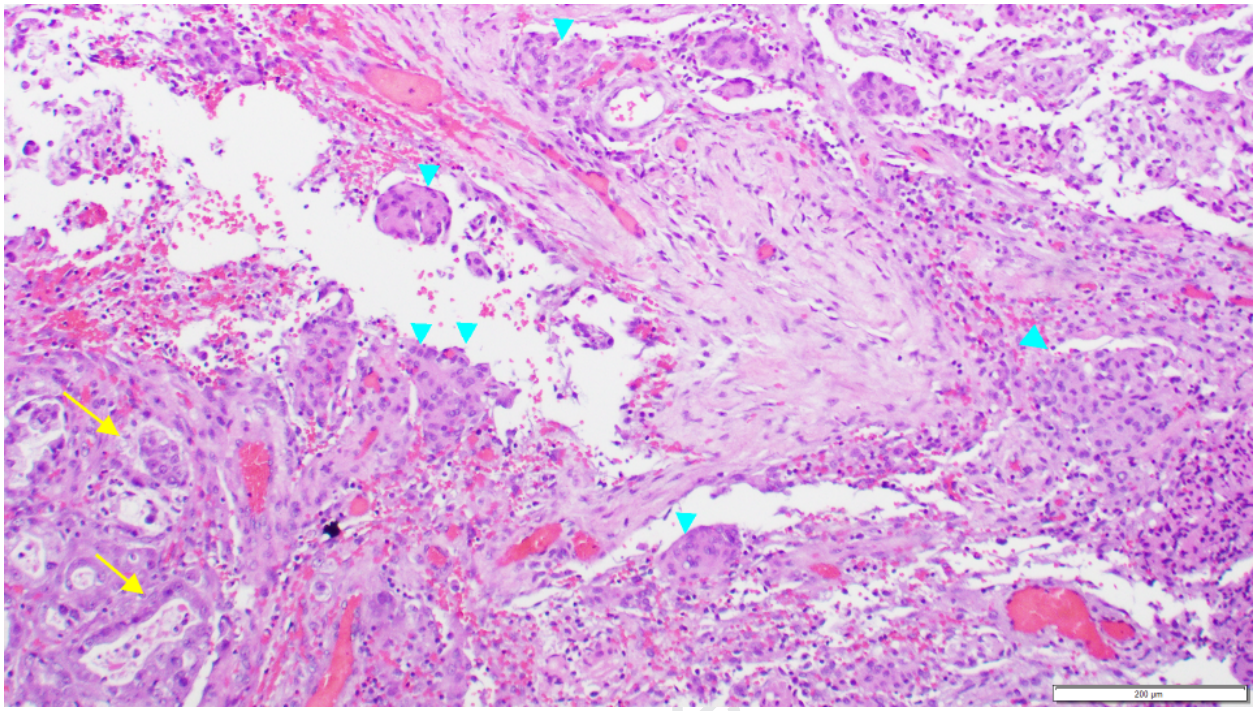


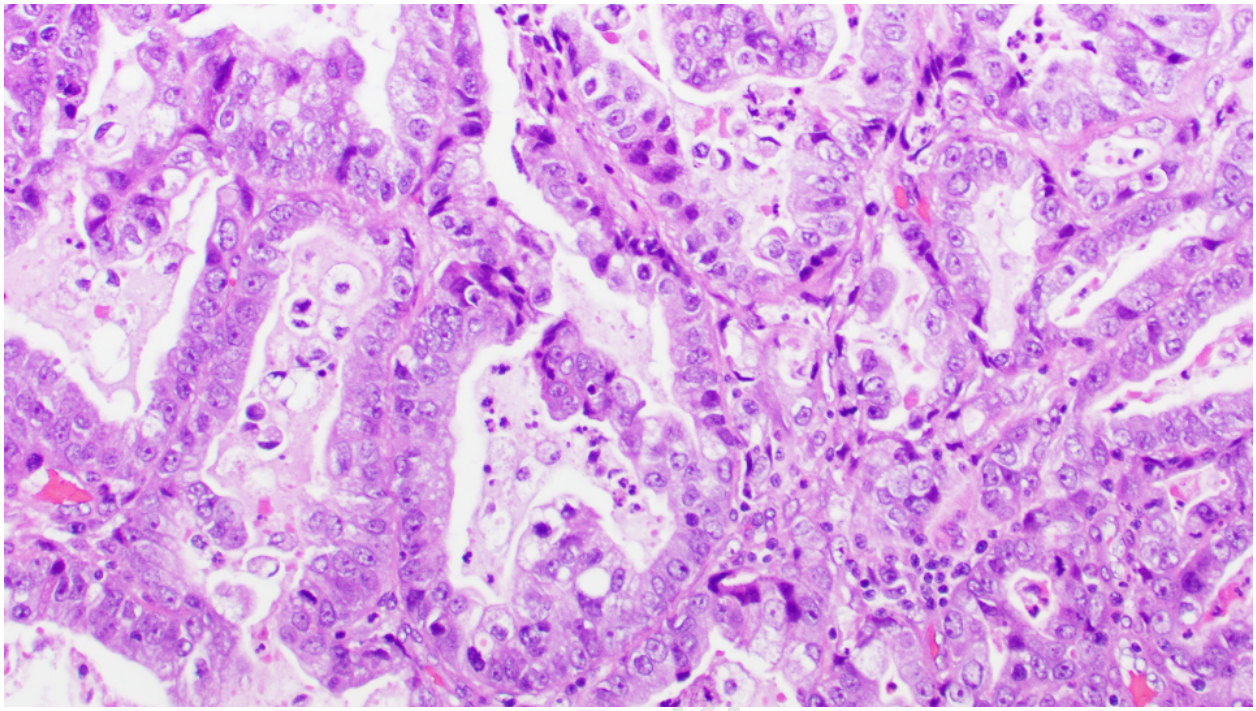


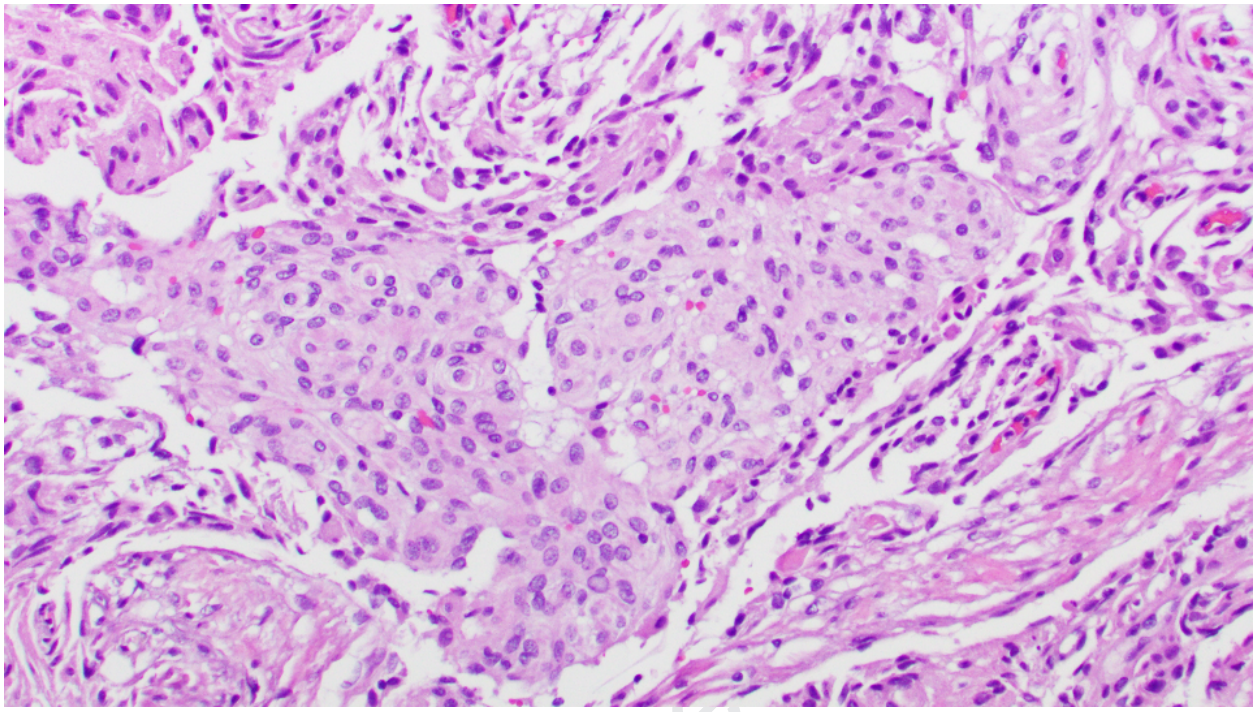


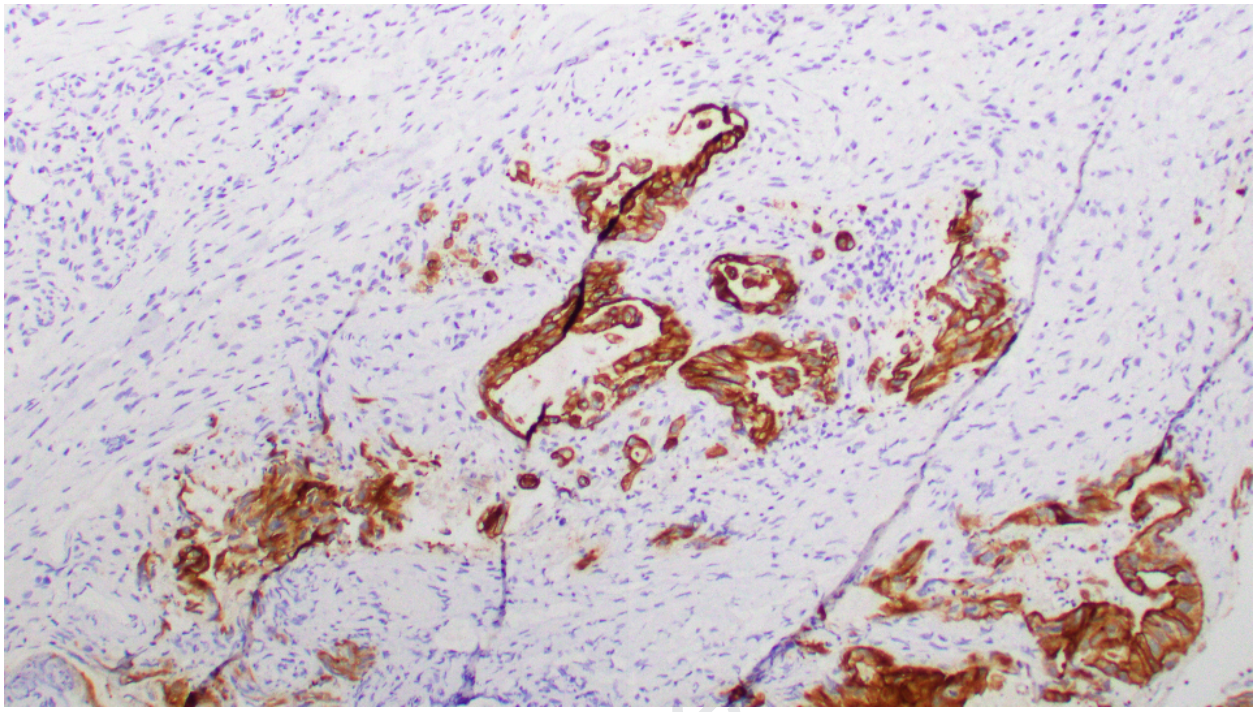


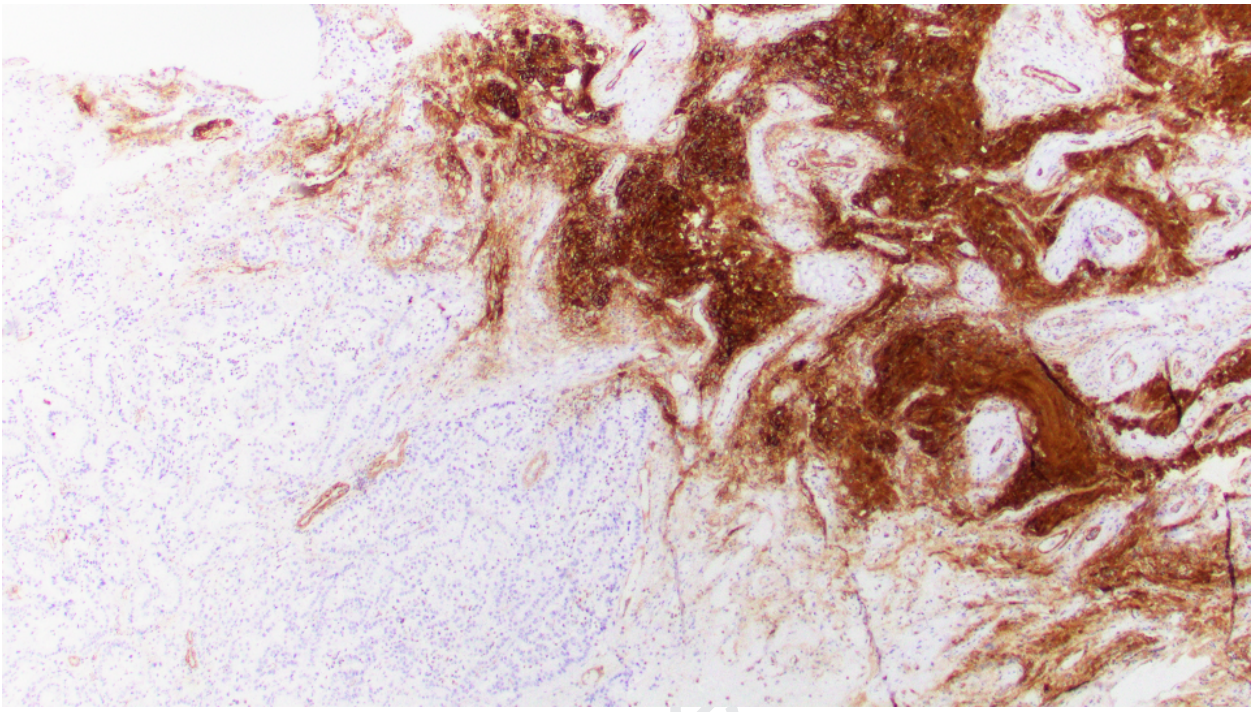












AICA: Anterior inferior cerebellar artery

cm: Centimeter

CPA: Cerebellopontine angle

CT: Computed tomography

F: Female

FLAIR: Fluid-attenuated inversion recovery

H&E: Hematoxylin and eosin

IHC: Immunohistochemical

M: Male

MRI: Magnetic resonance imaging

N/A: Not applicable

NCBI: National Center for Biotechnology Information

TTM: Tumor-to-tumor metastasis

WHO: World Health Organization

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: