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Case Report

# Simultaneous cerebrospinal fluid and hematologic metastases in a high-grade ependymoma

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## Abstract

**Background:** Ependymomas are relatively uncommon tumors that constitute about 7% of all primary intracranial neoplasms. Among these, high-grade ependymomas are locally aggressive and recur most commonly at the primary site following resection. Ependymomas are also known to be the one glial neoplasm that tends to frequently metastasize inside and outside the central nervous system (CNS) that complicates workup and management. Metastasis due to surgical manipulation is common and neurosurgeons should be well-versed in the most effective methods to remove these tumors in order to avoid such metastases.

**Case Description:** Here, we report a case of a 28-year-old female who initially presented with a parenchymal World Health Organization (WHO) grade III anaplastic ependymoma of the occipital lobe without metastasis. After multiple resections, the patient showed no evidence of disease recurrence for 2 years. During follow-up, new metastasis to the frontal lobe as well as to the lung were discovered 2 years after the initial surgery, without recurrence at the tumor's primary site.

**Conclusions:** While uncommon, this case demonstrates the possibility for ependymomas to metastasize via cerebrospinal fluid to other locations within the CNS and hematologically to extraneural locations without recurring locally.

**Key Words:** Cerebrospinal fluid metastasis, ependymoma, hematologic metastasis

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## INTRODUCTION

Ependymomas are primary glial cell tumors that arise from ependymal cells lining the ventricular system.[1] These neoplasms constitute 6.8% of all primary intracranial neoplasms; in adults, these tumors make up < 4% of primary central nervous system (CNS) tumors.[3,9,19] In adults, ependymomas are found most commonly in the spinal cord (46%), infratentorial (35%), and supratentorial (19%) locations within the posterior fossa.[26]

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The World Health Organization (WHO) grade classification system outlines three grades of this disease—with the most malignant subtype being grade III, anaplastic ependymoma.[10,15] These grade III neoplasms are locally aggressive and recur most commonly at the primary site following resection.[29,31]

At present, the primary therapeutic intervention for intracranial ependymomas is surgery.[9] However, due to a high rate of local recurrence, many patients require adjuvant radiotherapy, chemotherapy, or surgical re-resection.[14,24] Ependymomas, like other gliomas, have been shown to also metastasize to extracranial sites, albeit at a very low rate; however, the incidence is difficult to calculate since this is a rare event.[1]

The majority of ependymomas are not located in the parenchyma but located within the cerebrospinal fluid (CSF) pathways and have a relatively high rate of metastasis compared to other brain tumors. Workup for these neoplasms, therefore, includes imaging of the entire cranio-spinal axis and between 8 and 20% of high-grade ependymomas demonstrate CSF spread at presentation.[32] High-grade, infratentorial ependymomas occurring in children are most likely to be associated with CSF seeding.[20] Due to CSF dynamics, the spinal cord is the most likely location for tumor seeding, though a very few case reports have demonstrated spinal cord and/or infratentorial to supratentorial spread as well.[2]

Here, we report a case of a 28-year-old female who initially presented with a WHO grade III anaplastic ependymoma of the occipital lobe without any signs of metastasis. After multiple resections, which were required for the index site, the patient showed no evidence of disease recurrence in the CNS for 2 years. At the 2-year follow-up appointment, new metastasis to the frontal lobe and lung were discovered in the absence of any recurrence at the tumor's primary site.

The case presented is of particular interest for multiple reasons. First, it is highly uncommon for an ependymoma to metastasize in retrograde to the primary lesion. Second, concurrent brain and lung metastases suggest sequential CSF and hematologic spread, which, to our knowledge, has yet to be reported within the literature.

## CASE REPORT

A 28-year-old female presented to an outside hospital in 2007 with fainting spells that were suspicious for seizures by family's report. A magnetic resonance imaging (MRI) was obtained and revealed a right occipital tumor. The patient underwent a right occipital craniotomy and image-guided resection of the lesion. It was noted that there were three areas which were concerning for tumor invasion of the surrounding parenchyma due to its general discoloration. Frozen biopsies were sent for evaluation. The pathology report came back negative for marginal tumor infiltration. The patient was incorrectly told that the tumor was meningioma due to an incorrect preliminary read and that no further treatment was necessary; however, the final pathological diagnosis revealed a WHO grade III anaplastic ependymoma. Unfortunately, the revised diagnosis was not made known to the patient, nor her future physicians. She did not undergo chemotherapy or radiation at that time.

In 2012, the patient presented to our hospital with severe (8/10) headaches, nausea, and photophobia. Computed tomography (CT) and MRI of the brain did not show any acute pathology or evidence of tumor recurrence. The patient was given a diagnosis of migraine headaches and treated medically.

The patient re-presented in 2014 with relapse of her headaches and fainting spells. An MRI of the brain was obtained, revealing a recurrent 4.1 cm enhancing mass in the right occipital lobe with surrounding edema (without evidence of drop metastasis or other enhancing lesions on spinal MRI [Figure 1]). In light of the rather rapid interval growth of the lesion, despite no new onset focal deficits, and concern for malignant transformation to a WHO grade IV glioma, the neurosurgical team recommended re-resection of the tumor. The patient underwent subsequently re-do craniotomy, and did well clinically postoperatively as she remained neurologically intact and showed improvement in her headaches. The postoperative MRI demonstrated a gross total resection and she subsequently underwent adjuvant radiotherapy.

Two years after her second resection, the patient presented to her primary care physician with a cough lasting for several weeks. A chest X-ray was performed, which revealed multiple, bilateral pulmonary nodules. The

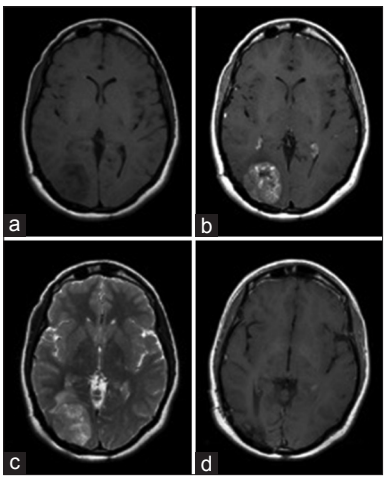


**Figure 1: Preoperative axial MR images showing an enhancing mass in the occipital lobe with isointensity on T1-weighted images (a), hyper intensity on a gadolinium enhanced T1-weighted image (b), and hyper intensity on T2-weighted image (c). Postoperative axial gadolinium enhanced T1-weighted image demonstrating complete resection of the mass with no regions of hyper intensity (d)**

largest lesion was seen in the left lower lobe, measuring 4.5 × 3.4 × 3.9 cm [Figure 2]. The second largest lesion was in the left upper lobe, in close proximity to the major fissure. Additional pleural-based masses were seen. A CT-guided biopsy of the mass was performed, confirming the diagnosis of grade III anaplastic ependymoma.

An MRI of the brain was obtained at the same time, which revealed the interval development of several new right-sided intracranial frontal extraaxial masses side, but without any evidence of tumor recurrence in the right occipital lobe tumor resection bed [Figure 3a–d]. The largest mass measured at 4.7 × 4.4 × 3.0 cm and was located along the right temporal–frontal convexity. Imaging displayed heterogeneous hyper-intense T2- and hypo-intense T1-signal characteristics and some foci of restricted diffusion. There was diffuse heterogeneous enhancement on postcontrast imaging. The lesion exerted significant mass effect upon the adjacent right temporal lobe gyri, uncus, and cerebral peduncle and a second mass (measuring 2.1 × 2.1 × 1.7 cm) and was located along the right posterior frontal convexity, also causing mass effect. Two additional masses were detected immediately anterior to the second largest mass along the right posterior frontal lobe, measuring 1.3 cm each in the greatest dimension. There was no evidence of recurrent disease at the initial occipital site of presentation, nor evidence of drop metastasis or other enhancing lesions on spinal MRI [Figure 3e, f].

The patient once again underwent respective surgery and all cranial tumors were removed successfully as seen on postoperative imaging [Figure 4].

The patient is currently under close follow-up, with adjuvant radiotherapy and chemotherapy for her lung metastases without evidence of intracranial recurrence 12 months following her most recent resection seen on imaging.

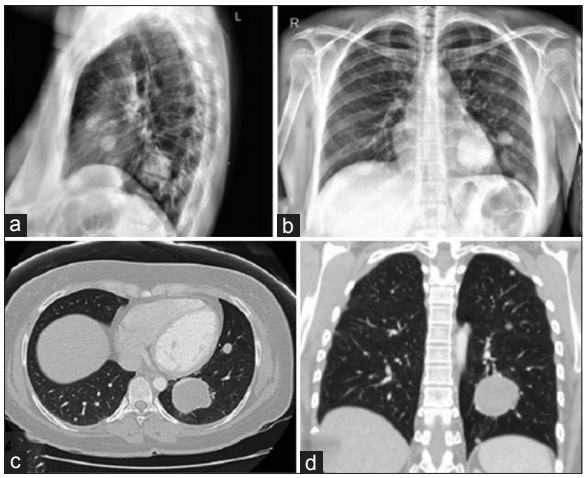


**Figure 2: Imaging of multiple pulmonary nodules in the left lower and upper lobe seen on lateral (a) and anterior posterior (b), X-ray views, as well as on sagittal (c) and axial (d) CT imaging**

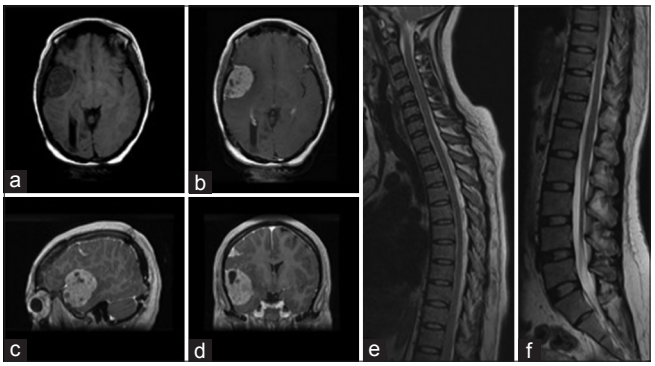


**Figure 3: Two year post operative MR axial images demonstrating T1 weighted a non enhancing fronto-temporal mass (a), with hyperintensity following gadolinium enhancement on T1-weighted axial (b), sagittal (c) and coronal views (d). Images demonstrating the absence of drop metastases or other enhancing lesions T1-weighted gadolinium enhanced images of thoracic (e), and lumbar (f) spinal cord**

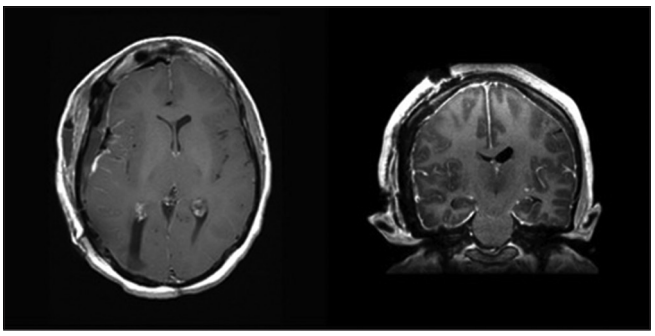

**Figure 4: Post-operative MR images showing complete resection of the tumor and the absence of hyper intense lesions near the site of tumor excision on axial gadolinium enhanced T1-weighted axial (Left), and coronal images (Right)**

## DISCUSSION

Ependymomas are primary tumors of the CNS that primarily affect children and young adults.[11,28] Traditionally, ependymomas were thought to originate from the lining of the ventricles, and believed to be of glial cell origin.[4] Management of ependymomas is largely limited to surgical resection and radiation therapy, with chemotherapy playing a minimal role.[13,18,23,25] Because of their locally invasive nature and their tendency to recur as well as the fact that the prognosis is correlated to the extent of tumor resection, aggressive gross total resection is the preferred treatment. Following appropriate treatment, adult 5-year overall survival ranges between 60 and 90%.[17,30] However, patients with aggressive recurrence and/or metastasis have worse prognoses. Unfortunately, the rarity of these conditions makes it difficult to establish an accurate survival rates.[2]

The scenario of intracranial tumors showing metastasis to an extraneural location has been intensely studied, but the mechanism of this spread of disease is not yet fully understood.[2,16,27] A clear prerequisite seems to be tumor access to extracranial soft tissue, blood, or CSF. Several hypotheses of the underlying mechanisms have

been brought up and include: direct tumor invasion of the dural sinuses, tumor access to local lymphatic vessels, spread to adjacent extracranial tissue, and, most commonly, CSF seeding via the ventricular system leading to drop or spinal metastases.[22]

Extracranial ependymoma metastases are exceedingly rare, and are most often found at the time of primary tumor recurrence.[4,5,12] Ependymomas, like all primary brain tumors, have low potential for spread outside the CNS due to the blood–brain barrier, matrix proteins, and microglia.[1] However, metastases of anaplastic ependymomas have been observed in the lungs, liver, and cervical lymph nodes, suggesting the possibility of both hematologic and lymphatic spread.[8,21]

Direct surgical manipulation of the tumor and CSF-shunt placement are potent avenues for intra- and extraneural metastasis formation in these cases. The physical disruption of the blood–brain barrier during surgery, combined with the dislodging of malignant cells

into local structures, following direct tumor manipulation, is likely to play a role in the formation of about 8.5% of extracranial metastases.[1,7,21] Studies of venous blood samples during and after surgery have also demonstrated a significant presence of brain tumor cells which gained access to the systemic circulation.[7] Additionally, direct seeding to the extraneural space may occur in setting to any placement of ventricular shunts and is associated with about 27.3% of extraneural metastases observed in cases of other primary CNS tumors.[4]

High-grade ependymomas are locally aggressive and recur most commonly at the primary site following resection. They are also known to be the glial tumor most prone to metastasis. Malignant cells have been identified within the CSF, drawn in the typical fashion of three vials of 2 cc. On average, 16% of patients with known ependymomas.[17] We speculate that it is through CSF dissemination that our patient's occipital lobe tumor reoccurred in the frontal/temporal region without recurrence at the primary site. Furthermore, this leptomeningeal spread occurred most likely after tumor cells were introduced into the subarachnoid space at the time of surgery.

Pulmonary metastases, on the contrary, are likely the result of hematogenous spread via tumor cells that gained access to the circulation during surgery. Such CSF seeding to extracranial sites is possible via mechanical disruption of the blood–brain barrier at the time of surgery allowing tumor cell to reach the venous system, which then permits hematogenous spread to the lung. Similarly, it is possible that the intracranial tumor could have spontaneously invaded either vascular or lymphatic structures, leading to seeding of tumor cells to the lungs.

While uncommon, and not extensively written about in the literature, this case demonstrates the possibility for ependymomas to simultaneously metastasize both through CSF to other CNS locations and hematologically to extraneural locations. Such pathways should be considered when routinely monitoring patients for tumor growth or recurrence.

## CONCLUSION

Ependymomas rarely metastasize without local recurrence. To the best of our knowledge, our case is the first report on anaplastic ependymoma with concurrent CSF and hematologic metastasis, occurring without recurrence at the primary site. This unusual pattern of neoplasm recurrence prompts a discussion of the pathogenesis of extraneural metastasis and highlights a possible risk of surgical intervention.

### Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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