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Case Report

# Preoperative and intraoperative perfusion magnetic resonance imaging in a RELA fusion-positive anaplastic ependymoma: A case report

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## Abstract

**Background:** Ependymomas are rare neuroepithelial tumors thought to arise from radial glial precursor cells lining the walls of the ventricles and central canal of the brain and spinal cord, respectively. Histopathological classification, according to World Health Organization criteria, has only recently defined the RELA-fusion positive ependymoma. These tumors may account for 70% of supratentorial ependymomas in children and represent an aggressive entity distinct from other ependymomas.

**Case Description:** Here we present the case of a patient with RELA-fusion positive ependymoma of the frontal lobe in whom we used preoperative and intraoperative magnetic resonance (MR) perfusion imaging. In this first demonstrated intraoperative evaluation of MR perfusion in ependymoma, increased peripheral perfusion of the lesion in a ring-like manner with a discrete cutoff around the surgical margin correlated with intraoperative findings of a clear border between the tumor and brain, as well as pathological findings of increased MIB index and hypercellularity—specifically within solid tumor components. An abnormal perfusion pattern also suggested an aggressive lesion, which was later confirmed on pathological analysis. In addition, intraoperative MR perfusion improved detection of tumor tissue in combination with traditional T1-weighted contrast-enhanced methods, which increased extent of resection.

**Conclusions:** MR perfusion imaging may be a useful method for delineating tumor aggressiveness and borders, which can be prognostic.

**Key Words:** Brain tumor, ependymoma, imaging, neurosurgery, perfusion magnetic resonance imaging, RELA fusion-positive

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## INTRODUCTION

Ependymoma is the third most common primary brain tumor in children.[6,10] It accounts for approximately 2–3% of primary tumors of the central nervous system and 25% of tumors originating in the spinal cord in both pediatric and adult populations.[14] These tumors are hypothesized to derive from radial glial precursor cells within the walls of the ventricles and central canal and can, therefore, arise along the length of the neuraxis.[20] Intracranial ependymoma is characterized by its aggressive clinical behavior portending a poor prognosis, whereas spinal ependymoma is often associated with an indolent clinical course and a low risk of recurrence after conventional therapy.[21]

The 2016 World Health Organization (WHO) classification formally introduced RELA-positive ependymomas, which result from chromothripsis of chromosome 11 resulting in a C11orf95–RELA fusion protein.[10,15] C11orf95–RELA fusion, which results in constitutive pathological activation of the nuclear factor-κB (NF-κB) signaling cascade, has been associated with 70% of aggressive supratentorial ependymomas in children.[2,10,16,18] Targeting of RELA-positive fusion proteins in these ependymomas and relevant downstream signaling pathways has been suggested as a strategy in treating these cases.[11,16] Histologically, the RELA-positive ependymomas possess clear cell morphology and prominent vascularity, but definitive pathological features are absent.[5,10] Genomic classification has supported the distinction of RELA-positive ependymomas from other tumor types along with a worse clinical course.[4,9,15]

Imaging of RELA-positive ependymomas often demonstrates a large mass that appears heterogeneous, with both solid and cystic components, but definitive diagnosis with conventional imaging alone remains challenging.[13,22] Magnetic resonance (MR) perfusion imaging may be helpful in the diagnosis of high-grade tumors and tumors with aggressive features. MR perfusion involves dynamic susceptibility contrast (DSC) and dynamic contrast-enhanced techniques that allow for quantification of several tumor parameters, including cerebral blood volume (CBV), cerebral blood flow (CBF), and other contrast-diffusion parameters.[17] Various studies have suggested the potential use of MR perfusion imaging in the diagnosis of high-grade gliomas,[8] differentiation of gliomas from lymphomas,[12] and prediction of tumor aggression and treatment response.[1] To date, the role of perfusion intraoperative magnetic resonance imaging (iMRI) in the surgical treatment of RELA-fusion positive ependymomas has not been thoroughly explored. We report on the clinical presentation, radiological evaluation, and pathological findings in a patient with RELA-fusion positive anaplastic ependymoma along with the utility of MR perfusion during the treatment.

## CASE REPORT

### History and examination

A previously healthy 19-year-old man presented with a 6-week history of word-finding difficulty and a 3-week history of headaches, nausea, and vomiting, but he was otherwise neurologically intact. Diagnostic T1-weighted imaging with contrast revealed a heterogeneously enhancing lesion in the left frontal lobe with significant mass effect and surrounding vasogenic edema, initially concerning for an astrocytoma or oligodendroglioma [Figure 1]. Given the concerns for possible language center and supplemental motor strip involvement, a functional MRI (fMRI) that included diffusion tensor tractography was performed. An awake craniotomy was not performed, as sufficient distance between the language activation center and the tumor edge was noted on preoperative fMRI. Informed consent was obtained for participation in an Institutional Review Board-approved protocol investigating the use of preoperative as well as perfusion iMRI in diagnosis and treatment.

MR perfusion was performed in addition to standard preoperative and intraoperative imaging sequences, including T1-, T2-, and diffusion-weighted imaging (DWI), fluid-attenuated inverse resonance imaging (FLAIR), gradient and spin echo imaging (GSE), and contrast-enhanced imaging as described earlier.[7] Images were acquired on a Siemens TIM Trio 3T (Siemens, Washington DC) or IMRIS 3T (IMRIS, Minnetonka, MN) scanner. MR perfusion images (TR 3.07, TE 1.01, 2-mm slices, 256-mm field of view, 75% field of view phase) were analyzed using Olea Sphere (Olea Medical Solution, http://www.olea-medical.com). An abnormal ring-enhancing pattern on MR perfusion was identified along with high peripheral CBV and CBF values, suggestive of a high-grade lesion.

### Operative and postoperative course

The patient underwent a stereotactic left frontal craniotomy and tumor resection with neuromonitoring and iMRI. Conventional intraoperative studies (T1 with and without contrast, T2, FLAIR, DWI/ADC, stereotactic T1) demonstrated gross total resection [Figure 2]; however, a 1-cm$^2$ hyperperfused area of tissue in the posterior aspect of the resection margin was identified. Although the findings on conventional iMRI were suggestive of residual tumor, perfusion iMRI solidified our concern for residual tumor. Several areas that demonstrated increased perfusion (CBV, CBF) of the ring-enhanced lateral, posterior, and deep margins of the resection cavity on preoperative MR perfusion imaging were biopsied intraoperatively. Initial intraoperative pathological analysis and all post-iMRI resections were determined to be a high-grade tumor. Postoperative recovery was uneventful, with a return to baseline mild

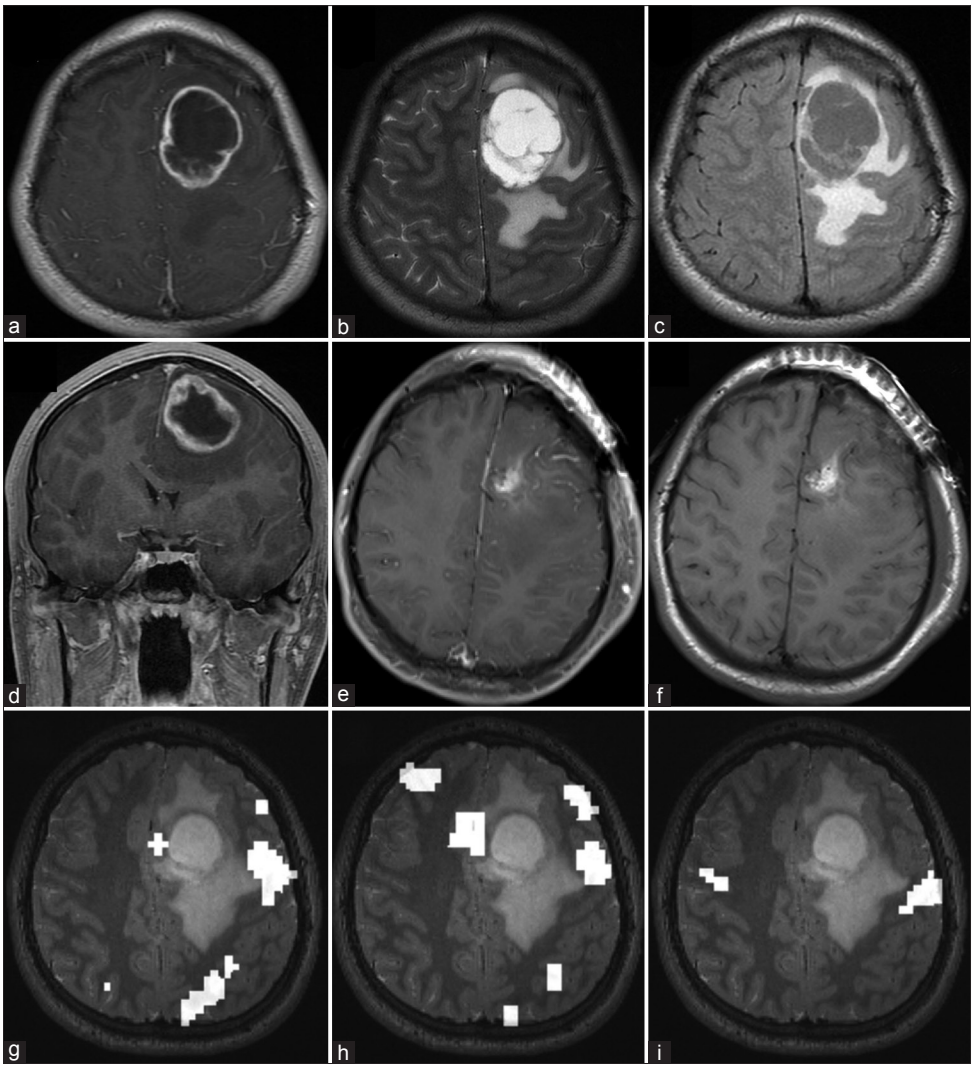


**Figure 1: Preoperative and postoperative MRI of RELA-fusion positive ependymoma. Preoperative axial (a) T1-weighted gadolinium-enhanced, (b) T2-weighted, (c) FLAIR, and (d) coronal T1-weighted contrast-enhanced imaging demonstrate a ring-enhancing lesion with cystic central component and perilesional edema in the left frontal cortex. Postoperative (e) T1-weighted contrast-enhanced and (f) T1-weighted nonenhanced imaging show a gross total resection. Functional MRI data for (g) reading, (h) word recognition, and (i) lip movement are shown. Compared with the tumor, language cortex localizes posterolateral while motor cortex is further posterior**

word-finding difficulty, and the patient was discharged home.

## Pathological analysis

The final pathological results of the original tumor and biopsy of lateral, posterior, and deep resection cavity margins were consistent with RELA-fusion positive anaplastic ependymoma [Figure 3]. Areas that had biopsies taken after iMRI were also positive for tumor. Two distinct areas of tumor were identified—solid and papillary components. The solid component more closely correlated with hyperperfusion biopsy sites on perfusion iMRI. Immunohistochemistry revealed the tumor to be positive for glial fibrillary acidic protein (GFAP), epithelial membrane antigen, and synaptophysin; the tumor was negative for pancytokeratins AE1/AE3 and isocitrate dehydrogenase I (IDH-1). The MIB index was as high as 60% within solid portions of the tumor. There was no BRAF-V600E mutation detected by a polymerase chain reaction (PCR) sequencing assay. Given the high-risk features noted on histopathologic examination (i.e., high MIB-I and tumor predominantly composed of sheets of poorly differentiated cells), the patient was referred for adjuvant chemoradiation therapy. A RELA-fusion was detected on subsequent PCR analysis.

# DISCUSSION

The 2016 WHO classification of ependymomas not only focuses primarily on histopathology but also incorporates a new genetically defined subtype—RELA-fusion positive ependymoma.[10,20] However, to date, a widely accepted, reproducible, and comprehensive prognostic classification of ependymomas has yet to be established. Imaging

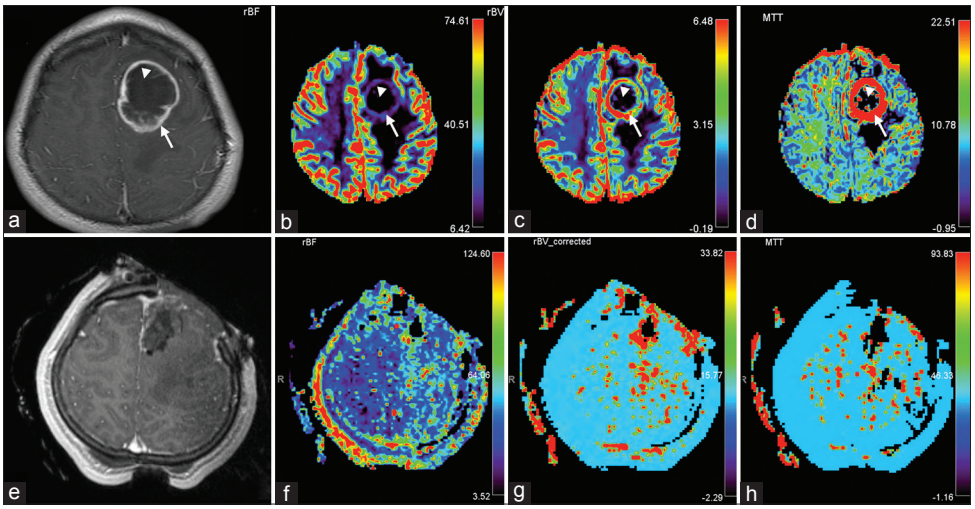


**Figure 2: Preoperative and intraoperative MR perfusion of RELA-fusion positive ependymoma. Preoperative (a) T1-weighted with contrast, (b) CBF, (c) CBV, and (d) mean transit time (MTT) imaging demonstrates increased diffusion in the ring-enhancing portion of the tumor, suggestive of an aggressive lesion (*arrow*). This perilesional area (*arrow*) correlated with the solid tumor component seen on pathological analysis [Figure 3a–c]. A central hypoperfusive tumor mass (*arrowhead* in a–d) correlated with the more papillary component of the tumor [Figure 3d–f]. Intraoperative (e) T1-weighted contrast-enhanced imaging suggested a gross total resection. However, intraoperative (f) CBF, (g) CBV, and (h) MTT demonstrated posterior perilesional hyperperfusion that was suggestive of residual tumor, a conclusion that was later confirmed**

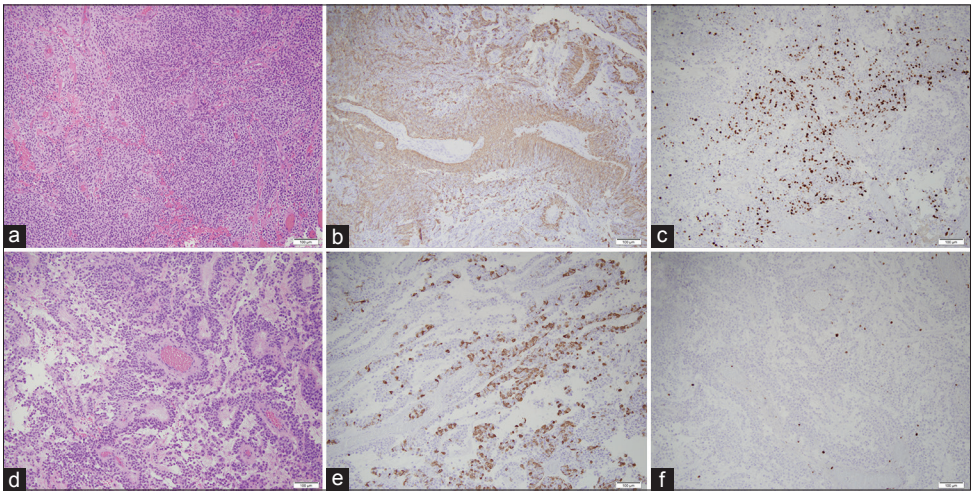


**Figure 3: Pathological analysis of RELA-fusion positive ependymoma. (a, d) The hematoxylin and eosin-stained tissue showed two morphologic patterns to the tumor. Some areas of the tumor consist of solid sheets of tumor cells (a–c), whereas other areas of the tumor have papillary architecture (d and f). The tumor nuclei are round and regular with evenly distributed chromatin. Areas with increased cellularity, predominately in the solid areas of the tumor, show up to six mitotic figures in ten high-power fields. Small foci of tumor necrosis (not pictured) are also identified. A prominent vascular network is present in the tumor with fibrotic vessels. The tumor cells cuff the vessels, although there is a lack of an acellular zone containing fibrillary projections. (b and e) The immunohistochemical stain for GFAP shows patchy positivity in the tumor cells, with the tumor cells surrounding the vessels being notably positive. (c and f) The MIB-1/Ki-67 stain is positive in approximately 60% of the tumor nuclei in the solid areas of the tumor (c), and occasional nuclei are positive in the papillary areas (f). The MIB-1/Ki-67 index overall is greater than 10% in the tumor. The immunohistochemical stain for IDH-1 is negative (not pictured). All photomicrographs taken at 100× total magnification**

determination of high-risk ependymomas using conventional imaging also remains limited, thus warranting additional study. We demonstrate that MR perfusion can be suggestive of higher-grade lesions, even before definitive pathological analysis is complete; can help identify tumor borders; and can support the identification of residual tumor after iMRI.

Ependymomas are often heterogeneous masses with cystic components, necrotic change, calcification, and hemorrhage. In particular, supratentorial intraparenchymal ependymomas can be highly variable in appearance and can be difficult to distinguish from other glial neoplasms with conventional imaging modalities such as computed tomography (CT) and MRI.[13,22] Therefore, advanced imaging techniques have proven to be helpful in the work-up and treatment of these tumors. MR perfusion was sought as one specific method to evaluate tumor

delineation and correlate imaging with pathological features.

### Imaging

Most intracranial ependymomas (60%) are located in the infratentorial posterior fossa and classically arise from the floor of the fourth ventricle and may exude through the foramina of Luschka and Magendie.[13,22] Infratentorial ependymomas are typically well-demarcated on both CT and MRI. In contrast, supratentorial ependymomas are often intraparenchymal and can appear as aggressive, large, highly variable, enhancing masses with solid and/or cystic components.[19] Both infra- and supratentorial ependymomas typically demonstrate low T1, high T2, and intermediate or high FLAIR signal intensity relative to brain parenchyma.[13,22]

MR perfusion has been shown to be helpful in the identification of more aggressive lesions. Delgado *et al*.[3] conducted a meta-analysis of 727 patients with grade II and III gliomas to investigate the diagnostic potential of MR perfusion imaging with DSC and to identify optimal cutoff values for rCBVmax to differentiate between WHO grades II and III gliomas. The authors concluded that WHO grade III gliomas had a higher relative maximal CBV compared with WHO grade II gliomas; they identified a mean rCBVmax of 1.76 and an optimal cutoff of 2.02 for the diagnosis of high-grade tumors. A heterogeneous pattern is observed among glial lesions, with increased perfusion in higher-grade lesions. In our study, semiquantitative analysis of MR perfusion showed discrete, hyperperfusion around the borders of the tumor. Moreover, these areas correlated with the solid, more aggressive tumor components on pathological analysis. Hyperperfusion on iMRI also helped delineate residual tumor after resection, which was positive on further pathological analysis. Two distinct patterns, one with hyperperfusion and one with similar perfusion to cortical tissue, were observed in our case. It may be concluded that this heterogeneity of MR perfusion pattern can distinguish more aggressive lesions, correlating with alterations in tumor vascularity. In addition, MR perfusion improved detection of intraoperative tumor, which could add another imaging sequence for identification of tumor margins.

### Limitations

Because this represents only a single case report with no other cases available for comparison, it is possible that the MR perfusion signal was artifactual. Further study of preoperative and intraoperative MR perfusion as a modality to understand glial tumor heterogeneity is currently underway at our institution.

## CONCLUSION

RELA-positive ependymoma is a newly defined clinical entity. Preoperative and perfusion iMRI could be used to better understand the progression of this tumor. Within the ring-enhancing rim of the tumor, increased tumor perfusion and vascularity was observed. In addition, this perfusion area correlated with the more aggressive, solid tumor components and a corresponding higher MIB index than other tumor parts. Perfusion iMRI also aided the resection of additional tumor. Additional studies with perfusion iMRI may aid in the identification of characteristic imaging findings that may be of diagnostic and prognostic significance in the preoperative setting.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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