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Case Report

Supratentorial ependymoma, zinc finger translocation-associated fusion positive, with extensive synaptophysin immunoreactivity arising from malignant transformation of clear cell ependymoma: A case report

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ABSTRACT

Background: We describe a case of a supratentorial ependymoma, zinc finger translocation-associated (*ZFTA*) fusion positive with extensive synaptophysin immunoreactivity arising from malignant transformation of an ependymoma with clear cell features in a patient with long-term follow-up.

Case Description: A 55-year-old woman presented with seizures and ataxia 15 years after an initial resection of a clear cell ependymoma, Grade 2. Imaging demonstrated an enhancing right paracentral mass and the patient underwent biopsy and resection. Microscopic analysis showed regions of the tumor with morphological and immunohistochemical features typical of ependymoma, including perivascular pseudorosettes and focal dot-like epithelial membrane antigen positivity, as well as high-grade features. In addition, the neoplasm contained large nodular regions of clear cells exhibiting extensive synaptophysin immunoreactivity, suggestive of neural differentiation, and only focally positive immunoreactivity for glial markers. Electron microscopy showed poorly formed and ill-defined junctional complexes, but no cilia, microvilli, or dense granules were seen. Molecular profiling revealed the presence of a fusion between *ZFTA* (previously known as *C11orf95)* and *RELA* fusion.

Conclusion: We report a case of extensive synaptophysin immunoreactivity in a *ZFTA-RELA* fusion-positive ependymoma that had undergone malignant transformation from a clear cell ependymoma and has long-term follow-up, contributing to the assessment of prognostic significance of synaptophysin immunoreactivity in supratentorial ependymoma, ZFTA fusion positive.

Keywords: Anaplastic ependymoma, *C11orf95*, Clear cell ependymoma, Neuronal differentiation, *RELA* fusion, Zinc finger translocation associated

INTRODUCTION

Ependymomas are primary tumors of the central nervous system (CNS) that may occur at any site along the neuraxis. Microscopically, ependymomas are classically characterized by

perivascular pseudorosettes, ependymal rosettes, glial fibrillary acidic protein (GFAP) reactivity, areas of fibrillary, and paranuclear dot and ring positivity for epithelial membrane antigen (EMA) immunohistochemical stain. Clear cell, papillary, and tanycytic ependymomas were once codified as distinct variants in previous editions of the World Health Organization (WHO) classification system,[21] but, in the fifth edition, are now recognized as histomorphologic patterns.[11] Neural differentiation has been described in small series of ependymomas[12] and *RELA* fusion-positive ependymomas,[13] though this finding is usually focal or patchy. Malignant transformation of ependymoma is rare; rarer still is malignant transformation of a clear cell ependymoma, which can be found in historical data published before the current classification system.[9]

The fifth edition of the WHO classification of CNS tumors divides ependymomas into prognostically relevant groups based on a combination of anatomic location (i.e., supratentorial, posterior fossa, and spinal compartments) and molecular features.[11,21] Within any of the three anatomic sites, a diagnosis of "ependymoma" Grade 2 or Grade 3 can be made based on histopathologic features; the term "anaplastic ependymoma" is no longer listed. Within the supratentorial compartment, ependymomas are classified according to the presence of fusions involving the zinc finger translocation-associated (*ZFTA*) gene or the Yes-associated protein 1 gene.

Supratentorial ependymoma, *ZFTA* fusion positive was originally codified in the revised fourth edition of the WHO classification system as ependymoma, *RELA* fusion positive. The discovery that *ZFTA*, previously known as *C11orf95*, may pair with fusion partners other than *RELA* to produce the same histomolecular neoplasm[20] spurred the fifth edition of the WHO classification of CNS tumors to change the name to the more representative designation of supratentorial ependymoma, *ZFTA* fusion positive.[11]

Intrachromosomal fusion between the *RELA* and *ZFTA* (previously known as *C11orf95*) forms an oncogenic driver of supratentorial ependymomas that are thought to be present in up to 70% of pediatric supratentorial ependymomas.[16] While its full pathogenesis has yet to be elucidated, Zhu *et al*. have shown that the fusion protein translocates spontaneously to the nucleus to activate NF-κB target genes, which rapidly drives ependymomagenesis in mice through enhanced chromatin interaction.[22] Pathological activation of NF-κB,[12,22] a known hallmark of many cancers, leads to induction of various target genes, such as pro-proliferative and antiapoptotic genes, promoting tumorigenesis.[6] Recent studies have suggested that the fusion protein additionally drives several other key biological processes such as cytokine production and vesicular transport, while also disrupting cell to cell adhesion.[14] The *ZFTA* fusion-positive ependymomas have the worst prognosis among the supratentorial ependymomas.[14,16] Long-term follow-up reports of patients with supratentorial ependymoma, *ZFTA* fusion positive exhibiting extensive neural differentiation are scarce.

CASE REPORT

A 55-year-old woman with a history of a right frontoparietal clear cell ependymoma treated with surgery, adjuvant radiation therapy, and infusional chemotherapy 12 years before presented with symptomatic recurrence of a right frontoparietal mass. The specimen obtained from the initial resection [Figure 1] was formalin fixed, paraffin embedded, and stained with hematoxylin and eosin, as well as the following immunohistochemical stains: GFAP, EMA, progesterone receptor (PR), and phosphohistone H3 (PHH3). Microscopic features demonstrated GFAP, EMA, and PR-positive tumor cells with round nuclei and perinuclear clearing; the tumor had focal perivascular pseudorosettes, a low mitotic rate on PHH3, and no high-grade features. A diagnosis of clear cell ependymoma was rendered at that time and no further molecular testing was performed. Retrospective review showed ependymoma, CNS WHO Grade 2, and NOS, with predominant clear cell morphology. Initial treatment consisted of involved field radiation to 5940 cGy over 33 fractions and systemic chemotherapy.

Twelve years later, the patient developed breakthrough seizures and progressive left-sided weakness. Follow-up magnetic resonance imaging (MRI) of the brain identified an enhancing lobulated cortical lesion within her right frontoparietal lobes, in the same location as her original mass that was compressing the primary motor and sensory cortices and extending into the dura [Figure 2a]. A right frontoparietal craniotomy for the resection of likely recurrent tumor with neuronavigation, somatosensory evoked potentials (SSEPs), motor mapping, and intraoperative microscope was performed. The lesion was yellow and well-circumscribed intraoperatively and, following excision, a small rim of residual tumor adherent to the functional cortex remained [Figure 2b]. Pathology demonstrated ependymoma with cytomorphologic characteristics similar to her original mass, including clear cells lacking high-grade features [Figure 3]. She then completed six cycles of palliative chemotherapy with cisplatin (80 mg/sqm) and etoposide (100 mg/sqm days 1–3) every 3 weeks. Radiation therapy was planned, but the patient did not follow-up with radiation oncology, in part because of limited transportation means and the distance between her home and our center.

Fifteen years after her original presentation and 3 years after the treatment of her first recurrence, she presented with ataxia and left-sided hemiparesis severe enough that she did not have functional use of the left upper or lower extremity. In the same region as her prior tumors, MRI demonstrated a new right posterior parietal convexity, heterogeneously

enhancing mass lesion arising along the superior aspect of the resection cavity within the right perirolandic cortex [Figure 4a], as well as multiple surrounding subcentimeter enhancing satellite nodules and a subcentimeter nodule in the corpus callosum. There were also adjacent pachymeningeal enhancement and vasogenic edema with leftward subfalcine herniation [Figure 4a]. After multidisciplinary evaluation at tumor board and discussion with the patient, the decision was made to perform a third craniotomy for palliative resection of the right perirolandic mass with plans for adjuvant radiation therapy for the treatment of the corpus callosum nodule. We recommended a more aggressive resection than the prior excision given the lack of functional use on the left and the aggressive behavior of the tumor. Due to severe scalp thinning, free flap reconstruction was also planned and performed in conjunction with plastic surgery. Neuronavigation, SSEPs, motor mapping, and intraoperative microscope were employed for safe resection. Frozen specimen was consistent with a glial neoplasm and the frontoparietal lesion and satellite lesions were completely resected on examination with the operative microscope. Postoperative MRI [Figure 4b] found enhancement along the resection cavity, but no nodular residual lesion was detected, consistent with gross total resection. Postoperatively, her course was complicated by infection of her free flap, which was treated with washout and debridement.

Microscopic analysis of the second recurrence [Figures 5a-i] showed regions of tumor with morphological and

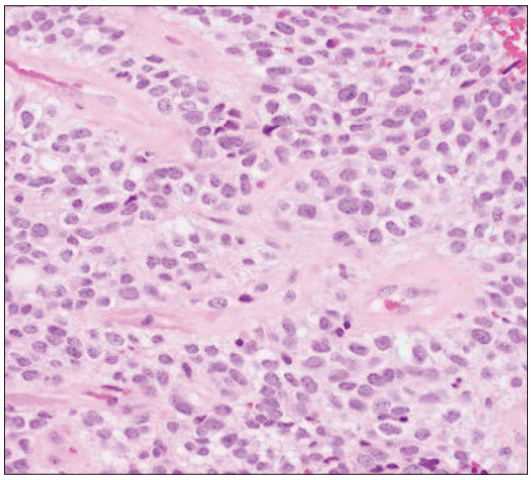

Figure 1: First resection (H&E, 200x) showing clear cell ependymoma with perinuclear clearing and vague perivascular pseudorosettes.

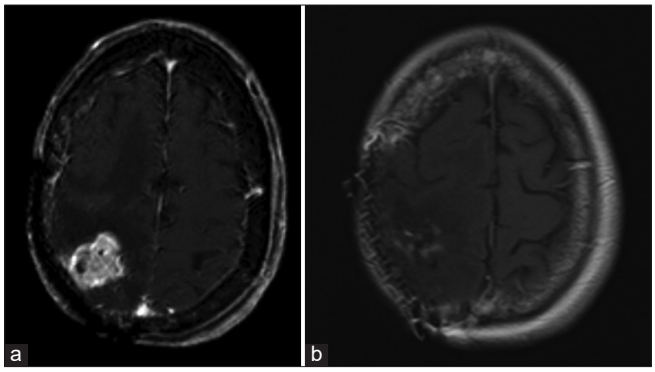

Figure 2: Axial T1-weighted imaging post contrast demonstrating (a) focal post-surgical changes from resection twelve years prior and an enhancing cortical lesion within the right parietal lobe concerning for recurrence. (b) immediate post-surgical changes of the right frontoparietal craniotomy for first recurrence with peripheral residual enhancement in resection cavity and mild enhancement in the superior aspect of the frontal lobe.

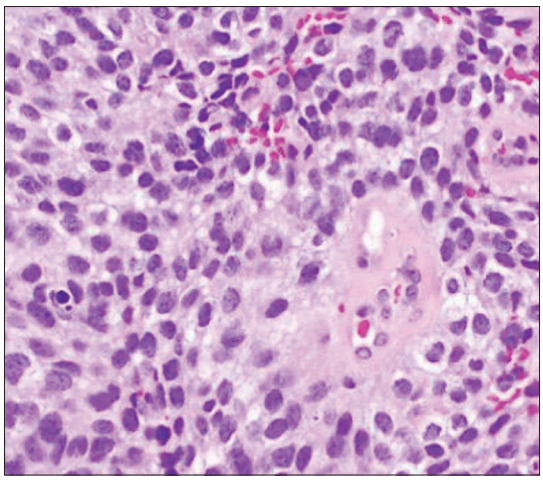

Figure 3: Second resection (H&E, 100x) showing clear cell ependymoma with perinuclear clearing and vague perivascular pseudorosettes.

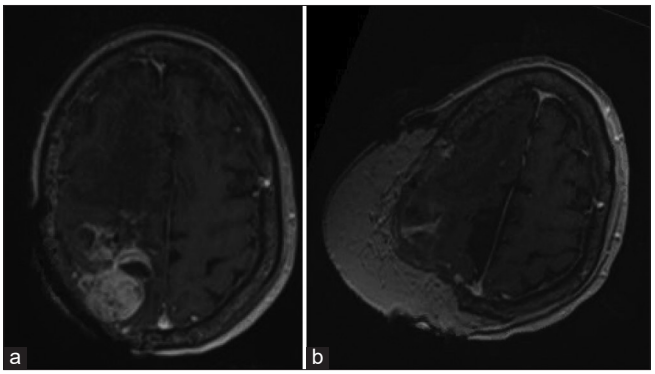

Figure 4: (a) Second recurrence seventeen months after second resection with interval increased size of right posterior parietal convexity heterogeneously enhancing mass lesion measuring 3.7 x 4.6 x 2.9 cm with additional minimal adjacent nodular enhancement seen within the right superior frontal sulci/gyri and pachymeninges with an increase in associated vasogenic edema (b) Immediate post-surgical changes of right posterior parietal convexity mass resection for second recurrence with irregular brain parenchymal enhancement about the resection site and parietal scalp free flap reconstruction.

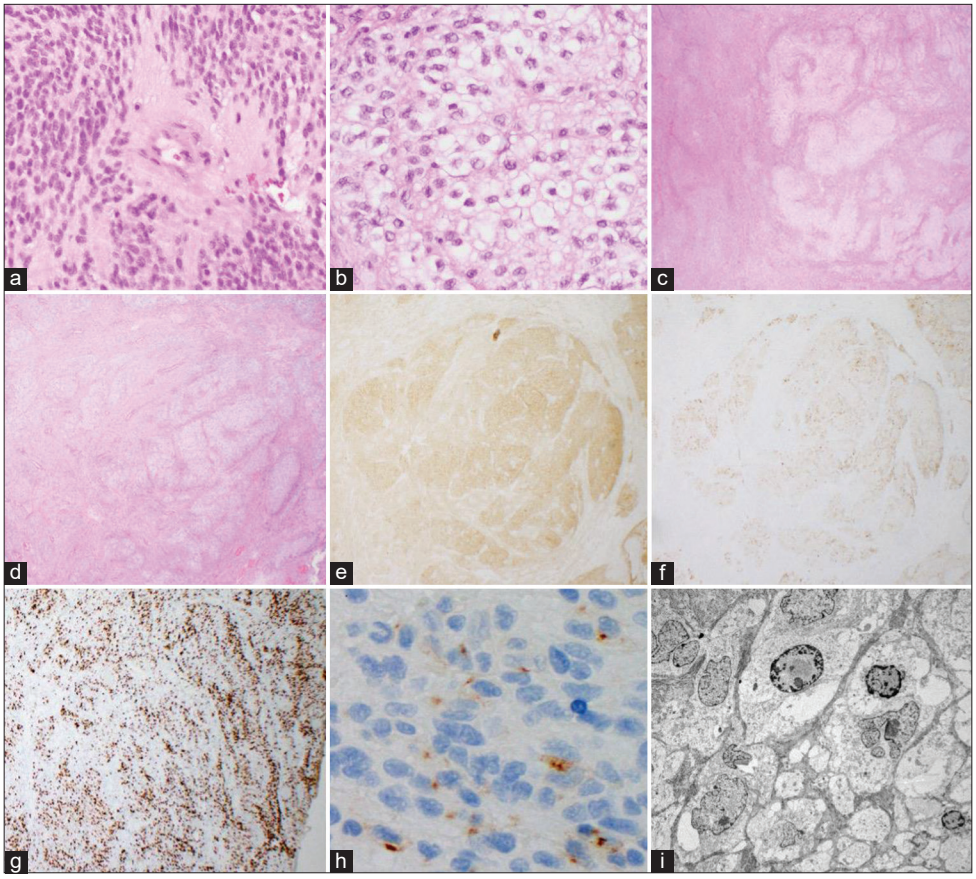

Figure 5: Third resection. High-power views of tumor with typical ependymoma features including relatively uniform ovoid cells with perivascular pseudorosettes (a; H&E, 200x) and areas with prominent clear cell change (b; H&E, 200x). Low power views (c-g, 20x) showing large nodules of tumor with clear cell morphology on H&E (c-d). A large nodule with clear cell morphology seen on H&E (d) is strongly positive for synaptophysin (e) and weakly positive for GFAP (f). Ki67 proliferation index is markedly elevated (g). EMA shows characteristic dot-like staining pattern (h; 400x). Transmission electron microscopy of clear cell regions with few poorly-formed intercellular junctions and intracellular glial-type filaments (i; magnification: 2500x).

immunohistochemical features typical of ependymoma, including perivascular pseudorosettes and focal dot-like EMA positivity, as well as malignant features including increased mitotic activity with elevated Ki67 proliferation index, marked hypercellularity, and microvascular proliferation. In addition, the neoplasm contained large nodular regions of clear cells exhibiting extensive immunoreactivity for synaptophysin as well as other markers suggestive of neural differentiation, including neuronal nuclei (NeuN) and insulinoma-associated protein 1 (INSM1). The tumor cells were focally positive for glial markers, including GFAP and oligodendrocyte transcription factor 2. Electron microscopy showed poorly formed and ill-defined junctional complexes, but no cilia, microvilli, or dense granules were seen [Figure 1]. The presence of a *C11orf95-RELA*, now known as *ZFTA-RELA*, fusion was detected on RNA sequencing, a highly sensitive and specific platform, thereby confirming the diagnosis of supratentorial ependymoma, *ZFTA* fusion positive. Immunohistochemical surrogate markers for *RELA* fusion, L1CAM and p65, were not performed due to cost restrictions and their inferior specificity compared to sequencing.[5] Next-generation DNA sequencing also identified a pathogenic *PTCH1* c.2084dupA mutation with p.D695fs protein alteration. Homozygous deletion of *CDKN2A/B*, a reported independent predictor of poor outcome in ependymomas with ZFTA: RELA fusions, was not detected.[7]

These findings were presented at tumor board and radiation therapy was recommended. Therapy was delayed in part due to her limited means of transportation. Planning MRI 3 months postoperatively showed an area of intense enhancement within the right frontoparietal vertex, concerning for a third recurrence. She received 3000 cGy in 10 fractions to the visualized tumor using image-guided intensity modulated radiation therapy (IG-IMRT). Two months later, there were moderately increased size and degree of enhancement of the affected area, as well as development of multiple satellite nodules. After another 2 months, the mass had demonstrated

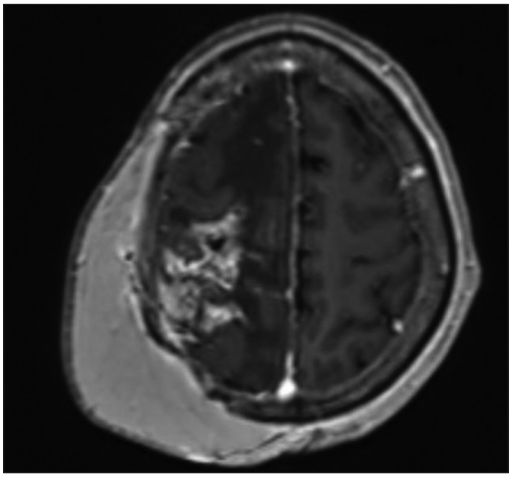

Figure 6: Four-month interval development of a solid tumor with a dominant 2.6 x 1.9 cm nodule with additional smaller nodules and right periolandic and deep white matter necrotic bubbly enhancement.

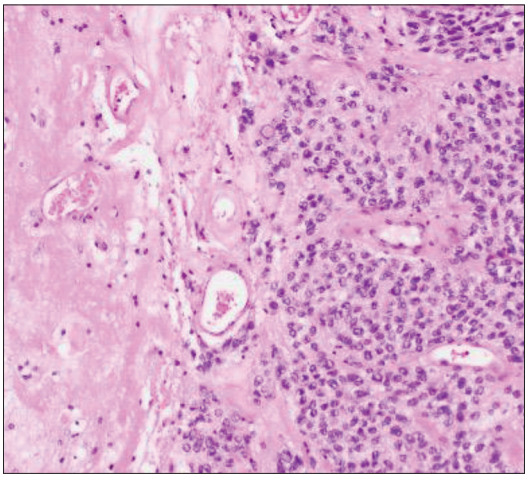

Figure 7: Fourth resection showing ependymoma (right half of image) with radiation-associated injury and necrosis of the adjacent brain tissue (left half of image) (H&E, 100x).

rapid growth with significant mass effect as well as necrotic bubbly enhancement of the perirolandic and deep white matter consistent with rapid tumor progression and radiation necrosis, respectively [Figure 6].

Her case was discussed at tumor board. Although she could lift her left arm, she had no functional use of the hand or lower extremity. A fourth resection was recommended to maximize her survival and allow for potential enrollment in a clinical trial. The resection was performed with neuronavigation, SSEPs, motor mapping, intraoperative microscope, ultrasonic aspiration, and plastic surgery management of her scalp flap. Intraoperatively, the tumor had a firm, gray and red center with an infiltrative border. After gross resection of the lesion, ultrasonic aspiration was used to remove all remaining lesion, with additional guidance based on neuronavigation. Pathology revealed an ependymal neoplasm and necrosis of brain parenchyma, compatible with radiation necrosis [Figure 7]; given the histomorphologic similarity to the prior specimens, molecular and immunohistochemical testing was not repeated. Postoperative MRI showed mild residual irregular enhancement along the inferior and superior aspects of the resection cavity, suggestive of a small amount of residual lesion. Unfortunately, her care was again delayed due to transportation issues, and she was unable to enroll in the clinical trial that had been planned. Given the presence of *PTCH1* mutation, she received targeted smoothened (SMO) inhibitor vismodegib therapy on a compassionate basis. She received three cycles of chemotherapy, but continued to decline clinically with worsening seizures managed on multiple antiepileptic medications. She was placed on hospice care 5 months after her fourth resection. Ultimately, she succumbed to her disease 16 years after her original diagnosis and 8 months and 23 days after her fourth surgery.

DISCUSSION

Before our understanding of the molecular underpinnings of ependymomas, prognosis was largely influenced by an amalgam of features that include histopathologic grading (e.g., anaplasia), as well as tumor size, location, and potential for gross total resection. Recent studies indicate that molecular subgrouping is superior to histopathological grading for risk stratification and predicting outcome.[15] This is especially important when considering that distinction between the ependymoma grades has been controversial and difficult to reproduce, as morphologic features can vary within different regions of a tumor.[3] Historically, clear cell ependymomas, especially those of the supratentorial compartment, have been thought to have worse outcomes. While more studies are needed, it has been suggested that ependymomas exhibiting clear cell morphology more frequently harbor the *RELA* fusion[4,16,17] and thus the clear cell appearance may be a microscopic indicator suggesting a worse prognosis.

Although rare, several reports of radiation-induced ependymomas exist in the literature.[8,19] Given that this tumor recurred in the prior radiation field and had an adequate latency period, the possibility that the neoplasm is a result of radiation must be considered. However, it is the opinion of the authors that the later tumors represent recurrence rather than radiation-induced neoplasms due to the histomorphologic similarities between the tumor specimens and the location arising in region of the prior.

Patients with ependymomas containing the *C11orf95-RELA* fusion are thought to have a worse outcome,[15] though much of the data supporting this argument is based on progression-free survival rather than overall survival due to short follow-up time. Survival analyses between subgroups conducted by Pajtler *et al*.

who showed a dismal outcome for the *RELA* fusion subgroup, with 10-year overall survival rates of 50% and progression-free survival rates of 20%.[15] Other authors, such as Malgulwar *et al*., experience difficulties in calculating overall survival analysis due to small numbers of overall deaths in patient with ependymoma of any subtype.[12] For the patient presented here, initial progression occurred 3 months or less after resection and diagnosis of her supratentorial ependymoma, *ZFTA* fusion positive (third surgery), and she died just under 19 months later. Progression also occurred 3 months or less after her fourth resection. The additional presence of a mutation in the tumor suppressor gene *patched 1* was likely an additional driver for the aggressive nature of her tumor. PTCH1 mutations are found in several malignant tumors, including 30% of sporadic medulloblastoma and 3.7% of anaplastic ependymomas,[2] and its presence leads to upregulation of important Sonic Hedgehog target genes and thus cellular proliferation.[10]

This tumor demonstrated extensive immunoreactivity for synaptophysin, as well as NeuN and INSM1, suggesting the presence of neural differentiation, though this was not confirmed on electron microscopy. Neural differentiation in ependymoma is rare and, when it does occur, it is usually a minor component comprising focal patchy areas or small neuropil islands interspersed among primarily glial components usually within a supratentorial neoplasm.[1] Few reported cases of ependymomas with neuronal differentiation were published before our collective knowledge of the *ZFTA-RELA* fusion, so the fusion status of these reported cases is unknown. In addition, given the rarity of neural differentiation in ependymoma, its application in prognostication is limited, though increased recognition of its presence with extended follow-up will permit better assessment of its significance.[18] The rapid tumor progression seen our patient suggests that extensive synaptophysin immunoreactivity does not provide prognostic favorability that might be seen in other CNS tumors with neural differentiation, such as ganglioglioma.

CONCLUSION

Whereas most documented reports of neural differentiation in ependymal neoplasms typically feature small islands of synaptophysin-positive neuropil, this case reports extensive synaptophysin immunoreactivity in an ependymoma with a *ZFTA-RELA* fusion that had undergone malignant transformation from a lower grade ependymoma with clear cell features diagnosed 16 years earlier. The presence of extensive synaptophysin positivity in ependymoma does not appear to confer a favorable outcome.

Declaration of patient consent

Patient's consent not required as patients identity is not disclosed or compromised.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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