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Supratentorial cortical ependymoma: A systematic literature review and case illustration

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Abstract

Cortical ependymomas are currently not considered a subgroup of supratentorial ependymomas; however, there is a growing body of literature investigating the natural history of these lesions compared to supratentorial ependymomas. We performed a systematic literature review of cortical ependymomas with a focus on the natural history, clinical characteristics, and clinical outcomes of these lesions as compared to supratentorial ependymomas. Our search revealed 153 unique cases of cortical ependymomas. The mean age on presentation was 21.2 years. Males and females comprised 58.8% (90/153) and 41.2% (63/153) of cases, respectively. The most common presenting symptom was seizure activity occurring in 44.4% of the cohort (68/153). The recently recognized *C11orf95-RELA* fusion was identified in 13.7% of the cohort (21/153) and 95.5% of cases (21/22) reporting molecular characterization. World Health Organization grades 2 and 3 were reported in 52.3% (79/151) and 47.7% (72/151) of cases, respectively. The frontal lobe was involved in the majority of cases (54.9%, 84/153). Gross total resection was achieved in 80.4% of cases (123/153). Tumor recurrence was identified in 27.7% of cases (39/141). Mean clinical follow-up was 41.3 months. Mean overall survival of patients who expired was 27.4 months whereas mean progression-free survival was 15.0 months. Comparatively, cortical ependymomas with *C11orf95-RELA* fusions and supratentorial ependymomas with *C11orf95 RELA* fusions exhibited differing clinical outcomes. Further studies with larger sample sizes are necessary to investigate the significance of *RELA* fusions on survival in cortical ependymomas and to determine whether cortical ependymomas with *C11orf95-RELA* fusions should be classified as a distinct entity.

Keywords

cortical ependymoma, ependymoma, insula, insular ependymoma, supratentorial cortical ependymoma

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Introduction

Ependymomas are a relatively uncommon entity, accounting for approximately 1.8% of all primary central nervous system (CNS) tumors and 6.8% of glial neoplasms.[1,2] These tumors arise from ependymal cells lining the ventricular system, choroid plexus, central canal of the spinal cord and filum terminale.[2] Given their embryonic origin, these neoplasms are most commonly found within the ventricular system (e.g. floor of the fourth

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ventricle, cervicothoracic cord, filum terminale); however, ependymomas can also be found throughout the neuroaxis, even outside the bounds of the ventricular system.[2] Such entities are known as supratentorial extraventricular ependymomas, which exhibit a low incidence and an unclear etiopathogenesis.[1,2]

New guidelines by the Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT-NOW) committee in 2020 have distinguished ependymal tumors according to methylome profiling data to indicate specific molecular groups based upon anatomic location.[3] These new molecular groups include ependymal tumors of the supratentorial, posterior fossa, and spinal compartments.[3] Specifically, *C11orf95* and *YAP1* fusion genes are now considered subgroups of supratentorial ependymomas with *C11orf95-RELA* fusions exhibiting the worst prognosis of all supratentorial ependymomas.[3–6] A small subset of supratentorial extraventricular ependymomas, known as cortical ependymomas, selectively involve the cerebral cortex without any ventricular involvement. Cortical ependymomas are currently not considered to be a distinct subgroup of supratentorial ependymomas; however, there is a growing body of literature specifically investigating the natural history and clinical outcomes of these lesions compared to supratentorial ependymomas as a whole.[7–48] In fact, several studies have demonstrated cortical ependymomas with high rates of *C11orf95-RELA* fusions exhibiting favorable outcomes, which is in contradistinction to the natural history of supratentorial ependymomas with *C11orf95-RELA* fusions.[41,43,48] Here, we describe a rare case of a 58-year-old female found to have an ependymoma of the insular cortex. We perform a systematic literature review of cortical ependymomas with a focus on the natural history, clinical characteristics, and clinical outcomes of these lesions as compared to supratentorial ependymomas as a whole.

Systematic literature review

A systematic literature review of cortical ependymomas was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The PubMed and Web of Science databases were searched through February 2022 using the following search terms: ("cortical ependymoma" [All Fields] OR "supratentorial cortical ependymoma" [All Fields] OR "insula ependymoma" [All Fields] OR "insular ependymoma" [All Fields]). A total of 279 records were returned using these search terms. The bibliographies of these papers were reviewed to search for any additional papers, which yielded five additional records due to the variability of nomenclature used to describe these lesions. These 284 records were screened for original reports of cortical ependymomas including case reports and case series while excluding preclinical or clinical studies, literature reviews, systematic reviews, and meta-analyses. A total of 42 studies met eligibility after applying inclusion and exclusion criteria and were included in the final analysis (Figure 1). These studies encompassed 153 unique cases of cortical ependymomas. Data collection and extraction were performed by one author (AS) with oversight and a second independent review by a second author (JC). Data gathered included: age, sex, gene fusion, tumor grade, location, presence of cystic component, treatment, recurrence, overall survival, progression-free survival, follow-up, and outcome. A summary of the data synthesized is listed in Table 1.

The average age on presentation was 21.2 years (range: 8–74 years). Males and females constituted 58.8% (90/153) and 41.2% (63/153) of cases, respectively. The most common presenting symptom was seizure activity observed in 44.4% (68/153) of cases. The *C11orf95-RELA* fusion was observed in 13.7% (21/153) of cases; however, the supratentorial ependymoma *C11orf95-RELA* fusion subgroup was only recently recognized as a variant by the cIMPACT-NOW committee in 2020.[3] As such, gene fusions were not investigated in the vast majority of cortical ependymomas reported to date. Of cases reporting molecular characterization, 95.5% (21/22) reported the presence of the *C11orf95-RELA* fusion. World Health Organization (WHO) grades 2 and 3 were reported in 52.3% (79/151) and 47.7% (72/151) of cases, respectively, documenting tumor grades. The most common location was the frontal lobe or at least involvement of the frontal lobe accounting for 54.9% (84/153) of cases. Gross total resection was achieved in 80.4% (123/153) of cases with adjuvant radiotherapy and/or chemotherapy utilized in 43.1% (66/153) and 3.3% (5/153) of cases, respectively. Tumor recurrence occurred in 27.7% (39/141) of cases. Mean clinical follow-up was 41.3 months (range: 2–347 months). Mean overall survival percentage at last known follow-up was 88.3% (128/145). Mean overall survival of patients who expired was 27.4 months (range: 4–72 months). Mean progression-free survival was 15.0 months (range: 4–32 months).

Case illustration

A 58-year-old female presented to the emergency department with three days of mild expressive aphasia and weakness of the right hand. Neurologic examination was otherwise unremarkable. Past medical history was unremarkable. Magnetic resonance imaging (MRI) of the brain demonstrated a heterogeneously enhancing lesion of the left insula with a large cystic component extending superiorly into the left frontal inferior gyrus with significant surrounding vasogenic edema (Figure 2). Metastatic workup was unrevealing. The patient was started on dexamethasone and medically optimized. Given the significant mass effect,

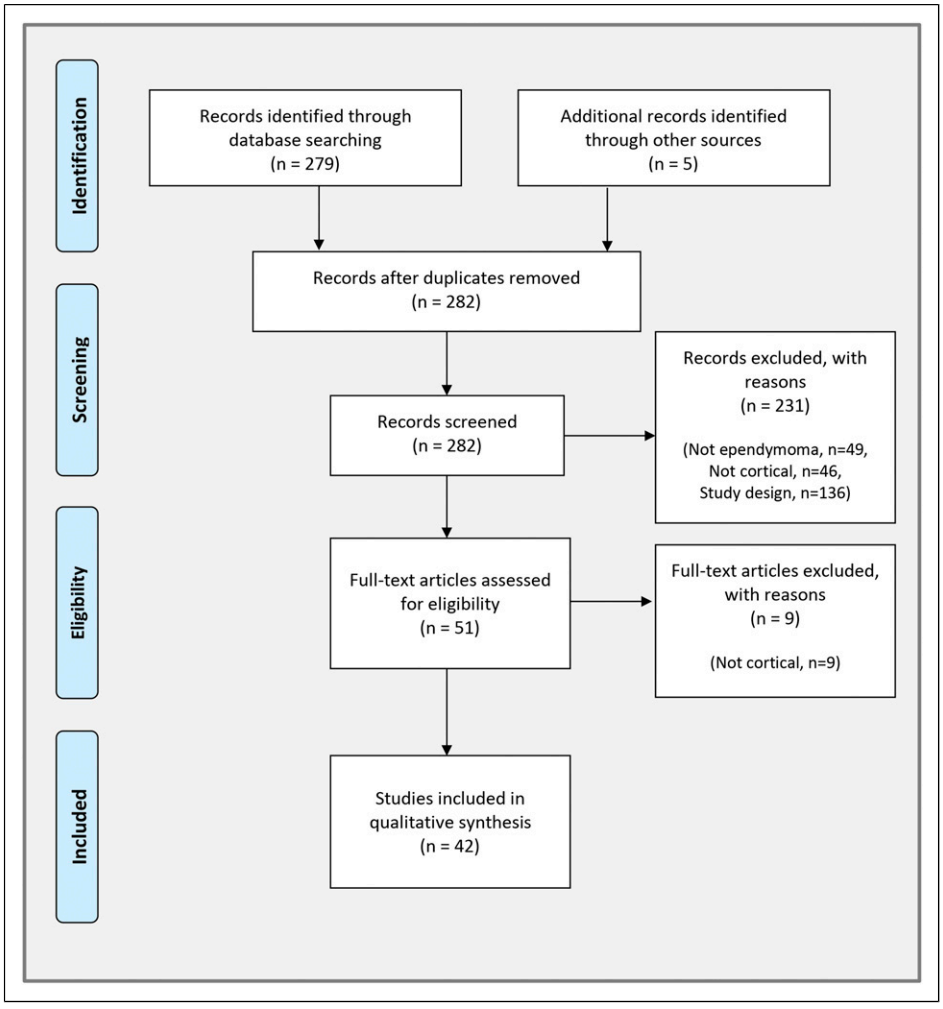

Figure 1. PRISMA study selection flowsheet for the systematic review of cortical ependymomas.

symptomatic edema, and need for tissue diagnosis, neurosurgical resection was recommended.

A stereotactic left craniotomy was performed for resection of the left insular lesion and superiorly extending cystic component. A subtotal resection was pursued given that the tumor was found to be encasing the vessels of the Sylvian fissure. The patient tolerated the procedure well and without complication. Postoperative neuroaxis MRI was unremarkable for drop metastases. Histopathology demonstrated cellular neoplastic tissue consisting of cords of relatively monomorphic tumor cells with perivascular pseudorosettes and focal true ependymal rosettes (Figure 3). There was evidence of focal tumor invasion into surrounding brain parenchyma, a feature that can rarely be seen in ependymoma.[15] The Ki-67 proliferative index was variable and focally ranged up to 20% in some areas. Neither necrosis, nor vascular proliferation, nor significant mitotic activity was identified. Tumor cells were strongly and diffusely reactive with glial fibrillary acidic protein (Figure 4). Synaptophysin and neuron-specific enolase highlighted neurons in the infiltrative areas. These stains exhibited limited reactivity in tumor cells; however, the reactivity was patchy and weak compared to the strong and diffuse glial fibrillary acidic protein immunostains. Additional immunostains including Melan-A, SOX10, cytokeratin AE1/AE3, cytokeratin 7, and CD45 were negative in all tumor cells, which ruled out metastatic melanoma, metastatic carcinoma, and lymphoma as potential diagnoses. Neuropathology confirmed a diagnosis of supratentorial ependymoma grade 2 not elsewhere classified according to molecular testing.[3] The patient underwent adjuvant Cyberknife radiosurgical treatment to the resection cavity eight weeks after surgery. The most recent repeat MRI imaging at 15 months revealed a stable disease burden.

Table 1. Systematic review of the literature pertaining to the natural history, clinical features, and treatment strategies of cortical ependymomas.

Author (Year)	Age/ Sex	Symptoms	Gene fusion	WHO grade	Location	Cystic	Treatment	Recurrence	OS (months)	PFS (months)	Last FU (months)	Outcome	Ref
Saito et al. (1999)	63F	Seizure	NR	2	L parietal	No	GTR + RT	No	NA	NA	14	Alive	7
Fujimoto et al. (1999)	13M	Hyperesthesia	NR	2	L frontoparietal	Yes	GTR	NR	NR	NR	NR	NR	8
Sato et al. (2000)	41F	Weakness	NR	3	L frontoparietal	Yes	GTR + RT	No	NA	NA	2	Alive	9
Takeshima et al. (2002)	70F	Incidental	NR	3	R frontal	Yes	GTR	No	NA	NA	14	Alive	10
Lehman et al. (2003)	10M	Seizure	NR	2	R frontal	Yes	GTR	No	NA	NA	19	Alive	11
Roncaroli et al. (2005)	52M	Seizure	NR	2	L frontal	No	GTR + RT	No	NA	NA	130	Alive	12
	34M	Seizure	NR	2	L temporal	No	GTR	No	NA	NA	100	Alive	
	7F	Seizure	NR	2	R parietal	No	GTR	No	NA	NA	48	Alive	
Miyazawa et al. (2007)	33M	Aphasia	NR	3	L parietal	No	GTR + RT + ChT	Yes	NA	6	7	Alive	13
Ghani et al. (2008)	4M	Seizure	NR	2	L frontoparietal	Yes	GTR +RT	Yes	NA	10	NR	Alive	14
Lehman (2008)	1F	Seizure	NR	3	R frontal	No	GTR	No	NA	NA	48	Alive	15
Grajkowska et al. (2009)	11F	Headache	NR	2	L frontoparietal	Yes	GTR + RT	No	NA	NA	72	Alive	16
Yadav et al. (2009)	15M	Headache	NR	2	L frontal	No	STR	Stable	NA	NA	20	Alive	17
Niazi et al. (2009)	36F	Seizure	NR	3	R frontal	Yes	GTR + RT	No	NA	NA	29	Alive	18
	18M	Seizure	NR	3	R frontoparietal	Yes	GTR + RT + ChT	Yes	14	6	14	Deceased	
	28F	Seizure	NR	2	L temporoparietal	Yes	GTR	No	NA	NA	42	Alive	
Yurt et al. (2010)	11M	Seizure	NR	2	L frontal	Yes	GTR	No	NA	NA	12	Alive	19
Lee et al. (2011)	2M	Seizure	NR	2	R frontoparietal	No	GTR	No	NA	NA	12	Alive	20
Van Gompel et al. (2011)	32F	Incidental	NR	2	L parietal	Yes	GTR	No	NA	NA	59	Alive	21
	43F	Seizure	NR	2	L frontal, insular	Yes	STR + RT	Stable	NA	NA	60	Alive	
	12M	Seizure	NR	3	R parietal	Yes	GTR + RT	Yes	NA	NR	101	Alive	
	40F	Seizure	NR	2	R frontal	Yes	GTR	No	NA	NA	131	Alive	

(continued)

Table 1. (continued)

Author (Year)	Age/ Sex	Symptoms	Gene fusion	WHO grade	Location	Cystic	Treatment	Recurrence	OS (months)	PFS (months)	Last FU (months)	Outcome	Ref
	25M	Seizure	NR	3	R frontal	Yes	GTR + RT	No	NA	NA	80	Alive	
	26M	Seizure	NR	2	R occipital	Yes	GTR	No	NA	NA	6	Alive	
	59F	Incidental	NR	2	L parietal	No	GTR	No	NA	NA	31	Alive	
	59M	Seizure	NR	3	R frontal	No	GTR + RT	Yes	NA	NR	47	Alive	
	25F	Seizure	NR	2	L frontal	Yes	GTR	No	NA	NA	39	Alive	
Davis et al. (2011)	22F	Headache	NR	3	R frontotemporal	Yes	GTR + RT	Yes	NA	20	55	NR	22
Romero et al. (2012)	23M	Seizure	NR	3	L frontal	Yes	GTR + RT	No	NA	NA	60	Alive	23
Ng et al. (2012)	51F	Incidental	NR	3	Bifrontal	Yes	GTR + RT	Yes	NA	4	8	Alive	24
Nakamizo et al. (2012)	20F	Seizure	NR	2	L frontoparietal	No	GTR	No	NA	NA	16	Alive	25
Ohla et al. (2012)	29M	Headache	NR	3	L parietal	No	STR + RT	Yes	15	14	15	Deceased	26
Rigante et al. (2013)	14M	Seizure	NR	2	R temporoparietal	Yes	GTR	No	NA	NA	12	Alive	27
Hiniker et al. (2013)	19F	Seizure	NR	NR	L frontotemporal	Yes	STR	Stable	NA	NA	4	Alive	28
Elsharkawy et al. (2013)	25M	Seizure	NR	3	R frontal	No	GTR	No	NA	NA	6	Alive	29
Kambe et al. (2014)	2M	Seizure	NR	2	R parietal	NR	GTR	No	NA	NA	NR	NR	30
Liu et al. (2014)	24M	Seizure	NR	2	R frontal	No	GTR	No	NA	NA	24	Alive	31
	30M	Seizure	NR	3	R parietal	No	GTR + RT + ChT	Yes	NA	NR	264	Alive	
	50M	Seizure	NR	3	L frontal	Yes	GTR + RT +ChT	Yes	72	NR	72	Deceased	
	50F	Seizure	NR	3	L frontal	No	GTR	Yes	NA	NR	150	Alive	
	2M	Hemiparesis	NR	3	L frontal	No	GTR	Yes	NA	NR	48	Alive	
	47F	Headache	NR	3	R frontal	Yes	STR	NR	<1	NR	<1	*Deceased Operative complications	
	54F	Headache	NR	3	R parietal	Yes	GTR	NR	48	NR	48	Deceased	
	52F	Confusion	NR	3	L frontal	No	GTR	Yes	NA	NR	36	Alive	

(continued)

Table 1. (continued)

Author (Year)	Age/ Sex	Symptoms	Gene fusion	WHO grade	Location	Cystic	Treatment	Recurrence	OS (months)	PFS (months)	Last FU (months)	Outcome	Ref
	15F	Hemiparesis	NR	3	L temporal	Yes	GTR + RT + ChT	No	NA	NA	11	Alive	
	20M	Seizure	NR	2	L temporal	No	GTR	No	NA	NA	6	Alive	
	63F	Headache	NR	3	L parietal	Yes	GTR + RT	NR	4	NR	4	Deceased	
Zhang et al. (2014)	1.5M	Seizure	NR	3	R frontoparietal	Yes	GTR	No	NA	NA	6	Alive	32
Tailor et al. (2015)	27F	Seizure	NR	2	L parietal	Yes	GTR	NR	NA	NA	NR	NR	33
Yamasaki et al. (2015)	10M	Seizure	NR	2	R parietal	N/A	GTR	No	NA	NA	12	Alive	34
Bijwe et al. (2015)	14F	Headache	NR	2	R frontal	Yes	GTR	No	NA	NA	6	Alive	35
Mohaghegh et al. (2015)	17M	Weakness	NR	3	L parietooccipital	Yes	GTR	NR	NA	NA	NR	NR	36
Kharosekar et al. (2018)	11F	Headache	NR	3	R frontoparietal	Yes	GTR	NR	NA	NA	NR	NR	37
Wang et al. (2018)	6M	Seizure	NR	2	R frontal	No	GTR	No	NA	NA	23	Alive	38
	13F	Seizure	NR	2	R parietal	Yes	GTR	No	NA	NA	48	Alive	
	46M	Seizure	NR	3	L parietal	No	GTR	No	NA	NA	46	Alive	
	5F	Headache	NR	2	L frontal	Yes	GTR	No	NA	NA	70	Alive	
	74M	Headache	NR	3	R frontal	Yes	GTR	Yes	20	11	20	Deceased	
	4F	Seizure	NR	2	R frontal	Yes	GTR	No	NA	NA	71	Alive	
	49M	Seizure	NR	2	L temporal	No	GTR	No	NA	NA	88	Alive	
	9M	Seizure	NR	3	R frontal	Yes	STR + RT	Yes	NA	NR	41	Alive	
	31F	Seizure	NR	2	R parietal	No	GTR	No	NA	NA	67	Alive	
	18M	Seizure	NR	3	L temporal	No	GTR + RT	No	NA	NA	39	Alive	
	53F	Seizure	NR	2	R temporal	No	GTR	No	NA	NA	51	Alive	
	51M	Seizure	NR	2	L parietal	No	GTR	No	NA	NA	75	Alive	
	45F	Seizure	NR	2	R parietal	Yes	GTR	No	NA	NA	35	Alive	
Beniwal et al. (2018)	3F	Dyskinesia	NR	3	L frontal	NR	GTR	No	NA	NA	12	Alive	39
Sun et al. (2018)	19M	Numbness	NR	2	L parietal	No	GTR	No	NA	NA	8	Alive	40
	26F	Headache	NR	3	R frontoparietal	Yes	GTR + RT	No	NA	NA	15	Alive	
	24M	Seizure	NR	2	L temporal	No	GTR	No	NA	NA	30	Alive	
	6M	Headache	NR	3	L frontal	No	STR + RT	Yes	25	18	25	Deceased	

(continued)

Table 1. (continued)

Author (Year)	Age/ Sex	Symptoms	Gene fusion	WHO grade	Location	Cystic	Treatment	Recurrence	OS (months)	PFS (months)	Last FU (months)	Outcome	Ref
	30F	Headache	NR	2	L occipital	No	GTR	No	NA	NA	25	Alive	
	22M	Headache	NR	3	R temporal	No	GTR + RT	Yes	22	15	22	Deceased	
	31M	Headache	NR	3	R frontal	Yes	STR + RT	No	NA	NA	28	Alive	
	18F	Dizziness	NR	2	L temporal	No	GTR	No	NA	NA	32	Alive	
	3F	Seizure	NR	3	R frontal	Yes	GTR + RT	No	NA	NA	15	Alive	
	22M	Seizure	NR	2	R temporal	Yes	GTR	No	NA	NA	14	Alive	
	11F	Vomiting	NR	2	L parietooccipital	Yes	GTR	No	NA	NA	8	Alive	
	48M	Headache	NR	2	L frontal	No	GTR	No	NA	NA	39	Alive	
	35F	Seizure	NR	3	R parietal	Yes	GTR + RT	Yes	NA	18	21	Alive	
Matsumoto et al. (2019)	9M	Headache	NR	3	R frontal	Yes	STR + RT	Yes	NA	32	347	Alive	41
	16F	Vomiting	NR	3	L frontal	Yes	GTR + RT	Yes	NA	19	23	NR	
	4M	Headache	NR	3	L frontal	Yes	GTR + RT	Yes	NA	16	74	Alive	
	6M	Hemiparesis	*RELA* fusion	2	L parietal	Yes	STR	Yes	NA	25	187	Alive	
	22M	Hemianopsia	*RELA* fusion	3	L parietal	Yes	GTR + RT	No	NA	NA	104	Alive	
	3M	Seizure	*RELA* fusion	3	R frontal	Yes	GTR + RT	No	NA	NA	136	Alive	
	24M	Seizure	*RELA* fusion	3	L parietal	Yes	GTR + RT	No	NA	NA	74	Alive	
	1F	Seizure	*RELA* fusion	3	L parietal	Yes	GTR	No	NA	NA	10	Alive	
*Khatri et al. (2019)	32M	Headache	NR	3	NR	NR	GTR + RT	No	NA	NA	101	Alive	42
	11M	Headache	NR	3	NR	NR	GTR + RT	No	NA	NA	101	Alive	
	12M	Headache	NR	3	NR	NR	GTR + RT	Yes	53	NR	53	Deceased	
	10M	Seizure	NR	3	NR	NR	STR + RT	Yes	NA	NR	88	Alive	
	5M	Headache	NR	2	NR	NR	GTR	No	NA	NA	48	Alive	
	12F	Headache	NR	3	NR	NR	STR + RT	No	NA	NA	47	Alive	
	16M	Seizure	NR	2	NR	NR	GTR	No	NA	NA	43	Alive	
	14F	Headache	NR	3	NR	NR	GTR + RT	No	NA	NA	26	Alive	
	46F	Headache	NR	2	NR	NR	GTR	No	NA	NA	16	Alive	
	21F	Headache	NR	3	NR	NR	GTR + RT	Yes	11	NR	11	Deceased	
	14F	Headache	NR	2	NR	NR	STR	No	8	NA	8	Deceased	
	8M	Headache	NR	2	NR	NR	GTR + RT	Yes	NA	NR	40	Alive	
	22M	Headache	NR	2	NR	NR	STR + RT	No	NA	NA	27	Alive	

(continued)

Table 1. (continued)

Author (Year)	Age/ Sex	Symptoms	Gene fusion	WHO grade	Location	Cystic	Treatment	Recurrence	OS (months)	PFS (months)	Last FU (months)	Outcome	Ref
	23M	Headache	NR	2	NR	NR	STR + RT	No	NA	NA	20	Alive	
	22M	Headache	NR	3	NR	NR	GTR + RT	No	NA	NA	14	Alive	
	14F	Headache	NR	2	NR	NR	STR + RT	No	NA	NA	11	Alive	
	42M	Seizure	NR	2	NR	NR	STR + RT	No	NA	NA	7	Alive	
	19M	Headache	NR	3	NR	NR	GTR + RT	No	NA	NA	7	Alive	
Wang et al. (2020)	26F	Seizure	NR	3	R frontal	Yes	STR	Yes	43	NR	43	Deceased	43
	48M	Headache	NR	2	L temporal	Yes	STR + RT	Yes	NA	NR	94	Alive	
	50M	Headache	*RELA* fusion	2	R frontal	No	GTR	No	NA	NA	24	Alive	
	5F	Seizure	NR	2	R frontal	No	GTR	No	NA	NA	24	Alive	
	5M	Headache	NR	3	L frontotemporal	Yes	GTR + RT	No	NA	NA	50	Alive	
	54F	Dizziness	No	3	R temporal	Yes	STR + RT	Yes	26	NR	26	Deceased	
	8F	Headache	NR	3	R temporooccipital	Yes	STR + RT	Yes	NA	NR	21	Alive	
	37M	Headache	NR	2	R temporal	No	STR + RT	Yes	NA	NR	36	Alive	
	22F	Headache	NR	2	R temporal	No	STR + RT	Yes	29	NR	29	Deceased	
	58M	Seizure	NR	2	R temporal	Yes	GTR	No	NA	NA	60	Alive	
	17M	Headache	NR	2	R frontotemporal	Yes	STR + RT	No	NA	NA	48	Alive	
	2F	Headache	NR	3	R frontal	Yes	GTR + RT	No	NA	NA	36	Alive	
	4M	Headache	NR	2	R occipital	Yes	GTR	No	NA	NA	36	Alive	
	6F	Hemiparesis	NR	2	R frontoparietal	Yes	GTR	No	NA	NA	30	Alive	
	5M	Seizure	*RELA* fusion	2	R frontal	No	GTR	No	NA	NA	29	Alive	
	7M	Headache	NR	2	R occipital	No	GTR	No	NA	NA	9	Alive	
	11F	Headache	NR	2	R temporal	Yes	GTR	No	NA	NA	36	Alive	
	6F	Seizure	*RELA* fusion	2	L temporooccipital	No	GTR	No	NA	NA	18	Alive	
	11M	Seizure	*RELA* fusion	3	L temporal	No	GTR + RT	No	NA	NA	18	Alive	
	13F	Headache	NR	3	R parietal	Yes	STR + RT	No	NA	NA	48	Alive	
	2M	Hemiparesis	NR	3	L frontoparietal	Yes	STR	Yes	24	NR	24	Deceased	
	19F	Seizure	NR	2	R temporooccipital	Yes	GTR	No	NA	NA	27	Alive	
	4M	Headache	*RELA* fusion	3	R parietal	No	GTR + RT	No	NA	NA	36	Alive	
	17M	Seizure	*RELA* fusion	2	R temporooccipital	Yes	GTR	No	NA	NA	8	Alive	

(continued)

Table 1. (continued)

Author (Year)	Age/ Sex	Symptoms	Gene fusion	WHO grade	Location	Cystic	Treatment	Recurrence	OS (months)	PFS (months)	Last FU (months)	Outcome	Ref
	22M	Seizure	*RELA* fusion	3	L parietal	No	GTR + RT	No	NA	NA	6	Alive	
	4M	Headache	NR	2	R temporal	No	GTR	No	NA	NA	65	Alive	
	5M	Headache	NR	3	R frontal	No	GTR + RT	Yes	NA	NR	72	Alive	
	14M	Hemiparesis	NR	2	R frontotemporal	Yes	GTR	No	NA	NA	24	Alive	
	11M	Hemiparesis	*RELA* fusion	3	R frontoparietal	No	STR + RT	Yes	NA	NR	7	Alive	
	0.75M	Vomiting	*RELA* fusion	3	R frontal	Yes	GTR	No	NA	NA	5	Alive	
Senthilvelan et al. (2020)	22M	Seizure	NR	2	L frontal	Yes	GTR	NR	NR	NR	NR	NR	44
Sallam et al. (2020)	9M	Facial droop	*RELA* fusion	2	L frontal	Yes	GTR	Yes	NA	5	5	Alive	45
Safavi et al. (2021)	2M	Headache	NR	NR	L frontal	Yes	GTR	NR	NR	NR	NR	NR	46
Lee et al. (2021)	25F	Seizure	*RELA* fusion	2	R frontoparietal	No	GTR	No	NA	NA	10	Alive	47
Wang et al. (2021)	6F	Seizure	*RELA* fusion	2	L temporooccipital	No	GTR	No	NA	NA	18	Alive	48
	11M	Seizure	*RELA* fusion	3	L temporal	No	GTR + RT	No	NA	NA	18	Alive	
	13F	Headache	NR	3	R parietal	Yes	STR + RT	No	NA	NA	48	Alive	
	2M	Weakness	NR	3	L frontoparietal	Yes	STR	Yes	24	20	24	Deceased	
	6F	Weakness	NR	2	R frontoparietal	Yes	GTR	No	NA	NA	30	Alive	
	5M	Seizure	*RELA* fusion	2	R frontal	No	GTR	No	NA	NA	29	Alive	
	7M	Headache	NR	2	R occipital	No	GTR	No	NA	NA	9	Alive	
	11F	Headache	NR	2	R temporal	Yes	GTR	No	NA	NA	36	Alive	
	4M	Headache	NR	2	R temporal	No	GTR	No	NA	NA	65	Alive	
	5M	Headache	NR	3	R frontal	No	GTR + RT	Yes	NA	24	72	Alive	
	14M	Weakness	NR	2	R frontotemporal	Yes	GTR	No	NA	NA	24	Alive	
	11M	Weakness	*RELA* fusion	3	R frontoparietal	No	STR + RT	Yes	NA	7	7	Alive	
	0.75M	Vomiting	*RELA* fusion	3	R frontal	Yes	GTR	No	NA	NA	5	Alive	
Current case	58F	Aphasia	No	2	L insula	Yes	STR + RT	No	NA	NA	15	Alive	

Abbreviations: WHO: World Health Organization; OS: overall survival; PFS: progression-free survival: FU: follow up; F: female; NR: not reported; L: left: GTR: gross total resection; RT: radiotherapy; NA: not available; M: male; R: right; ChT: chemotherapy; STR: subtotal resection.

*Overall, the frontal lobe accounted for nine cases, parietooccipital lobe for four cases, frontotemporoparietal region for three cases, and temporal lobe for two cases. Fourteen patients had a cystic appearing tumor.

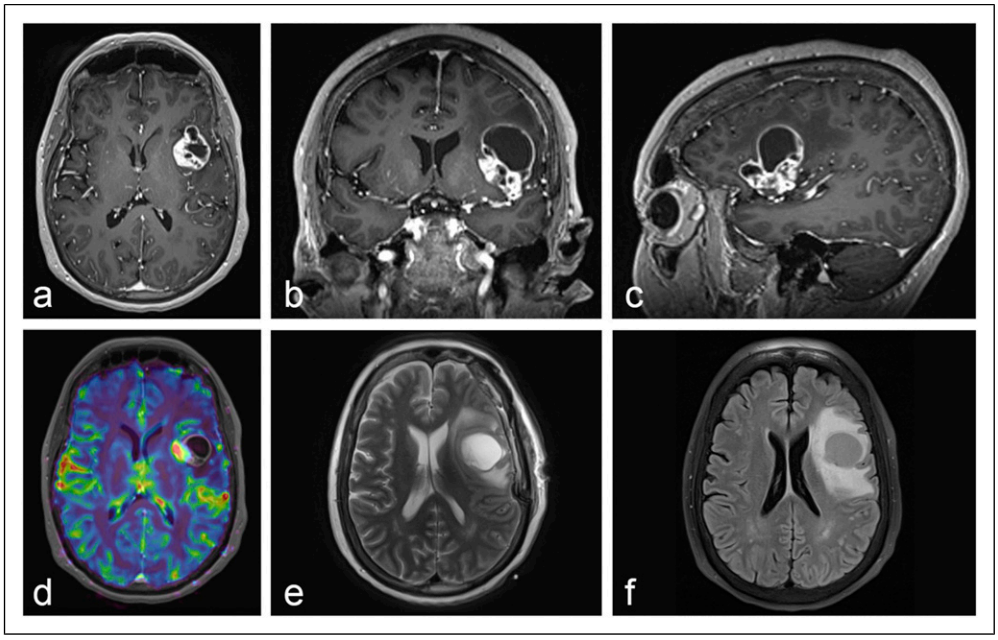

Figure 2. Initial MRI of the Brain. (a–c) T1-weighted imaging with a heterogeneously enhancing lesion of the left insular cortex with a large cystic component extending superiorly into the left inferior frontal gyrus with significant surrounding vasogenic edema. (d) Perfusion-weighted imaging with metabolically active tumor within the left insular cortex. (e) T2-weighted imaging with a moderately-sized cystic component extending superiorly into the left inferior frontal gyrus. (f) Fluid-attenuated inversion recovery imaging confirming vasogenic edema surrounding the tumor of the left insular cortex and cystic component.

Discussion

Classification of ependymal tumors based upon the anatomical location is a fundamental principle of the recent cIMPACT-NOW guidelines.[3] This reclassification was prompted by molecular profiles to suggest distinct genetic profiles observed in the supratentorial, posterior fossa, and spinal compartments.[3] Specifically, supratentorial ependymomas are now classified according to the genes, *C11orf95* and *YAP1*, which contribute the most significant pathogenic gene fusions in each group with grade defined by morphological criteria.[3] These two groups of supratentorial ependymomas have been distinguished by their clinical characteristics in most studies.[3–6] For example, Pajtler et al. demonstrated that supratentorial ependymomas harboring a *YAP1* fusion are clinically and molecularly distinct from those with a *RELA* fusion.[4] Importantly, the authors found that the *RELA* subgroup exhibited a 10-year overall survival and progression-free survival of 50% and 20%, respectively, whereas patients in the *YAP1* subgroup all survived.[4] Comparatively, Merchant et al. found that patients in the *RELA* subgroup did not have uniformly poor survival when treated with immediate postoperative radiotherapy.[49] In fact, the authors found that the five-year event-free survival differed significantly by tumor grade but not age, location, *RELA* fusion status, or posterior fossa grouping.[49] Additional fusions genes have been identified in supratentorial ependymomas, such as *C11orf95* with *MAML2* and *YAP1*, and *YAP1* with *FAM118B*; however, the clinical significance of these rare gene fusions remains to be elucidated.[3] Lastly, in some cases, supratentorial ependymomas are without a detectable fusion gene.[3]

Cortical ependymomas are currently not considered to be a distinct subgroup of supratentorial ependymomas; however, there is a growing body of literature specifically investigating the natural history and clinical outcomes of these lesions compared to supratentorial ependymomas as a whole. Recent studies have demonstrated a higher incidence of *C11orf95-RELA* fusions in cortical ependymomas (90–100%) compared with supratentorial ependymomas (65.1–70%).[4,41,43,48,50,51] Interestingly, Matsumoto et al. found that cortical ependymomas exhibited a comparatively favorable outcome while demonstrating high rates of *C11orf95-RELA* fusions.[41] Similarly, Wang et al. (2020) found that cortical ependymomas exhibit a higher rate of *C11orf95-RELA* fusions with 9 of 10 patients being *RELA* fusion positive.[43] Importantly, the authors found that the nine patients with *RELA* fusions had favorable outcomes with all patients currently living at last known follow-up.[43] Similar results were published by Wang et al. (2021) in a pediatric population with all *RELA* fusion positive patients exhibiting favorable outcomes with no deaths at last known follow-up.[48] Some authors have attributed favorable outcomes to the superficial location of cortical ependymomas

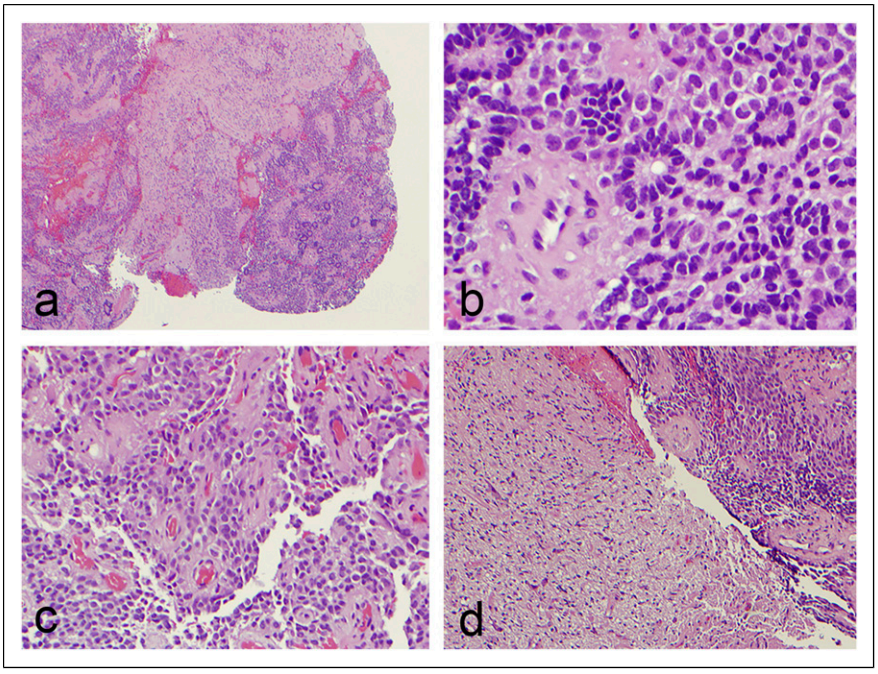

Figure 3. Histopathology consistent with WHO grade 2 ependymoma. Histopathology demonstrated cellular neoplastic tissue consisting of cords of relatively monomorphic tumor cells with perivascular pseudorosettes and focal true ependymal rosettes. Neither necrosis, nor vascular proliferation, nor significant mitotic activity was identified. (a–b) Hematoxylin and eosin stain at ×40 and ×400 magnification, respectively, showing true ependymal rosettes consisting of columnar cells around central lumens. (c) Hematoxylin and eosin stain at ×200 magnification with pseudorosettes. (d) Hematoxylin and eosin stain at ×100 magnification with focal tumor invasion into surrounding brain parenchyma, a feature that is seen more often in supratentorial ependymomas.

and achievable gross total resection.[41,43,48] Moreover, given these data, some authors have suggested the classification of cortical ependymomas as a new distinct subtype of supratentorial ependymoma.[12,41] Further studies with larger sample sizes are necessary to investigate the significance of *RELA* fusions on survival in cortical ependymomas.

The etiopathogenesis of cortical ependymomas remains ambiguous. In many regards, the clinicopathologic characteristics of cortical ependymomas are similar to ectopic ependymomas, that is, ectopic ependymomas are typically low-grade tumors with indolent behavior.[11,21,38] Historically, it has been suggested to group ependymomas based upon their location within the CNS, as natural history, operative mortality, and postoperative survival are known to be closely dependent on tumor location.[11,21,38] Nevertheless, cortical ependymomas and ectopic ependymomas have been considered distinct diagnostic entities. Ectopic ependymomas have been reported to involve the trigeminal nerve, neurohypophysis, sella turcica, falx, posterior fossa, and cavernous sinus.[52–57] Importantly, all of these sites are devoid of ependymal cells, which suggests that ectopic and cortical ependymomas may originate from a cell line distinct from mature differentiated ependyma.[11,21,38] Vernet et al. proposed the etiopathogenesis of ectopic ependymomas to be potentially due to one of several mechanisms including: (i) a migration disorder of the germinal matrix, (ii) primitive neuroectodermal neoplasms differentiating into the ependymal lineage, or (iii) unregulated neoplastic growth of an ependymal cell of ectopic origin.[58] Moreover, Hegyi et al. reported a case of an ectopic retinal ependymoma hypothesized to arise from Muller cells, which would imply that glial cells with progenitor potential may be the origin of these ependymomas rather than matured differentiated ependyma.[59] Extra-axial ependymomas, such as those occurring in ovarian teratomas, further support that these tumors of ectopic origin arise from a progenitor cell line.[21] As such, a progenitor cell line could also be the cell origin of cortical ependymomas. Although several hypotheses have been put forth to explain this phenomenon, the exact pathogenesis of cortical ependymomas has yet to been established.[21]

Currently, there is no consensus regarding the treatment of cortical ependymomas as clinical data is based upon limited case series.[7–48] Although gross total resection is preferred when feasible, the necessity and efficacy of adjuvant therapy remain debated. Indeed, treatment algorithms for cortical ependymomas remain largely dependent upon clinical studies addressing classical supratentorial intraventricular or infratentorial ependymomas.[60–62] There

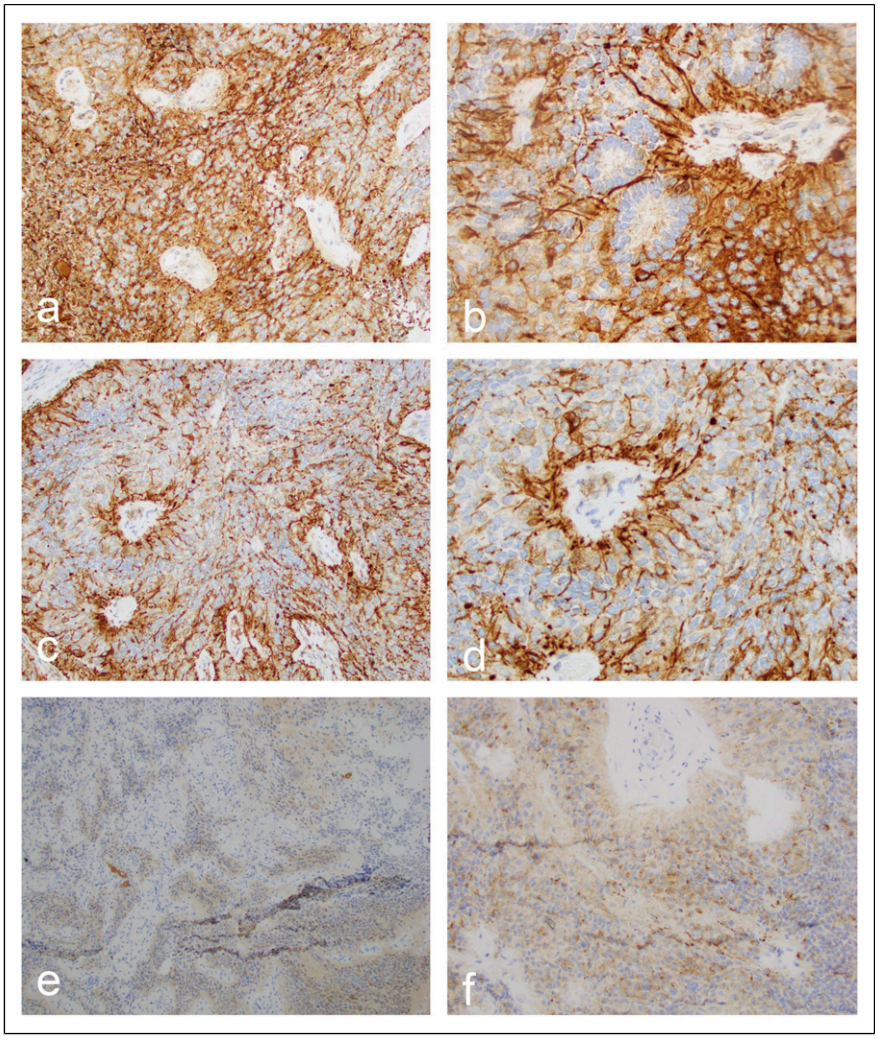

Figure 4. Immunohistochemistry consistent with ependymoma. (a–b) GFAP immunostain at ×200 and ×400 magnification, respectively, shows minimal staining in the ependymal cells of these true rosettes. (c–d) GFAP immunostain at ×200 and ×400 magnification, respectively, highlights the ependymal cell processes in pseudorosettes. (e) NSE immunostain at ×100 magnification shows weak staining in pseudorosettes. (f) Synaptophysin immunostain at ×100 magnification shows weak staining in pseudorosettes.

is widespread agreement in the oncology community favoring adjuvant radiotherapy for adults with WHO grade 3 anaplastic ependymomas regardless of the degree of resection and WHO grade 2 ependymomas after subtotal resection.[60–62] Conversely, adjuvant radiotherapy for WHO grade 2 ependymomas after gross total resection remains controversial.[62,63] Based upon an institutional experience of 13 patients with cortical ependymomas, Wang et al. (2018) advocated for adjuvant radiotherapy for all WHO grade 3 ependymomas regardless of extent of resection and WHO grade 2 ependymomas only in the context of a subtotal resection.[38] In the largest series to date, Wang et al. (2020) performed a comprehensive institutional analysis in 30 patients with cortical ependymomas, in addition to a systematic review of 106 cases previously reported in the literature.[43] The authors found that 69.1% (47/68 cases) of patients with WHO grade 3 cortical anaplastic ependymomas received postoperative adjuvant radiotherapy, which provided a significantly longer overall survival compared to those without irradiation.[43] Importantly, postoperative radiotherapy did not prolong overall survival in patients with WHO grade 2 cortical ependymomas.[43] These data further support widespread favor for adjuvant radiotherapy for WHO grade 3 ependymomas regardless of intracranial location. However, the clinical benefit of adjuvant radiation on disease control in patients with WHO grade 2 cortical ependymomas should be taken with caution, as prospective studies are necessary to validate this finding.[43] Regarding chemotherapeutics, the role of adjuvant chemotherapy, particularly in children, remains unproven despite extensive

investigation, as no chemotherapeutic regimen to date has demonstrated significant clinical benefit.[64]

Based upon our literature review, there is only one prior report of a cortical ependymoma with insular involvement.[21] Van Gompel et al. described a case of a 43-year-old female who presented with seizures and imaging demonstrating a left frontal tumor with insular involvement.[21] The patient was treated with subtotal resection followed by radiotherapy for the WHO grade 2 lesion.[21] Per report, the patient was alive with a stable disease burden at 60 months[21] Similarly, we report a case of a 58-year-old female with a WHO grade 2 ependymoma of the insular cortex extending into the left frontal cortex. Specifically, our tumor was primarily located in Zone 1 (anterosuperior) of the insula as per the Berger-Sanai classification system.[65–67] Our patient also underwent subtotal resection followed by radiotherapy and is currently with a stable disease burden 15 months post-operatively. Although gross total resection is preferred, it may not always be a feasible option, especially when dealing with tumors of eloquent areas, such as the insula. Indeed, the clinical consequences of gross total resection in eloquent areas may supersede disease control when dealing with tumors with more indolent behavior.

Conclusions

Cortical ependymomas are currently not considered to be a distinct subgroup of supratentorial ependymomas; however, there is a growing body of literature specifically investigating the natural history and clinical outcomes of these lesions compared to supratentorial ependymomas as a whole. Preliminary reports describe differing clinical outcomes between cortical ependymomas with *C11orf95-RELA* fusions and supratentorial ependymomas with *C11orf95 RELA* fusions. As such, further studies with larger sample sizes are necessary to investigate the significance of *RELA* fusions on survival in cortical ependymomas and to determine whether cortical ependymomas with *C11orf95-RELA* fusions should be classified as a distinct entity.

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Ethics approval

Our institution does not require ethical approval for reporting individual cases.

Informed consent

Written informed consent was obtained from the patient for their anonymized information to be published in this article.

Contributorship

JAC and ALO conceived the study idea. MSS, JJE, MRW, and ALO provided guidance and oversight. All authors (JAC, ACS, BMS, MSS, JJE, MRW, ALO) made substantial contributions to study planning and data collection. JAC and ALO drafted the original manuscript. MSS provided pathology images. All authors (JAC, ACS, BMS, MSS, JJE, MRW, ALO) critically reviewed and revised the final manuscript for important intellectual content. All authors (JAC, ACS, BMS, MSS, JJE, MRW, ALO) approval the final version of the manuscript.

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