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Coexistent pathology in chronic epilepsy patients with neoplasms

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Neoplasms are a well-established cause of medically intractable or chronic epilepsy. Certain tumors, including gangliogliomas and dysembryoplastic neuroepithelial tumors, are well known to be associated with cortical dysplasia. This study retrospectively examines the incidence of coexistent pathology in patients with tumors and chronic epilepsy. This study is a retrospective review of 270 tumors arising in patients with medically intractable epilepsy encountered during a 20-year period (1989–2009). Coexistent pathology was noted in 50 of 270 (17.8%) patients, including 27 males (54%) with a mean age at surgery of 18 years (range 1–52 years). The vast majority of lesions ($n=40$) (80%) were located in the temporal lobe and less commonly in the parietal lobe ($n=4$) and the occipital lobe ($n=3$). Tumor diagnoses included ganglioglioma ($n=29$), dysembryoplastic neuroepithelial tumor ($n=10$), low-grade glial/glioneuronal neoplasm ($n=5$), low-grade astrocytoma ($n=2$), angiocentric glioma ($n=1$), low-grade mixed glioma ($n=1$), dysembryoplastic neuroepithelial tumor/ganglioglioma mixed tumor ($n=1$), and meningioangiomatosis ($n=1$). Forty-one (82%) tumors represented WHO grade-I neoplasms. Concomitant pathology included malformation of cortical development (cortical dysplasia) in 40 patients (80%) (Palmini *et al* type-I: $n=37$; Palmini *et al* type-II: $n=3$). Hamartias were identified in 10 patients (20%), hippocampal sclerosis in four patients (8%), and nodular heterotopia in one patient (2%). The true incidence of coexistent pathology (17.8% in this study) was likely underrepresented, given the limited extent of adjacent non-tumoral tissue sampling in cases of resected tumor. Coexistent pathology may account for the incidence of recurrent or residual epilepsy in patients who undergo tumor resection.
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The pathologic substrates underlying medically intractable chronic epilepsy are well established and most commonly include hippocampal sclerosis, malformations of cortical development (cortical dysplasia), tumors, and remote ischemic events/infarcts. A number of series have examined the incidence of various tumor types encountered in the setting of medically intractable epilepsy.[1–6] The prevalence of tumors in this setting has ranged from 12.6 to 56.3%.[7–10] In a subset of these tumors, which are generally low-grade glial or glioneuronal neoplasms, multiple pathologies, which potentially may contribute to the genesis of these seizures, are identifiable (dual pathology).[11–16] Among these, there is a well-established association of certain neoplasms with malformations of cortical development (cortical dysplasia), particularly dysembryoplastic neuroepithelial tumors and gangliogliomas.[17–20]

The purpose of this study is to systematically review one institution's experience with neoplasms associated with identifiable coexistent pathology arising in the setting of chronic epilepsy. The study also offers an opportunity to explore some of the challenges in identifying coexistent pathology in this setting.

Materials and methods

After Institutional Board Review approval, the Surgical Pathology database was searched for patients with chronic epilepsy who had a diagnosis of tumor during a 20-year period (1989–2009). From this group, patients with coexistent pathology,

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including malformation of cortical development (cortical dysplasia), mesial temporal sclerosis (hippocampal sclerosis), hamartia, and nodular heterotopia, were identified. Patients with this dual pathology formed the study group.

Tumor classification was based on the most recent World Health Organization (WHO) Classification of Tumors of the Central Nervous System published in 2007.[21] In many cases, there was limited tissue adjacent to the tumor available for examination and evaluation of coexistent pathology was not possible. Malformations of cortical development or cortical dysplasia were identified and classified according to a simplified version of what was described by Palmini *et al*.[22] Due to overlap between the pathology of certain tumors and malformations of cortical development, the limited amount of tissue available for assessment in some cases, and the known lack of reproducibility in the classification (particularly in the Malformation of Cortical Development and Focal Cortical Dysplasia type-I categories; see Table 1), the Palmini *et al* classification was simplified to include only type-I and type-II forms. Table 1 summarizes the terminology and classification of malformations of cortical development and focal cortical dysplasia per Palmini *et al* and the classification used in this study.[22] Mesial temporal sclerosis or hippocampal sclerosis was defined by a characteristic loss of neurons and gliosis in the hippocampal region, preferentially involving the dentate, CA4, CA3, and CA1 regions.[23] Hamartias were defined as collections of small neurons marked by scant cytoplasm and pericellular clearing.[24] Heterotopias were marked by the presence of disordered gray matter tissue in the white matter.[25]

Two hundred and seventy tumors were identified in chronic epilepsy patients in the 20-year period studied. Of those, 50 patients had histologically identifiable coexistent pathology and formed the study group. These patients included 27 males (54%) and 23 females (46%), who at the time of initial surgery had a mean age of 18 years (range 1–52 years).

Results

Tumors originated most commonly in the temporal lobe ($n=40$, 80%). Less common sites of tumor origin included the parietal lobe ($n=4$, 8%), the occipital lobe ($n=4$, 8%), the frontal lobe ($n=1$, 2%), and the temporal–parietal lobe ($n=1$, 2%). In one case, the exact tumor location was not known. Twenty-two tumors were situated on the right side (44%), 24 on the left side (48%), and laterality was not designated in the remaining four tumors (8%).

Table 2 summarizes the salient clinicopathologic features of patients who had tumor and dual pathology of the tumors encountered in this study; the majority were gangliogliomas, WHO grade-I, which were diagnosed in 29 patients (58%). Dysembryoplastic neuroepithelial tumors were diagnosed in 10 patients (20%) (Figure 1a–c). Less commonly encountered neoplasms included low-grade astrocytoma (WHO grade-II) in two patients (4%), angiocentric glioma (WHO grade-I) in one patient (2%) (Figure 2), low-grade mixed glioma or oligoastrocytoma (WHO grade-II) in one patient (2%), and meningioangiomatosis (no WHO grade) in one patient (2%) (Figure 3). One patient had a tumor, which represented a dysembryoplastic neuroepithelial tumor/ganglioglioma composite neoplasm. The remaining five tumors were difficult to classify definitively and were designated as low-grade glioneuronal tumor (WHO grade-I) or low-grade glioma (WHO grade-II) neoplasm, due to the limited tissue sampling. In three of these tumors, the lesion had a morphology suggestive of either a dysembryoplastic neuroepithelial tumor or a low-grade oligodendroglioma; the remaining two tumors had features suggestive of either a low-grade astrocytoma or ganglioglioma.

Malformations of cortical development or focal cortical dysplasia were identified in 40 of 50 patients with tumors. Thirty-seven of 40 cases showed a type-I pattern (Figure 1c), which was observed in 23 gangliogliomas, seven dysembryoplastic neuroepithelial

Table 1 Classification of MCD and FCD (Palmini *et al*[22]), and modification for the current study

Palmini et al classification	*Current study*	*Criteria*
Mild MCD		
Type-I	Type-I	Ectopically placed neurons in or adjacent to layer-I
Type-II		Microscopic neuronal heterotopia outside layer-I
FCD		
Type-I		
A		Isolated architectural abnormalities (dyslamination, accompanied or not by other abnormalities of mild MCD)
B		Architectural abnormalities, plus giant or immature, but not dysmorphic, neurons
Type-II		
A	Type-II	Architectural abnormalities with dysmorphic neurons but without balloon cells
B		Architectural abnormalities with dysmorphic neurons and balloon cells

Abbreviations: FCD, focal cortical dysplasia; MCD, malformation of cortical development.

Table 2 Summary of the clinicopathologic features of coexistent pathology patients

Patient	*Age (yrs)*	*Gender*	*Location*	*Tumor*	*MCD (type)*	*HS*	*Hamartia*
1	10	F	Temporal	LGA	–	+	–
2	12	M	Temporal–parietal	GG	I	–	–
3	3	F	Temporal	AG	I	–	+
4	2	M	Temporal	GG	–	–	–
5	23	M	Temporal	GG	I	–	–
6	6	F	Temporal	GG	–	+	–
7	11	M	Occipital	GG	I	–	–
8	7	M	Occipital	GG	I	–	–
9	52	M	Temporal	GG	I	–	–
10	8	M	Temporal	LGM	–	–	+
11	28	M	Temporal	DNET	–	+	+
12	44	F	Temporal	GG	I	–	–
13	34	M	Temporal	LGA	–	–	+
14	24	M	Temporal	GG	I	–	+
15	12	M	Temporal	GG	I	–	–
16	4	M	Parietal	Mening.	–	–	+
17	19	F	Temporal	GG	I	–	–
18	36	F	Temporal	DNET	I	–	–
19	1	M	Frontal	GG	I	–	–
20	13	M	Parietal	DNET	II	–	–
21	12	F	Temporal	GG	I	–	+
22	9	F	Temporal	DNET	II	–	–
23	20	F	Temporal	G/GN	I	–	–
24	17	M	Temporal	GG	I	–	–
25	34	F	Temporal	GG	–	–	+
26	11	M	Temporal	G/GN	I	–	+
27	17	M	Temporal	GG	I	–	–
28	4	M	Occipital	GG	II	–	–
29	6	F	Temporal	GG	I	–	–
30	4	M	Temporal	GG	-	+	+
31	16	F	Temporal	DNET	I	–	–
32	37	M	Temporal	G/GN	I	–	–
33	15	F	Temporal	GG	I	–	–
34	36	F	Temporal	DNET-GG Comp.	I	–	–
35	17	F	Temporal	GG	–	+	–
36	15	F	Temporal	DNET	I	–	–
37	16	F	Temporal	GG	I	–	–
38	16	F	Parietal	DNET	I	–	–
39	16	M	Temporal	DNET	I	–	–
40	26	F	Temporal	GG	I	–	–
41	26	F	Temporal	GG	I	–	–
42	28	M	Temporal	DNET	I	–	–
43	31	M	Temporal	GG	I	–	–
44	5	F	Temporal	GG	I	–	–
45	5	F	Temporal	G/GN	I	–	–
46	36	F	Temporal	GG	I	–	–
47	5	M	NS	DNET	I	–	–
48	8	F	Temporal	GG	I	–	–
49	29	M	Parietal	G/GN	I	–	–
50	19	M	Temporal	GG	I	–	–

Abbreviations: AG, angiocentric (WHO grade-I); comp., composite; DNET, dysembryoplastic neuroepithelial tumor (WHO grade-I); F, female; G/GN, glial/glioneuronal neoplasm (WHO grade-I or II); GG, ganglioglioma (WHO grade-I); LGA, low-grade astrocytoma (WHO grade-II); LGM, low-grade mixed glioma (WHO grade-II); mening., meningioangiomatosis; M, male; NS, not specified; yrs, years.

tumors, five glial/glioneuronal neoplasms, one angiocentric glioma, and one dysembryoplastic neuroepithelial tumor/ganglioglioma composite tumor. Three tumors had a coexistent type-II malformation of cortical development/cortical dysplasia (Figure 4), including two dysembryoplastic neuroepithelial tumors and one ganglioglioma.

Coexistent hamartias (Figure 5) were identified in 10 patients with tumors including four gangliogliomas, one angiocentric glioma, one low-grade mixed glioma, one low-grade astrocytoma, one meningioangiomatosis, one dysembryoplastic neuroepithelial tumor, and one low-grade glial/glioneuronal neoplasm. Mesial temporal or hippocampal sclerosis was identified in the hippocampus associated with four tumors including two gangliogliomas, one dysembryoplastic neuroepithelial tumor, and one low-grade astrocytoma. One ganglioglioma (patient 9) was noted to have an associated nodular heterotopia.

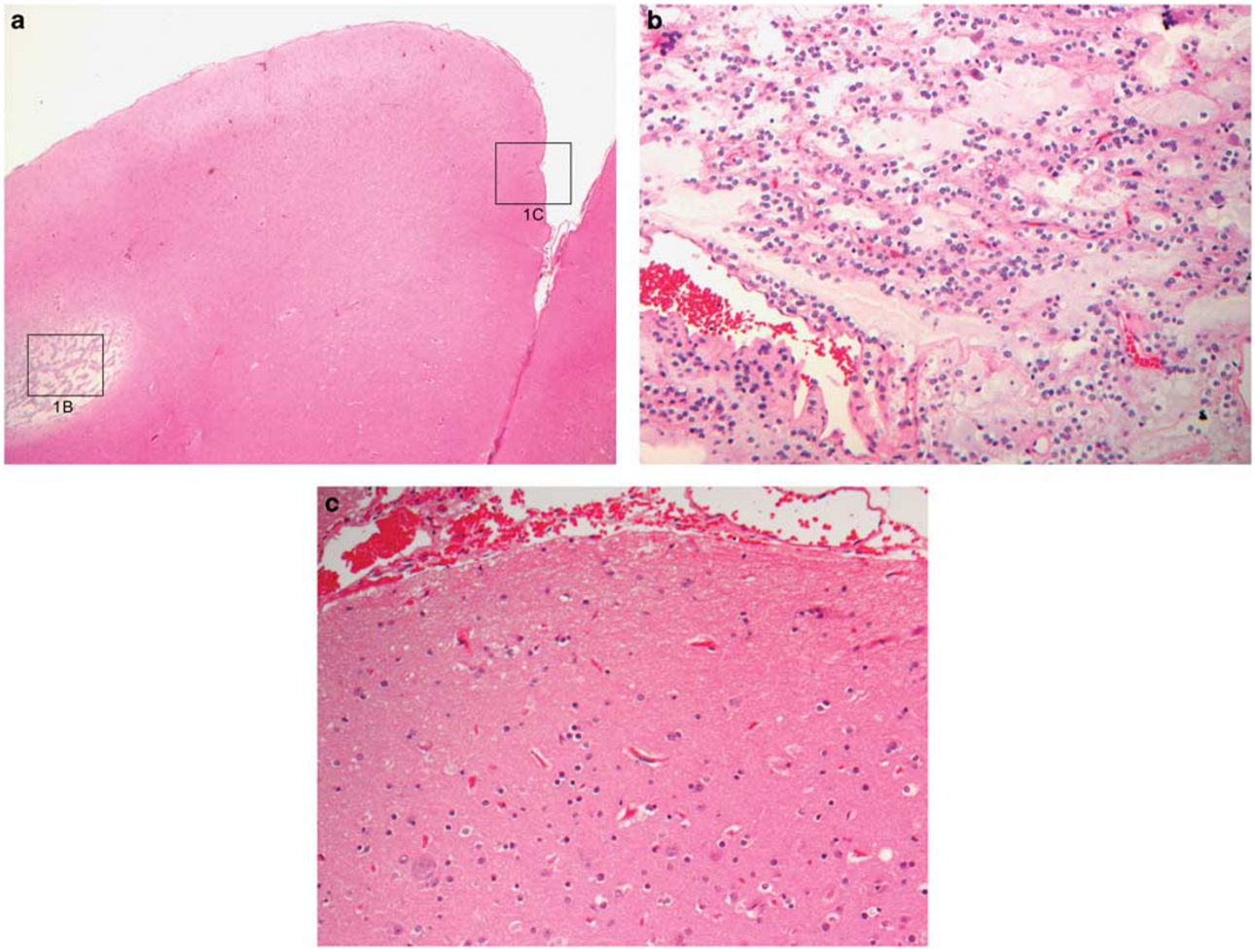

Figure 1 (**a**) A low-magnification appearance of a temporal lobe resection in a patient diagnosed with a dysembryoplastic neuroepithelial tumor illustrating the relationship between tumor (1B, box) and adjacent malformation of cortical development (1C, box) (hematoxylin and eosin, original magnification ×20). (**b**) A high-magnification appearance of the box area in 1B showing a dysembryoplastic neuroepithelial tumor characterized by a microcystic background and cells with rounded nuclei (resembling oligodendrocytes) with interspersed normal-appearing neurons (hematoxylin and eosin; original magnification ×200). (**c**) A higher magnification appearance of the box area in 1C showing a disordered cortical architecture indicated by absence of cortical layer 2 (type-I pattern) (hematoxylin and eosin; original magnification ×200).

Discussion

A variety of tumors are preferentially encountered in association with medically intractable seizures. If one examines the larger series that has been reported, gangliogliomas, dysembryoplastic neuroepithelial tumors, and low-grade astrocytomas are the most commonly encountered neoplasms.[1–6] In general, these tumors tend to present earlier in life, frequently in childhood, and generally represent low-grade lesions (WHO grade-I or II tumors). The incidence of various tumor types in this study in patients with dual pathology seems to be consistent with these findings in that gangliogliomas and dysembryoplastic neuroepithelial tumors represent the two most commonly encountered tumor types. Again, similar to what has been reported previously in the literature, the temporal lobe is the most common site of origin of these lesions. It is not surprising, given the well-established association of dysembryoplastic neuroepithelial tumors and gangliogliomas with malformations of cortical development, that malformations of cortical development are the most commonly encountered second component in the coexistent pathology setting in this study. Interestingly, a small number of other neoplasms, which are not thought to be typically associated with coexistent pathology, were also observed, including rare cases of low-grade astrocytoma and a low-grade mixed glioma. Rare instances of cortical dysplasia have been described in association with other glioma types.[16] Although no pleomorphic xanthoastrocytomas were diagnosed in this series, cases of this tumor and coexistent cortical dysplasia have been reported by others.[26] Two lesions encountered in the current series, which have typically not been reported to be associated with malformation of cortical development,

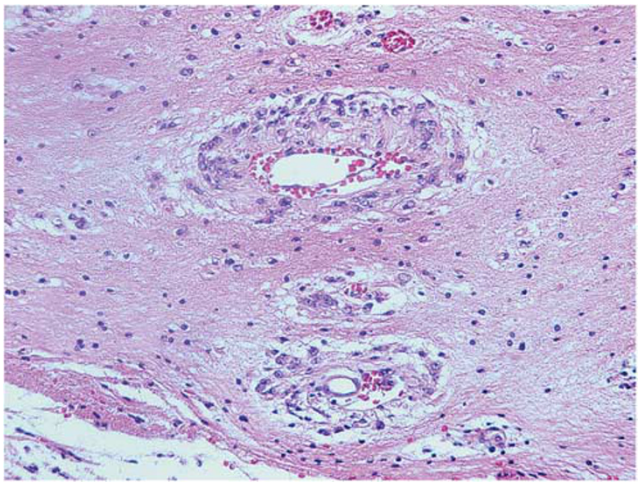

Figure 2 Angiocentric gliomas are marked by proliferation of elongated glial cells around blood vessels, forming a perivascular pseudo-rosetted structure (hematoxylin and eosin; original magnification $\times 200$).

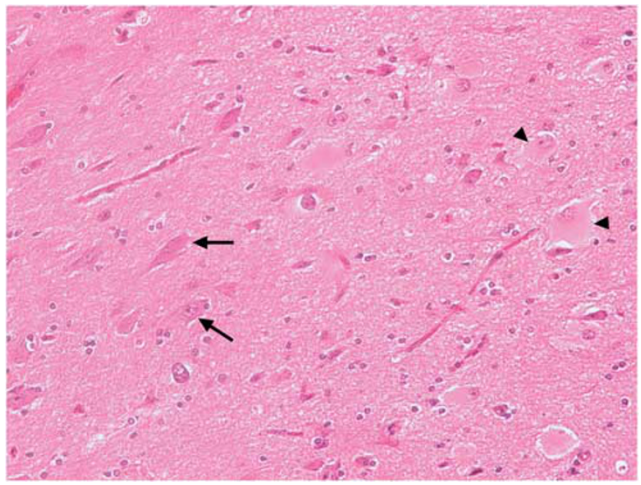

Figure 4 A type-II malformation of cortical development seen adjacent to a dysembryoplastic neuroepithelial tumor and marked by neuronal cytomegaly (arrows) and balloon cells (arrowheads) (hematoxylin and eosin; original magnification $\times 200$).

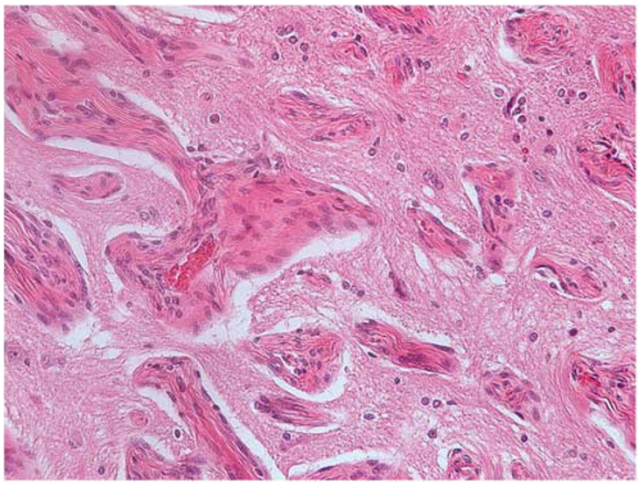

Figure 3 Perivascular proliferations of meningothelial cells characterize meningioangiomatosis (hematoxylin and eosin; original magnification $\times 200$).

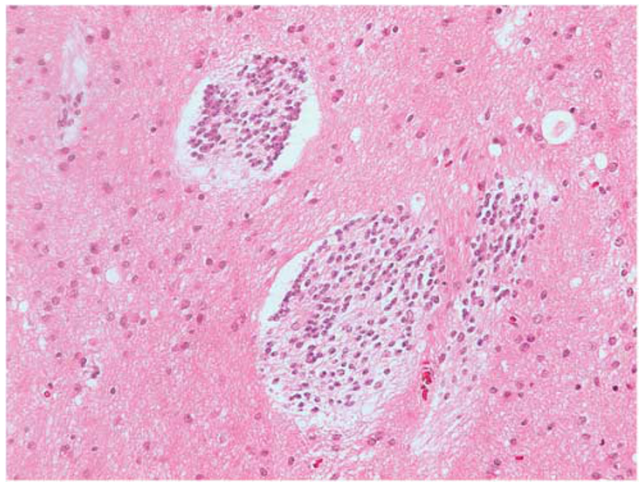

Figure 5 Hamartia adjacent to a ganglioglioma and characterized by aggregates of small neurons (hematoxylin and eosin; original magnification $\times 200$).

include the newly codified angiocentric glioma and meningioangiomatosis;[27–31] the significance of this finding in these rare lesions is not known and may warrant a more systematic examination of these lesions to look for for coexistent malformation of cortical development. The exact nature of the relationship between malformations of cortical development and glioneuronal tumors remains conjectural. Whether the lesions merely coexist and are different phenotypic manifestations of disrupted or abnormal development, whether they represent the opposite ends of the same spectrum, or whether the tumors arise out of the malformation of cortical development is not known.

An interesting category of lesions includes composite tumors, which appear to have geographically distinct areas resembling different glioneuronal neoplasms. The current series contained one case of a dysembryoplastic neuroepithelial tumor/ganglioglioma composite lesion. Rare similar cases have been reported in the literature.[32–34] The finding of an associated malformation of cortical development adjacent to this lesion is not surprising, given the association with both of these tumor entities. Similarly, composite tumors, marked by a mixture of pleomorphic xanthoastrocytoma and ganglioglioma, have also been reported.[35–38] Although pleomorphic xanthoastrocytoma has conventionally been considered a form of astrocytoma, immunohistochemical studies have suggested that a subpopulation of cells in the tumor do show evidence of neural differentiation by immunostaining, raising the question as to whether these tumors may be more glioneuronal in nature than purely astrocytic.[39]

Five tumors in the current series were classified more generally as glial/glioneuronal neoplasms.

With a limited pathologic specimen, the obvious overlap between certain glioneuronal tumors and low-grade gliomas, such as a dysembryoplastic neuroepithelial tumor and a microcystic low-grade oligodendroglioma or a ganglioglioma and a low-grade astrocytoma, are obvious. This underscores the importance of sampling in arriving at a correct pathologic diagnosis in these lesions. The atypical ganglion cell component in the ganglioglioma may be only focally present in the tumor.[17] If this component is not sampled, an erroneous diagnosis of low-grade glioma will be made. Sometimes, the presence of other pathologic findings, such as prominent perivascular lymphocytes or eosinophilic granular bodies, suggests a ganglioglioma diagnosis in the absence of ganglion cells; the findings are typically not salient features of the typical diffuse or fibrillary low-grade astrocytoma.[17,21] Similarly, on a limited biopsy, the areas of a dysembryoplastic neuroepithelial tumor may resemble an infiltrating low-grade microcystic oligodendroglioma. Key to the diagnosis of dysembryoplastic neuroepithelial tumor is recognition of the predominant cortical location of the neoplasm and multinodular architecture.[19,21] All five of these cases in the current series showed evidence of a coexistent malformation of cortical development; this would suggest that these lesions are perhaps more likely glioneuronal tumors than real gliomas.[17–21]

The diagnosis of malformation of cortical development or focal cortical dysplasia in the setting of a ganglioglioma is potentially challenging. There are focal areas of some gangliogliomas, particularly those that are ganglion cell-rich, which can resemble a malformation of cortical development.[17] At times, making the decision at what point the tumor ends and at what point dysplasia or coexistent malformation might begin is subjective. Many cases of coexistent cortical dysplasia are likely not diagnosed, because the findings are simply attributed to the ganglioglioma.

Small hamartias are commonly observed in the hippocampus and amygdala in patients with chronic epilepsy and likely represent small foci of disorganized or incomplete development.[24] Their significance and contribution to epilepsy is uncertain. The presence of hippocampal sclerosis was a relatively rare occurrence in this study. The etiology of hippocampal sclerosis is uncertain. A variety of explanations have been provided.[23,40] Whether the morphologic findings of hippocampal sclerosis are secondary to chronic epilepsy related to the coexistent tumor or whether the coexistence of hippocampal sclerosis represents serendipity, is uncertain.

The clinical significance of identifying coexistent pathology lies within the potential implications for seizure management and control. In many cases, the tumor itself is electrically silent and the origin of seizures is from the tissue adjacent to the tumor.[41] Abnormalities in the adjacent tissue, accounted for by a second epileptogenic pathology, would provide an explanation for seizures in this setting. The potential implication is that, with excision of the tumor, in the tissue-sparing procedure, an epileptogenic lesion, such as a malformation of cortical dysplasia, may be left behind and serve as a focus for recurrent or continued epilepsy. Particularly in tumors that are well known to be associated with cortical dysplasia, this has implications with regard to the extent of resection patients undergo. In the current series, there were many cases in which tissue adjacent to the tumor was not adequate to make a proper assessment for coexistent pathology. It is, therefore, likely that the true incidence of coexistent pathology is higher than the number of cases that are reported in this series. Despite limitations to the reproducibility of diagnoses in the arena of malformation of cortical development/cortical dysplasia,[42] particularly when dealing with the Palmini *et al* Malformation of Cortical Development/Focal Cortical Dysplasia type-I lesions, attempts should be made to identify these findings when evident.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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