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Malignant Transformation Potential of Dysembryoplastic Neuroepithelial Tumors

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Abstract

Dysembryoplastic neuroepithelial tumor is a relatively recently recognized neuropathological entity that was first proposed in 1988. It is typically considered either a quasi-hamartomatous lesion or a benign, low-grade mixed glioneuronal tumor, and is of World Health Organization grade I classification. Earlier studies suggested the clinical stability of this entity given the predominant lack of regrowth or recurrence on long-term follow-up, even in setting of subtotal resection. However, there is increasing evidence to suggest the possibility of atypical behavior including post-resection recurrence and malignant transformation. Mutagenic effects of adjuvant radiotherapy, subtotal resection, contrast enhancement, and high proliferative activity as reflected by Ki67 labeling index have been postulated as risk factors to malignant transformation. However, ultimately, the rare occurrence, limited descriptions, and conflicting findings in the literature preclude confidently making any meaningful conclusions on this phenomenon.

Keywords: Magnetic resonance imaging; Dysembryoplastic neuroepithelial tumor; Astrocytoma; Oligodendroglioma; Malignant transformation

Introduction

First described by Daumas-Duport et al. [1], dysembryoplastic neuroepithelial tumor (DNET) is considered by some as a malformative, hamartomatous lesion [2], and given its proliferative features, is considered by others as a benign mixed glioneuronal neoplasm. It is included in the current World Health Organization (WHO) classification as a grade I glioneuronal tumor [3]. They typically occur in children and young adults and are not an uncommon cause of epileptic seizures refractory to pharmacologic treatment. The typical magnetic resonance imaging (MRI) appearance of DNET includes a cortically based, T1-hypointense, T2-hyperintense lesion that is most commonly seen in the temporal and frontal lobes, and does not typically exhibit mass effect or vasogenic edema [4]. Three histological forms of DNET have been described, including simple, complex, and nonspecific [5]. Although DNET has been classically described as a benign entity, there is increasing evidence to suggest malignant transformation is possible [6].

Discussion

Malignant transformation of DNET has been predominantly observed in case reports and small case series (Table 1). Most DNETs demonstrate extremely low proliferative activity as measured by Ki67 labeling indices, but this finding may appear less consistent in those of complex and nonspecific histological forms [7]. In contrast, all cases with available Ki67 labeling indices with malignant transformation demonstrated significantly higher values [6,8-12]. Given malignant transformation is a rare yet distinctly recognized phenomenon, the presence of an abnormally high Ki67 labeling index in an otherwise histologically and radiologically classic-appearing DNET should raise suspicion for a possibly atypical or malignant entity. However, the approach to calculating the Ki67 labeling index may influence the perceived proliferative activity, with Duggal et al. [13] arguing the high-power field of highest labeling density may be more representative than the average value over 10 random high-power fields. Given DNET glial nodules on histology bear the majority of proliferative activity, random field acquisition may underestimate true level of proliferation, whereas a select high-power field is more likely representative of the region with highest proliferative potential and risk of malignant transformation. Duggal et al. [13] further cautions that the Ki67 labeling index should not be interpreted in isolation, but in the context of other histological features. Accurate histological interpretation is further obfuscated by the observation that concerning histological features may not necessarily translate into clinically aggressive behavior [10,14]. Moreover, despite the absence of mitoses, endovascular proliferation, and necrosis on histology, subsequent growth of

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Table 1: Summary of Reported Cases Demonstrating Malignant Transformation of DNET.

Year	Author	Age	Sex	Site	ME	VE	Gad	Diff	Cal	Surg	Diagnosis	Ki67[a]	XRT[b]	Chem[b]	EFS[c]
2000	Hammond et al. [11]	29	M	F	-	-	Y	-	-	STR	Astrocytoma IV	35	N	N	132
2003	Rushing et al. [12]	14	M	TP	-	-	Y	-	-	STR	Astrocytoma III	12	Y	Y	36
2008	Duggal et al. [13]	29	M	F	-	-	Y	-	-	STR	Astrocytoma IV	-	-	-	132
2009	Ray et al. [10]	12	F	FP	Y	Y	Y	-	-	STR	Astrocytoma III	8.5	Y	N	80
2011	Thom et al. [26]	12	-	T	N	N	Y	-	-	STR	Glioneuronal III	-	N	N	36
2013	Mano et al. [8]	4	F	P	N	N	Y	-	Y	STR	ODG III	30	-	-	20
2014	Chuang et al. [6]	2	F	FP	N	Y	Y	Y	Y	None	Astrocytoma IV	-	N	N	12
2016	Heiland et al. [9]	28	M	O	N	N	Y	-	-	STR	Astrocytoma IV	10	Y	N	60

- = not available; F = female; M = male; P = parietal lobe; F = frontal lobe; T = temporal lobe; O = occipital lobe; Y = yes; N = no; ME = mass effect; VE = vasogenic edema; Gad = presence of gadolinium contrast enhancement; Diff = presence of increased diffusivity; Cal = presence of calcification; Surg = extent of resection; STR = subtotal resection; ODG = oligodendroglioma; III = WHO grade III; IV = WHO grade IV; Ki67 = Ki67 labeling index (%); XRT = adjuvant radiotherapy; Chem = adjuvant chemotherapy; EFS = event-free survival;

[a] = Ki67 labeling index corresponds to regions of malignant neoplasm and not of DNET

[b] = denotes use of adjuvant therapy following initial resection and prior to recurrence with malignant transformation

[c] = denotes months of disease-free survival until recurrence with malignant transformation

residual tumor and recurrence following resection have nevertheless occurred [15].

In several studies [10,12,13], at the time of repeat resection of the subsequently recurrent tumor, the original histopathological diagnosis was retrospectively reviewed and revised to DNET, albeit with two of the cases being originally diagnosed prior to the inception of DNET as a distinct entity. Nevertheless, this may underscore the potential difficulty with ascertaining an accurate diagnosis when confronted with the diagnostic possibility of DNET. Specifically, the heterogeneity of histological features, the growing recognition of varying morphologic subtypes [16,17], and multitude of cellular elements resembling oligodendrogliomas, oligoastrocytomas, or astrocytomas associated with DNETs altogether contribute to the diagnostic challenge of this entity. Therefore, it would not be surprising in rare instances if the reported diagnosis of DNET may not be accurately reflective of the true nature of the underlying neoplasm.

In three cases, malignant transformation occurred following radiation [9,10,12], and raises implication for the potential mutagenic effect of adjuvant radiotherapy on subsequent risk of malignant transformation, which have been similarly observed in cases of pilocytic astrocytoma [18,19]. It should be noted, however, the original study by Daumas-Duport et al. [13] demonstrated no difference in recurrence or survival in the 13 who underwent adjuvant radiotherapy versus the 26 who did not. Overall, the limited number of cases with malignant transformation precludes the ability to confidently identify any trends and make meaningful conclusions.

With the exception of two studies [6,8], the remaining cases demonstrated recurrence of malignant transformation following initial surgical resection. For studies reporting malignant DNET prior to surgery, Chang et al. [6] observed a new enhancing mass along the lateral aspect of the original unresected biopsy-proven DNET. Mano et al. [8] demonstrated two histopathologically distinct entities in the same mass preoperatively, with the enhancing portion corresponding to anaplastic oligodendroglioma, and the non-enhancing portion corresponding to DNET. These cases suggest the possibility of two coexisting primary neoplasms arising separately rather than malignant transformation of a benign neoplastic entity. It is unclear how often the improbable occurrence of two coexisting primary neoplasms may be seen, particularly in potential scenarios in which a second benign primary neoplasm coexisting with DNET is entirely resected along with DNET at the time of surgical intervention, and therefore may reduce the observed incidence of such postulated coexistence. In the case of Chuang et al. [6], the relatively large size of the lesion may have led to sampling error, and argues for the possibility of under-sampling of a separate coexisting neoplasm that was subsequently interpreted as transformation at the time of recurrence.

Interestingly, Heil et al. [9] observed two recurrences and malignant transformation in an originally diagnosed DNET case, and was histologically bearing all hallmark features of a glioblastoma at the time of recurrence (glial markers, high proliferation, necrosis, and angiogenesis). However, the epigenetic signature and methylation patterns of both the first and second recurrent glioblastoma exhibited striking similarity to that of the original DNET, especially when comparing it to the more distinctly different established methylation patterns typically seen in glioblastomas [9]. The similar epigenetic signatures suggest a common molecular and cellular origin, and further supports the process of malignant neoplasms arising from a benign neoplastic entity (malignant transformation), rather than arising *de novo* and incidentally coexisting within the same lesion. Indeed, despite the histological hallmarks of glioblastoma, the authors argue the recurrent tumor should be termed a "malignant DNET" given its strong epigenetic association with the tumor of origin [9].

Contrast enhancement, whether heterogeneous, ring, or nodular in pattern, may be normally seen in 20% of cases, and doesn't necessary imply a high-grade behavior [10]. Enhancing portions of the tumor have been observed to correlate significantly with the complex form of DNET on histopathology [5,8]. However, all cases exhibiting malignant transformation also demonstrated contrast enhancement. Therefore, while contrast enhancement may be considered a imaging finding that is consistent with features of a classic, benign DNET, the potential presence of malignant transformation should be a considered a rare possibility. The possibility of tissue enhancement in the relatively earlier period (several months) following surgical resection may also further obfuscate determination of the presence of recurrence and a more aggressive entity. However, this may not be particularly relevant as the time to malignant transformation was 20 months following resection at the earliest in cases summarized here [8].

The incidence of recurrence with malignant transformation

occurring predominantly in subtotal resection cases within the existing literature may underscore the importance of a total resection as a means to mitigate such risk of recurrence and malignant transformation. However, the original study by Daumas-Duport et al. [1] demonstrated that of 17 cases with subtotal resection, no evidence of recurrence was found on long-term follow-up. In another study, a subset of patients with DNET who underwent en bloc resection also did not demonstrate any evidence of recurrence [20]. Lee et al. [21] reported gross total resection in 14 patients with DNET without evidence of tumor on follow-up with MRI, with a mean follow-up interval of 21 months. Stanescu Cosson et al. [4] reported no recurrence following resection on radiological follow-up of 4.5 years in 49 patients. In contrast, Daghistani et al. [15] reported 6 of 18 patients with subtotal resection exhibited increasing size of the residual tumor. More interestingly, 3 of 30 patients with gross total resection also had tumor recurrence [15]. Such occurrences with gross total resection have been reported in other studies as well [10,22-26]. Therefore, subtotal resection alone may not be a significant predisposing risk factor for malignant transformation.

Overall, the limited characterization of malignant transformation of DNETs in the literature may be partly due to the relatively short duration of time this entity has been in existence since the first description in 1988 [1]. It is possible certain mixed glial, astrocytic, and oligodendroglial tumors implicated in malignant transformation prior to 1988 may have in retrospect possessed histological features suggestive of DNET, but instead were reported in the literature under another glial entity.

Conclusions

DNET is a relatively new entity in the WHO classification that is classically considered a benign, low-grade mixed glioneuronal neoplasm. Rare reports of malignant transformation into high-grade oligodendrogliomas, astrocytomas, and mixed glioneuronal tumors suggest the behavior of DNETs may not be as benign as initially suggested. The limited descriptions in the literature obviate any ability to perform meaningful statistical analysis and make confident conclusions on risk factors and pathogenesis, but nevertheless suggest that malignant transformation should be recognized as a possible but rare occurrence.

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