Dysembryoplastic Neuroepithelial Tumor: A Review

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Most DNETs are benign, low-grade lesions. However, a small number appear to have the potential for malignant transformation. We report a patient with a biopsy-proven DNET with features of an ogliodendroglioma and review the clinical features of DNETs and their potential for malignant transformation.

Key Words: dysembryoplastic neuroepithelial tumor, malignant transformation

Abbreviations Used: DNET, dysembryoplastic neuroepithelial tumor; MR, magnetic resonance; SGNE, specific glial neuronal element; WHO, World Health Organization

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In 1988 Dumas-Duport et al. first used the term dysembryoplastic neuroepithelial tumor to describe low-grade tumors found in young patients with intractable partial seizures.[4] In 1993 the distinct pathological entity known as DNET was given a place in the WHO classification of brain tumors as a grade I tumor of neuroepithelial origin.[3,10,11] Many studies have reported successful surgical management of this low-grade tumor in the treatment of refractory epilepsy. We report the case of a young man who experienced possible seizure activity and was found to have a biopsy-proven DNET.

Case Report

A 30-year-old man with no significant medical history experienced the sudden onset of right facial numbness, which resolved completely within hours. When questioned he stated that he had experienced occasional sensory abnormalities in his right arm and leg throughout the previous year. Computed tomographic scans showed a nonhemorrhagic hypodense lesion in the mesial temporal lobe, thalamus, and posterior limb of the internal capsule. The lesion was hyperintense on T2-weighted MR images, hypointense on T1-weighted images, and nonenhancing (Fig. 1). Based on the imaging studies, the diagnosis was unclear and we recommended that the patient undergo a needle biopsy to guide further treatment.

An intraoperative frozen specimen was interpreted as either an oligodendroglioma or a DNET. The final pathological evaluation described nodular, neoplastic, glioneuronal elements with oligoden-

droglial-like features and areas of microcystic change and hyalinization. On immediate postoperative MR imaging, a small hemorrhage was visible in the tumor bed. The patient suffered no adverse events and was discharged home neurologically intact after a brief period of observation. Interestingly, on follow-up imaging the lesion had partially regressed. We hypothesized that the compressive forces of the intraoperative hemorrhage had partially obliterated the tumor.

Discussion

In 1988 Dumas-Duport and colleagues first characterized DNETs when they described neuroepithelial tumors in 39 patients with medically intractable partial complex seizures.[4] Their cohort was a combination of epilepsy patients undergoing surgery at St. Anne Hospital in France and at the Mayo Clinic in Rochester, Minnesota. They noted a distinct cortical tumor with multinodular architecture, associated cortical dysplasia, and both neuronal and glial elements. After resection their patients were followed a mean of 9 years. Their outcomes were excellent. Of the 39 patients, 30 were seizure free, 4 experienced only rare seizures, and the number of seizures was reduced significantly in the remaining 3 patients. Two patients died. Despite being seizure free, one patient committed suicide 3 months after surgery. The second patient received whole brain radiation and polychemotherapy and was found to have extensive radionecrosis at autopsy.

Although the report by Dumas-Duport et al. is considered the first to describe these tumors and their specific histology,[4] they did credit Cavanagh of London who published an article in 1958 called, *On Certain Small Tumors Encountered in the Temporal Lobe*.[1] The multinodular lesions that Cavanagh described were found while he performed temporal lobectomies for temporal lobe epilepsy. Cavanagh described the lesions as hamartomas but opined that areas of "early neoplastic change" were susceptible to malignant transformation into gliomas. Dumas-Duport et al.[4] considered the tumor to be at least partially neoplastic and argued that these lesions formed during embryonic development.

Dumas-Duport's argument that DNETs had embryonal origins was four-fold. First, these tumors exhibited multiple cell lineages that could arise from multipotent cells present during early development. Second, these tumors manifest early in life. Third, there is often an adjacent bone deformity, which suggests that the tumors are long standing with an early onset. Finally, the presence of cortical dysplasia implies that these lesions occur during cortical formation and are not neoplasms that arise within normally developed cortex. The actual origins of these indolent tumors and whether they are truly neoplastic are still debated.

Classification

The original paper describing DNETs focused on the theory that these tumors had embryonal origins. However, it was clear that their clinical course differed from that of tumors classified as embryonal tumors of neuroepithelial origin. Tumors listed in the WHO classification scheme as embryonal are all considered WHO grade IV lesions (Table 1).[12] Thus the term *dysembryoplastic* was coined to indicate both the origin of these tumors and the observation that they share features with less aggressive, dysplastic lesions. However, the authors did not think that the term was an entirely accurate description of these tumors, which share some similar histologic features with neoplastic lesions. Nonetheless, the term dysembryoplastic still served to denote the predominantly benign clinical course of these tumors.

In 1993 DNETs were placed in the WHO brain tumor classification scheme as a neuronal/mixed glial-neuronal tumor of neuroepithelial origin.[3,10,11] They are

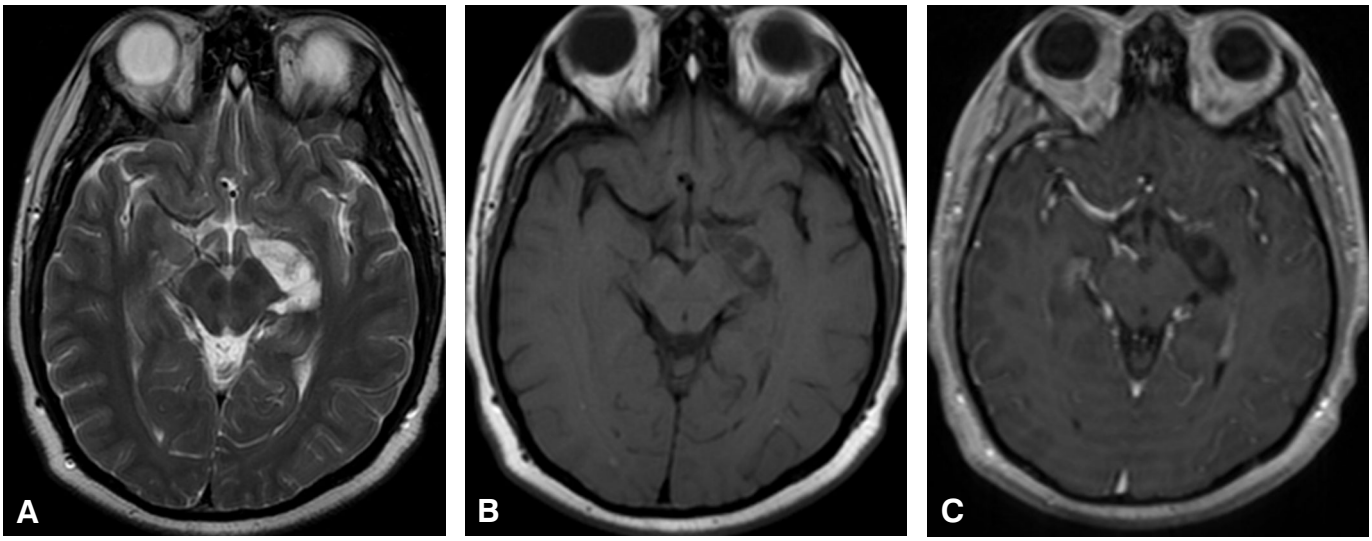

Figure 1. (*A*) Axial T2-weighted MR image shows a hyperintense lesion in the mesial temporal lobe. Axial T1-weighted MR images (*B*) with and (*C*) without contrast show a hypointense lesion that does not enhance.

Table 1. Tumors classified as embryonal within category of tumors with neuroepithelial origins.† [12]

Medulloblastoma
Desmoplastic/nodular medulloblastoma
Medulloblastoma with extensive nodularity
Anaplastic medulloblastoma
Large cell medulloblastoma
CNS primitive neuroectodermal tumor
CNS neuroblastoma
CNS ganglioneuroblastoma
Medulloepithelioma
Ependymoblastoma
Atypical teratoid/rhabdoid tumor

†According to the 2007 WHO classification of brain tumors.

Table 2. Tumors classified as neuronal and mixed neuronal-glial tumors within category of tumors with neuroepithelial origins[12]

Dysplastic gangliocytoma of cerebellum (Lhermitte-Duclos)
Desmoplastic infantile astrocytoma/ganglioglioma
Dysembryoplastic neuroepithelial tumor
Gangliocytoma
Ganglioglioma
Anaplastic ganglioglioma
Central neurocytoma
Extraventricular neurocytoma
Cerebellar liponeurocytoma
Papillary glioneuronal tumor
Rosette-forming glioneuronal tumor of fourth ventricle
Paraganglioma

classified as Grade I tumors along with the other low-grade neuronal tumors such as gangliogliomas and gangliocytomas (Table 2).[12] Although still debated, most contemporary neurosurgeons consider these tumors to be frankly neoplastic.

Histology

Three histologic forms of DNET have been described: complex, simple, and nonspecific.[2] The complex form (Fig. 2), which is the type originally described by Dumas-Duport et al.,[4] consists of SGNE (Fig. 3), glial multinodular architecture, and associated cortical dysplasia. The nodular component of a DNET contains both glial and neuronal components and can resemble both gliomas and gangliogliomas. The neuronal component often consists of neurons "floating" in a basophilic mucinous matrix (Fig. 4). The axons are surrounded by "tumoral" oligodendrocyte-like cells. These cells exhibit oligodendroglial features, including prominent perinuclear halos (Fig. 5). The simple form, which was also described by Dumas-Duport et al.,[4] consists only of the SGNE. The nonspecific form is more controversial: It has neither the SGNE nor the multinodular architecture. It resembles a low-grade astrocytoma but has clinical and radiological features more consistent with a DNET.[5]

Imaging Features

On neuroimaging DNETs are cortical lesions with little mass effect and a predilection for the temporal lobes. On computed tomography DNETs are typically well-demarcated, hypodense, cortical lesions that can be associated with deformation of the overlying skull. In a radiological study, fewer than 20% contained calcifications in contrast to gangliogliomas, which had a much higher rate.[16] MR images often show a solid and cystic mass with the cystic portions appearing slightly more intense than cerebrospinal fluid. A cystic signal pattern is not specific to DNET; the pattern is also found in other tumors frequently associated with epilepsy such as gangliogliomas and gliomas. The solid components often appear multinodular, hypointense on T1-weighted MR images, hyperintense on T2-weighted MR images, and occasionally weakly enhancing.[6,17]

Clinical Course

Consistent with their original description, DNETs are tumors associated with epilepsy in young adults. In 2006 Chan et al. reported the outcomes of patients who underwent surgical removal of a DNET for seizure control and reviewed the published series of DNETs.[2] The mean long-term outcome of 18 patients with DNETs surgically resected for the treatment of epilepsy was 10.8 years. They found that 66.7% of their patients achieved Engel Class I outcomes, indicating that they were free of disabling seizures. In the reviewed series of surgical outcomes for DNETs, 52.4 to 90% of the patients achieved Engel Class I. Interestingly, the results that they had previously reported for the same group of patients at a mean of 2.7 years of follow-up were predictive of their long-term outcomes. Their results, combined with those of other studies, led them to conclude that a patient who is seizure free 3 years after resection of a DNET can be considered cured.

Nonetheless, DNETs can recur as Nolan et al. reported in 2004.[13] Of 26 children who underwent surgical resection of their tumor for seizure control, 3 demonstrated a recurrence within 1 to 5 years. In this series, the rate of incomplete resection was high (63%), and all patients who experienced a recurrence showed some degree of residual tumor on postoperative imaging.

Potential for Malignant Transformation

In published series the clinical course of DNETs has been stable. Only rarely does diagnostic imaging reveal a postoperative recurrence. Recent case reports, however, have shown that these

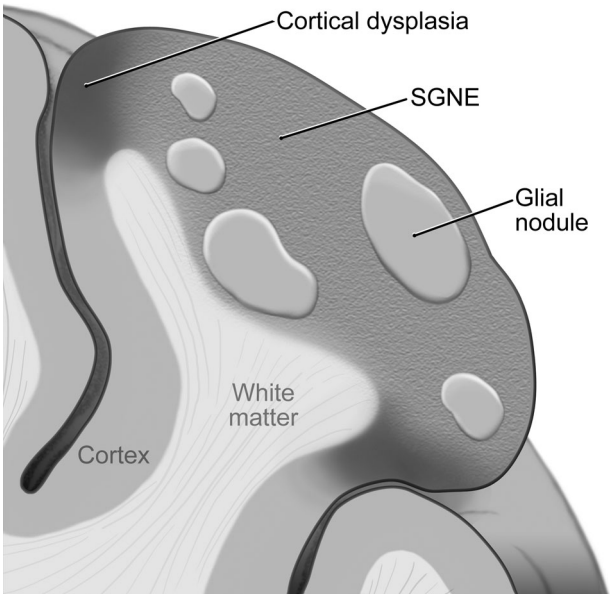

Figure 2. Schematic representation of the complex form of DNET.

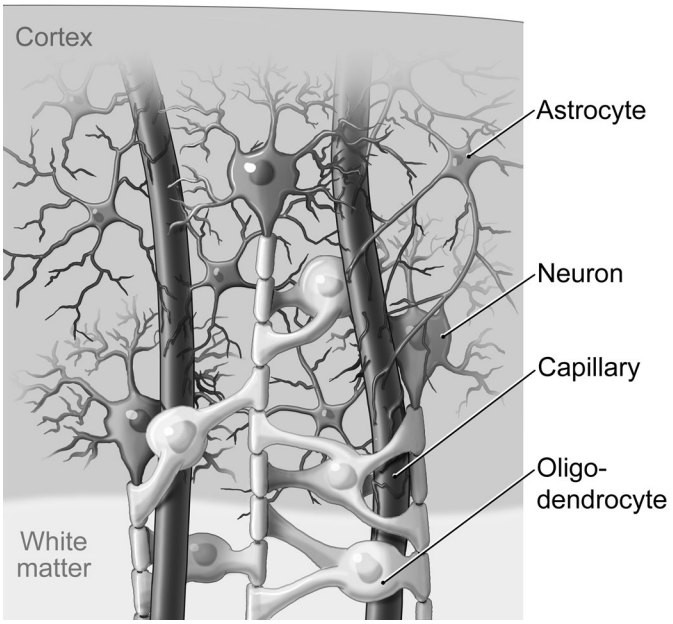

Figure 3. Schematic representation of the SGNE of a DNET showing the neuronal elements that form the columnar structures perpendicular to the cortical surface.

lesions may undergo malignant change. In 2000 Hammond et al. reported the first malignant transformation of a DNET that had been surgically resected.[7] The patient, a 29-year-old man who suffered from partial seizures, had a nonenhancing lesion in his left frontal cortex. He first underwent surgery in 1984, when his tumor was labeled as a "fibrillary astrocytoma." The surgeons reported subtotal resection. The patient received no radiation or chemotherapy, but 11 years later his seizures recurred. MR imaging showed a partially enhancing cystic lesion. After repeat resection the pathology was confirmed as a grade IV astrocytoma. Retrospective histological review of the initial tumor found it to be a DNET with SGNEs, glial nodules, and associated cortical dysplasia.

In 1974 Rushing et al. described a 14-year-old boy who underwent subtotal resection of a tempoparietal mass for the treatment of epilepsy.[14] The pathology, which was originally diagnosed as a "mixed oligoastrocytoma," was later shown to be a DNET. The patient received postoperative radiation therapy. One year later MR imaging showed the formation of a cyst that was drained via a craniotomy. After this procedure the patient underwent a 6-week course of chemotherapy. Three years later, his seizure activity resumed and a tumor recurrence was found. The patient underwent a third surgery, and the pathologic diagnosis of the lesion was consistent with progression to an anaplastic astrocytoma.

Three other studies also suggest the potential for transformation or progression of a DNET. Josan et al. reported a 3-year-old girl with seizures who was found to have a DNET. She was managed conservatively.[9] At the age of 14 years, follow-up MR imaging showed a large cystic lesion, which was resected. The lesion was diagnosed as a pilocytic astrocytoma within a surrounding DNET. In a 9-year-old with seizures, Sampetrean et al. described a DNET with a small ring-enhancing core; the size of the lesion tripled in 3 months.[15] Surgical resection confirmed the diagnosis of DNET. Five years after surgery, the patient remained seizure free without a recurrence. Jensen et al. reported a 46-year-old patient who had medically refractory seizures with a nonenhancing, low-intensity lesion in the mediotemporal lobe.[8] The patient opted for conservative management until the tumor developed contrast enhancement after 15 years. Surgical pathology revealed a DNET without atypical changes. These findings suggest that on imaging these tumors can show progression that does not necessarily imply malignant transformation.

Because DNETs have only been discovered within the last 20 years, their natural history is not yet completely defined. The literature, however, suggests that these lesions hold the potential for malignant change. It is possible that the discovery of a higher-grade lesion within a histologically proven DNET is simply coincidental. Given that some DNETs display high mitotic activity based on the Ki-67 proliferation labeling index, it seems likely that these tumors arise from neoplastic cells within the DNET itself.[2] These findings support the argument that a DNET is at least partially a neoplastic lesion, although its nature is still debated. Although some of these tumors progress, most are stable and rarely recur after surgery. Possibly, a subset of these tumors yet to be identified has the propensity

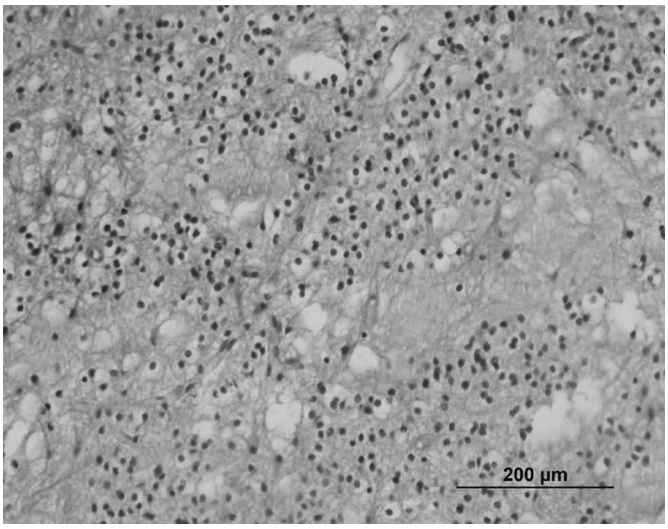

Figure 4. Low-power view of oligodendrocyte-like cells with prominent perinuclear halos embedded in a background of abundant basophilic mucin (hematoxylin and eosin, original magnification x200).

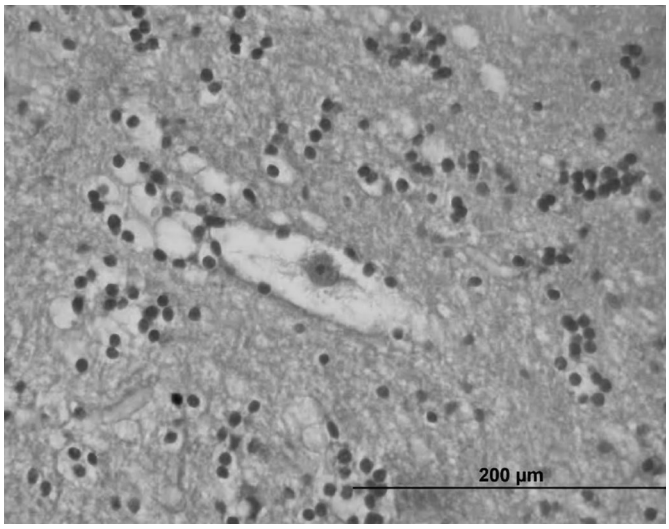

Figure 5. High-power view of a floating neuron (hematoxylin and eosin, original magnification x400).

for malignant transformation. When the natural history of these tumors is better defined with longer follow-up, we also may find that a greater percentage progress to more aggressive lesions than previously thought. For now these reports demonstrate the importance of regular follow-up, both clinical and radiographic, for patients who harbor DNETs.

Conclusion

Since their discovery in 1988, much has been learned about the characteristics and clinical course of DNETs. It is widely accepted that patients with seizures attributable to these lesions are excellent surgical candidates who achieve good outcomes and low recurrence rates without the use of adjunct therapies. Although most DNETs are benign, low-grade lesions, it is becoming increasingly apparent that a small number will progress to more aggressive lesions. Consequently, we recommend that these patients have regular follow-up examinations to identify progression at its early stages. As the natural history of DNETs is better defined, it should become increasingly possible to tailor treatments and follow-up regimens to individual patients.

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