Malignant transformation of a dysembryoplastic neuroepithelial tumor

Case report

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A 29-year-old man presented in 1984 with a recent onset of partial seizures marked by speech arrest. Electroencephalography identified a left frontotemporal dysrhythmia. Computerized tomography (CT) scanning revealed a superficial hypodense nonenhancing lesion in the midleft frontal convexity, with some remodeling of the overlying skull. The patient was transferred to the London Health Sciences Centre for subtotal resection of what was diagnosed as a “fibrillary astrocytoma (microcystic).” He received no chemotherapy or radiation therapy and remained well for 11 years.

The patient presented again in late 1995 with progressive seizure activity. Both CT and magnetic resonance imaging demonstrated a recurrent enhancing partly cystic lesion. A Grade IV astrocytoma was resected, and within the malignant tumor was a superficial area reminiscent of a dysembryoplastic neuroepithelial tumor (DNT). Data on the lesion that had been resected in 1984 were reviewed, and in retrospect the lesion was identified as a DNT of the complex form. It was bordered by cortical dysplasia and contained glial nodules, in addition to the specific glioneuronal element. The glial nodules were significant for moderate pleomorphism and rare mitotic figures. The Ki67 labeling index averaged 0.3% in the glial nodules and up to 4% focally. Cells were rarely Ki67 positive within the glioneuronal component. This case is the first documented example of malignant transformation of a DNT. It serves as a warning of the potential for malignant transformation in this entity, which has been traditionally accepted as benign. This warning may be especially warranted when confronted with complex forms of DNT. The completeness of resection in the benign state is of paramount importance.

Key Words • dysembryoplastic neuroepithelial tumor • malignant transformation • neoplasm • hamartoma

Since the original description by Daumas-Duport, et al., in 1988, the DNT has attained widespread recognition as a benign quasineoplastic or hamartomatous entity associated with chronic refractory epilepsy. In centers with large epilepsy services, at which DNT cases have now been followed for more than 10 years, the tumor has become virtually commonplace. The present case is the first known example of malignant transformation of a DNT.4

The clinical behavior of these lesions as a group is unquestionably benign; however, the 11-year period during which the entity has been recognized is still too short for a complete assessment of their potential. Our case and others provide evidence of the neoplastic nature of DNTs and their full biological potential.

The clinicopathological identity of the DNT was first brought to light by Daumas-Duport, et al., In a large collection of patients treated by lobectomy for chronic refractory epilepsy, a distinct multinodular intracortical entity emerged as a novel diagnostic category. In this landmark paper, the defining features of 39 cases of simple and complex DNTs were presented. Since then, their striking histopathological characteristics and their pattern of association with chronic partial seizures have been extensively corroborated.5,7,8 Although malignant degeneration has not previously been described, Daumas-Duport and others have occasionally noted mitotic activity and focal proliferative indices (using MIB1 labeling) more typical of high-grade gliomas.2,6 Furthermore, enlargement of DNTs has been noted on serial imaging studies.7 These findings and the example of the present case support the neoplastic nature of the DNT and further justify follow-up observation in such cases, as for any low-grade glioma.

Case Report

History. This 29-year-old right-handed man originally presented with a recent onset of seizures. His first seizure was grand mal in nature, whereas subsequent events were focal and typified by periods of speech arrest lasting from a few minutes to 1 hour. In retrospect, his wife described possible absencelike spells (periods in which the patient displayed blank staring and inattention to voice) dating back to adolescence. The new seizures proved to be refractory to phenytoin and carbamazepine. Neurological

Abbreviations used in this paper: CT = computerized tomography; DNT = dysembryoplastic neuroepithelial tumor; MAP2 = microtubule-associated protein–2; MR = magnetic resonance; OLC = oligodendroglia-like cells.
findings were normal, apart from mild hyperreflexia on the right side. Electroencephalography revealed a focal left frontotemporal dysrhythmia.

Head CT scans revealed a superficial nonenhancing hypodense lesion in the superior middle convexity of the left frontal lobe, with thinning and scalloping of the overlying skull (Fig. 1a).

The patient underwent surgery during which the tumor was found to be a well-demarcated pale elliptical mass restricted to an expanded left midfrontal gyrus (Fig. 1b). It measured approximately 6.5 × 3 cm at the pial surface and was firm in comparison with surrounding brain. The posterior portion of the tumor bordered on the precentral gyrus at the wrist area, as determined by cortical stimulation. The latter portion was not completely resected. The inferior resection was limited by speech arrest. The lesion was diagnosed as a fibrillary astrocytoma, and no adjuvant therapy was given.
Examination. After 11 years, the patient presented again with progressive seizures. Imaging revealed a recurrent left midfrontal mass with cystic components and enhancement (Fig. 1c). The malignant lesion fulfilled all criteria for a World Health Organization Grade IV astrocytoma (Fig. 1d), displaying marked nuclear pleomorphism, mitotic activity, endothelial hyperplasia, and necrosis. Scattered tumor cells expressed glial fibrillary acidic protein and the average Ki67 index was 35% (in 10 random high-power fields). However, within the frankly malignant glioma were infiltrated components reminiscent of a DNT (Fig. 1e and f). The original resected specimen was reviewed and found to be a multinodular low-grade intracortical tumor (Fig. 2a). The latter was bordered by a short

Fig. 2. Photomicrographs of tissue specimens obtained at the original resection. a: Intracortical microcystic tumor in which multinodularity (arrows) can be observed around one sulcus. Note that the subcortical white matter (at the bottom) is uninvolved. H & E, original magnification × 10. b: Bordering regions of cortical dysplasia with disruption of the laminar architecture and neuronal polarity. H & E, original magnification × 10. c: Cellular atypia within glial nodules. H & E, original magnification × 400. d: Mucin-filled microcysts (M), OLCs (arrows), and “floating neurons” (arrowheads) of the specific glioneuronal element. H & E, original magnification × 400. e: Many OLCs and floating neurons (arrow) expressing the neuronal marker MAP2. Immunoperoxidase staining with anti-MAP2, original magnification × 400. f: Occasional floating neurons (arrow) demonstrating cytoplasmic expression of synaptophysin. Immunoperoxidase staining with antisynaptophysin, original magnification × 400.
Malignant transformation of a DNT

span of dysplastic cortex (Fig. 2b) and contained glial nodules (Fig. 2c), as well as the specific glioneuronal element (Fig. 2d), highlighted by mucin-filled microcysts containing “floating neurons” and lined by OLCs. The glial nodules were notable for mild pleomorphism (Fig. 2e), rare mitotic figures, and a random Ki67 index of 0.3% (three per 1037 cells in 10 random high-power fields) and a maximum Ki67 index of 4% (six per 139 cells in one high-power field). Within the specific glioneuronal element there were no mitoses and Ki67 labeling was rare (< 0.1%). Several large “floating” neurons and many small neurons of the specific glioneuronal element strongly expressed MAP2 (Fig. 2e). Occasional floating neurons also displayed weak expression of synaptophysin in the perinuclear cytoplasm (Fig. 2f). The patient died 3 months after the second resection.

Discussion

This case is the first recognized example of malignant transformation in a DNT. Other examples likely exist, in which tumors have been classified as other low-grade gliomas before the recognition of DNTs as a distinct entity. The present case was recognized in retrospect by examining the remnant of DNT in the second resection and by comparing it with the original tumor. Dysembryoplastic neuroepithelial tumors have only existed in the realm of diagnostic neuropathology for 11 years—too short a period for a complete assessment of their potential for malignant transformation. However, given no similar reports, these lesions in large part behave in a very benign fashion, as originally predicted.

Several authors have noted evidence of a wide range of proliferation in DNTs. The vast majority show negligible proliferation, and this appears to be particularly true in the neuronal and OLC components. However, there are several examples in the literature of more alarming anaplasia, MIB1 labeling, and mitotic activity within the glial nodules. The fact that examples of malignant degeneration have not previously been documented may be due to a number of factors, including the uncommon nature of DNTs and their early detection and treatment. Furthermore, DNTs presenting before 1988 would certainly have been diagnosed as astrocytic, oligodendrogial, or mixed glial tumors in which malignant degeneration would be expected. Indeed, most DNTs encountered before 1988 would have given rise to examples of “gliomas” that were cured by excision. Finally, tumor-growth kinetics is an equation balanced by a number of factors, whereby mitotic activity may be countered by apoptosis and other factors. As such, despite anaplastic appearances, some mitotically active tumors may be relatively inhibited at the molecular level from aggressive behavior.

Dysembryoplastic neuroepithelial tumors have been described as hamartomas with neuronal and glial components. This fits well with their morphological characteristics, immunohistochemical or ultrastructural characterization, and usually benign course. Other authors favor their designation as true neoplasms, owing to their proliferative activity and other variable anaplastic features. Both considerations have merit, and it is recognized that other mixed glioneuronal lesions sharing hamartomatous and neoplastic features (such as gangliogliomas) occasionally give rise to malignant tumors, despite a traditionally benign nature. Such occurrences have led to speculation about the relationship between glioneuronal dysmorphogenesis and neoplasia. Our case draws further attention to this association and the overlap between developmental and neoplastic biology.

The present case is instructive in a number of practical points. It serves to underscore the importance of a complete resection, when possible, to minimize the risk of tumor recurrence and malignant transformation. Therefore, DNTs also merit follow-up observation for malignant transformation, especially when resection is not complete. Finally, it reminds us of the importance of reviewing and correlating tumor histopathological findings with findings from previous resections whenever the opportunity exists.

Dedication

This paper is dedicated to the late Dr. Patrick A. Gill.

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References


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