Histology and Molecular Aspects of Central Neurocytoma

Phillip A. Bonney, MD[a], Lillian B. Boettcher, BA[a], Richard S. Krysiak III, BS[a], Kar-Ming Fung, MD, PhD[b], Michael E. Sughrue, MD[a,c,*]

KEYWORDS

• Central neurocytoma • Review • Brain tumor • Histology • Molecular pathways

KEY POINTS

- Central neurocytoma (CN) is a well-differentiated tumor of neural cells occurring within the ventricles. It is composed of monomorphic cells with round, regular nuclei within clear cytoplasm and must be distinguished from other clear cell tumors.
- Immunohistochemical markers include synaptophysin and neuronal nuclear antigen.
- Chromosomal abnormalities that have been reported in CN include trisomy 7; chromosome 17 deletion; and gains in 2p, 10q, 13q, and 18q.
- Microarray analyses have identified many overexpressed genes in CN, including those of the insulin-like growth factor 2 (IGF2) and Wnt pathways; other pathways that may be involved in tumorigenesis include neuregulin 2, N-Myc, and platelet-derived growth factor. Pathways that have not been linked to CN include p53, epidermal growth factor receptor, and BCL-2.

INTRODUCTION

Neurocytoma is a rare tumor of mature neural cells within the central nervous system. It was first described arising from the ventricular system, although since then an extraventricular variant has been well documented. Central (intraventricular) neurocytoma is a low-grade tumor (World Health Organization [WHO] grade II) that occurs in young adults. It typically presents with signs of increased intracranial pressure. It is rare, representing less than 0.5% of brain tumors. Overall, the disease is associated with a favorable prognosis with treatment and in many cases surgical resection is curative, although a subset of central neurocytoma (CN) is clinically aggressive and necessitates adjuvant therapy. This article reviews the literature regarding the microscopic characteristics that define this tumor and the insights made into the molecular pathways by which tumorigenesis and progression occur.

HISTOLOGY

Hassoun and colleagues[1] first described CN in 1982, presenting 2 similar cases of tumors with extensive calcifications arising from the third ventricle and sharing histologic features of mature neuronal differentiation. Under light microscopy, clusters of tumor cells with regular, round nuclei

Disclosures: The authors have nothing to disclose. They have no relevant funding sources and no conflicts of interest.

[a] Department of Neurosurgery, University of Oklahoma Health Sciences Center, 1000 North Lincoln Boulevard, Suite 4000, Oklahoma City, OK 73104, USA; [b] Department of Pathology, University of Oklahoma Health Sciences Center, 940 Stanton L. Young Boulevard, BMSB 451, Oklahoma City, OK 73104, USA; [c] Oklahoma Comprehensive Brain Tumor Clinic, Oklahoma City, OK 73104, USA

* Corresponding author. University of Oklahoma Health Sciences Center, 1000 North Lincoln Boulevard, Suite 4000, Oklahoma City, OK 73104.

E-mail address: michael-sughrue@ouhsc.edu

Neurosurg Clin N Am 26 (2015) 21–29
http://dx.doi.org/10.1016/j.nec.2014.09.001
1042-3680/15/$ – see front matter

and clear cytoplasm occurred in a matrix of fibrillary stroma. Electron microscopy revealed synapses, dense-core and clear vesicles, and parallel microtubules indicating differentiated neuronal tissue without evidence of glial cells.

The salient cytologic features on light microscopy (uniform, regular nuclei containing granular chromatin and accompanied by perinuclear halos) closely resemble those of oligodendroglioma (Fig. 1A). Tumor cells are arranged in sheets, often interspersed between acellular fibrillary regions also known as neuropil islands.[2] Perivascular pseudorosettes[2] and Homer Wright rosettes[3] have been reported but are rare. Calcifications are also rare, but when they occur they tend to be within the tumor as opposed to the peripheral calcifications seen in oligodendroglioma.[4] However, without en bloc neurosurgical resection, it is difficult to appreciate this feature. Necrosis, hemorrhage, and mitoses are seen rarely.

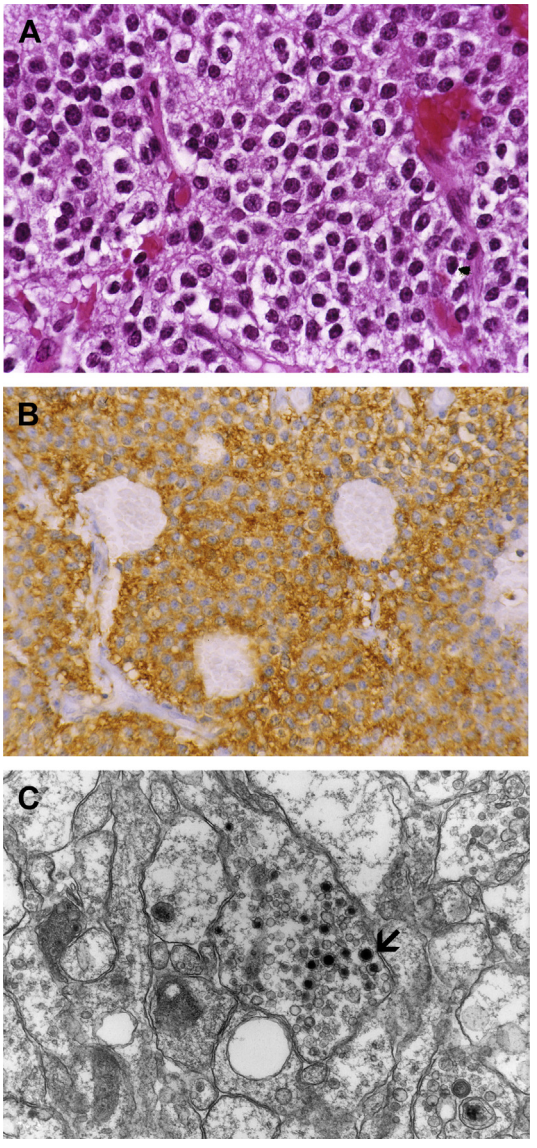

Fig. 1. CN. (*A*) Light microscopy reveals oligodendrogliomalike cells with round to ovoid nuclei within clear cytoplasm. (*B*) Immunostaining for synaptophysin occurs extracellularly within tumor stroma. (*C*) Electron microscopy shows neural elements including synapses with dense-core (*arrow*) and clear neurosecretory granules.

Immunohistochemical staining shows positivity for synaptophysin within fibrillary areas (see Fig. 1B). Neuron-specific enolase is universally positive in CN, as in many central nervous system tumors.[5] Neuronal nuclear antigen (NeuN) immunoreactivity occurs diffusely in nuclei of tumor cells and has been noted as a more specific marker for CN.[6–8] Neuronal cell adhesion marker is also reactive.[9] Neuron-associated class III beta-tubulin (Tuj-1) and microtubule-associated protein 2 (MAP2) staining occurs within microtubules.[6,10] S100 protein and retinal S-antigen have been reported to stain positively with some regularity.[11] Glial fibrillary acidic protein (GFAP) staining occurs intermittently and is typically attributed to reactive astrocytes.[2,12] However, immunoreactivity for GFAP has also been reported to occur in neoplastic cells in histologic variants.[13–15] Rare staining for neurofilament protein has been documented as well, in association with ganglion cells.[13] Focal OLIG2 staining may occasionally occur.[16]

The histologic appearance of CN shares similarities with several other tumors of the central nervous system. Before a distinct entity was identified, these tumors were usually deemed to be oligodendroglioma or ependymoma.[13,17] In relation to CN, oligodendroglioma cells share similar morphology, and they may even stain lightly for synaptophysin[7]; in addition, focal OLIG2 staining may be seen in CN. However, oligodendroglioma lacks the neuropil islands seen in CN, and oligodendroglioma cells have widespread immunoreactivity to OLIG2 and are negative for NeuN. Further, oligodendroglioma is usually hemispheric and rarely occurs as a ventricular mass. Non–clear cell ependymoma can usually be distinguished from CN based on morphology alone. However, clear cell ependymoma may require additional evaluation. Distinction can be made given that ependymoma cells are usually extensively positive for GFAP and are often positive for epithelial membrane antigen. Ultrastructural examination is occasionally used to diagnose CN, in which mature neural elements, including neurosecretory granules, may be seen (see Fig. 1C). Other neoplasms that may be considered in the differential