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Case study

Central neurocytoma represents a tumor consisting of diverse neuronal phenotypes

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ABSTRACT

Central neurocytoma (CN) has long been regarded as a neuronal tumor based on the immunohistochemical expression of synaptophysin and the ultrastructural observation of neurosecretory granules, neurites, and synapses. Having diagnosed 11 CNs at our institution over the past thirty years, we set out to conduct an immunohistochemical study to assess the expression profile of neuronal markers across our cases. Markers of interest included synaptophysin, alpha-synuclein, chromogranin, neurofilament, and calretinin. Intriguingly, we observed a dichotomous expression profile between neurofilament and calretinin, suggesting the presence of histologic variants of CN based on the degree of neuronal maturation. We have further provided an overview of the clinico-pathologic heterogeneity within our series with respect to age of onset, overall outcome, and presence of anaplastic features. In highlighting the case of an infant with an incidental CN diagnosed at autopsy, we have discussed the role of a primitive neural cell of origin for driving tumor formation and accounting for our proposed differences in neuronal maturation within CN.

1. Introduction

Central neurocytoma (CN) represents a rare low-grade intraventricular tumor that typically occurs in young or middle-aged adults. Given that most CNs arise in the lateral ventricle near the foramen of Monro, these tumors were historically diagnosed as either intraventricular oligodendrogliomas or ependymomas [1,2]. Their recognition as a distinct entity came in 1982 with the use of electron microscopy and immunohistochemistry, which clarified their neuronal phenotype [3]. While CNs are generally benign, non-recurrent tumors with a favorable post-operative prognosis, atypical neurocytomas have been described to contain anaplastic features and an aggressive clinical course in those tumors with a MIB labeling index of greater than 2% [4]. With the demonstration of marker expression unique to glial cells, recent reports have indicated a more primitive bipotential cell of origin from the periventricular matrix [5]. These findings have suggested CNs to exist on a spectrum of neuronal differentiation, which may correlate with differences in histology and clinical outcome.

The recent *in vivo* and genomic characterization of primary human CN cells has provided further evidence to support a neuronal transit-amplifying progenitor cell of origin [6]. Additional studies have demonstrated the capacity of cultured human CN cells to generate action potentials, contain voltage-gated Ca^{2+} channels, and express ionotropic and metabotropic neurotransmitter receptors [7]. In light of these findings, we set out to conduct an immunohistochemical study to assess the expression profile of neuronal markers across 11 CNs diagnosed at our institution in the past thirty years. Markers of interest include synaptophysin, alpha-synuclein, neurofilament, and calretinin. In serving as the universal diagnostic marker for tumors of neuronal origin, synaptophysin is recognized as a glycoprotein on the presynaptic vesicles of neurons [8,9]. While alpha-synuclein is traditionally used to mark pathologic intracytoplasmic inclusion bodies (Lewy bodies) in Parkinson's disease, it also functions as component of the presynaptic terminals of neurons [9,10]. Neurofilament is a major cytoskeletal element in axons and dendrites, indicating the development of a more mature neuronal phenotype [9] among tumor cells such as gangliocytic differentiation. Calretinin is a member of calcium-binding family of proteins and has been shown to iden-

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tify a subset of GABAergic interneurons in the mammalian neocortex [9,11,12]. In considering the expression profile of these neuronal markers with their corresponding clinico-pathological determinants, we describe CN to be a tumor of varying neuronal phenotypes in support of a neuronal precursor cell of origin.

2. Materials & methods

The present study reviewed all cases of CNS CN at our institution over a 30-year period ranging from 1987 to 2017. Medical records of patients with CN were retrieved from our clinical and pathology database at Hamilton General Hospital, McMaster University. Clinical data included: age gender, tumor location, clinical history, presence of hydrocephalus, extent of resection, and outcome. Pathological data included: type of neurocytic differentiation, type of glial morphology, presence of mitosis, necrosis, endothelial proliferation, pleomorphism, and extent of cellularity. Immunostains were performed for the following antibodies within our clinical laboratory facility: glial fibrillary acidic protein (RTU (ready-to-use) rabbit polyclonal; Dako; Carpinteria, CA, USA), synaptophysin mouse monoclonal antibody (RTU; Dako; Carpinteria, CA, USA), neurofilament mouse monoclonal (RTU; Dako; Carpinteria, CA, USA), alpha-synuclein mouse monoclonal (1:100; Dako; Carpinteria, CA, USA), calretinin mouse monoclonal (RTU; Dako; Carpinteria, CA, USA), p53 mouse monoclonal (RTU; Dako; Carpinteria, CA, USA), and Ki-67 mouse monoclonal (RTU; Dako; Carpinteria, CA, USA). Both authors (BM, JPP) independently evaluated the intensity and extent of cell positivity within each specimen using 10 fields at high magnification (×400). Intensity was evaluated on a scale of 1–3 (1 = low, 2 = moderate, 3 = high). Immunonegative samples were denoted with "–". The extent of immunopositivity was assessed as either focal or diffuse.

3. Results

3.1. Clinical features

In the thirty-year span from 1987 to 2017, we have diagnosed 11 CNs at our institution. Available demographic data (Table 1) from our case series identified no gender differences (F: 5; M: 6) and an average age of onset of 34.9 years (range 1–63 years old). Clinical data was limited for Cases 1 and 2 due to minimal historical records for these cases. Of particular interest is case 6, which was a CN incidentally identified in a 1-year old boy at autopsy following a head injury and skull fracture of the left occipit. In addition, case 7 was a recurrent CN, which was previously treated at another institution. Clinically, patients' symptoms were often related to increased intracranial pressure with nausea, headache, and vomiting being the most common symptoms. All tumors were located in the ventricular system: 2 in bilateral ventricles, 1 in bilateral ventricles and extending into foramen of Monro, 5 in the left lateral ventricle, 2 in the right lateral ventricle, and 1 extending from the left lateral ventricle into the 3rd ventricle. Hydrocephalus was present in the majority of cases (n = 7), with only one case having normal ventricular size. Historical records from the remaining 3 cases were not available to determine the presence of hydrocephalus. Given the location of these tumors and their propensity to extend throughout the ventricular system, gross-total resection (GTR) is often challenging and therefore only achieved in 4 cases. Subtotal resections (STR) were performed in 5 cases with one of these cases receiving adjuvant radiotherapy. One case (case 4) required multiple surgical resections, resulting in two STRs. Given the lack of historical records for case 2 and the incidental autopsy finding of CN in case 6, surgical details were not available for these cases. Post-operative intraventricular hemorrhage (IVH) was the primary complication, which was described in 2

Table 1
Clinical Summary.

Case	Age	Gender	Diagnosis	Location	Clinical History	Hydrocephalus	Extent of Resection	Outcome
1	35	M	Central neurocytoma	L lateral	N/A	N/A	STR	Intraventricular hemorrhage resulting in death within 1 month post-surgery
2	39	M	Central neurocytoma	Bilateral	N/A	N/A	N/A	Alive 11 years post-surgery
3	57	F	Central neurocytoma with ganglionic differentiation	L lateral	Short-term memory loss	Y	GTR	Alive within 2 years post-surgery
4a, 4b	53	M	Central neurocytoma	L lateral	Nausea, headaches, loss of contact with surroundings	Y	STR	Intraventircular hemorrhage and malignant brain swelling with cardiac arrest resulting in death within 1 month post-surgery
5	32	F	Central ganglioneurocytoma	L lateral, foramen of Monro	Vomiting, headaches	Y	GTR	Alive 3 years post-surgery
6	1	M	Central neurocytoma	L lateral	Post-head injury and skull fracture of left occipit	N/A	N/A	Dead
7	30	F	Recurrent central neurocytoma	R lateral	Nausea, headaches, short term memory loss	N	STR + radiation	Alive 4 years post-surgery
8	22	F	Central neurocytoma	L lateral, foramen of Monro, 3rd ventricle	Visual problems, hand tingling, nausea, vomiting, headaches	Y	STR	Alive 3 years post-surgery
9	34	M	Central liponeurocytoma	Bilateral, foramen of Monro	Visual problems, headache	Y	GTR	Alive 2 years post-surgery
10	63	F	Central ganglioneurocytoma	R lateral, foramen of Monro	Headache, unsteady gait	Y	GTR	Alive 1 year post-surgery
11	18	M	Central neurocytoma	Bilateral	Unsteady gait	Y	STR	Alive 1 month post-surgery

M male, *F* female, *L* left, *R* right, *Y* yes, *N* no, *STR* subtotal resection, *GTR* gross total resection, *N/A* not available.

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