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CASE REPORT

Central Neurocytoma with Malignant Course

Neuronal and Glial Differentiation and Craniospinal Dissemination

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Central neurocytoma is a benign neuronal tumor of young adults in the lateral cerebral ventricles with characteristic X ray and light microscopic findings. In many respects typical central neurocytoma is reported below, with recurrence in the third month requiring reoperation. Death ensued in the fifth postoperative month. Subsequent histology proved progressive vascular proliferation and increasing, unusual glial differentiation of the neuronal tumor. At autopsy tumorous seeding blocked the liquor circulation. A thin tumorous layer covered the surface of all ventricles, the cerebellum and medulla oblongata. The GFAP positive cells out-numbered the synaptophysin positive ones. Increase of GFAP positivity and vascular proliferation of the central neurocytoma may be alarming signs suggesting a malignant course in addition to the other atypical features. (Pathology Oncology Research Vol 5, No 2, 155–159, 1999)

Keywords: central neurocytoma, atypical central neurocytoma, glial and neuronal differentiation, ganglioglioma.

Introduction

Some controversy exists as to whether there is a malignant variant of central neurocytoma (CN). More than one hundred CN cases have been reported in the literature,[8,16] but only few malignant tumors are mentioned.[6,22,31] In the following we give account of a 19-year old woman with CN rapidly progressing to death.

Methods

Tissues were fixed in buffered formalin and paraffin embedded. Conventional sections were HE stained. Immunohistochemistry was carried out by the indirect method, visualisation by APAAP kit for Synaptophysin and by PAP kit for other antigens. Appropriate normal tissues were used as positive controls and normal serum instead of immune serum as negative control. Marker sera are listed in *Table 1*.

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Clinical history

19 year old girl was admitted with a month's history of early morning headache, dizziness, nausea, vomiting and speach difficulties. On admission she had right sided hemiparesis, hemisensory loss, sensomotoric dysphasia, and conjugate deviation of the eyes to right with decreased consciousness. CT and MRI showed a left thalamic 4x3.5x3.5 cm tumor bulging into the lateral ventricle. The greyish, reddish tumor was transventricularly partially removed by a left parasagittal parietal craniotomy. She was discharged from the hospital two weeks later with a slight left sided hemiparesis, apraxia in the left hand, minimal motoric dysphasia, and right sided homonymous hemianopia. After two months she started vomiting and headache, drowsiness, dysphasia were registered. Again, CT showed a rapidly growing tumor in the left thalamus which blocked the left temporal horn of the ventricle at the trigone. A second operation was performed through the previous craniotomy three months after the first one. The recurrent tumor was partially removed but tumor invasion was seen in the direction of the hypothalamus. After the second operation she developed a severe sensomotoric

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Table 1. **Primary antibodies in the analysys of CN case**

Antigen	*Antibody/clone*	*Source and dilution*	*Major specificity*
Synaptophysin	SY38	DAKO A/S, 1:10	Fraction of presynaptic vesicle protein in neural and neuroendocrin tissue, tumors
SNP88		BioGenex, 1:1	
Synaptophysin	rabbit	DAKO A/S, 1:100	
GFAP	GF2	DAKO A/S, 1:100	Astrocytes
NSE	BBS/NC/VI-H14	DAKO A/S, 1:50	Nerve and glial fibres
Ki-67	Ki-67	DAKO A/S, 1:100	Proliferating cells

aphasia, right sided hemiparesis, hemiapraxia, hemisensory loss. After the fifth day of the postoperative radiotherapy intracranial pressure increased. Radiotherapy was stopped and a ventriculo-peritoneal shunt was put in, but improvement was only temporary and she died 5 months after her first operation.

Pathologic findings

Histology of the first operation. – The tumor appeared cellular in conventional HE sections (*Figure 1a*).The tumor cells were small, round with ill defined borders and round or oval nucleus. On some fields the cytoplasm was scanty. Clear cells were characteristic giving the tumor honeycomb appearence as in oligodendroglioma. Patchy irregular fibrillar zones alternated by moderately dense areas of cells were sometimes circularly arranged (as rosettes) around blood capillaries. Mitosis was only occasional and no necrosis was seen. Only one or two larger (ganglioid) cells were present in the whole specimen. Calcifications were common. Cells and fibrillar networks around them were synaptophysin positive (*Figure 1b*). There were glial cells focally and fibres mostly perivascularly, and these areas showed GFAP positivity (*Figure 1c*). The final diagnosis was central neurocytoma. The histology of the second specimen differed from the first one only in the presence of more vascularised areas and the lack of calcifications and ganglioid cells. Synaptophysin was positive again. GFAP staining showed more astrocytes than previously seen (*Figure 2a*). The diagnosis was again central neurocytoma.

Autopsy. – Only the cranium was opened. The grayish, white soft tumor recurrence in the left lateral ventricle was 3x2x1 cm in diameter. Thin layer covered the upper surface of the cerebellum and the initial part of the medulla spinalis. This opalescent film was microscopically subarachnoid tumor tissue (*Figure 2b*). Such thin tumorous infiltration was present along the wall of all ventricles. In the fourth ventricle pseudopapillary tumorous growth blocked the liquor circulation. Tumor cells were more polymorphic, than in the previous histological samples but the cytoplasm was broader than that of neuroblastoma

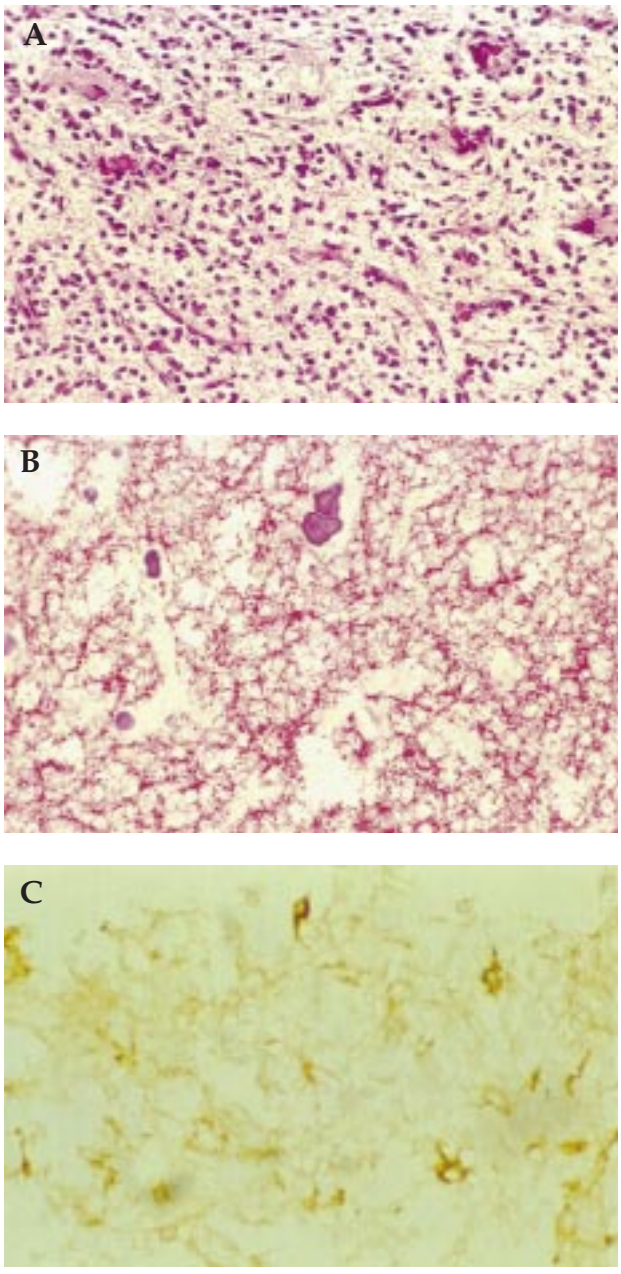

Figure 1. *First biopsy of central neurocytoma, A) HE, vascularisation is scanty, B) synaptophysin is diffusely positive (see calcifications), x 120, C) GFAP labels only few cells, x200*

cells. The endothel proliferation in the vessels was occasionally glomeruloid. GFAP positive cells outnumbered the synaptophysin positive ones in some places (*Figure 2c*) and the same picture could be seen both in the ventricular and leptomeningeal dissemination (*Table 2*).

Discussion

The main features of CN include conventionally: 1. lateral ventricular location,[8,13]; 2. occurrence in young adults,[4,9]; 3. characteristic radiological findings,[3,16,21,28,36]; 4. resemblance to oligodendroglioma or ependymoma on light microscopy,[3,13,18,27,34]; 5.neuronal origin seen on immunohistochemical (synaptophysin)[4,5,13] or electron microscopic [14,18,19] examination; 6. favourable prognosis with benign biological behaviour.[13,16,26]

The first five conditions are fulfilled in our case with the exception of the sixth. What is the reason for this difference? Deviating cases have been discovered recently, for example unusual localisation,[2,12,20,25,30] but what more important is that there are rapidly progressing, rare variants.[22,33]

Incomplete macroscopic removal of tumor is not exceptional for profuse intraoperative bleeding. Shunt implantation may be necessary 1 or 2 months after operation.[34] The prognosis ranges from fair to excellent even if the tumor is resected subtotally and no radiotherapy is given.[16,18] Subtotal removal have only marginal significance in the poor prognosis of our case. CN is supposed to originate from remnants of periventricular germinal matrix[5,6,30] (subependymal plate). The hypotheses are the followings[20]:

1. Neurocytoma cells could be immature neuronal cells intermediate between neuroblast and gangliocyte. Differentiation of neurocytoid cells into ganglioid elements is mentioned in CN,[3,6,11,27,33] but it is rare. According to this supposition occasionally bimodal i.e. neuronal and glial differentiation can not be excluded in a fraction of the tumor cells.[35] Consequently malignant CN might be a tumor with malignant change restricted to the glial elements. If it contained poorly differentiated neuronal cell population it should be called neuroblastoma.

2. CN cells may be mature cells which resemble small granular neurons. These are committed to neuronal differentiation and in this case bipotential so that glial maturation

Table 2. **Evolution of histological features**

	Operation time		*Autopsy (5th month)*	
	first	*second*	*at the site of tumor*	
	0	*3rd month*	*origin*	*dissemination*
Perinuclear halo	+	++	+	–
One cell necrosis	–	–	+	+
Ganglion like cell	+	–	+	–
Calcification	+	–	+	–
Rosettes	+	+	–	+
Fibrillary stroma	++	+	++	+++
Blood vessels	±	+	±	+++
Mitoses	++	+	+	+++
Synaptophysin	+++	++	±	+
GFAP	–	±	+++	++
Ki-67 (% of + cells)	4.4	4.8	2.4	4.3

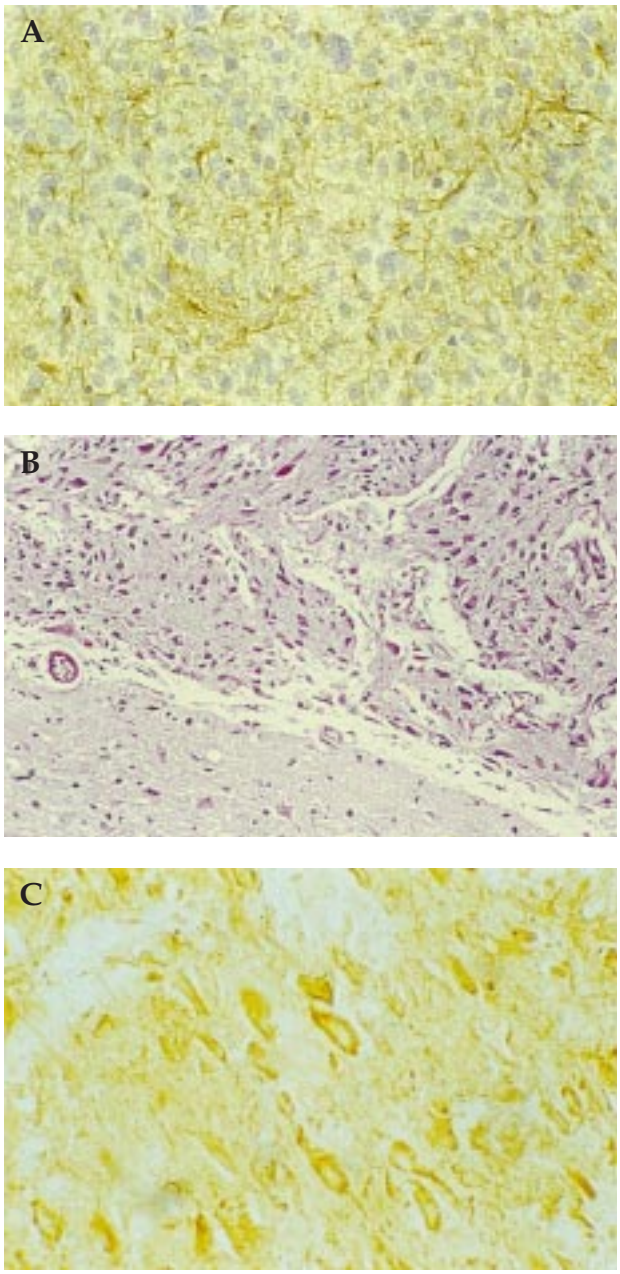

Figure 2. *Second biopsy of central neurocytoma three months later, A) GFAP stains larger number of cells around small vessels, x 120. B) Leptomeningeal infiltration at autopsy (five months later), larger vessels in tumor tissue, x 120. C) GFAP shows considerable number of positive cells in leptomeningeal infiltration at autopsy (compare it with Fig. 1C), x200.*

is not to be expected. "Malignant central neurocytoma" is not an adequate name, primitive neuroectodermal tumor (PNET) should be used instead.[4,9] The occasionally seen transformation of CN cells into ganglioid elements may indicate a separate entity: ganglioneurocytoma.[11,24,27,33] The sparsity of ganglioid cells in our case made however this diagnosis unjustified.

Somewhat controversial is the question of whether occasional cases of CN express GFAP – that is whether glial differentiation is possible or not. GFAP positive cells are generally confined to blood vessels and have characteristic features of entrapped[3,15] or reactive[18,24] astrocytes. A few cases of CN have been described showing considerablely more GFAP positivity and authors concluded that these GFAP positive cells represent neoplastic cells which undergo glial differentiation rather than reactive astrocytic cells.[1,5,6,17,32] Localisation of GFAP positive cells in the leptomeningeal tumorous seeding in our case excludes their entrapped or reactive origin. Some rare cases were mentioned even producing mesenchymal tissue by pluripotent differentiation.[2,17,25] Neuroglial evolution is not always associated with a malignant course[6,17,33] and a less favorable outcome is possible from craniospinal dissemination alone without bimodal differentiation.[8,33] These data demonstrate that bimodal growth (in the direction of glial differentiation) is very rare event in CN.[13]

What morphologic indices are associated with poor prognosis? Some percent of recurrent cases show atypical light microscopy (necrosis, invasive growth,[15,20,31], endothelial proliferation,[41] mild nuclear pleomorphism and mitoses[15,34]). These features might indicate an increased proliferative potential[13,21] (atypical CN). Immunoreactivity to proliferating nuclear antigen (Ki67, MIB1), varies from 0.1 % to 5.6, indicating, that some of these tumors have proliferative potential similar to that of anaplastic astrocytoma.[10,15,23,36] Ki67 in our case varied from 3-4.5 %. Vascular proliferation seems to correlate with recurrences[29] as it was in our case too.

Radiation and chemotherapy should be recommended for progressive, recurrent or atypic variant of CN.[7,26,28,34] Summarising: our CN case showed both seeding along all ventricles and increasing vascularisation, with GFAP positivity. A certain degree of endothelial proliferation and GFAP positivity may indicate a less benign prognosis in a tumor resembling CN.

CN is a rare tumor – it represents approximately 0.1% of all primary central nervous system tumors.[13,26,34] Its histogenesis is debated but a neuronal origin is widely assumed. Analysis of unusual CN cases might have not only clinicopathological but histogenetic significance as well. Occasional malignant cases might indicate that this tumor arises from an undifferentiated precursor cell with the capacity of bipotential (neuroglial) differentiation.

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References

1. *Akimoto J, Itoh H, Itoh Y, et al:* Histogenesis of central neurocytoma:an immunohistochemical and electronmicroscopic study of four cases. No Shinkei Geka 23:1083-1091, 1995.
2. *Alleyne CH, Hunter S, Olson JJ, et al:* Lipomatosus glioneurocytoma of the posterior fossa with divergent differentiation. Neurosurgery 42:639-643, 1998.
3. *Barbosa DM, Balsitis M, Jaspan T, et al:* Intraventricular neurocytoma: a clinical and pathological study of three cases. Neurosurgery 26:1045-1054, 1990.
4. *Burger PC, Scheithauer BW:* Tumors of the central nervous system. Atlas of tumor pathology, third series, AFIP, Fascicle 10:178-184 and 193-194, 1994.
5. *Deimling A, Kleihues P, Saremaslani P, et al:* Histogenesis and differentiation potential of central neurocytomas. Lab Invest 64:585-591, 1991.
6. *Deimling A, Janzer R, Kleihues P, et al:* Patterns of differentiation in central neurocytoma. Acta Neuropathol 79:473-479, 1990.
7. *Dodds D, Nonis J, Mehta M, et al:* Central neurocytoma: a clinical study of response to chemotherapy. J Neurooncol 34:279-283, 1997.
8. *Eng DY, DeMonte F, Ginsberg L, et al:* Craniospinal dissemination of central neurocytoma. J Neurosurg 86:547-552, 1997.
9. *Figarella-Branger D, Pellissier JF, Daumas-Duport C, et al:* Central neurocytomas: critical evaluation of a small cell neuronal tumor. Am J Surg Pathol 16:97-106, 1992.
10. *Fujimaki T, Matsuno A, Sasaki T, et al:* Proliferative activity of central neurocytoma: doubling time, MIB-1 and bromodeoxyuridine labeling index. J Neurooncol 32:103-109, 1997.
11. *Funato H, Inoshita N, Okeda R, et al:* Cystic ganglioneurocytoma outside the ventricular region. Acta Neuropathol 94:95-98, 1997.
12. *Giangaspero F, Cenacchi G, Losi L, et al:* Extraventricular neoplasms with neurocytoma features. Am J Surg Pathol 21:206-212, 1997.
13. *Hassoun J, Soylemezoglu F, Gambarelli D, et al:*Central neurocytoma: a synopsis of clinical and histological features. Brain Pathol 3:297-306, 1993.
14. *Horoupian DS, Shuster DL, Kaarsoo-Herrick M, et al:* Central neurocytoma: one associated with a fourth ventricular PNET/medulloblastoma and the second mixed with adipose tissue. Hum Pathol 28:1111-1114, 1997.
15. *Kim DG, Kim JS, Chi JG, et al:* Central neurocytoma: proliferative potential and biological behavior. J Neurosurg 84:742-747, 1996.
16. *Kim DG, Paek SH, Kim IH, et al:* Central neurocytoma: the role of radiation therapy and long term outcome. Cancer 79:1995-2002, 1997.
17. *Kim DH, Suh YL:* Pseudopapillary neurocytoma of temporal lobe with glial differentiation. Acta Neuropathol 94:187-191, 1997.
18. *Kubota T, Hayashi M, Kawano H, et al:* Central neurocytoma: immunohistochemical and ultrastructural study. Acta Neuropathol 81:418-427, 1991.
19. *Langford LA:* Central nervous system noplasms: indications for electron microscopy. Ultrastruct Pathol 20:35-46, 1996.

20. *Louis DN, Swearingen B, Linggood RM, et al:* Central nervous system neurocytoma and neuroblastoma in adults. J Neurooncol 9:231-238, 1990.
21. *Mineura K, Sasajima T, Itoh Y, et al:* Blood flow and metabolism of central neurocytoma. Cancer 76:1224-1232, 1995.
22. *Mrak RE:* Malignant neurocytic tumor. Hum Pathol 25:747-752, 1994.
23. *Nishio S, Fujiwara S, Tashima T, et al:* Tumors of the lateral ventricular wall, especially the septum pellucidum. Neurosurgery 27:224-230, 1990.
24. *Nishio S, Takeshita I, Fukui M:* Primary cerebral ganglioneurocytoma in an adult.Cancer 66:358-362, 1990.
25. *Pal L, Santosh V, Gayathri N, et al:* Neurocytoma/rhabdomyoma of the cerebellum. Acta Neuropathol 95:318-323, 1998.
26. *Schild SE, Scheithauer BW, Haddock MG, et al:* Central neurocytomas. Cancer 79:790-795, 1997.
27. *Schweitzer JB, Davies KG:* Differentiating central neurocytoma. J Neurosurg 86:534-546, 1997.
28. *Sgouros S, Carey M, Aluwihare N, et al:* Central neurocytoma: correlative clinicopathologic and radiologic analysis. Surg Neurol 49:197-204, 1998.
29. *Soylemezoglu F, Scheithauer BW, Esteve J, et al:* Atypical central neurocytoma. J Neuropathol Exp Neurol 56:551-556, 1997.
30. *Tatter SB, Borges LF, Louis DN:* Central neurocytomas of the cervical spinal cord. J Neurosurg 81:288-293, 1994.
31. *Tomura N, Hirano H, Watanabe O, et al:* Central neurocytoma with clinically malignant behavior. Am J Neuroradiol 18:1175-1178, 1997.
32. *Tsuchida T, Matsamuto M, Shirayama Y, et al:* Neuronal and glial characteristics of central neurocytoma. Acta Neuropathol 91:573-577, 1996.
33. *Yamamoto T, Komori T, Shibata N, et al:* Multifocal neurocytoma/gangliocytoma with extensive leptomeningeal dissemination in the brain and spinal cord. Am J Surg Pathol 20:363-370, 1996.
34. *Yasargil MG, Ammon K, Deimling A, et al:* Central neurocytoma: histopathological variants and therapeutic approaches. J Neurosurg 76:32-37, 1992.
35. *Valdueza JM, Westphal M, Vortmeyer A, et al:* Central neurocytoma: clinical, immunohistologic and biologic findings of a human neuroglial progenitor tumor. Surg Neurol 45:49-56, 1996.
36. *Zentner J, Peiffer J, Roggendorf W, et al:* Periventricular neurocytoma. Surg Neurol 38:38-42, 1992.