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Ganglioneurocytoma (central neurocytoma with diffuse ganglionic differentiation) with neuraxis dissemination. Case report and review of the literature

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We report the case of a 46-year-old man with ganglioneurocytoma, initially managed by subtotal resection. The location of the tumour was typical for central neurocytoma, but there was a rapid local progression (in 3 months) mimicking malignant tumour with simultaneous dissemination in the brain as evidenced by magnetic resonance imaging (MRI). The histological appearance of this tumour lacked features of malignancy and showed two neoplastic cells types – a predominance of neurocytes with some ganglion cells scattered singly and in clusters in all parts of the tumour. An immunostain for synaptophysin was typical for neuronal tumours. The proliferative potential of the tumour was low, as indicated by an MIB1 immunostain. The disease was managed at progression with radiotherapy delivered to the whole brain (42 Gy in 15 fractions) and with a boost to the primary site (2 fractions of 2 Gy). Four months after radiotherapy the neurological status of the patient had improved and he no longer required steroid administration. MRI revealed tumour stabilisation. We conclude that neuronal tumours like ganglioneurocytoma or central neurocytoma with diffuse ganglionic differentiation may not be as benign as previously thought and discuss other data reporting malignant behaviour of such tumours. Aggressive tumour behaviour can occur in the absence of the described histopathological signs of poor prognosis, making clinical predictions from the pathological data uncertain. The predictive value of the proliferative index, reported by some authors, is not always a reliable predictor of aggressive behaviour, as exemplified by the case now reported.

**Ganglioneurocytoma z rozsiewem w centralnym układzie nerwowym.
Opis przypadku i przegląd piśmiennictwa**

Przedstawiono przypadek 46-letniego mężczyzny, u którego dokonano subtotalnej resekcji guza mózgu, zlokalizowanego w okolicy otworu Monroe prawej komory bocznej. W badaniu histopatologicznym zdiagnozowano guz pochodzenia neuronalnego, złożony z 2 typów komórek nowotworowych – neurocytów i komórek zwojowych. Ostatecznie postawiono rozpoznanie histopatologiczne – ganglioneurocytoma. Na podstawie morfologii guza (brak atypii, pleomorfizmu, martwicy) oraz niskiego potencjału proliferacyjnego, oznaczonego za pomocą przeciwciał MIB1, określono, że chodzi o wysokozróżnicowany, dobrze rokujący nowotwór. Stan ogólny i neurologiczny chorego uległ, w ciągu 3 miesięcy po zabiegu operacyjnym, znacznemu pogorszeniu. W rezonansie magnetycznym mózgu wykazano bardzo dużą progresję miejscową nowotworu, z jednoczesnym rozsiewem wzdłuż komór, charakteryzującym się obecnością satelitarnych guzów w rogu skroniowym i potylicznym komory bocznej prawej i jednoczesnym wzmocnieniem kontrastowym wzdłuż komory III. W badaniu cytologicznym płynu mózgowo-rdzeniowego z punkcji lędźwiowej nie znaleziono komórek nowotworowych. Chory został napromieniony na mózg i C1-C2, do dawki 42 Gy w 15 frakcjach, z podwyższeniem dawki na obszar wznowy miejscowej do 46 Gy. Cztery miesiące po zakończeniu radioterapii stwierdzono stabilizację choroby w badaniu radiologicznym i lekką poprawę stanu neurologicznego.
Dokonano przeglądu piśmiennictwa dotyczącego tego rzadkiego nowotworu. Zaznaczono, że według niektórych autorów, ganglioneurocytoma nie jest oddzielną jednostką chorobową, lecz odmianą neurocytoma centrale ze znacznym rozległym różnicowaniem w kierunku gangliocytoma. Szybka progresja nowotworu z jednocześnie stwierdzonym rozsiewem wzdłuż układu komorowego, chociaż niezgodna z opisem łagodnego nowotworu pochodzenia neuronalnego, nie stanowi wyjątku. Istnieją w piśmiennictwie doniesienia o takiej właśnie ewolucji choroby. Nieznane są czynniki rokownicze, które pozwoliłyby przewidzieć niekorzystny przebieg choroby. Podaje się w piśmiennictwie, że wysoki potencjał proliferacyjny nowotworu jest najważ-

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niejszym czynnikiem prognostycznym. W przedstawianym przypadku potencjał proliferacyjny był niski, podobnie jak w kilku innych doniesieniach, gdzie również doszło do rozsiewu choroby drogą płynu mózgowo-rdzeniowego. Przedstawiany chory odniósł korzyść z radioterapii. Większość danych z piśmiennictwa potwierdza pozytywną rolę radioterapii w leczeniu tego nowotworu w przypadkach nieradykalnej resekcji i w razie progresji lub nawrotu.

Key words: ganglioneurocytoma, neurocytoma, dissemination, radiotherapy
Słowa kluczowe: ganglioneurocytoma, neurocytoma, rozsiew, radioterapia

Introduction

The first recognition of intraventricular (central) neurocytoma as a distinct clinicopathological entity appeared 20 years ago. Hassoun et al. described such neoplasms in the region of the foramen of Monroe as a rather indolent ("benign") neuronal origin tumour developing in young adults from the ventricular walls or septum pellucidum [1]. Neurocytomas are composed of neurocytes – cells, which while relatively small are not immature neuroblasts, (earlier case reports had described these tumors as "differentiating intraventricular neuroblastomas") [2] but neither are they large ganglion cells; instead they are the neoplastic counterparts of the small granular neurones of the cerebellar cortex, dentate gyrus, or the second and fourth neocortical laminae. To our knowledge, about 200 cases of neurocytoma have been published. Central neurocytoma was listed in WHO CNS tumours classification as a benign, grade I tumour [3]. Although benign biological behaviour of this tumour is emphasised in most publications, many reports show a completely different character of its clinical course, with rapid recurrences and even craniospinal dissemination [4-7]. Histopathological variants, mainly with admixed ganglionic differentiation, and sometimes with astrocytic differentiation, have also been reported [7-9]. Whether extraventricular or parenchymal neurocytic tumors are the same neoplasm [10-12], as in the intraventricular examples, has been a controversial issue, and need not be further discussed herein.

We present a case of neurocytoma in its typical location, but with a component of neoplastic ganglion-cell-like cells allowing us to make a diagnosis of a combined tumour – ganglioneurocytoma. Additionally, the presented case has shown a clinical course similar to the malignant brain tumours with rapid local progression and dissemination in the CNS.

Case report

Presentation and initial management

A 46-year-old man presented with a one-week history of generalized weakness. There was no significant past medical history. Neurological examination showed no abnormalities, except for decreased strength in the upper and lower extremities. CT brain scans showed a 6 cm (largest diameter) tumour extending from the wall of the right ventricle to the genu of the corpus callosum and the region of the right basal ganglia. Compression of the ventricle, midline shift and mild ventriculomegaly were also present. Contrast enhancement was extensive and heterogeneous, mimicking a malignant tumour. The patient underwent a removal of ventricular obstruction at the foramen of Monroe and a subtotal resection of the tumour under microscopic vision. The tumour extended from the foramen of Monroe to the right fornix and into the frontal horn of the right ventricle. Two days after the first craniotomy the patient became slightly lethargic and a CT brain scan showed increased size of the lateral right ventricle. A right frontal ventriculostomy was placed. Ten days later a ventriculoperitoneal shunt was created, which was removed 15 days later because of infectious complications. The patient was fit to be discharged from the hospital 1 month after the resection, in stable condition, however with maintained generalized weakness.

Pathologic findings

The tumour tissues were fixed in 10% buffered formalin, processed routinely into paraffin. The sections were stained with hematoxylin and eosin (HE), and with immunohistochemical stains (for antibodies see Table I)

Table I. Antibodies for immunohistochemistry

Antibody (clone)	Source	Type
Synaptophysin (SY38)	Boehringer-Mannheim	m
GFAP	Dako	P
Neurofilament Protein (RMD020)	Zymed	m
Neu-N (MAB 377)	Chemicon	m
Ki67/MIB1	AMAC	m

Abbreviations: m mouse monoclonal; p polyclonal; GFAP Glial Fibrillary Acidic Proten

using standard avidin-biotin immunoperoxidase techniques with diaminobenzidine as the final chromagen. The tumour was a uniform neoplasm composed of two admixed cell types: the first, and more numerous, present at a moderate cell density and consisting of back-to-back medium size cells with polygonal-to-round cell bodies with clear cytoplasm and centrally placed bland round nuclei (Figure 1A-B), and the second, less numerous, large neuronal cells – ganglion cells – many of which had peculiar shapes, cell bodies with eosinophillic cytoplasm pushing the Nissi granules peripherally, and rarely, two nuclei (Figure 1B-C). The first cellular component,

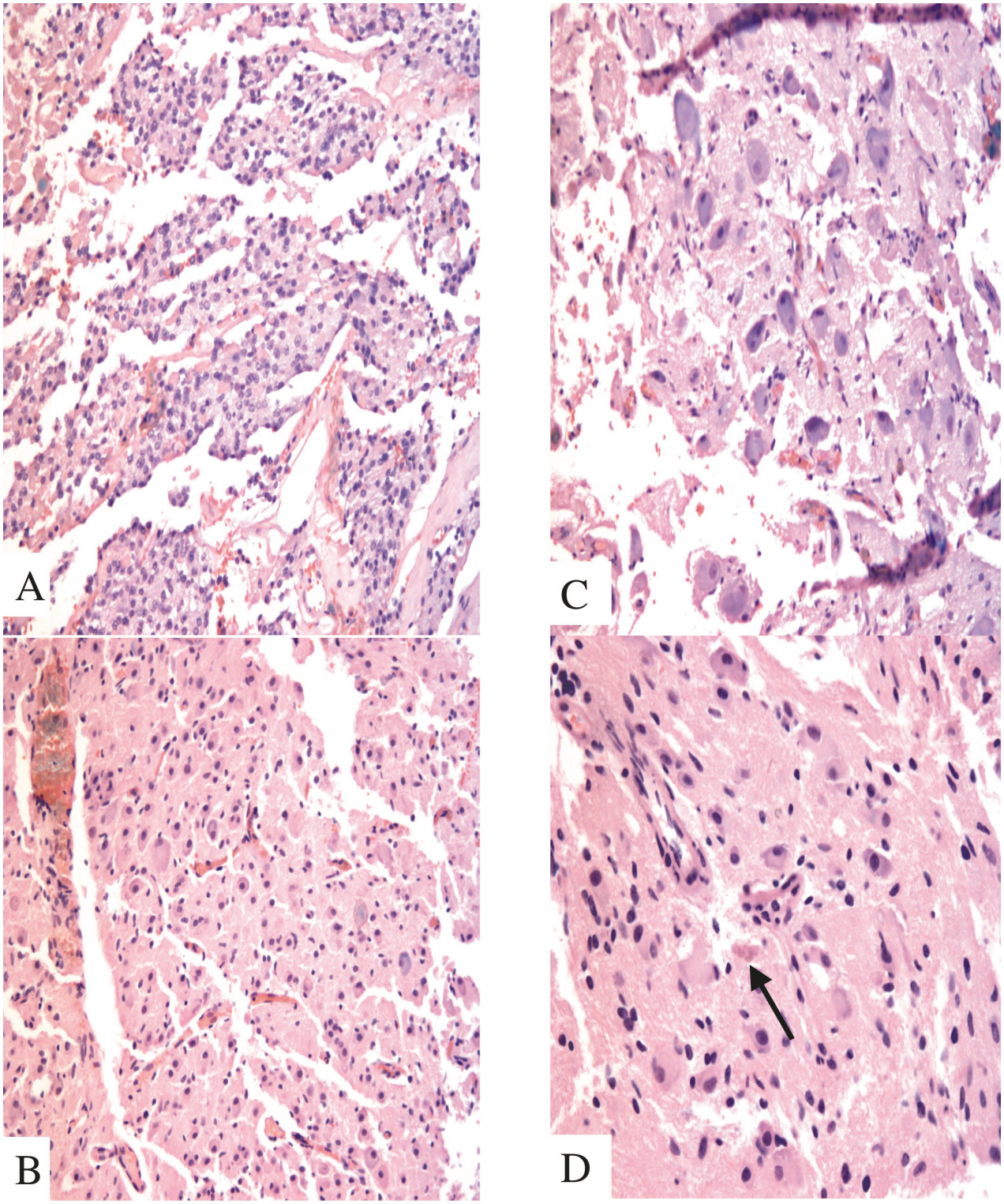

Figure 1. Histopathology of the presented intraventricular tumor. A) The predominant component of the tumor is a population of medium-size cells with centrally placed round nuclei in cell bodies which are often clear in H&E stains, ie the typical picture of "oligodendroglioma-like" tumor cells characteristic of central neurocytomas. H&E, original magnification 358x. B) Scattered throughout the tumor are larger neurons – ganglion cells. H&E, original magnification 358x. C) In small foci the ganglion cells are more numerous. H&E, original magnification 358x. D) The finely fibrillary tumor background contains a few eosinophilic granular bodies (arrow). H&E, original magnification 726 x.

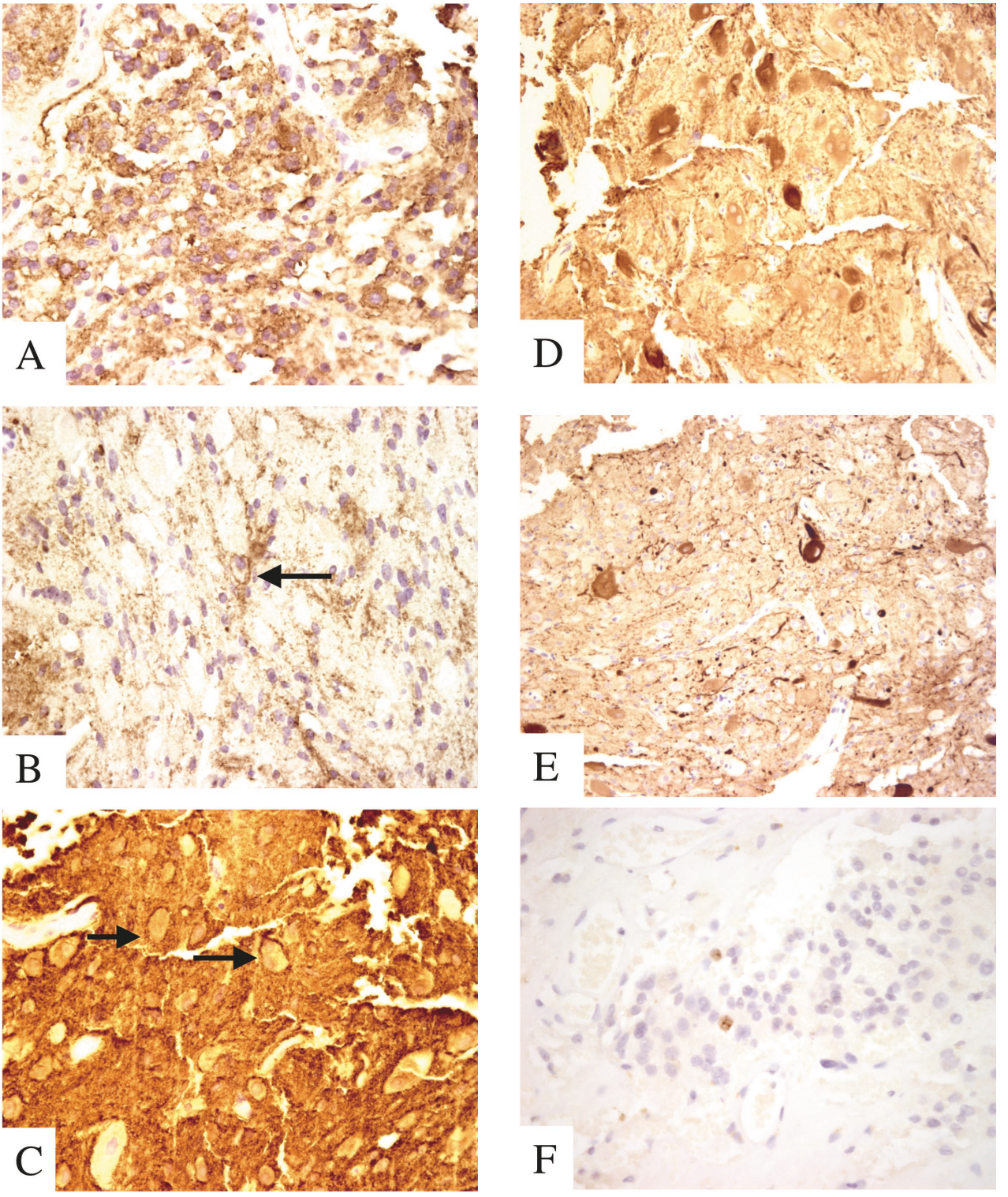

Figure 2. Immunostains of the intraventricular tumor. A) A synaptophysin immunostain shows a diffuse granular immunopositivity in a neuropil pattern. Original magnification 726x. B) In foci the neuropil pattern of synaptophysin immunopositivity is not very dense, and single ganglion cells with perikaryal surface immunopositivity (arrow) are apparent. Original magnification 726x. C) In other areas the background synaptophysin immunoreactivity is very dense, but the clusters of larger neurons still have discernible surface perikaryal immunoreactivity (arrows). Original magnification 726x. D) Neurofilament protein (antibody RMDO20) immunostains show that many of the larger neurons have cytoplasmic immunopositivity. Original magnification 358x. E) A few of the smaller neurocytoma cells are also RMDO20 immunopositive. Original magnification 358x. F) An MIB1 immunostain shows a low labeling index (2.7% actual count of multiple fields). Original magnification 726x.

the neurocytic cells, had the usual resemblance to “oligodendroglioma". There was no vascular hyperplasia, and no definite necrosis. There were scattered eosinophilic granular bodies among the tumour cells (Figure 1D).

There was almost no GFAP (glial fibrillary acidic protein) immunopositivity in the tumour, except at the edges, which contained gliotic brain tissue. There was a strong diffuse granular immunoreactivity with antibody to synaptophysin (Figure 2A-C). Additionally, the large neuronal cells (ganglion cells) were, almost uniformly, surrounded by a densely granular synaptophysin immunopositivity on the perikaryal surfaces, while the cell body cytoplasm was immunonegative (Figure 2B-C). An immunostain with the antibody RMD020, identifying intermediate molecular weight neurofilament protein, marked the cytoplasm of most or all of the large ganglion cells, many axons, and a few of the smaller “oligodendroglioma”-like cells (Figure 2D-E). Antibody Neu-N (a neuronal nuclear antigen) was mostly negative; however, there were rare positive nuclei. An MIB1 immunostain (Ki67) showed a low proliferative index (2,7%), in accordance with the low grade appearance of the tumour (Figure 2F).

Finally, the combination of the histopathologic patterns and the immunophenotypes pointed to the diagnosis of a low grade neuronal neoplasm of mixed ganglion cell and neurocytoma cell elements – “ganglioneurocytoma".

Clinical course and postoperative radiotherapy

One month later the patient was evaluated by a radiation oncologist with a diagnosis of ganglioneurocytoma subtotally removed, with a Karnofsky Performance Status score of 80, a moderate weekness of the extremities more pronounced on the left, without headache and other neurological abnormalities. In view of the usual good prognosis of the diagnosed tumour an MRI examination was performed before the final treatment decision. MRI of the brain revealed an approx. 5 cm tumour in the primary location with a dissemination of the disease along ventricular walls; and two other tumour masses, one in the right temporal horn and another in the right occipital horn. Lumbar CSF cytology was negative for malignant cells. The neurological condition of the patient rapidly deteriorated, with an aggravation of generalized weakness and the emergence of a definite left hemiparesis. The patient had episodes of frank lethargy. Steroid administration was started and an irradiation of the whole brain and the 2 first cervical spinal segments was given to a dose of 42 Gy in 15 fractions. A boost of 4 Gy in two fractions was added to the primary site of the tumour. The patient required steroids throughout the duration of radiotherapy, as the neurological problems aggravated in the early phases of treatment. MRI of the brain performed 1 month after radiotherapy revealed the disease to be stable. The general and neurological state of the patient improved. Steroids were progressively reduced and, ultimately, stopped. Four months after radiotherapy the neurological improvement persists.

Discussion

We have described the clinical and pathological features of a case of an intraventricular tumour in the classic location at the foramen of Monroe – central neurocytoma, as first described by Hassoun et al. and subsequently verified by many others [1, 3]. Histopathologically, two cell types were found in the tumour. The predominant one was identical to the usual “oligodendroglioma-like” of central neurocytomas. While this histopathological pattern in a tumour from this location should be expected to result in a diagnosis of central neurocytoma, the final diagnosis as neurocytoma depends on either ultrastructural or immunohistochemical verification of neuronal differentiation of the tumour cells – specifically positive immunostains for synaptophysin and other neuronal antigens such as neurofilament protein and Neu-N. Given the tendency for histological misdiagnosis based on the H&E appearance of tumors resembling “oligodendroglioma”, the actual number of central neurocytomas has almost certainly been historically underreported.

The second type of neoplastic cells in this tumor comprised large, often dysplastic or atypical, neurons (ganglion cells). These had the typical immunophenotypic profile of neoplastic ganglion cells, including the typical perikaryal surface immunopositivity for synaptophysin [13]. Although WHO brain tumours classification does not recognise ganglioneurocytoma as a distinctive entity, there were several pathologic and clinical reports claiming its approval as a separate tumour of the neuronal origin [8, 10]. For others the presence of ganglionic differentiation in neurocytomas, which has no demonstrable prognostic significance (in the small number of reported cases), should not be cause to recognize a distinctive type of tumour, but as a morphological type or variation within the category of central neurocytoma [6]. Future editions of the WHO classification of brain tumours will have to take these controversies into consideration.

Early descriptions of central neurocytomas considered these tumours as “benign” lesions. One of the two described cases in the report of Hassoun et al. died 14 months after surgery, apparently from meningitis, without evidence of tumor progression in CT exams; MRI was not available at that time, and no autopsy was performed [1]. While the WHO classification of brain tumours has agreed with this “benign” characterization of neurocytomas, there are multiple reports showing a rather different, more aggressive clinical course in some patients, with local rapid progression or craniospinal dissemination [4-7]. The initial pathologic appearance of the tumour in the case we have presented was that of a low grade neurocytomatous neoplasm, but clinically this was regarded as a prediction of a “benign” clinical course of the disease. Atypia, vascular proliferation, pleomorphism, and necrosis were absent. Additionally, an MIB1

immunostain showed a low labelling index, indicating a low proliferative potential of the tumour. Despite this, the tumour followed the aggressive course we have described. It is of crucial importance to find prognostic factors allowing more accurate predictions of the clinical behaviour of tumours such as this, which seem uncommonly, but not extremely rarely, unpredictable to date. While a high proliferative index estimated by Ki67 immunostains predicts a poor prognosis according to some reports [6-7, 14-15] our present case is not the only reported example of unfavourable clinical course with craniospinal dissemination of a central neurocytoma despite a low proliferative index and the absence of other aggressive histopathological features [3] Others have reported local recurrences not predicted by histopathological features ("anaplasia") or proliferation measurement [16]. Other potential prognostic factors, such as age [6] might be relevant to our case (the patient was 45 years old) but this has not been a consistent finding among reported cases either.

The generally accepted treatment of choice for intraventricular neurocytomas is complete surgical resection. No patient undergoing gross total resection recurred in the two reported series of 10 and 14 patients, respectively [6, 17], but in another series of 15 patients 3 had symptomatic recurrences following gross total excision [7]. The role of postoperative radiotherapy for incompletely resected tumours has been debated. Radiosensitivity of neurocytomas has been shown in retrospective series [17, 18]. Schild et al. [17] reported 100% 5-year local control rate for patients irradiated after incomplete resection, in comparison with 50% for those who did not undergo postoperative radiotherapy. The latest data support the use of stereotactic radiosurgery for incompletely resected tumours which show any sign of progression after surgery [18, 19]. In our case “extended field” radiotherapy was used, due to dissemination of the disease in the brain. The radiotherapy delivered in the presented case stopped the rapid disease progression and was certainly beneficial, at least on a short term basis. This observation supports other data suggesting a useful role of radiotherapy in this disease. Rapid cerebral dissemination of the disease could also be an indication for the use of chemotherapy. Brandes et al. [20] have reported 3 cases of recurrent neurocytoma with long term disease stabilisation after a chemotherapy regimen containing cisplatin, etoposide and cyclophosphamide. In our case the poor general status of the patient was thought to preclude the use of chemotherapy at the time of diagnosis of dissemination. Chemotherapy remains advisable in case of recurrence after radiotherapy.

Conclusions

The presented case of ganglioneurocytoma (central neurocytoma with diffuse ganglionic differentiation) is an example of an unusual, but not unprecedented, unfavourable clinical course of this disease. Our review of the literature shows that the course of intraventricular ganglioneurocytoma or central neurocytoma is not predictable at the present day and merits further study.

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