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RESEARCH

Clinical Course of Central Neurocytoma with Malignant Transformation—An Indication for Craniospinal Irradiation

Petra Mozes · Erika Szanto · Laszlo Tiszlavicz · Pal Barzo · Adrienne Cserhati · Emese Fodor · Katalin Hideghety

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Abstract Central neurocytoma is generally considered to be a benign tumor and the literature suggests that a cure may be attained by surgery ± adjuvant focal irradiation. However, there is a need for change in the therapeutic strategy for the subgroup of patients with aggressive central neurocytoma. An example case is presented and the literature on central neurocytoma cases with malignant features and dissemination via the cerebrospinal fluid is reviewed and the radiotherapeutic strategies available for central neurocytoma treatment is discussed. Nineteen cases including the present report with a malignant course and cerebrospinal fluid dissemination have been described to date, most of them involving an elevated MIB-1 labeling index. Our case exhibited atypical central neurocytoma with an initially elevated MIB-1 labeling index (25–30 %). The primary treatment included surgery and focal radiotherapy. Three years later the disease had disseminated throughout the craniospinal axis. A good tumor response and symptom relief were achieved with repeated radiation and temozolomide chemotherapy. Central neurocytoma with an initially high proliferation activity has a high tendency to spread via the cerebrospinal fluid. The chemo- and radiosensitivity of the tumor suggest a more aggressive adjuvant therapy approach. Cases with a potential for malignant transformation should be identified and treated appropriately, including irradiation of the entire neuroaxis and adjuvant chemotherapy may be considered.

Keywords Central neurocytoma · Craniospinal dissemination · Radiotherapy · MIB-1 labeling index

P. Mozes (✉) · E. Szanto · A. Cserhati · E. Fodor · K. Hideghety
Department of Oncotherapy, University of Szeged, Albert Szent-Györgyi Clinical Center, 6720 Szeged, Korányi fasor 12, Hungary
e-mail: mozespetra@gmail.com

L. Tiszlavicz
Department of Pathology, University of Szeged, Albert Szent-Györgyi Clinical Center, 6720 Szeged, Állomás u. 2., Hungary

P. Barzo
Department of Neurosurgery, University of Szeged, Albert Szent-Györgyi Clinical Center, 6720 Szeged, Semmelweis u. 6., Hungary

Introduction

Detection of the malignant transformation of central neurocytoma (CN) at the time of the diagnosis is a rare feature of this basically benign tumor, which is mainly associated with a favorable outcome. Before the entity of neurocytoma was described by Hassoun et al. [1] in 1982 such tumors were referred to intraventricular ependymomas or sometimes oligodendrogliomas. The latest WHO classification categorizes CN as a grade II tumor [2–5]. Following the cellular origin, it has been established that neurocytoma has the properties of bipotential precursor cells, which can exhibit both glial and neuronal differentiation [6]. Immunohistochemical studies have identified markers of neuronal differentiation such as neuron-specific enolase and synaptophysin [7, 8], this staining confirming the diagnosis of neurocytoma. This tumor entity, which accounts for only 0.1–0.5 % of all brain neoplasms [9–12], displays a slow and benign clinical course with a low recurrence rate and a low tendency to spread. Most neurocytomas arise from the septum pellucidum, fornix or walls of the lateral ventricles, with relatively frequent extension to the lateral and third ventricles, often causing obstructive hydrocephalus in relation to the foramen of Monro. The lesions are mainly located in the midline supratentorially, and more commonly on the right side [13]. The occurrence of such tumors outside the cerebral ventricular system is infrequent [14], reported first in 1989 [15], and these lesions have been termed extraventricular neurocytomas. CN develops mainly in young adults around the third decade of life

[10, 12] (ranging from childhood to 70 years). It has been detected with higher incidence in Asian populations, than among Caucasians. The majority of the case reports and accounts of small series originate from India [16–20], China [21–23], Japan [7, 24–29], and Korea [11, 30–34]. Gross total resection (GTR) ensures high progression-free and overall survival rates without recurrence [5], but rare cases of more aggressive behavior with dissemination in the craniospinal axis have been reported. On the basis of the histological findings, such as nuclear atypia, anaplasia, vascular endothelial proliferation, focal necrosis, and/or an increased mitotic index [2, 5, 35–37] a subgroup of this tumor entity is defined as atypical neurocytoma. An MIB-1 labeling index (MIB-1 LI) of ≥2 % or >3 % has been claimed to be associated with a significantly poorer survival and to correlate with a higher risk of relapse; moreover an MIB-1 LI of >4 % correlates significantly with an unfavorable clinical course [38, 39]. Such a high proliferation index is quite uncommon and the detection of malignant transformation at the time of the diagnosis is extremely rare. Adjuvant radiotherapy (RT) has been stated to be beneficial for patients with such atypical neurocytoma and incomplete resection. In general, irradiation of the whole craniospinal space is not recommended, but evidence has recently been accumulating of tumors that disseminate in the central nervous system.

Presentation of Our Example Case

In February 2007, a 40-year-old man presented to our hospital with a history of a few weeks of visual impairment, and diplopia. MRI revealed a mass at the bottom and in the posterior third of the third ventricle, which constricted the aqueduct and caused an occlusive hydrocephalus. Via an endoscopic ventriculostomy, aspiration biopsy was performed. The cytopathological analysis demonstrated a cell-dense tissue, with mild cellular atypia reminiscent of ependymal cells. A focal rosette structure was observed, but there was no glomeruloid vessel proliferation, necrosis, palisade necrosis or mitosis. At that time a WHO grade II ependymoma was diagnosed. One week later, GTR of the tumor was carried out through an occipital osteoplastic craniotomy. In the early postoperative period the patient was somnolent and displayed slowness of movements. Because of the abnormality of the CSF circulation, a ventricular drain was inserted. Several febrile episodes recurred and lumbar punctures demonstrated an elevated leukocyte count in the CSF; parenteral antibiotic was therefore administered, which resulted in an improvement of the condition of the patient and the circulation of the CSF normalized. The patient still presented diplopia, but no other neurological symptoms.

Cytopathological analysis demonstrated a cell-dense, well-vascularized tumor tissue. The nuclei were normal, and the cytoplasm was moderately granulated. The cells were positive for synaptophysin and negative for GFAP. The MIB-1 LI was 25–30 %. These findings corresponded to a diagnosis of WHO grade II CN (Figs. 1, 2 and 3).

The patient was prepared for whole-neuraxis irradiation, but the CSF was negative for tumor cells and there was no suggestion in this respect in the literature overview, so he finally participated in adjuvant, local RT by the 3D conformal technique with a cummulative dose of 60 Gy in daily fractions of 1.8 Gy to the primary tumor bed.

Until 2010 the patient was symptom-free, but in March of that year there were signs of muscle weakness, an increase in the deep tendon reflexes, moderate numbness in the left arm and paresthesia in the lateral proximal region (headzone C 7–8). A spinal MRI showed numerous small cervical, two thoracal and several lumbar, mostly extramedullary manifestations (Fig. 4.). Reoperation was performed and all tumor-seeming tissue was removed from the thoracal IV-VI region through hemilaminectomia and dura mater opening. The postoperative period was uneventful. Cytopathological analysis indicated a hypercellular, undifferentiated tumor tissue. Moderate cell atypia and several mitoses were observed. Immunohistological analysis demonstrated GFAP and CK-KL1 negativity, synaptophysin positivity, a highly positive MIB-1 LI of >40 %, NF: +/−, and CD99: +/−. This was characteristic of malignantly transformed, disseminated CN of WHO grade III. Postoperative, conformal irradiation of the whole spinal cord was performed in a total dose of 36 Gy in conventional fractionation, and a 10 Gy boost was delivered to the tumor bed in the thoracal IV–VI region.

In November 2010, the patient presented with severe pain in the shoulders, numbness in both arms and hands and moderate muscle weakness in the right arm. CT showed moderate tumor progression in the cervical spinal cord. At that time the patient underwent simultaneous chemoradiotherapy with 200 mg/m^2

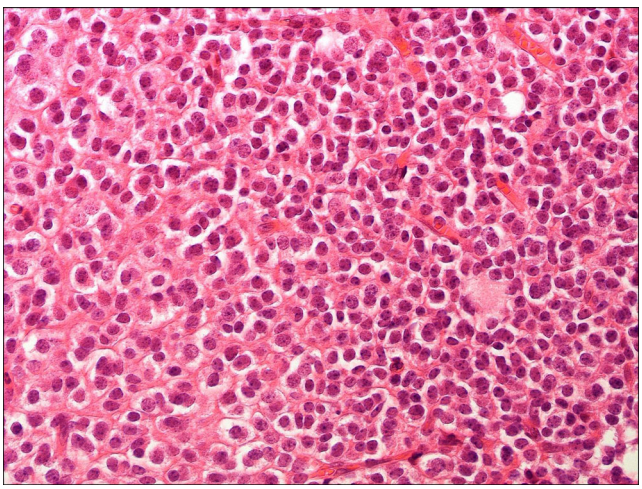

Fig. 1 Microphotograph of a central neurocytoma (hematoxylin and eosin stain, 40×). Well-vascularized tumor tissue and numerous round nuclei with a moderately granulated cytoplasm

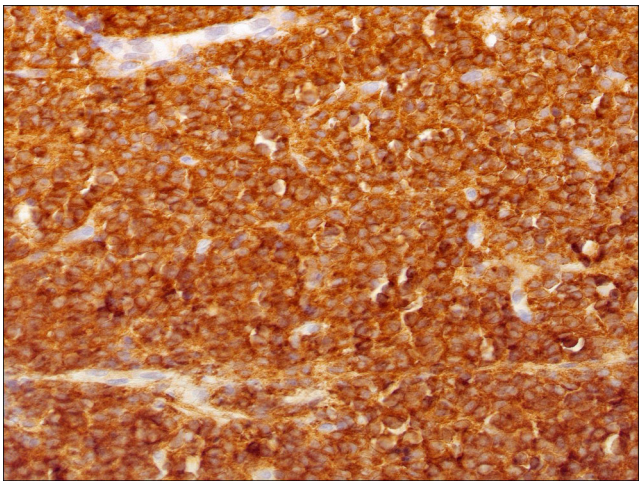

Fig. 2 Microphotograph of a central neurocytoma (40×) displaying strong synaptophysin positivity

temozolomide five times per week in 28-days cycles and received an irradiation dose of 22.5 Gy in 1.5 Gy daily fractions to the cervical spinal region. He was then placed on 200 mg/m^2 temozolomide monotherapy. He remained stable and symptom-free, and the repeated MRI examinations showed mild tumor regression until November 2011, when the follow-up MRI detected tumor recurrence in the left frontal lobe, in the occipital lobes on both sides, and in the left cerebellum (Figs. 5 and 6). Reirradiation was carried out to the whole brain in a cumulative dose of 27 Gy in 1.8 Gy daily fractions, with initial tumor bed avoidance, and an additional boost dose of 8 Gy in 1 Gy daily fractions to the cerebral and cerebellar manifestations. For a few months the good condition of the patient persisted, but a slow deterioration of his physical performance started in February 2012 and he died in April 2012, 62 months after the initial diagnosis and operation. Permission for autopsy was not granted by the family.

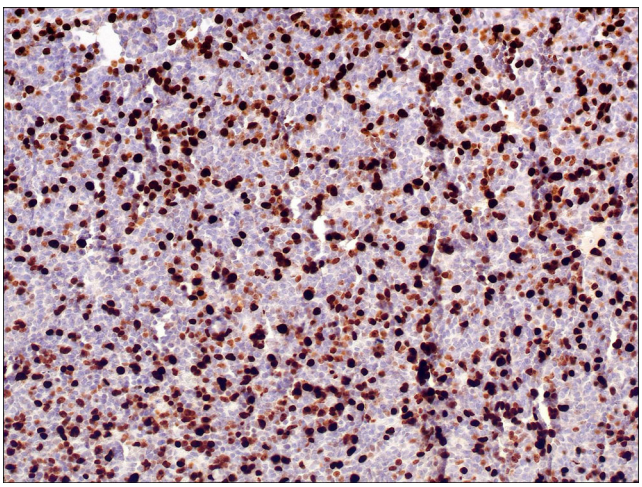

Fig. 3 Microphotograph (40×) demonstrating the immunoreactivity of Ki-67. The MIB-1 LI was reported to be 25–30 %

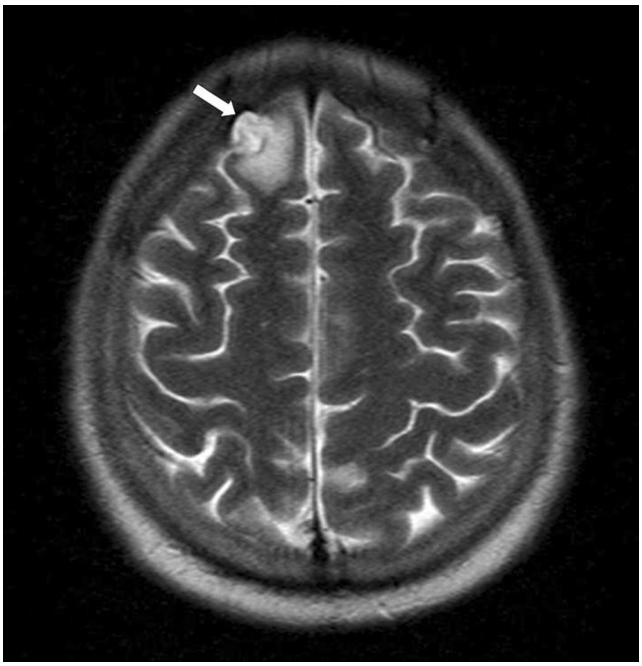

Fig. 4 Axial T2-weighted MRI showing hyperintense frontal metastasis

Discussion

There has so far been no randomized clinical trial involving CN because of the rarity of this tumor. Only case reports, retrospective case studies and meta-analyses of small numbers of patients are available with therapeutic recommendations.

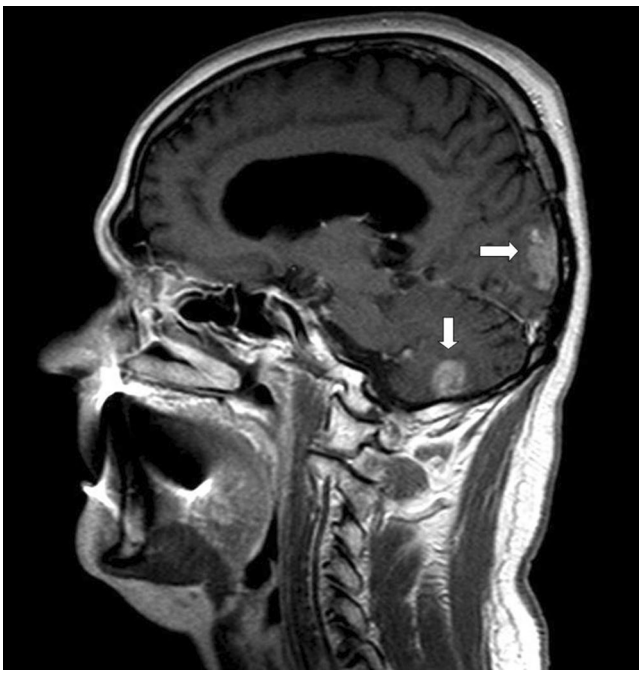

Fig. 5 Sagittal T1-weighted MRI showing hyperintense, contrast-enhancing metastases with perifocal edema in the left cerebellum and occipital lobe

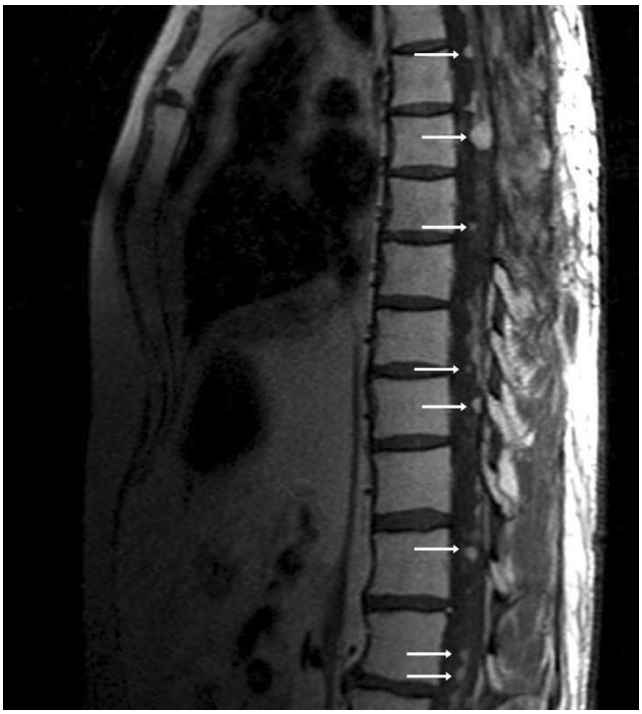

Fig. 6 Transversal T1-weighted MRI showing hyperintense, contrast-enhancing, intradural metastases in the thoracal spinal canal

GTR provides the best local control and survival rates. Postoperative irradiation is beneficial after STR and for atypical CN cases [2, 40]. Peak et al. [41] reported on 6 cases of CN (no allusion to the typ of CN), who underwent postoperative RT after GTR (3 cases) or STR (3 cases). The patients were treated with Co-60 gamma-irradiation. The median total dose to the primary tumor was 54 Gy. At the last follow-up, the KPS scores had deteriorated, due to white-matter demyelination. This report demonstrates that RT can control residual CN effectively and is beneficial, but more sophisticated irradiation techniques should be used to avoid serious late sequelae.

There have been several reports on small numbers of CN cases treated with conformal, adjuvant RT. Kim et al. [31] concluded that better local control rates can be achieved with RT. Schild et al. [42] and Rades et al. [43] retrospectively analyzed the available CN small-series literature reports and archives from their institution (32 and 85 cases, respectively). Those authors concluded that postoperative RT should be considered only in cases of STR and should involve only the initial tumor bed, because CNs neither infiltrate the brain parenchyma nor metastasize.

Rades et al. [44] reviewed and retrospectively analyzed 89 published incompletely resected cases of CN and recommended a guideline for the local RT: the target volume should include the preoperative tumor volume and 2 cm safety margin and should be irradiated with a total dose of 54–62.2 Gy. Leenstra et al. [2] likewise concluded that postoperative RT significantly improved the local control rate. They confirmed a nonsignificant tendency toward a better local control rate at 5 years when the MIB-1 LI was ≤2 %. This demonstrated that the MIB-1 LI could be used as a predictive marker of the clinical outcome. Several reports have been published on the usage and effectiveness of the gamma knife and stereotactic radiosurgery (SRS) for typical CN [34, 45].

In opposite to the localised benign CN, 19 cases including the present report have been described in the literature with unfavorable clinical course and rapid progression: high rates of local recurrence and craniospinal dissemination prior to the diagnosis or following surgical resection (Table 1). 11 of the 13 patients for whom data were accessible had an initial MIB-1 LI >2 %. The MIB-1 LI was not significantly higher among the patients who died because of disease progression. For the group of patients in whom the first tumor recurrence or dissemination occurred within 12 months, a higher mean MIB-1 LI was observed (mean 17.82 %, range 4.4–37.3 %). There was a nonsignificant tendency toward an unfavorable clinical course if the MIB-1 LI was initially elevated. The same phenomenon was observed for the patients who developed spinal metastases, who exhibited an initial mean MIB-1 LI of 13.4 %.

There were no differences in age and gender distribution and in localisation between the typical and atypical CN. Malignant CN arises mainly from the septum pellucidum ($n=4$), fornix or walls of the ventricles (lateral ($n=8$), third and ($n=1$), fourth ventricles ($n=1$)) with relatively frequent spreading to the surrounding structures: to the thalamus ($n=5$), the frontal lobe ($n=1$) and the ventricles($n=4$) and in one case the tumor was already multifocally spread. Due to the diffuse growth toward the adjacent structures GTR could be carried out in only 3/18 cases, 13 patients underwent STR, and 2 biopsy only. Reoperation was carried out in 4 cases.

16/18 patients received adjuvant treatment, i.e. RT ± chemotherapy. A huge variety of RT techniques (SRS=3, conformal RT=12), doses (25–66 Gy) and cytotoxic agents and combination were used (etoposide, carboplatin, cyclophosphamide, cisplatin, vincristine, cytarabine, ifosfamide, imatinib, temozolomide, toptecan, thioTEPA, and nimustine). Four patients received only chemotherapy and two patients did not get any postoperative treatment. The whole craniospinal axis was treated only in the cases with proven manifestation in the spinal cord ($n=2$). In case 8 [51], 39.6 Gy was administered to the entire neuraxis and an additional 14.4 Gy to the thoracal spine, sequential to cyclophosphamide, etoposide, and cisplatin. In case 17 [58], the craniospinal axis was treated with 36 Gy, and a 20 Gy boost was given to the tumor bed and to the upper cervical spine. Reirradiation was carried out in 3 cases, and diverse chemotherapeutic regimes were performed for the treatment of recurrences. In our patient temozolomide resulted in good response lasting for 12 months.

The clinical outcome was available for all cases. 7 patients died because of tumor dissemination and disease progression.

Table 1 A summary of all the reported cases of central neurocytomas with a malignant course

A/S	Localisation	MIB-1 LI(%)	Chronologyof dissemination	Treatment	Progr.	Follow-up af D	Ref.
3,M	3rdv, l th	–	STR,24 mo LC, STR2, 19 mo rapid LC & PD	ETO,CPT, DOXO, CTX	24 mo	E43 mo	[46]
3,M	WholeCSA	6,7	Diffuse,multifocal with leptomeningeal dis	VCR,CPT	–	SD18 mo	[47]
5,M	Rlat. v, r front	37,3;23,8	GTR,12 mo later R in frontal lobe/GTR, 5 mo later CSF spreading into frontal horn of l lat v, 9 mo later R in 4th v, 2 mo later L3–L4 drop metastasis, 10 mo later multiple metastases	VCR,CDDP, CTX/R2 INN, locRT: 50 Gy + TMZ, TMZ/R3 IT Ara-C + SRS:16 Gy/R4 Ara-C, TOPO, CPT, IFO, thioTEP, + ASCT, RT: 36 Gy + 6 Gy to L3-L4/R5 RT, ETO	12 mo	SD46 mo	[48]
19,F	Lth, lat vs	4,6	STR,2 mo later LR in l th l temp., 2nd STR	RT	2 mo	E5 mo	[49]
21,F	Latvs	–	Biopsyand RT, 15 mo later dis	RT50 Gy	15 mo	Dis15 mo	[16]
22,F	SP,3rd, lat. vs	3,3	GTR,36 mo later R in 3rd, 4th and lat vs, Th8	ETO,CDDP, CTX	–	SD36 mo	[50]
22,F	Rlat and 3rd v	1,8;4,1	STR,20 mo later R in lat v, 2nd STR, 14 mo later dis to lat vs and spinal leptomeninges	ETO,CDDP, CTX	20 mo	SD34 mo	[50]
22,F	SP,3rd, lat vs	–	GTR,36 mo LC, dis walls of the vs & at Th8	AfterP CTX, ETO, CDDP, RT: 39, 6 Gy CSA + 14,4 Gy to Th8	36 mo	SD72 mo	[51]
31,F	Rlat v, r th	15	STR,24 mo later LC, multiple dis in CSA	IFO,CDDP, ETO, RT: 50 Gy	24 mo	E37 mo	[52]
31,F	SP,lat vs mult	7–8	STR	–	–	SD7 mo	[53]
34,M	Corp.callos	25	STR,12 mo later LC and spinal dis	SRS:25 Gy, after R RT: 60 Gy, CDDP, ETO	12 mo	E23 mo	[54]
71,F	Corp.callos	14,4	STR	RT:60 Gy, ACNU	22 mo	E46 mo	[54]
35,F	Llat v	4,6	Biops,11 mo P, spinal dis at Th4 level, STR	RT:brain 66 Gy, spinal cord Th2–Th5 46 Gy	11 mo	SD14 mo	[55]
42,M	Latvs	high	STR,24 mo later meningeal dis		24 mo	E24 mo	[56]
43,M	SP	–	STR,2 mo later dis to v's walls	RT:60,6 Gy	2 mo	E17 mo	[57]
46,M	Llat v, th	–	STR,5 mo later P in 3rd v, 2 mo later dis	RT:60 Gy, after R RT: 56 Gy	5 mo	InP 7 mo	[57]
59,F	4thv	<1	D,7 mo STR, dis in v, cerebell & C spinal cord	RT:36 Gy CSA + 20 Gy to tumor beds	5 mo	DSF9 mo	[58]
		7,8	STR,R, dis into 4th v	RT,ChT		DSF132	[59]

ACNU nimustine, *Ara-C* cytarabine, *ASCT* autologous stem cell transplantation, *CDDP* cisplatin, *ChT* chemotherapy, *CPT* carboplatin, *CSA* cerebrospinal axis, *CTX* cyclophosphamide, *D* diagnosis, *dis* dissemination, *DOXO* doxorubicin, *ETO* etoposide, *E* exitus, *GFAP* glial fibrillary acidic protein, *IFO* ifosfamide, *IHC* immunohistochemistry, *INN* imatinib, *IT* intrathecal, *l* left, *LC* local recurrence, *mo* months, *Neu-N* neuron-specific nuclear protein, *NF* neurofilament, *NSE* neuron-specific enolase, *P* progression, *PD* peritoneal dissemination, *R* recurrence, *r* right, *SD* standard disease, *SP* Septum pellucidum, *SRS* stereotactic radiosurgery, *Syn* synaptophysin, *th* thamus, *TOPO* topotecan, *TMZ* temozolomide, *v* vtricle, *VCR* vincristine

The estimated mean survival was 27.9 months (range 5–46). 7 patients were in a stable condition at the time of their last follow-up examination. The mean follow-up period was 32.4 month (range 7–72). 2 patients were in disease progression at their last follow-up 15 and 7 months after the first operation. 2 patients were disease-free 9 and 132 months after the first tumor removal. The estimated mean progression-free survival was 15.3 months, ranging from 2 to 36 months.

One patient had multifocal disseminated disease at the time of the diagnosis. In the other cases, recurrence was always observed. CSF spreading was detected in 16/18 cases (ventricular $n=5$ on average 11 months after the first operation and spinal metastases $n=11$ an average of 21.1 months (range 5–36)). One patient exhibited peritoneal dissemination through the ventriculo-peritoneal shunt 43 months after the diagnosis.

In our case, we planned irradiation of the entire neuraxis as initial therapy, but the literature review at that time led us to change our treatment strategy to focal irradiation only. Irradiation of the recurrencies resulted in a good tumor response lasting from some months to years. The clinical course of the disease proved the inappropriateness of our decision on the postoperative treatment (local irradiation only), because this review of the separately reported malignant CN cases shows high probability of spread via the CSF (89 %) and the tumor exhibits good radiosensitivity.

Conclusions

There is currently no standard accepted therapeutic option for atypical CN; a rare central nervous system malignancy. The patients are treated with a large variety of different approaches. The conclusions drawn from meta-analyses of reports on benign CN can not be applied in cases with aggressive behavior. Our systematic evaluation of the available sporadic case reports has demonstrated that the cases with potential malignant transformation should be differentiated, and treated accordingly. Apart from the nuclear atypia, anaplasia, vascular endothelial proliferation, focal necrosis, and/or an increased mitotic index, correct evaluation of the MIB-1 LI can help in the identification of these patients. In that cases after the largest possible surgical removal, adjuvant neuroaxis irradiation should be considered.

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