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中枢神経系原発悪性リンパ腫

Ⅰ．中枢神経系原発悪性リンパ腫の標準治療と問題点

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はじめに

中枢神経系原発悪性リンパ腫（PCNSL）は，中枢神経系外に病巣をもたないリンパ球由来の悪性腫瘍で，わが国では原発性脳腫瘍のうち約3%程度を占めている[1]。本来リンパ系を有しない神経系で原発する理由は不明であるが，高齢者の発生頻度が高く，近年増加している腫瘍の一つである。組織学的には95%以上がびまん性大型B細胞性リンパ腫（DLBL）であるため，本稿ではPCNSLのうちDLBLに対する標準治療について述べる。本腫瘍は放射線感受性が高い腫瘍であるが，放射線単独療法では生存期間中央値が約12か月で，5年生存率が約18%という報告がなされ，奏効率は高いものの，長期間の抗腫瘍効果が低いことが示されている[2]。また，全身性節外性DLBLの標準的治療法であるCHOP（D）療法（サイクロフォスファミド/ドキソルビシン/ビンクリスチン/デキサメサゾン）と全脳への放射線照射との併用療法も，生存期間中央値が16か月と有意な上乗せ効果が確認できなかった[3]。これは主に，サイクロフォスファミド，ドキソルビシンが脳血液関門を通過しない薬剤であることが原因と考えられている。これに対して1990年代以降，大量のメソトレキサートを急速に点滴静注し，これと他の薬剤や放射線治療を併用することで，放射線照射単独療法と比較して無増悪生存期間と全生存期間が延長できることが明らかになった。高い血中濃度を得ることによって脳血液関門を通過させることができるようになり，またロイコボリンの投与にて正常細胞を救援することで，神経系への毒性を抑えたまま抗腫瘍効果を高められると考えられている。その後，メソトレキサートを上回る効果を示した抗腫瘍薬や代替療法が出現していないため，現時点では大量メソトレキサートを中心とした化学療法と全脳放射線照射の併用が事実上の標準治療となっている。

1．PCNSLの標準治療

大量メソトレキサート/ロイコボリン救援療法（HD-MTX）を中心とした化学療法＋全脳放射線照射は標準治療であると同時に，エビデンスを備えているといえる唯一の治療法でもある。米国のNational Comprehensive Cancer Network（NCCN）や英国のBritish Committee for Standards in Haematology（BCSH）のガイドラインでは，初発症例に対する治療として推奨されている。これまでに報告された前向きで症例数が25例以上の治療について主なものを表1に示す[4-22]。メソトレキサートは3 g/m^{2}以上用いられることが多く，2～3週間間隔で繰り返されている。これらの治療では，奏効率，著効率は化学療法後でそれぞれ72～94%と18～67%，放射線治療追加後にはそれぞれ68～94%と33～87%に達している。2年生存率と5年生存率はそれぞれ50～75%，26～51%で初期治療が奏効する割合は高いといえるものの，効果の乏しい症例や無効例が少なからず存在することと，長期生存の割合も高いとはいえないこともわかる。本邦における多数例の報告には，Hiragaらの報告[23]とPCNSL研究会による多施設第Ⅱ相試験の報告[24]がある。前者では，3.5 g/m^{2}のメソトレキサートを3時間で急速点滴静注した群と，6時間で点滴静注した群を比較し，3時間点滴静注群のほうが6時間点滴静注群よりも髄液中への薬剤移行が有意に促進されること，腫瘍縮小効果も有意に高くなることが報告された。また，2群間で有意差はみられなかったが，3時間点滴静注群の無増悪生存期間と生存期間の中央値は，メソトレキサート単独＋放射線照射で50か月と60か月以上という成績であった。後者では，3.5 g/m^{2}でのHD-MTXを2週間間隔で3コース行い，30～40 Gyの全脳照射を加えるというプロトコールが用いられた。中間報告では，放射線治療追加群55例における奏効率85%，生存期間中央値が44か月とされている。臨床試験では，年齢に上限が定められていることも少なくないため，非高齢者で比較的performance status（PS）のよい症例に対する標準治療の成績は奏効率80%，CR達成率70%程度で，全生存期間の中央値3～4年程度といえよう。メソトレキサートの量，コース数，各コース間の間隔などについてはまだ

表 1

症例数	初期治療					観察期間	生存率（%）		神経毒性
	療法	使用薬剤	Mの投与量	全奏効率（%）	著効例（%）	中央値（月）	2年	5年	（%）
化学療法のみ									
31[5]	化療単独	M	8 g/m²/14 d	100	NR	31	63	NR	0
25[6]	化療単独	M	8 g/m²/14 d	74	52	23	70	NR	5
65[7]	化療単独	M＋VICA	5 g/m²/28 d	71	61	26	69	43	3
37[8]	化療単独	M	8 g/m²/14 d	35	30	56	51	25	20
HD-M 単剤＋放射線治療									
25[9]	化療＋放	M	3.5 g/m²/21 d	88-92	56-88	60	58	38	8
46[10]	化療＋放	M	1 g/m²/7 d	NR-95	NR-82	36	62	37	22
31[11]	化療＋放→化療	M	1 g/m²/7 d	64-87	NR-87	97	72	22	32
HD-M を含む多剤併用＋放射線治療									
25[12]	化療＋放	AaCMOP	3 g/m²/21 d	72-72	67-78	24	70	58	0
57[13]	化療＋放→化療	ABnMO±CHOP	1.5-3 g/m²/14 d	68-71	62-64	59	60	36	NS
56[14]	化療＋放	BnMNP	1.5 g/m²/28 d	71-100	53-61	8	86	NS	29
31[15]	化療＋放	ABCMOP	2 g/m²/15 d	89-67		24	48	36	7
52[16]	化療＋放→化療	MNO	3.5 g/m²/7 d	90-94	56-87	60	75	40	25
102[17]	化療＋放	MNO	2.5 g/m²/14 d	94-NR	58-NR	56	64	32	15
52[18]	化療＋放	BnMOP	3 g/m²/14 d	NR-81	33-69	27	69	NR	12
41[19]	化療＋放	AIMT	3.5 g/m²/21 d	76-83	44-56	49	50	41	NR
30[20]	化療＋放→化療	MNOR	3.5 g/m²/14 d	93-NR	44-77	37	67	NR	NR
無作為化試験									
79[21]	化療＋放	M	3.5 g/m²/21 d	40-40	18-30	30	39	26	20
		Ma	3.5 g/m²/21 d	69-74	46-64		56	48	6
551[22]	化療±放	M or Ml	4 g/m²/14 d	54-NR	35-80（＋放）	50.7	60	32	49
				65	42			26	

NR: not reported，化療: 化学療法，放: 放射線療法，→化療: 化学療法後放射線治療を行いさらに化学療法追加，d: day
初期治療に使用された薬剤: A もしくは H: アドリアマイシン，a: シタラビン，B: ブレオマイシン，Bn: BCNU，C: サイクロフォスファミド，E: エトポシド，HD-M: 大量メソトレキサート，I: イフォスファマイド，M: メソトレキサート，N: プロカルバジン，O: ビンクリスチン，P: プレドニゾロン，R: リツキシマブ，T: チオテパ，Te: テモゾロミド，V: テニポシド

標準化がなされていない。これらの臨床試験では年齢の上限が定められていたり，PSの悪い症例は除外されていることが多く，70歳以上の高齢者の占める割合が高く，PSの悪い症例も多い臨床現場に適応する際には考慮が必要と考える。

2．標準治療における問題点と対策

現在，本疾患は標準治療後，著効例であっても再発はほぼ避けられない。一方，再発時の治療法は確立していない。同様にHD-MTXの効果が低い，あるいは抵抗性の症例に対する治療法も同様である。さらに，高齢者においてことに問題になる放射線治療後の遅発性神経毒性の問題も無視できない。

化学療法の治療強度を高める試みは，放射線障害を回避するために化学療法単独での治療成績改善を目的として計画されることが多く，メソトレキサートを増量する単独療法，多剤併用療法，超大量の化学療法に造血幹細胞移植を併用する方法が主なアプローチである。増量したメソトレキサート単剤療法では8 g/m²を用いた報告が多く，その一つであるNABTT 96-07で，6.5年以上観察した長期成績が2008年に報告された。著効例12例のうち，5例が中央値6.8年間，無再発で経過している[25]。生存期間の中央値は55.4か月であったが，原疾患死に関しては72か月でも中央値に到達していない。観察期間が約2年の時点での報告では23例中12例(52%)がCRで，全奏効率は72%，無増悪生存期間の中央値は12.8か月であった[6]。増量したメソトレキサート単剤投与ではgrade 3，4の有害事象は少なく，安全に実施できるとされる。一方で，放射線治療を追加しなければ，著効例でも比較的早期に再発するという傾向が指摘されている[16]。

HD-MTXを中心とし，様々な薬剤を併用した多剤併用療法も試みられている。最近，二つの無作為化試験の

結果が報告された。HD-MTX単独とそれに高用量のシタラビンを併用する群を比較した第Ⅱ相試験では，全奏効率が単独群40%（95% CI: 25-55），併用群69%（95% CI: 55-83）で（p=0.009），CR達成率も単独群18%（95% CI: 6-30），併用群46%（95% CI: 31-61）と，ともに有意差が認められた（p=0.006）。さらに，3年後の無増悪生存率についても単独群21%，併用群31%で有意差を認めているが（p=0.001, hazard ratio: 0.54, 95% CI: 0.31-0.92），3年後の全生存率は単独群32%，併用群46%で有意差は得られなかった[21]。これらの点から，高用量のシタラビン併用は治療効果を高め，無再発生存期間を延長できると考えられた。また，本試験では放射線治療を全例に併用していたが，HD-MTXとイフォスファマイド併用群のHD-MTX単独に放射線治療を追加した群に対する全生存期間における非劣勢を検討したG-PCNSL-SG-1試験の結果が2010年に報告された[22]。全生存期間の中央値は放射線併用群では32.4か月（95% CI: 25.8-39.0），化学療法単独群では37.1か月（95% CI: 27.5-46.7）であり，両者間に有意差はみられなかったが，hazard ratio: 1.06（95% CI: 0.80-1.40, p=0.71）で仮説は証明されなかった。さらに，本試験では初期治療中の死亡率が13%であった。このように初期治療としての多剤併用療法はHD-MTX単独＋放射線治療に対して予後を改善できる可能性が示唆されるものの，その成績を大きく凌駕することはできていない。また，再発時などに多くの症例で放射線治療を行わざるを得ず，神経毒性の軽減という点でも課題が残されている。

化学療法を強化する方法のもう一つは，造血幹細胞移植併用大量化学療法である。2006年にIllerhausらは，65歳以下の症例に対して，8 g/m^{2}のHD-MTX後にカルムスチン，チオテパを用いて自家造血幹細胞移植併用大量化学療法を行った治療成績を報告している。登録症例30例中，幹細胞移植を併用した症例は23例で，5年後の生存率87%，全症例5年生存率は69%であったが，放射線治療群の24%で強い白質脳症が出現したと報告している[26]。彼らはさらに69歳以下を対象として，CR例には放射線治療を行わない方針で行われた研究の結果を2008年に報告しているが，ここでは観察期間の中央値25か月で，3年生存率は77%，良好な認知能が維持できているという[27]。このように，本療法には良好な治療成績を収めたものもあり，魅力的な方法ではあるが治療関連死が3%以上に上るなど，限られた症例に対して行われる研究段階の治療にとどまっているといえる[28]。

高齢者には高率に生じる，放射線治療による認知機能の低下も依然大きな問題である。65歳以上を対象として，3 g/m^{2}のMTX投与に放射線治療を延期させる方針で30例に行われた前向きの研究では，観察期間の中央値が78か月の時点での無増悪生存期間と生存期間の中央値はそれぞれ5.9か月と15.4か月であったが，8例が生存しており，3年後と5年後の生存率はともに33%であった[29]。心機能や腎機能が保たれていれば，HD-MTXは高齢者にも比較的安全に実施可能だが，容易に化学療法を強化できないため，治療成績改善のためには若年者とは異なるアプローチが必要である。テモゾロミドやリツキシマブの併用が報告され，高齢者の治療成績の改善が期待されている[30,31]。

おわりに

本疾患は希少癌腫のため，大規模な試験や無作為化試験の遂行が困難なこと，脳血液関門のために効果が得られる薬剤が限られるといった問題があり，他臓器の悪性腫瘍に比べ治療法の進歩が遅れているといわざるを得ない。しかしながら，リツキシマブの効果やラパチニブのような低分子薬品の登場を考慮すると，今後，中枢神経系外のDLBLに対する新規治療薬剤が本疾患の標準治療薬となる可能性があると期待してよいのではないだろうか。

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CASE REPORT

A case of metastatic brain tumor causing multifocal cerebral embolism

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Abstract The patient was a 72-year-old woman who had previously undergone treatment for femoral chondrosarcoma (histologically rated as myxofibrosarcoma). She suddenly developed left homonymous hemianopsia and was diagnosed with cerebral embolism. Because she had atrial fibrillation, we treated her for cardiogenic cerebral embolism. About 3 months later, however, she developed left hemiplegia, and head magnetic resonance imaging revealed multiple tumorous lesions affecting the previously detected infracted area and several new areas. We assumed that a tumor embolus had caused cerebral embolism, which resulted in growth of the tumor from the embolus and formation of a metastatic brain tumor. The metastatic foci formed from the tumor embolus were visualized by diagnostic imaging, and histological examination of the resected tumor confirmed that the brain tumor had occluded the brain vessel (tumorigenic cerebral embolism). No such case has been reported to date, and this case seems to be important.

Keywords Tumor embolus · Cerebral embolism · Metastatic brain tumor · Chondrosarcoma

Introduction

Metastasis of malignant tumors to the brain is usually considered to assume the form of blood-borne metastasis. The involvement of tumor embolus in such conditions is also well known. We recently encountered a case of femoral chondrosarcoma in which detection of brain metastasis was triggered by the appearance of the signs of cerebral embolism. In this case, metastatic foci were formed in the brain because of the growth of the tumor from the tumor embolus (tumorigenic cerebral embolism). The presence of the tumor embolus within cerebral vessels was confirmed in the pathology specimens. We have reported this noteworthy case.

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Case report

Case

Patient 72-year-old woman.
Chief complaint Left homonymous hemianopsia.
Disease history Right femoral chondrosarcoma resected 2 years ago (which showed remission in response to postoperative radiotherapy) and atrial fibrillation.
History of present illness Left homonymous hemianopsia developed suddenly, and the patient was brought to our hospital in an ambulance. Upon arrival, echocardiography and electrocardiography revealed no thrombus, but atrial fibrillation was confirmed. Hematologically, no elevation of tumor markers was noted. Chest computed tomography (CT) scans revealed no abnormal shadow. Head magnetic resonance imaging (MRI) findings revealed multifocal cardiogenic embolism affecting the right occipital lobe as well. Anticoagulant therapy was thus started (Fig. 1).

Three months later, the woman visited the hospital with chief complaints of left hemiplegia and generalized malaise. At that time, head MRI revealed expansion of the previous lesions and presence of new lesions in the right

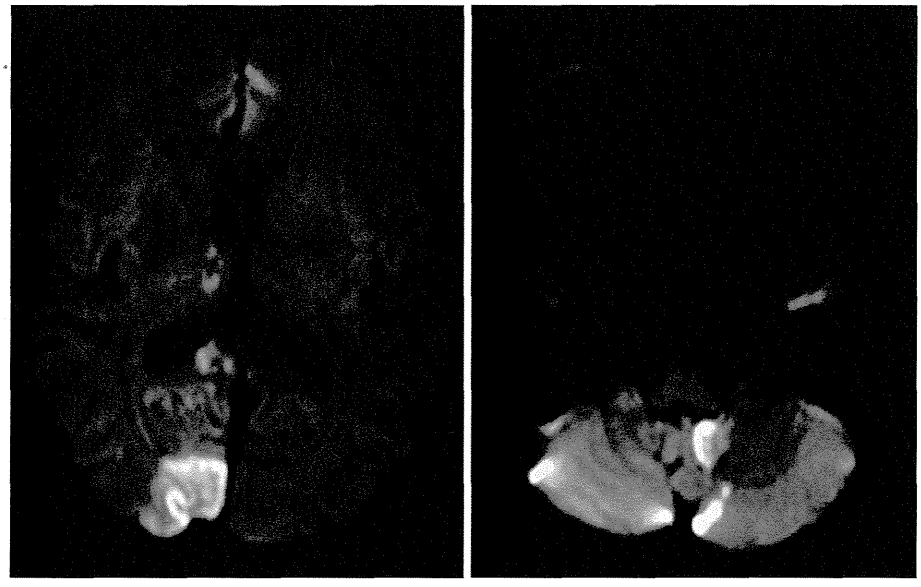


Fig. 1 Diffusion-weighted images showing high signal intensity areas in the cerebella, corpus callosum, thalamus, and right-posterior lobe on admission

thalamus and the splenium of corpus callosum (Fig. 2, 3, 4). Chest CT scans did not reveal any primary or metastatic tumor or any other abnormality. Decompression was achieved, and definite histological diagnosis was established by surgical resection of the brain tumor using a right occipital approach.

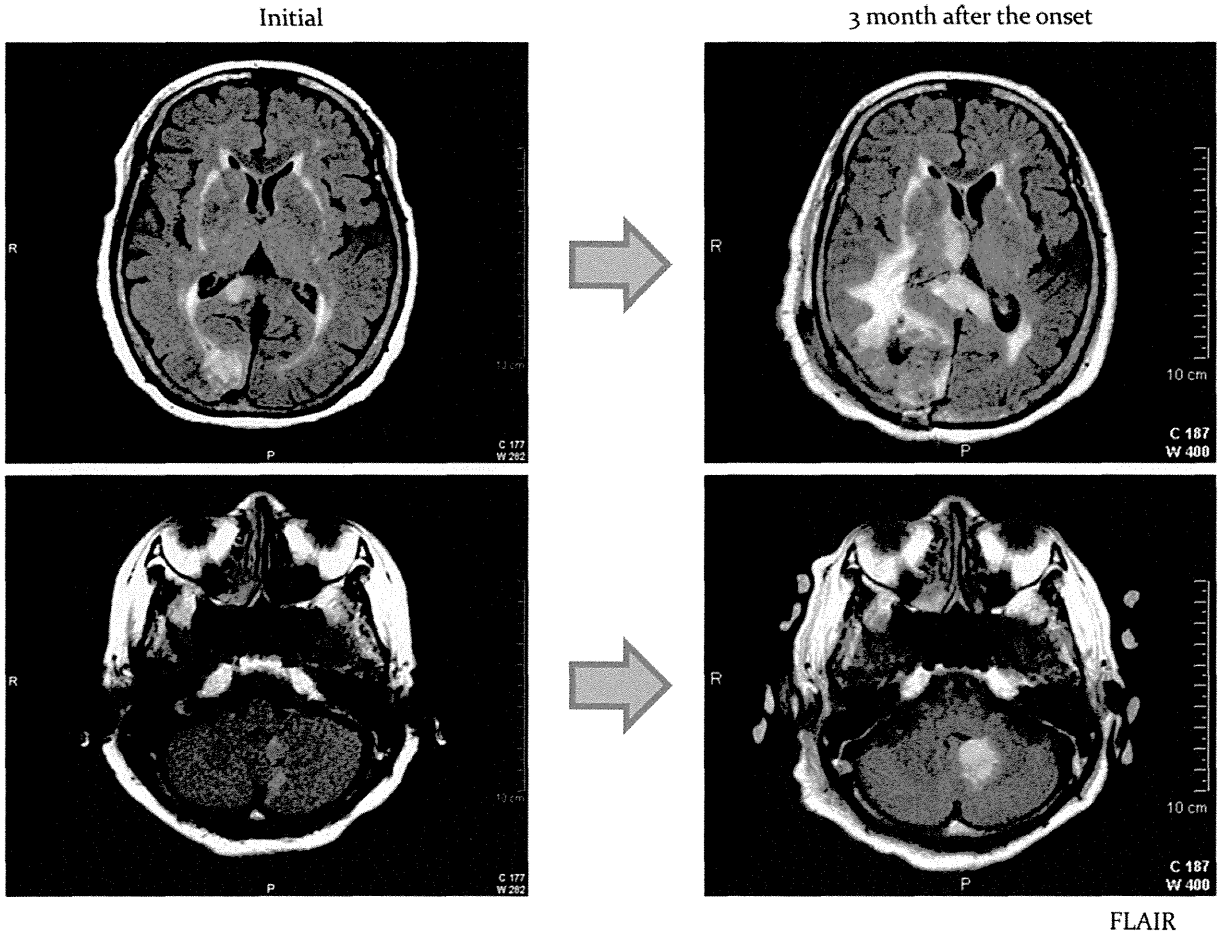
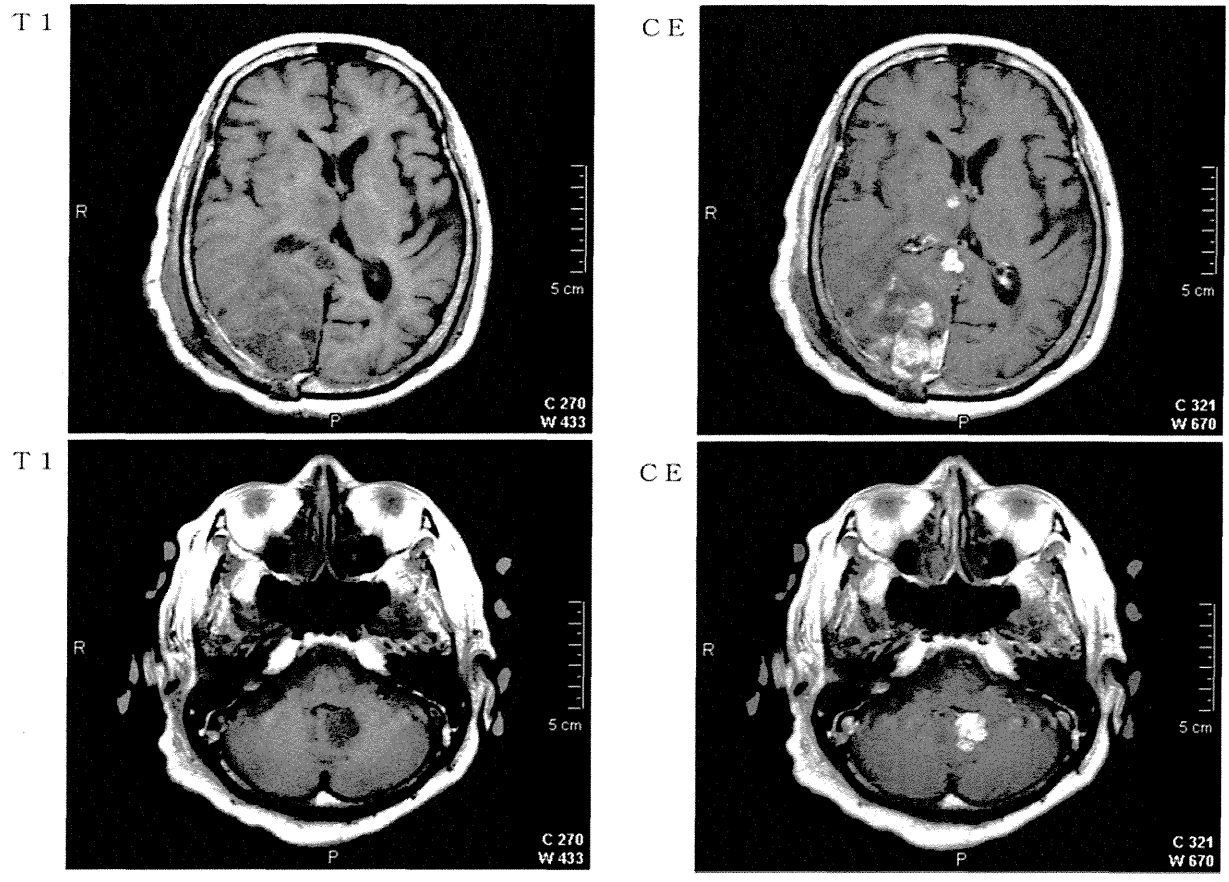


Fig. 2 Fluid attenuated inversion recovery (FLAIR) images obtained 3 months after the onset of cerebral embolism showing multiple high signal intensity areas located in the area identical to the areas that showed high signal intensity in the initial FLAIR images



Figs. 3, 4 Enhanced magnetic resonance (MR) image obtained 3 months after the onset of cerebral embolism showing enhanced areas in the same places where high signal intensity areas were initially observed (Fig. 2)

We planned to administer postoperative radiotherapy. However, the postoperative tumor progression was very rapid, and deterioration of the general condition was observed. Hence, the patient died 2 months after the surgery before postoperative radiotherapy could be administered.

Histological findings

Histological examination of the resected tissue with hematoxylin-eosin staining revealed that the cells had assumed a spindle form and were atypical, presenting with well-developed cell processes and close linkage between cells. Mucinous material was found in the stroma, cell density was high, and signs of cell division were noted, which suggested malignancy (Figs. 5, 6). These tumor cells filled the vascular lumen, and there were many sites within the brain parenchyma where no tumor infiltration was visible. These findings suggested arterial embolization by tumor cells (Fig. 5). The tumor was negative for cytokeratin (CK), alpha-SMA, and CD34, and was thus rated as myxofibrosarcoma.

Similar to the brain tumor, the primary lesion (femoral soft tissue tumor) was composed of spindle cells that were highly atypical and were linked by processes to each other; based on these observations, myxofibrosarcoma was diagnosed (Figs. 7, 8).

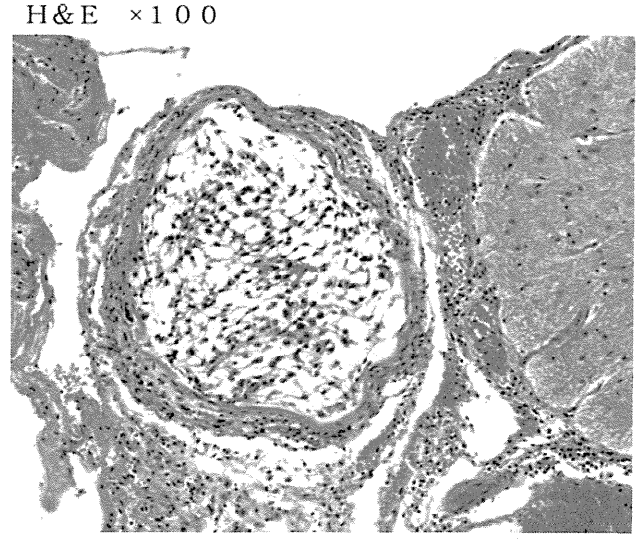


Fig. 5 Right posterior artery occluded by cells of myxofibrosarcoma. Recent infarction is present surrounding the embolus (hematoxylin-eosin, original magnification ×100)

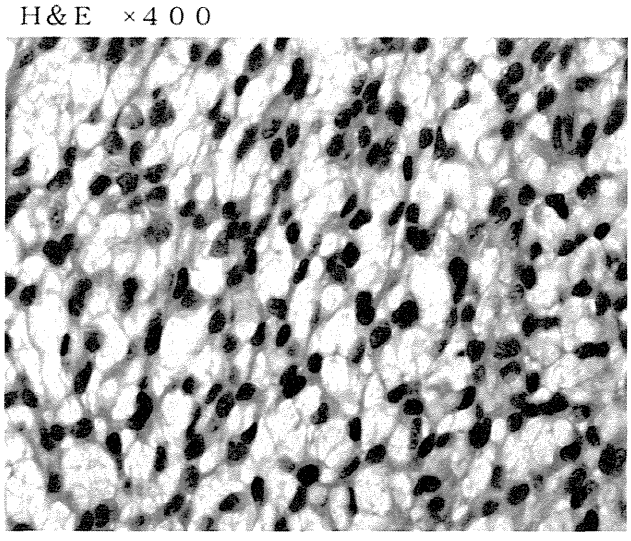


Fig. 6 Right posterior artery occluded by cells of myxofibrosarcoma (hematoxylin-eosin, original magnification ×400)

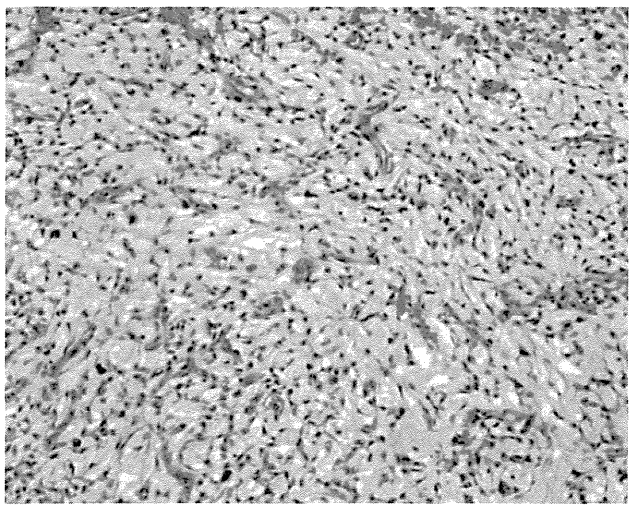


Fig. 7 Primary femur myxofibrosarcoma (hematoxylin-eosin, original magnification ×100)

On the basis of these findings, the brain tumor in this case was considered as having metastasized from the femoral chondrosarcoma.

Discussion

A very small number of reports are available on intracranial metastasis of myxofibrosarcoma in which metastasis occurs from the heart (primary lesion); further, according to our literature search, no case of intracranial metastasis from the femoral region has been reported thus far [1, 2].

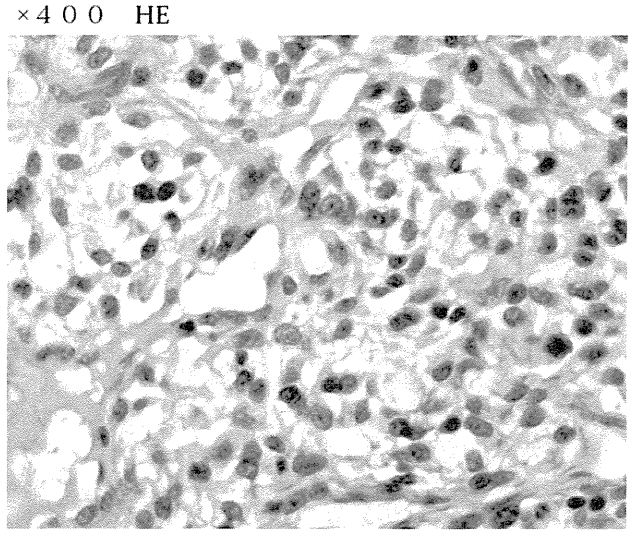


Fig. 8 Primary femur myxofibrosarcoma (hematoxylin-eosin, original magnification ×400)

In the case described in this paper, the patient had developed left femoral chondrosarcoma and undergone surgical resection of the tumor; the histological diagnosis was myxofibrosarcoma [3, 4]. The patient later received radiotherapy, and no sign of recurrence was found on periodic follow-up imaging examinations.

The patient recently presented with clinical signs of cerebral embolism. Some time after receiving treatment for cerebral embolism, she developed new neurological symptoms and was found to have a tumor in the embolized region of the brain. The findings from diagnostic imaging and histological examination were evaluated.

Imaging findings revealed high signal intensity on diffusion-weighted images (DWI), isosignal intensity on T1-weighted images, and slightly high signal intensity on T2-weighted images. The surrounding tissue was free of edema, and no sign of compression was observed; thus, infarction was speculated. Other features (sudden onset, consistence with the vascular region, and interruption of posterior cerebral artery on angiogram) did not contradict the diagnosis of cerebral embolism. It was estimated that the tumor had grown from the embolus in the embolized area, leading to the formation of the metastatic brain tumor.

It is quite rare that a tumor embolus serves as the cause of cerebral embolism. Cerebral embolism usually arises from cardiac tumor or primary/metastatic lung tumor [5–7]. Although transesophageal ultrasonography was not performed in this case, the possibility of paradoxical embolism cannot be ruled out in view of the fact that chest CT scans revealed no lesion in the lung.

According to our literature search, in addition to cases in which cerebral embolism arises from cardiac tumors, only

five cases of cerebral embolism caused by brain metastasis of primary/metastatic lung tumor have been reported [5, 8, 9]. There is no report on patients who might have paradoxical embolism of the brain in the absence of primary/metastatic lung tumor.

In the present case, at the time of definite histological diagnosis, the tumor was already progressive in nature and was accompanied by deterioration of the general condition. Hence, we were unable to begin radiotherapy. In the cases of metastatic brain tumors, measures need to be taken to reduce the tumor volume, if necessary, and radiotherapy should be administered after definite histological diagnosis. However, metastatic brain tumors due to tumor embolus often show multifocal dissemination.

In all of the cases reported to date, symptoms advanced progressively, leading to death within several months [9]. Early diagnosis is therefore essential.

Differential diagnosis of this condition on the basis of symptoms is difficult. However, the following findings seem helpful.

Navi et al. [9] reported that in this condition, tumor embolus is large in size and causes more extensive embolization.

Although recanalization of obstructed vessels is seen in 40–75% of all cases with cerebral embolism, reperfusion is less likely to occur in cases of tumorigenic embolism because of the large size and other properties of the tumor embolus [7].

It is therefore advisable to consider the possibility of tumor embolism and to check tumor infiltration of brain parenchyma from the embolized area through frequent diagnostic imaging in patients free of atherosclerosis, patients with obstruction of relatively large vessels, patients without recanalization, patients having lung/heart tumor, and patients showing left-to-right shunt of the heart despite absence of lung/heart tumor.

The present case seems to be valuable because very few reports are available on cases in which the formation of metastatic foci from a tumor embolus could be confirmed by diagnostic imaging and the presence of an intravascular tumor embolus could be confirmed by pathological examination of resected brain tumor. Therefore, it is desirable to explore the methods for making the differential diagnosis of this condition in the future and to collect data from additional cases.

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ORIGINAL ARTICLE

Glioblastoma with oligodendroglial components: glioblastoma or anaplastic oligodendroglial tumors

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Abstract There have been some recent reports about glioblastoma with oligodendroglial (OG) components and malignant glioma with primitive neuroectodermal tumor (PNET)-like components. We investigated whether the presence and extent of OG components and PNET-like components influenced the prognosis in patients with glioblastoma. Eighty-six patients with glioblastoma were divided into an OG group (28 %), which revealed areas with a honeycomb appearance, and a non-OG group (72 %) without a honeycomb appearance. Patients with glioblastoma were also divided into a PNET group (27 %), which revealed areas with PNET-like features defined as neoplastic cells with high N/C ratios and hyperchromatic oval–carrot-shaped nuclei, and lacked the typical honeycomb appearance, and a non-PNET group (73 %) without PNET features. There were no significant differences in overall survival among the OG, the non-OG, the PNET, and the non-PNET groups. Two patients who survived longer than 36 months had both OG and PNET components with 1p or 19q loss of heterozygosity. Perinuclear halo, which is a characteristic feature of oligodendrogliomas, is an artifact of tissue fixation. Therefore, we should not readily use the term glioblastoma with OG components. PNET-like components, which are considered rare in malignant gliomas, may be frequently identified in glioblastomas.

Keywords Glioblastoma · Oligodendroglioma · PNET

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Introduction

Oligodendroglioma is defined as glioma composed of neoplastic cells morphologically resembling oligodendroglia, as there are no established diagnostic procedures for oligodendroglioma [1]. Therefore, diagnosis of oligodendroglioma is mainly confirmed by the presence of morphological features including typical clear cells with perinuclear halos, referred to as a honeycomb appearance. However, this histological feature is an artifact of fixation or staining. Previously, we reported glioneuronal tumors with oligodendrolioma-like and primitive neuroectodermal tumor (PNET)-like features. Neuronal differentiation and 1p/19q loss of heterozygosity (LOH) were identified in these tumors [2, 3]. PNET-like cells were also identified in anaplastic oligodendroglioma.

Recently, glioblastomas with oligodendroglial components have been reported [4–9]. However, clinical outcomes, histological evaluation, and molecular markers varied among these reports. In general, patients with malignant gliomas (including glioblastomas) with oligodendroglial components and 1p and/or 19 LOH survived longer than those with other malignant gliomas [4–6, 8, 9]. On the other hand, long-term survival in cases with classic glioblastoma is considered to be unrelated to 1p/19q loss [10–12]. In addition, this favorable association of the combined loss of 1p and 19q was not evident in patients with astrocytoma or mixed oligoastrocytoma [13]. Some studies have suggested

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that a contamination of glioblastoma patient groups by the oligodendroglial lineage occurs [2, 3].

The first description of an oligodendroglioma was published by Bailey and Cushing [14], followed by the classic paper of Bailey and Bucy [15]. When classified, oligodendrogliomas were linked directly to medulloblastomas (PNETs). Perry et al. [16] reported that malignant gliomas with PNET-like components were relatively rare and were considered to be secondary glioblastomas with metaplastic processes of tumor stem cell clones, and were equal to classic glioblastomas in terms of overall survival. In our previous reports, the prognosis of patients with glioneuronal tumors with PNET-like components was relatively favorable [2]. We investigated whether the presence of oligodendroglial and/or PNET-like features influenced the prognosis in patients with glioblastoma.

Materials and methods

This study was approved by the Institutional Review Board of the University of Fukui Hospital. After approval, discharge databases of the neurosurgical department were reviewed to identify all patients who had undergone surgical resection or had biopsy between January 1, 1986 and December 31, 2010. The available hospital charts and clinical records were reviewed retrospectively to extract relevant data. Eighty-six patients with glioblastoma from the archives of the University of Fukui, classified according to the WHO 2000 criteria as glioblastomas (WHO grade IV), were reevaluated in order to identify the distinctive histological features of oligodendroglial or PNET components. All patients were identified from the files of the Neurosurgical Department at the University of Fukui Hospital. The overall survival was evaluated in each patient after discharge from the first operation. Follow-up periods were measured from the date of the first surgery for the glioblastoma.

Oligodendroglial components

Oligodendroglial components were defined as clusters of neoplastic cells that consisted of round nuclei with cellular monomorphism with a honeycomb appearance and occupied at least 10 % of the entire specimen. All 86 patients with glioblastomas were divided into an OG group, which revealed areas with a honeycomb appearance consisting of typical clear cells identified in oligodendrogliomas, and a non-OG group without a honeycomb appearance.

PNET-like components

All patients with glioblastoma were divided into a PNET group, which revealed areas with PNET features defined as neoplastic cells with high N/C ratios and hyperchromatic oval–carrot-shaped nuclei and which lacked the typical honeycomb appearance, and a non-PNET group without PNET features.

Statistical methods

Statistical analysis of the differences between the early and late groups was performed using Student's t test. A p value of less than 0.05 was considered significant.

Results

Twenty-four patients (28 %) were assigned to the OG group and 62 (72 %) to the non-OG group; 23 patients (27 %) were assigned to the PNET group and 63 (73 %) to the non-PNET group according to H&E staining. There were 14 patients (16 %) with both OG and PNET components.

Table 1 shows a summary of the clinical features in the OG and non-OG groups and the PNET and non-PNET groups.

Oligodendroglial components

In the OG group, there were 12 women and 12 men who ranged in age from 23 to 85 years (mean 58.8 years) at their time of operation. Overall survival time ranged from 1 to 69 months (mean 12.4 months). In the non-OG group, there were 19 women and 43 men who ranged in age from

Table 1 Summary of the clinical features in the OG and non-OG groups and the PNET and non-PNET groups

	OG component (86 cases)		PNET component (86 cases)	
	OG group	Non-OG group	PNET group	Non-PNET group
Cases	24 (28 %)	62 (72 %)	23 (27 %)	63 (73 %)
Gender (male:female)	12:12	43:19	16:7	39:24
Age (years-old)	59 ± 16 (p = 0.07*)	66 ± 14	58 ± 17 (p = 0.046*)	66 ± 13
Survival time (months)	12.4 ± 10.9 (p = 0.66*)	13.5 ± 7.7	13.2 ± 10.8 (p = 0.98*)	13.2 ± 7.8

Mean ± SD (* t test, $p < 0.05$ is significant)

38 to 88 years (mean 65.7 years). Overall survival time ranged from 3 to 36 months (mean 13.5 months). The mean age of the first operation in the OG group was lower than that in the non-OG group, but not significantly ($p = 0.07$).

PNET components

In the PNET group, there were 7 women and 16 men who ranged in age from 23 to 80 years (mean 57.8 years) at their time of operation. Overall survival time ranged from 1 to 69 months (mean 13.2 months). In the non-PNET group, there were 24 women and 39 men who ranged in age from 38 to 88 years (mean 65.9 years). Overall survival time ranged from 3 to 36 months (mean 13.2 months). The mean age of the first operation in the PNET group was significantly lower than that in the non-PNET group ($p = 0.046$).

There were no significant differences among the OG, the non-OG, the PNET, and the non-PNET groups in the Kaplan–Meier survival curves (Fig. 1). Table 2 shows the clinicopathological features of patients with glioblastomas who survived more than 24 months after the first surgery (Table 2). Two patients who survived longer than 36 months had both oligodendroglial and PNET components with 1p or 19q LOH (Fig. 2; Table 2).

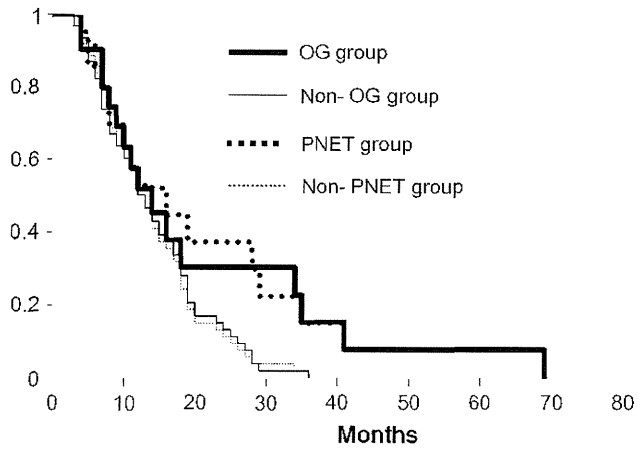

Fig. 1 Kaplan–Meier survival curves of the OG, the non-OG, the PNET, and the non-PNET groups. There were no significant differences among groups

Discussion

Previous studies have demonstrated that patients with glioblastoma with oligodendroglial components have longer overall survivals than patients with classic glioblastoma associated with 1p19q codeletion [4–6, 8, 9, 17]. 1p19q codeletion and EGFR receptor amplification provides a simple, clinically relevant prognostic subclassification of grade III gliomas [18]. However, Pinto et al. [7] demonstrated that the overall survival of patients with glioblastoma with oligodendroglial components without 1p19q codeletion was equal to those with classic glioblastoma. In addition, the long-term survival in cases of classic glioblastoma was suggested to be unrelated to a 1p/19q loss [10–12]. Recently, Hegi et al. [19] reported that GBM with an oligodendroglioma-like component (GBM-O) was not associated with a more favorable outcome in the EORTC study. Our study also demonstrated that there were no differences between overall survival in glioblastomas with or without oligodendroglial components, which suggested that oligodendroglial features such as a honeycomb appearance may be fixation artifacts and may not

Table 2 Clinicopathological features of patients with glioblastomas who survived more than 24 months after the first surgery

Case	Age	Gender	Survival time (months)	Diagnosis	Extent of resection	Temozolomide	OG component	PNET-like component	1p LOH	19p LOH
1	61	M	69	GBM	PR	−	+	+	+	+
2	61	M	41	GBM	STR	−	+	+	−	+
3	75	M	36	GBM	GTR	+	−	−	ne	ne
4	42	F	35	GBM	GTR	+	+	+		
5	35	M	34	Giant cell GBM	GTR	+	+	−	−	−
6	62	F	29	GBM	GTR	−	−	+	ne	ne
7	51	M	28	GBM	PR	−	−	−	ne	ne
8	72	M	28	GBM	GTR	−	−	+	ne	ne
9	66	F	27	GBM	GTR	−	−	−	ne	ne
10	72	M	26	Gliosarcoma	STR	−	−	−	ne	ne
11	68	M	25	GBM	GTR	−	−	−	ne	ne

OG oligodendroglial, *GBM* glioblastoma, *PR* partial resection, *STR* subtotal resection, *GTR* gross total resection, *LOH* loss of heterozygosity, *ne* not examined

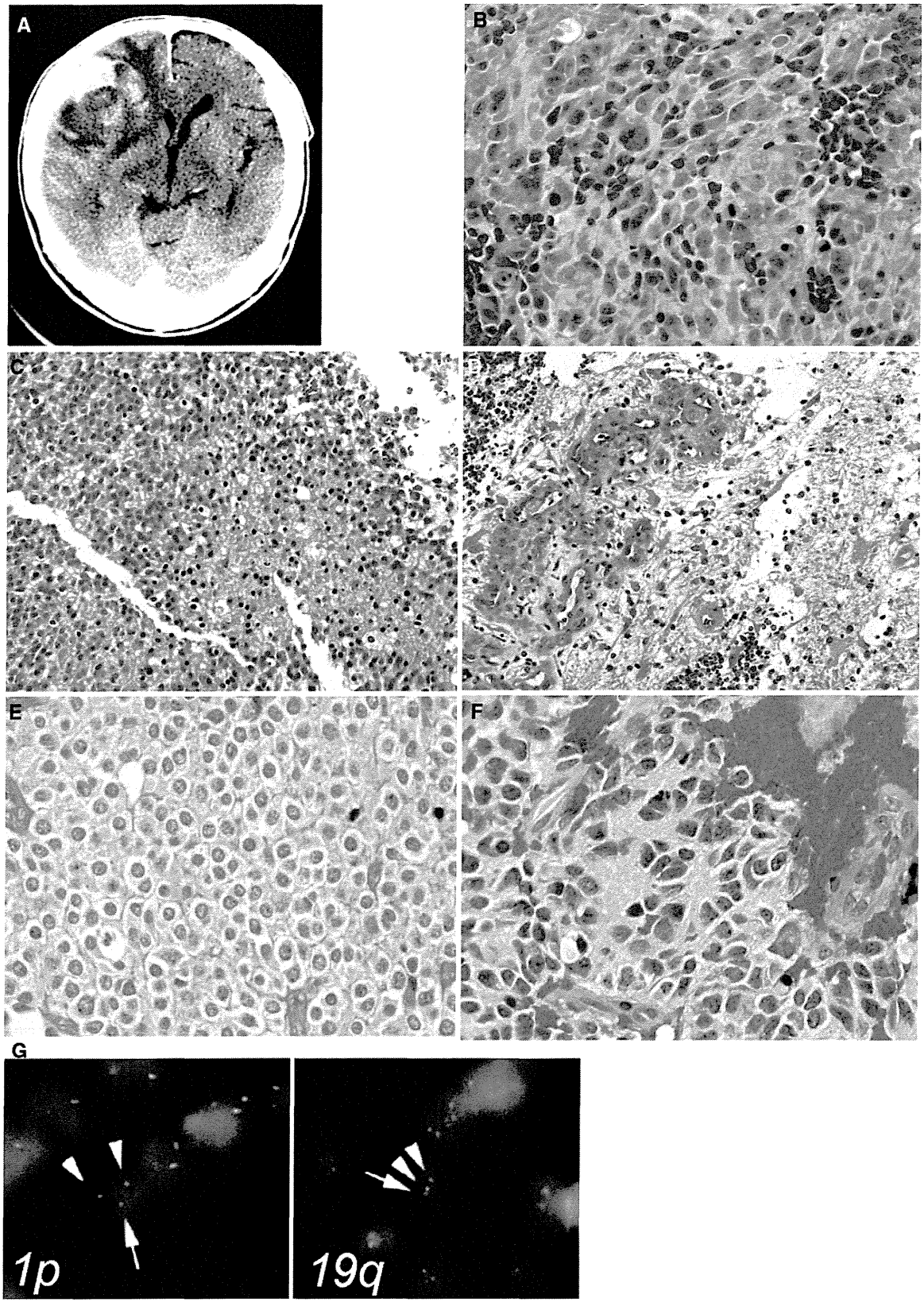

Fig. 2 A representative case of glioblastoma with oligodendroglial components. A 61-year-old man. Enhanced computed tomography shows a heterogeneous enhanced tumor in the right frontal lobe (**a**). The tumor consisted of atypical cells with brisk mitosis (**b** ×400), necrosis (**c** ×400), microvascular proliferation (**d** ×400), oligodendroglial components (honeycomb appearance, **e** ×400), and PNET-like components (**f** ×400). 1p 19q codeletion was identified by FISH (**g**). The overall survival time of the patient was 69 months

reflect biological features. However, two patients who survived longer than 36 months had both oligodendroglial and PNET components with 1p/19q deletion.

The relationship between PNET-like components and glioblastoma has not been clarified. In our previous study, 1p19q deletion was identified in long-survival (more than 2 years) patients with malignant glioma with PNET-like components [2]. However, Perry et al. [16] reported that malignant glioma with PNET-like components was relatively rare and had a poor prognosis equal to that of classic glioblastoma. In this study, a PNET-like appearance was often identified in glioblastoma cases, and the overall survival of patients with glioblastoma with PNET-like components was almost equal to that of patients with classic glioblastoma. We considered that the differences in frequency and prognosis were associated with differences in the definition of PNET-like components. In general, PNET features are defined as neoplastic cells with high nuclear/cytoplasmic ratios, hyperchromatic oval–carrot-shaped nuclei, high Ki-67 labeling indices, and immunoreactivity for GFAP or synaptophysin. In our study, PNET-like components were defined as a resemblance of morphological features in H&E stain. Therefore, in our study, there were no definitive demarcated, markedly hypercellular nodules, and no definitive synaptophysin immunoreactivity; those were characteristic findings of malignant glioma with PNET.

Morphologically, it may be difficult to make a differential diagnosis between anaplastic oligoastrocytoma and glioblastoma. Necrosis and microvascular proliferation are common in anaplastic oligodendroglioma and do not influence survival [1]. On the other hand, the presence of necrosis is a less favorable prognosis in anaplastic oligoastrocytoma [13, 20]. Therefore, these tumors are controversial and it was suggested that they should be designated as glioblastomas with oligodendroglioma components in the 2007 WHO classification of tumors of the central nervous system. In our study, oligodendroglial components were investigated in glioblastoma specimens, and there were no significant differences in overall survival time between patients with glioblastoma with oligodendroglial components and those without oligodendroglial components. He et al. [4] and Salvati et al. [8] reported that 10q deletion was identified in glioblastoma with oligodendroglial components. However, other reports suggested that 10q deletion was not always seen in cases of glioblastoma with oligodendroglial components [5, 6]. In summary, in order to be diagnosed as glioblastoma with oligodendroglial components, 1p19q10q codeletion must be confirmed. In order to be diagnosed as an anaplastic oligodendroglioma, a 1p19q codeletion and intact 10q must be confirmed. In other words, oligodendroglial or PNET-like components dominant malignant glioma with 1p19q codeletion may be assigned to anaplastic oligodendroglioma or oligoastrocytoma. Glioblastoma with oligodendroglial components with intact 1p19q and 10q deletion may be designated to classic glioblastoma.

Conclusions

The honeycomb appearance and PNET-like features identified in anaplastic oligodendroglioma were also frequently identified in specimens with glioblastoma. These histological features may be a fixative artifact. There may be of little benefit when attempting to diagnose some glioblastomas as glioblastomas with oligodendroglial components if genetic analysis is not performed.

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２．BNCT の課題と展望

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はじめに

ホウ素中性子捕捉療法（BNCT）はホウ素化合物が腫瘍（細胞）に選択的に集積すれば腫瘍（細胞）に対する略選択的な放射線照射が可能な治療であり、その放射線は生物効果の極めて大きい高 LET 粒子線であることから、二重の意味で X 線抵抗性、低感受性の腫瘍の治療法として期待が大きい。これまでの臨床研究でも有効性が示されており更なる発展が期待されている[1]。本稿では、BNCT 研究の到達点を概観しつつ今後の課題と展望を述べる。

１．中性子源開発

最初の臨床研究が 1950 年代に米国で行われて以来、中性子源には専ら研究用の原子炉が用いられてきた。その理由は、本法が中性子とホウ素原子核との反応による粒子を腫瘍細胞の破壊に利用するため、この反応確率が生体構成元素のそれに比して桁違いに大きいとは言え、大量の中性子を必要とする為である。しかもホウ素原子核と反応を起こすのは低速の熱中性子である。熱中性子は通常、速中性子を減速して得る。この減速過程での中性子フラックス（中性子強度：n/cm^2s）の減弱も勘案すると大量に速中性子を生み出す中性子源が必要で、その為には研究用の原子炉が適している。我が国では京都大学原子炉(KUR)と日本原子力研究開発機構の４号炉(JRR4)が BNCT に利用可能な原子炉であるが、JRR4 は東日本大震災の大地震以降は運転を止めおり、BNCT 研究に利用できる研究炉は、現在、KUR のみである。

片や原子炉に替わる加速器中性子源の開発も世界的に行われてきた。しかし、用いる一次粒子のエネルギーの高低に関わらず大電流の加速器とそれに耐える標的の開発が障壁なって成功していなかった。京大原子炉実験所では 2004 年から速器中性子源の開発研究を本格化させ、2009 年に住友重機械工業株式会社との共同によって BNCT の実臨床に使用可能な性能の世界初の加速器中性子源の開発に成功した[2]。サイクロトロンで 30MeV に加速した 1mA の陽子を Be 標的に衝突させて速中性子を発生させ、減速し熱外中性子ビームを生成する。加速器本体は最大長が約 3m であり、6m x 6m の部屋に充分に収まる。ビーム輸送系、標的・中性子生成系と照射室が必要となるが、将来は高度機能病院であれば設置可能なサイズである。本装置による体表面でのフラックスは KUR の約 1.8 倍、5cm 深部での生成熱中性子フラックスは約２倍である。従って、これまで 60 分の照射が必要な患者は 30 分の照射で済み、患者の身体的負担の軽減と照射精度の向上が期待できる。本装置の体表面でのフラックスは JRR4 の 1/2 から 1/2.5 であり、将来は電流量を増やして中性子フラックスを更に２倍程度高めることが望ましい。サイクロトロンの能力としては 2mA の陽子まで加速可能であることが確認済みである。電流量を増やすには、それに耐える標的システムの開発が重要課題となる。

加速器中性子源では、加速陽子のエネルギーにより最適標的金属と必要電流量が決まる。中性子の減速体系を小型化する意図で陽子エネルギーを下げると電流量を増やさねばならない。陽子エネルギーを 2.5MeV に下げると標的は Li となるが、Li での中性子収率は 30MeV 陽子―Be 系の約 1/200 である。片やγ線発生率は 1/10 もあり、同量の中性子を得ようとすると、数十倍の電流が必要となる。その場合、標的の熱除去や標的等への水素蓄積によるブリスタリング（標的表面が毛羽立ち脆弱化すること）をどう防ぐか困難な問題が存在する。陽子エネルギーを少し上げて Be 標的を用いる場合も類似の困難に直面する。Be は Li と異なり熱耐性が大きいが、陽子エネルギーが低いと陽子が標的金属に蓄積し、Li 同様のブリスタリングが避けられない。30MeV 陽子では Be 中の飛程が 5.8mm あるので、Be 厚をこれより若干薄くし陽子を冷却水中に回収することでブリスタリングを巧く回避できる。この標的システムは最低１年間交換無しに使用可能と考えている。低エネルギー陽子・大電流加速器は静電加速器にせよ直線加速器にせよ実現の可能性はあり得る。しかし、安定した長期間に亘って無交換で使える標的システムの開発には難しい課題が多い。

２．線量評価

現在尤もらしく用いられている BNCT の線量評価には重大な問題点がある。特に腫瘍に対する線量がそうだ。BNCT で組織や細胞に与えられる線量は、中性子と窒素原子核の核反応による陽子(a)、中性子とホウ素原子核との核反応によるα粒子と Li 原子核(b)、そしてビームに混在する一次γ線(c)および中性子と水素原子核の反応による二次γ線(d)の成分より構成される。これらの線量成分の中で、(b)以外は核反応の対象となる元素が組織や細胞に均一に分布していると見なし得るし、その濃度も分かっている。また、中性子、生成熱中性子の分布は相当正確な推定が可能である。このプログラムにはオハイオ州立大学で開発されたシステム SERA と原子力研究開発機構での開発になる JCDS がある。これらの線量は腫瘍非選択的線量でもある。問題は(b)の線量成分であり、これはホウ素濃度に依存して大きく変わる。そのホウ素濃度が個々の患者で正確に推定できるかと言えば「出来ない」。

BPA(paraboronophenylalanine)の場合、腫瘍細胞の増殖状態や細胞周期によって取り込みが大きく変わることが分かっている[3]。それ故に腫瘍内のホウ素の不均一分布は不可避である。また、ホウ素化合物は血流を介して腫瘍内に分布するので、腫瘍血管の分布や血流の状態の不均一にも由来してホウ素化合物の分布は不均一にならざるを得ない[4]。中性子とホウ素原子核の反応によって放出されるα粒子や

Li 原子核の飛程が、仮に 100μm もあればホウ素化合物分布の不均一は問題にならない。ホウ素化合物を取り込んだ細胞から放出される粒子の飛程が取り込まない細胞をも充分に含むからである。しかし、実際には粒子の飛程は極短いので線量分布は不均一になる。この問題の解決には腫瘍細胞に遍く集積する新規のホウ素化合物の開発が必要である。

BPA では ^{18}F で標識し[5]、PET で腫瘍集積の程度を予測することがある程度は可能である[6]。しかし、解像度の限界やトレーサー量の ^{18}F-BPA で得た集積比が 250-500mg/kg 体重と言う大量の治療量の投与時にも適応できるのか、あるいは BPA を取り込まない組織中の結合組織などの非細胞成分の多寡をどの様に評価するのか、等々、未解決の問題が多い。現状の ^{18}F-BPA PET で得た腫瘍：正常組織の集積比を用いて腫瘍の線量評価を行うとする試みは、BNCT に対する一知半解によるものであり、他の放射線治療の線量評価と同一視され、誤解を増幅する危険があり、行うべきではないと考える。

正常組織ではホウ素化合物の分布に個体差が小さいと考えられるので、血中ホウ素濃度と中性子量から計算した線量に実験で得た係数(CBE factor)を乗じることによって求めた生物学的 X 線等価線量を評価に使うことは合理的である[7]。従って、現状の BNCT では線量の制限を正常組織線量で考えるのが妥当である。何れにせよ現状の線量評価は大きな問題を内蔵しており、斬新なアイデアの出現に期待したい。

3．対象腫瘍種の拡大

嘗て BNCT は専ら悪性神経膠腫と皮膚の悪性黒色腫を対象に有効性と有用性の研究がなされた。しかし、これらの腫瘍は何れも本邦では発生頻度があまり高くない。例えば原発性脳腫瘍の 10 万人当たりの発生頻度 12 人程度であり、その 22%が星細胞腫（WHO グレードⅠ～Ⅳ）である[8]。BNCT の対象としているのはグレードⅢとⅣで、年間 2000 人強の新規患者が発生している。悪性黒色腫は白人で紫外線に曝露し易い環境にある場合には発生頻度が高いが、有色人種である日本人では高くない。また、注意すれば早期の発見と切除による治療が可能で、BNCT の相対的重要性は低くなる。

21 世紀に入り、唾液腺腫瘍を始めとして再発頭頸部癌等にも研究の対象が拡大し[9]、有効性が示されているが、BNCT の癌治療全体に対する役割を増すには発生頻度の高い他の腫瘍に適応を拡大する必要がある。更に言えば一次治療としての有効性を示す必要がある。しかし、既に相当の治療成績を上げている疾患に適応拡大を図ることは難しい。従って現行の放射線治療で制御に難渋している腫瘍、更には陽子線や重イオン線による治療の適応にならないものや治癒困難が予想されるものが当面の対象になる。

BNCT の原理や腫瘍の性質も勘案すると、BNCT が適応となる腫瘍には次の条件が必要である。① 腫瘍細胞の X 線感受性が低く、腫瘍治癒線量が周辺正常組織の耐容線量を越える。②細胞の放射線感受性は通常であるが、腫瘍が広範囲に侵潤あるいは侵潤する性質を持ち、根治には大照射野が必要で正常組織の耐容線量の点から根治照射が困難である。③硼素化合物が腫瘍に選択的に集積する。④術中 BNCT でない場合は標的病巣が浅在性である。

これら条件に適合する腫瘍として以下のものが考えられる。

3．1パンコースト型肺癌、胸壁侵潤の肺癌(T3)、悪性胸膜中皮腫

パンコースト型肺癌は高 LET 放射線治療の有効性が確認済みであり、病巣も比較的浅い。神経や血管を巻き込んで進展するため治療では病巣内の正常構造と腫瘍が選別照射されることが望ましい。従って、将来の適応癌腫として研究を進めるべきである。胸壁侵潤型の肺癌(T3)も同様の理由で対象とするべきである。悪性胸膜中皮腫は病巣の三次元形状が複雑で腫瘍の下は耐容線量の低い肺組織である。高精度の三次元X線集光照射を用いても対応が困難な腫瘍である。

3．2頭頸部癌の再発固定リンパ節

速中性子線治療で高 LET 放射線の有用性が認められている。放射線治療後の再発は X 線抵抗性の細胞成分が残った結果であり、低 LET 放射線による制御は困難である。この対策には高 LET 放射線の利用が効果的である。またこの領域の腫瘍では照射の標的体積に神経、血管などを含むので、とりわけ再照射治療にあっては細胞レベルでの選択的な照射が強く望まれる。

3．3骨肉腫、軟部腫瘍

代表的なX線低感受性腫瘍である。骨肉腫の場合、一回大線量照射が可能なX線術中照射が腫瘍の制御には有効である。しかし、化骨細胞と破骨細胞の両者が非選択的に破壊される結果、長管骨では腫瘍治癒後に病的骨折が高率に生じる。これを防ぎつつ治癒を得るには細胞レベルでの選択的照射が行える BNCT が適している。四肢病巣の場合は体位を変え２方向からの照射も容易に行えるので、腫瘍内の中性子分布を均一化し易く、細胞レベルでの選択的照射の特長を活かし易い。

3．4肝癌（転移性肝癌を含む）

単一病巣の場合は陽子線治療や IVR 治療によって優れた成績が得られる。片や複数病巣の場合、外照射法では広範囲の肝組織に可成りの線量が照射され、治療可能比が著しく低下する。更に医用画像では確認不可能なミクロの娘病巣は照射できない。これに対し細胞レベルでの線量集中が可能な BNCT では有効な線量を与え得る。肝動脈と門脈の血流二重支配を利用する IVR の手技を用いれば現在のホウ素化合物でも病巣に高濃度かつ選択的に集積させることも可能である[10,～,12]。

3．5再発乳癌

乳癌は標的病巣が体表面から浅く、その点で BNCT には好都合である。乳房の圧迫によって深度を更に浅くすることも可能である。腫瘍切除と術後X線治療を組み合わせた乳房温存療法が標準治療として確立されているが、乳癌によく集積するホウ素化合物があれば切除を BNCT に置き換えることも将来は可能になるかも知れない。その為には当面、局所再発乳癌を対象とした臨床研究が求められる。

3．6膵癌

極めて予後不良の癌である。腹膜播種、肝転移が生じ易