Levetiracetam versus phenytoin for seizure prophylaxis during and early after craniotomy for brain tumours: a phase II prospective, randomised study

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J Neurol Neurosurg Psychiatry published online December 15, 2014

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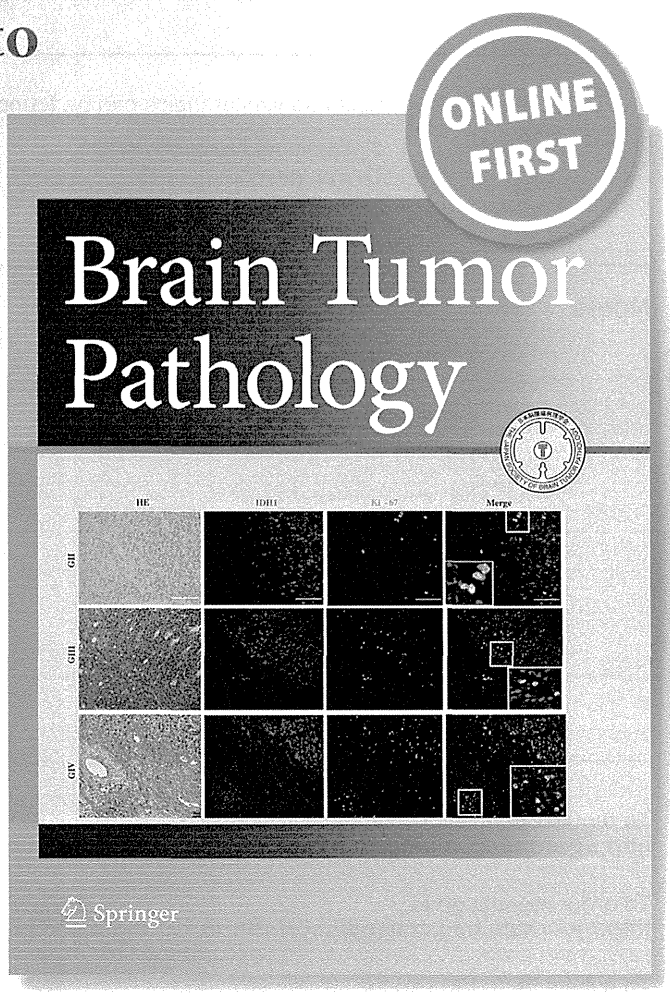
Brain Tumor Pathology

ISSN 1433-7398

Brain Tumor Pathol
DOI 10.1007/s10014-014-0210-4



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Brain Tumor Pathol
DOI 10.1007/s10014-014-0210-4

CASE REPORT

Findings from positron emission tomography and genetic analyses for cerebellar liponeurocytoma

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Received: 18 August 2014 / Accepted: 8 December 2014

Abstract Cerebellar liponeurocytoma is a rare tumor that usually develops in adult patients, and is categorized as World Health Organization grade II. Because of the small number of reports on its radiological and pathological features, the disease remains poorly characterized. The current case involved a 59-year-old man with tumor in the upper cerebellar vermis. Preoperative positron emission tomography (PET) showed high uptake on ^{11}C-methionine PET, but low uptake on ^{18}F-fluorodeoxyglucose PET. These findings resemble those of central neurocytoma and oligodendroglioma, but are incompatible with other brain tumors. Subtotal tumor removal was performed by suboccipital craniotomy. Histopathological examinations showed sheets of small, isomorphic cells with round nuclei and clear cytoplasm, and focal vacuolated cells resembling adipose cells. On immunohistochemistry, tumor cells were positive for synaptophysin and NeuN. Vacuolated cells were immunoreactive for perilipin. Based on these findings, cerebellar liponeurocytoma was diagnosed. Genetic analyses revealed absences of both chromosome 1p/19q loss and isocitrate dehydrogenase 1 mutation, further ruling out oligodendroglioma. These radiological and genetic aspects of cerebellar liponeurocytoma, which are mostly in common with central neurocytoma, should prove helpful in differentiating this rare tumor from other tumors with similar morphology.

Keywords Cerebellar liponeurocytoma · IDH · Immunohistochemistry · PET

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Introduction

Cerebellar liponeurocytoma is a rare neoplasm that was first introduced to the World Health Organization (WHO) classification in 2000 as a distinct clinicopathological entity among the central nervous system tumors [11]. In the 2007 WHO classification, cerebellar liponeurocytoma is defined as WHO grade II [14]. This neoplasm develops predominantly in the cerebellar hemispheres and vermis, and is characterized morphologically by focal lipidization within sheets of small, isomorphic round cells expressing both neuronal and glial markers [2, 9]. Cerebellar liponeurocytoma resembles neurocytoma microscopically, and expression profile analyses have also identified a close relationship to central neurocytoma [9]. Although findings from computed tomography (CT) and magnetic resonance imaging (MRI), pathological and immunohistochemical characteristics, and clinical behaviors have been reported in the literature [1, 4, 10], the characteristics of this tumor are still poorly understood. Because previous reports have demonstrated that patients with cerebellar liponeurocytoma usually show a favorable clinical course without adjuvant therapy after surgical removal [4, 10], accurate differential diagnosis of this rare pathology from other brain tumors is important in order to avoid unnecessary aggressive adjuvant therapies. However, differentiating neurocytoma and liponeurocytoma from other tumors such as oligodendroglial tumors, clear cell

Published online: 20 December 2014

ependymomas, dysembryoplastic neuroepithelial tumors (DNTs) and medulloblastomas is sometimes difficult under light microscopy, given the similar histological patterns such as perinuclear halo with round nuclei and cells [14]. We report herein an additional case, focusing on positron emission tomography (PET) findings and genetic perspectives that may prove useful in identifying this rare neoplasm.

Case report

A 59-year-old man visited the hospital after experiencing sporadic headaches and vertigo. Physical examination showed no neurological abnormalities. CT revealed an isodense to slightly hyperdense mass within the upper cerebellar vermis. The diameter of the mass was approximately 3.5 cm. MRI showed iso-intensity on T1-weighted imaging, heterogeneous intensity on T2-weighted imaging, high intensity on diffusion-weighted imaging, and slight hyperintensity on fluid-attenuated inversion recovery (FLAIR) imaging. Slight enhancement was observed after gadolinium administration (Fig. 1a–f). No feeding arteries were apparent on angiographic studies. To evaluate the metabolic activity of the tumor, radioisotope examinations were performed. Lower tumor accumulation was seen with ^{18}F-fluorodeoxyglucose (FDG) PET compared with normal cerebellar cortex, showing a lesion-to-normal cerebral cortex accumulation ratio (L/N) of 0.62, whereas the tumor showed higher accumulation on ^{11}C-methionine PET (L/N, 2.73) (Fig. 2a, b).

Preoperative differential diagnoses included anaplastic astrocytoma, oligodendroglial tumor, ependymoma, malignant lymphoma, and extraventricular neurocytoma. Since the tumor was relatively large in the posterior fossa, methionine PET demonstrated relatively high uptake, and diagnosis was difficult based solely on imaging examinations, we proceeded with surgical removal of the tumor by suboccipital craniotomy using a supra-cerebellar approach.

Under operative microscopy, the tumor showed generally whitish coloration, with moderate vascularity and mixed consistency. A clear cleavage plane was evident on the side of the cerebellar cortex, but no clear plane was seen on the side of the vermis, which was considered as the site of tumor origin. The patient was administered 5-aminolevulinic acid (5-ALA) preoperatively, resulting in no fluorescence at the tumor under violet–blue excitation light intraoperatively. Since the inferior vermian vein limited the operative approach, only subtotal resection could be achieved.

Histologically, the tumor comprised small, monomorphous cells with round nuclei and lightly eosinophilic to clear cytoplasm (Fig. 3a). Rare tumor cells showed intracytoplasmic vacuoles, reminiscent of lipid droplets (Fig. 3b). Mitosis was rarely observed. Immunohistochemical analysis was performed using a BenchMark XT automated immunostainer (Ventana Medical Systems, Inc., Tucson, AZ). Tumor cells were diffusely immunoreactive for synaptophysin (monoclonal, MRQ-40, Roche, Fig. 3c). Vacuolated cells were immunoreactive for perilipin, a lipid-droplet associated protein (polyclonal, Progen Biotechnik, Fig. 3d). Tumor cells were moderately stained for NeuN (monoclonal, MAB377, Merck Millipore, Fig. 3e). Immunoreactivity to GFAP was observed, largely on non-neoplastic astrocytes (monoclonal, 6F-2, Dako, Fig. 3f). Tumor cells were totally negative for Olig2 (polyclonal, IBL, Fig. 3g). Ki67-labeling index was 2 % (monoclonal, MIB-1, DAKO, Fig. 3h). On the basis of these histopathological findings, cerebellar liponeurocytoma was diagnosed.

To further confirm the differential diagnosis, genetic analyses were performed. Chromosome 1p and 19q co-deletion was not detected in the microsatellite analysis performed as described previously [29]. The presence of *IDH1* mutation was also denied by direct Sanger sequencing targeting codon 132 [17]. This genetic information indicated that oligodendroglial tumor was unlikely.

Although localized residual tumor was present on postoperative MRI, since the clinical course of cerebellar liponeurocytoma is generally reported to be slow and pathological features were benign in the current case, the patient was not treated with adjuvant therapy. At outpatient follow-up 2 years postoperatively, the small residual tumor showed no enlargement and the patient remained without any neurological disability.

Discussion

This case report suggests that preoperative PET and postoperative genetic analyses of tumor tissue might be useful for diagnosing liponeurocytoma.

Although PET findings for central neurocytoma have been documented in a small number of cases, findings for cerebellar liponeurocytoma have not been reported. Central neurocytoma generally shows low uptake on FDG-PET, reflecting low glucose metabolism [16, 27]. An exception was reported by Mineura et al., who described high uptake on FDG-PET for a tumor that showed regrowth 7 months after partial removal. Their report suggests that increased FDG uptake can be interpreted as predicting rapid tumor progression and a malignant prognosis [16]. On ^{11}C-methionine PET, central neurocytoma usually shows higher accumulation than normal cortex [16]. In a study of two cases of central neurocytoma by Takao et al. [27], L/N ratios as high as 1.68 and 2.80 were reported. In the current case, the

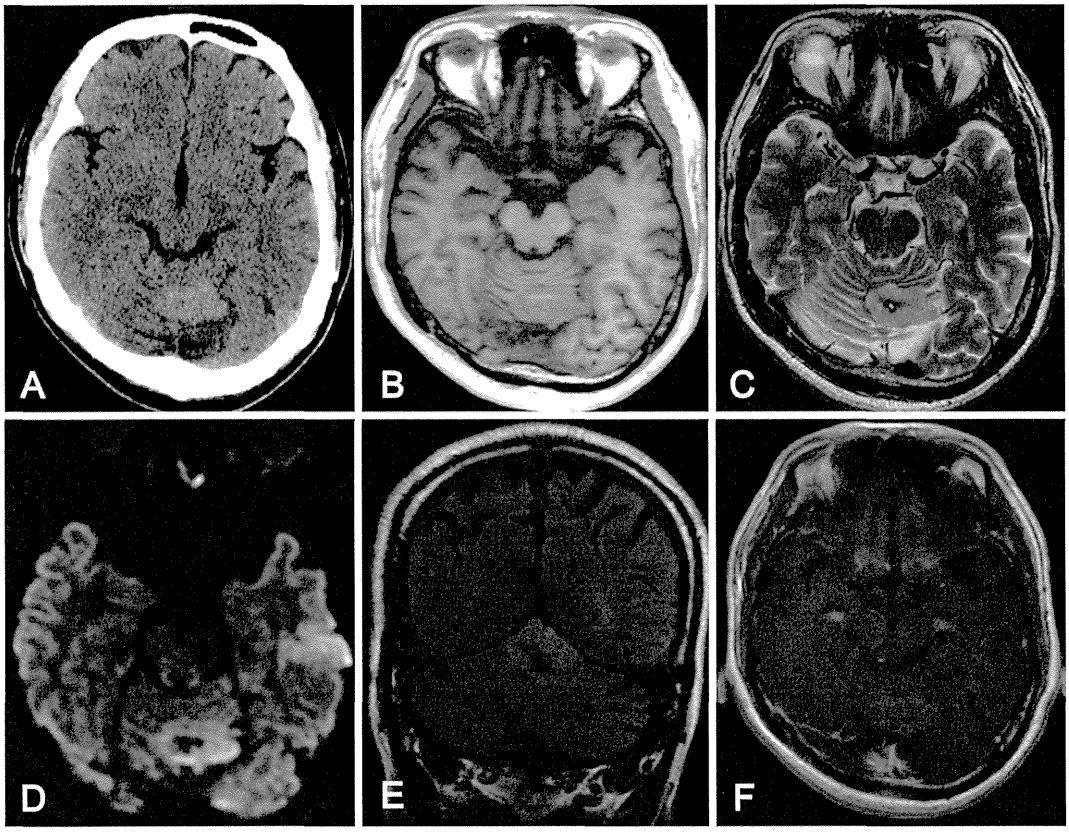

Fig. 1 Computed tomography (CT) and magnetic resonance imaging (MRI). **a** Axial CT, **b** T1-weighted axial MRI, **c** T2-weighted axial MRI, **d** diffusion-weighted axial MRI, **e** coronal fluid-attenuated inversion recovery MRI, **f** gadolinium-enhanced T1-weighted axial MRI. These images show a lesion measuring 3.5 cm in diameter in the upper cerebellum, with an indefinite boundary and without surrounding edema. Contrast enhancement is only slightly observed in the tumor

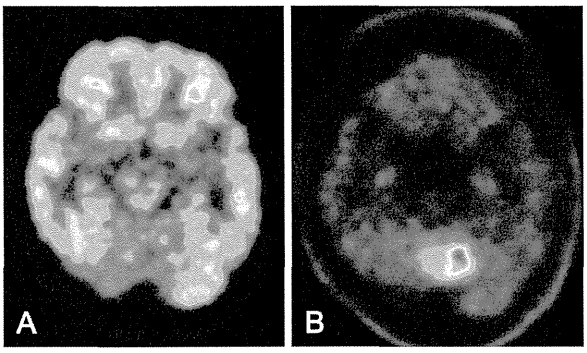

Fig. 2 Results for ^{18}F-fluoro-deoxy-glucose (FDG) (**a**) and ^{11}C-methionine (**b**) positron emission tomography (PET). Compared with normal cerebellar cortex, lower (L/N, 0.62) and higher (L/N, 2.73) accumulations are observed, respectively

tumor showed lower uptake on FDG-PET, but higher uptake on ^{11}C-methionine PET; these uncorrelated PET findings were consistent with previous observations of central neurocytoma, indicating that these two pathological entities may have similar metabolic traits.

Oligodendrogliomas also show somewhat similar findings on FDG and ^{11}C-methionine PET. In the study by Giammarile et al. [7], all 8 cases of oligodendroglioma showed a tumor/normal tissue ratio of around 1 (range 0.9–1.8) and higher accumulation (range 1.4–5.9) on FDG and methionine PET, respectively. Ependymomas and medulloblastomas tend to show higher uptake on both FDG and methionine PET [3, 8, 19, 28], whereas DNTs show lower and normal to slightly higher uptake compared with normal cortex on those studies, respectively [22]. These differences on FDG and methionine PET studies according to the differing histologies would help in preoperative diagnosis.

With regard to histopathological features, liponeurocytoma is a neurocytic neoplasm showing focal lipomatous change and astrocytic differentiation, evidenced by focal immunoreactivity to GFAP, which is also observed in most cases [14]. Immunohistochemical studies have indicated

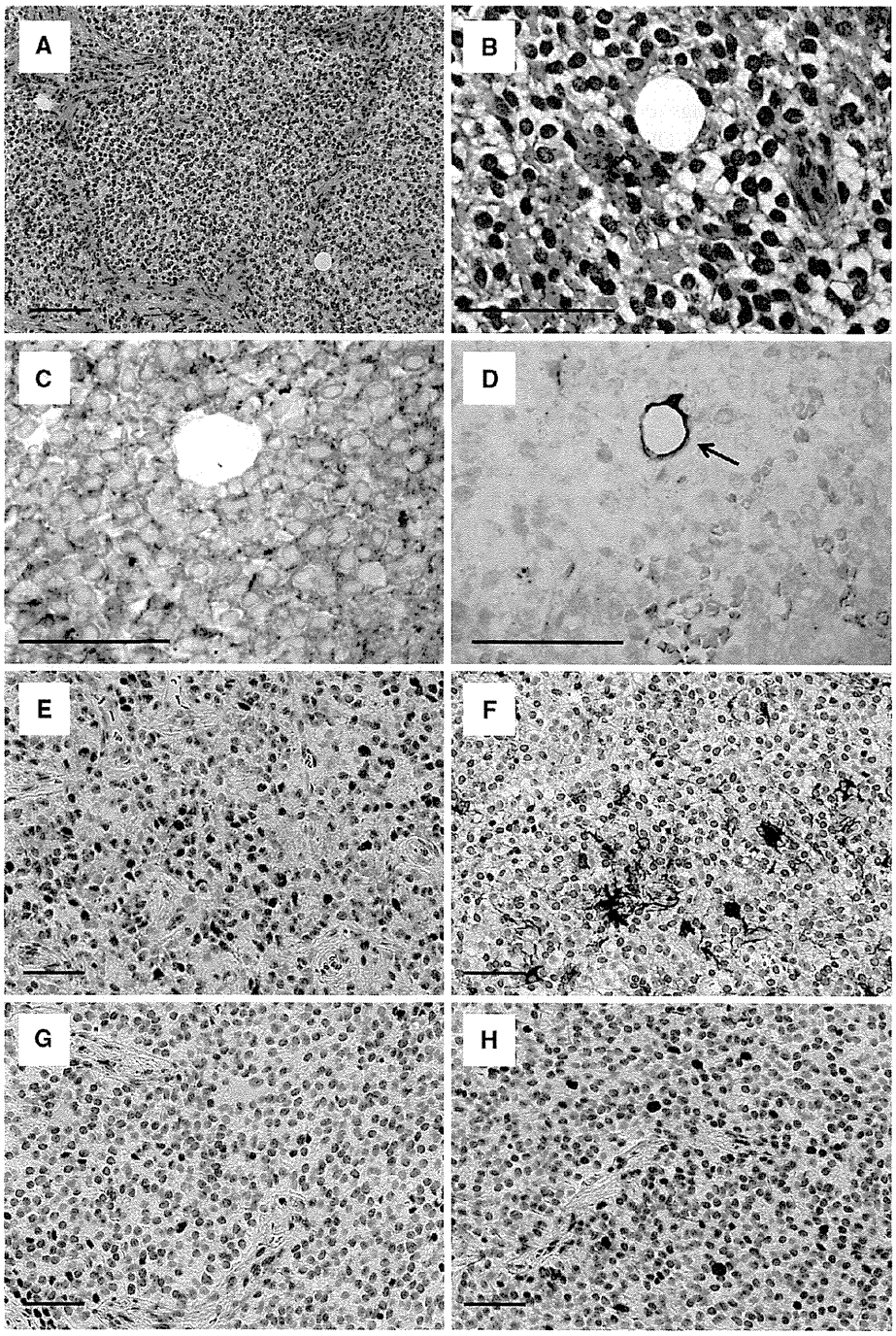

Fig. 3 Histological (**a**, **b**) and immunohistochemical (**c**–**h**) findings. **a** H&E-stained section shows sheets of relatively monomorphous cells with round nuclei and clear cytoplasm. Rare cells contain large intracytoplasmic vacuoles. **b** Tumor cells have round nuclei with indistinct nucleoli and fine chromatin on a cytology specimen (H&E). **c** Tumor cells are diffusely immunoreactive for synaptophysin. **d** A vacuolated cell is immunoreactive for perilipin (*arrow*). **e** GFAP is largely negative on tumor cells. **f** Tumor cells are completely negative for Olig2. **g** Tumor cells are moderately positive for NeuN. **h** Ki67-labeling index is 2 %. *Black bars* indicate 50 μm (**b**–**h**) or 100 μm (**a**)

that the lipomatous cells are not true adipose cells, instead representing neuroepithelial tumor cells with lipid accumulation. The pathogenesis of differentiation into lipid-producing cells in neuroepithelial tumors has not been discussed in the literature as far as we know, and remains to be elucidated.

Oligodendrogliomas occasionally demonstrate neuronal differentiation, resulting in a tumor possessing glial and neuronal characteristics. In this sense, oligodendrogliomas can show similar pathological findings to liponeurocytoma [5, 6, 12, 18, 21, 24, 26], although Olig2 immunohistochemistry is reported to show a high possibility of positive results in oligodendroglioma, while neurocytomas are mostly negative [15, 20, 23].

With genetic analysis, 50–80 % of oligodendrogliomas are known to show chromosome 1p/19q co-deletion, while neurocytoma is considered to be devoid of 1p/19q deletion [25, 30]. In addition, Capper et al. [5] reported that *IDH1* R132H mutation was negative in all of 35 central neurocytomas and 4 extraventricular neurocytomas, as well as in 2 cerebellar liponeurocytomas, while oligodendrogliomas showed a high frequency (>90 %) of *IDH1* mutation in addition to 1p/19q co-deletion [13]. We therefore propose that the absence of both chromosome 1p/19q loss and *IDH1* mutation, as observed in our case, is very useful in reaching a pathological diagnosis by eliminating the possibility of oligodendroglioma.

Conclusion

This case report suggests that cerebellar liponeurocytoma shows characteristic PET and genetic findings, including negative results for both *IDH1* mutation and chromosome 1p19q co-deletion, somewhat resembling the findings for neurocytoma. These findings will be helpful in differentiating the rare disease of cerebellar liponeurocytoma from more common neoplasms with similar pathological morphology. Further accumulation of findings from tumor investigations is necessary to definitively establish the characteristics of cerebellar liponeurocytoma.

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Neurologia medico-chirurgica

Vol. 55, No. 1, January, 2015

Pathophysiology, Diagnosis, and Treatment of Radiation Necrosis in the Brain

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REVIEW ARTICLE doi: 10.2176/nmc.ra.2014-0188
Neurol Med Chir (Tokyo) 55, 50–59, 2015 Online December 20, 2014

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Abstract

New radiation modalities have made it possible to prolong the survival of individuals with malignant brain tumors, but symptomatic radiation necrosis becomes a serious problem that can negatively affect a patient's quality of life through severe and lifelong effects. Here we review the relevant literature and introduce our original concept of the pathophysiology of brain radiation necrosis following the treatment of brain, head, and neck tumors. Regarding the pathophysiology of radiation necrosis, we introduce two major hypotheses: glial cell damage or vascular damage. For the differential diagnosis of radiation necrosis and tumor recurrence, we focus on the role of positron emission tomography. Finally, in accord with our hypothesis regarding the pathophysiology, we describe the promising effects of the anti-vascular endothelial growth factor antibody bevacizumab on symptomatic radiation necrosis in the brain.

Key words: bevacizumab, positron emission tomography, pseudoprogression, radiation necrosis

Introduction

Most patients who develop radiation necrosis in the brain originally received radiation treatment for either brain tumors or head and neck cancers. In rare cases, radiation treatment for vascular lesions such as arteriovenous malformations may cause radiation necrosis, but the treatment modality and doses are quite different between the treatments for tumors and vascular lesions. In this review, therefore, we focus on radiation necrosis in the brain that is derived from radiation treatment for brain tumors and, head and neck cancers.

Radiation necrosis in the brain is often encountered after the treatment of metastatic brain tumors, especially by stereotactic radiosurgery, the incidence rate following stereotactic radiosurgery for such tumors is up to 68%.[1–4] Numerous reports have also linked radiation necrosis to the treatment of primary brain tumors. The incidence of radiation necrosis in the setting of focal radiotherapy has been estimated as 3–24%.[5–11] The most important factors in the risk of cerebral radiation necrosis are the radiation dose, the fraction size, and the subsequent administration of chemotherapy.[8] A smaller fraction size even with the same total radiation dose will increase the biological effective dose and subsequently the incidence of radiation necrosis. For concurrent chemotherapy for malignant gliomas, the incidence increases by threefold.[12–14] At least in patients who receive radiosurgery, the irradiated volume is also critical in terms of the risk of radiation necrosis[7,15–17] and re-irradiation or additional boost radiation treatment by stereotactic radiotherapy pose additional risk as well.[8]

There are two distinct concepts of radiation-induced injury in the brain. One is pseudoprogression and the other is radiation necrosis. Generally speaking, pseudoprogression occurs relatively earlier (i.e., 2–5 months after the initiation of adjuvant treatment), and is generally detected by contrast enhancement in neuro-imaging modalities such as magnetic resonance imaging (MRI). Pseudoprogression usually shows a self-limited course and eventual resolution, both clinically and radiographically.[12–14,18] Radiation necrosis occurs rather later than pseudoprogression, after the treatment, and often does not subside without intensive treatment. Histologically, radiation necrosis is found mainly in white matter with endothelial damage, perilesional edema, and gliosis, as described below.[19–24] Sometimes pseudoprogression also shows symptoms,[25] and occasionally it is difficult to differentiate pseudoprogression and radiation necrosis. In addition, pseudoprogression, radiation necrosis, and tumor recurrence are difficult to differentially diagnose, especially with

Received May 22, 2014; Accepted October 14, 2014

neuroimaging modalities such as MRI.

Clearly, the risk of radiation-induced injury that attends radiation treatment is a significant challenge.

Pathophysiology of Radiation Necrosis

The histopathological characteristics of radiation necrosis include coagulation and liquefaction necrosis in the white matter, with capillary collapse and wall thickening and hyalinization of the vessels.[26–30] Telangiectasia is also reported to be a result of the genesis of collateral blood flow against ischemia caused by the obstruction of small venules and arterioles, as reported in a monograph by Burger and Boyko.[31] These histological changes seem to be caused by chronic inflammation and microcirculatory impairment.[19,21–23,32–34]

With respect to the cause of radiation necrosis, two hypotheses have been put forward. One postulates that the necrosis arises due to direct injury of the brain parenchyma, especially glial cells. According to this hypothesis, radiation treatment directly injures the brain parenchyma, leading to secondary damage to vessels. The primary damage is focused on glial cells, especially oligodendrocytes, creating demyelination in the white matter.[35,36] However, this hypothesis is not supported widely because even low doses of radiation that cannot result in histological necrosis cause a decrease in the number of glial cells.[30,37] The other hypothesis is that the direct primary injury to the blood vessels causes the brain parenchymal injury as secondary damage.[38] This hypothesis has been widely accepted because vascular injury was observed prior to the development of radiation necrosis in a rodent radiation necrosis model.[39–41]

We recently published our original hypothesis based on histopathological findings from human radiation necrosis surgical specimens (Fig. 1).[42] We considered that the first step in the development of radiation necrosis in a brain that has undergone radiation treatment is blood vessel damage just around the tumor. This is associated with hypoxia close to the irradiated tumor tissue, which causes the upregulation of hypoxia inducible factor-1 alpha (HIF-1α) in human glucose transporter 5 (hGLUT5)- and CD68-positive microglia. We based this hypothesis on our finding that HIF-1α is upregulated in the perinecrotic area in radiation necrosis specimens (Fig. 2).

Because HIF-1α is well known as a transactivator of vascular endothelial growth factor (VEGF) and CXCL12/CXCR4 signaling,[43,44] the upregulation of HIF-1α augments VEGF and CXCL12 expression in glial fibrillary acidic protein-positive reactive

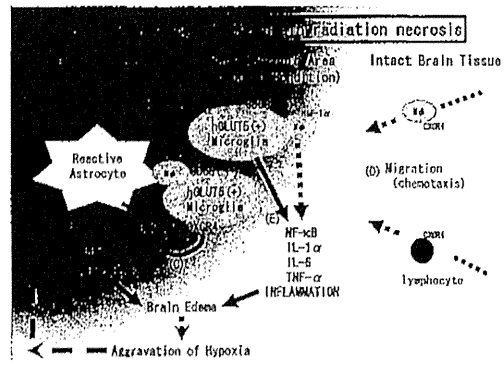

Fig. 1 The pathophysiology of brain radiation necrosis: our hypothesis. A: Vascular damage around the irradiated tumor tissue causes tissue ischemia. This hypoxia induces hGLUT5-positive microglia to express hypoxia inducible factor-1 alpha (HIF-1α) around the necrotic core. B: Under HIF-1α regulation, vascular endothelial growth factor (VEGF) is expressed in reactive astrocytes, causing leaky and fragile angiogenesis. C: CXCL12/CXCR4 signaling is also regulated by HIF-1α. D: CXCL12-expressing reactive astrocytes might draw CXCR4-expressing macrophages and lymphocytes by chemotaxis into the perinecrotic area. E: These accumulated hGLUT5-positive microglia producing NF-κB and pro-inflammatory cytokines seem to aggravate radiation necrosis. This figure was taken from our recent publication (Reference 42) with the permission of the publisher. CXCL12: C-X-C motif chemokine 12, CXCR4: C-X-C chemokine receptor type 4, hGLUT5: human glucose transporter 5, IL: interleukin, NF-κB: nuclear factor-kappa B, TNF: tumor necrosis factor.

astrocytes. The VEGF expression produces the leaky and fragile angiogenesis and the subsequent perilesional edema in radiation necrosis (Fig. 3).[45] The C-X-C motif chemokine 12 (CXCL12) expression might draw C-X-C chemokine receptor type 4 (CXCR4)-expressing hGLUT5-positive microglia and CXCR4-expressing lymphocytes by chemotaxis to the perinecrotic area. The production of pro-inflammatory cytokines [interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)-α] by these accumulated hGLUT5-positive cells seem to aggravate the perilesional edema.

However, we found that although some CD45-positive lymphocytes gathered in the perinecrotic area, they were not involved in pro-inflammatory cytokine production. Nuclear factor-kappa B (NF-κB), a key player in inflammation, would be expected to play a significant role in radiation necrosis. The aggravation of edema could lead to the further development of focal ischemia, which augments the expression of HIF-1α in the microglia in the perinecrotic area. Here, both angiogenesis and inflammation may contribute

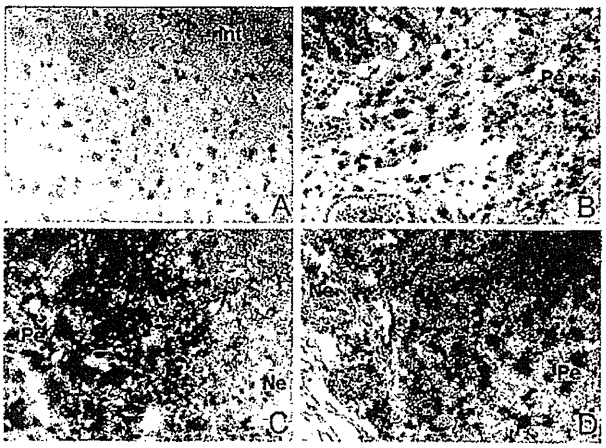

Fig. 2 Hypoxia inducible factor-1 alpha (HIF-1α) immunohistochemistry of radiation necrosis. A, B: The results of HIF-1α immunohistochemistry on the radiation necrosis in a patient with recurrent glioblastoma multiforme (GBM) who was treated by re-irradiation with boron neutron capture therapy (BNCT). The (A) intact brain area and (B) peri-necrotic area are shown. C, D: HIF-1α immunohistochemistry in patients with radiation necrosis from GBM and metastatic brain tumors, respectively. The former was treated with proton beam radiation and X-ray treatment as an initial treatment, while the latter was treated with repetitive BNCT at the recurrence. Int: intact brain, Ne: necrotic center, Pe: peri-necrotic area. The original objective magnification is ×40.

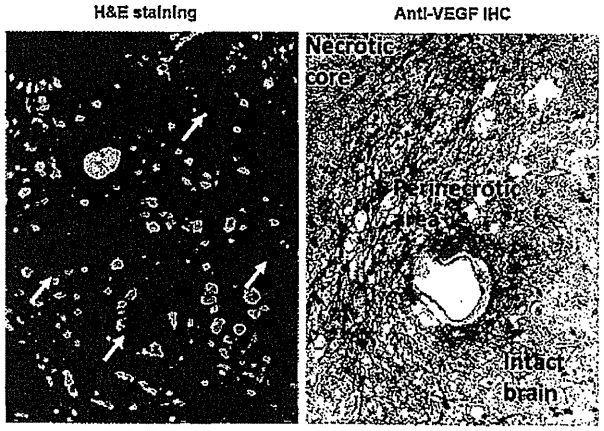

Fig. 3 Surgical specimen of radiation necrosis derived from a metastatic brain tumor caused by stereotactic radiosurgery (SRS). Hematoxylin and Eosin staining shows marked angiogenesis (indicated by *white arrows*) with perilesional edema. Anti-vascular endothelial growth factor (VEGF) immunohistochemistry shows the abundant expression of VEGF in the perinecrotic area. The VEGF-producing cells seemed to be reactive astrocytes.

to a synergistic and malignant cycle in radiation necrosis. In any case, our observations suggest that inflammation participates in the pathophysiology of brain radiation necrosis, as Yoshi suggested.[34]

Among the proinflammatory cytokines, one key upstream player is TNF-α, which regulates other cytokines to increase the blood-brain barrier's permeability, increase leukocyte adhesion, activate astrocytes, and induce endothelial apoptosis.[32,46,47] An important downstream molecule is intercellular adhesion molecule-1 (ICAM-1), which is expressed on the surface of endothelial cells and is a principal mediator of leucocyte-endothelial cell adhesion.[47–52] Our recent study provided evidence that platelet-derived growth factors (PDGFs) and their receptor families also play a significant role in cerebral radiation necrosis from the viewpoints of angiogenesis and inflammation.[53] However, to save the space of this article, we will omit the details of the participation of PDGFs and their receptor families in radiation necrosis.

Diagnosis of Radiation Necrosis

There is no question that surgical exploration including biopsy is the gold standard for the histological confirmation of radiation necrosis or tumor progression. Irradiation is generally applied to surgically inaccessible lesions. In addition, biopsies occasionally show a mixture of radiation necrosis in most parts of the specimen but some viable tumor cells in other parts. It is important for clinicians to determine the next best treatment based on the correct diagnosis of radiation necrosis or tumor progression. When we encounter increasing edema and a contrast-enhanced lesion after the radiation treatment of a brain tumor or head or neck cancer, this next best treatment must be identified. If we judge the cause of increasing edema as radiation necrosis, we can choose from among several treatment options including bevacizumab, as described below. In contrast, if we judge the cause of edema as tumor progression, re-irradiation may be preferable.[54]

I. MRI, ADC, MRS, and MR perfusion imaging

A typical characteristic of radiation necrosis in Gd-enhanced T_1-weighted MRI is called "Swiss cheese" or "soap bubble" enhancement.[6] However, conventional MRI is not sufficient to differentiate tumor progression/recurrence from treatment-related effects.[5,6,11,55]

The apparent diffusion coefficient (ADC) may be important to differentiate tumor recurrence and radiation necrosis. In tumor recurrence, the ADC is low, because high cellularity restricts water mobility.

An increased ADC is ascribed to increased water mobility in radiation necrosis.[56–58] Several research groups have attempted to differentiate radiation necrosis from tumor recurrence by magnetic resonance spectroscopy (MRS) from the viewpoint of metabolism.[11,59–61] In radiation necrosis, N-acetyl aspartate (NAA) and creatinine (Cr) generally decrease, whereas high choline (Cho) is correlated with tumor progression.[61–67] The Cho/Cr ratio and the Cho/NAA ratio have been described as good landmarks for differential diagnosis.[59,60,68] MR perfusion techniques using contrast enhancement can measure the relative cerebral blood volume (rCBV) and estimate the vascularity and hemodynamics. Hyperperfusion is seen in tumor progression, and hypoperfusion is seen in radiation necrosis.[69–71] Sugahara et al. reported that rCBV values < 0.6 suggest radiation necrosis and values > 2.6 suggest tumor progression.[72]

II. Positron emission tomography (PET)

PET scan can directly demonstrate the metabolism of the brain or lesions such as radiation necrosis or tumor progression. Several studies using fluorine-18 fluorodeoxyglucose (^{18}F-FDG) as a tracer initially suggested good sensitivity and specificity,[73–78] but there is a paucity of histological correlations in these reports. Other studies using the same tracer showed unpromising results with decreased sensitivity and specificity.[79–83]

The main reasons for this uncertainty about the utility of this tracer for the differentiation of radiation necrosis and tumor progression are as follows. The brain shows high sugar metabolism, and FDG-PET reveals a very high metabolic background in the normal brain. Moreover, FDG accumulates well in cases of inflammation.[84] However, inflammatory cells commonly infiltrate at the radiation necrosis border as well as in normal brain tissue.[26,85] It thus remains rather difficult to apply FDG-PET to discriminate between radiation necrosis and tumor progression.[86] Indeed, it has been reported that some radiation necrosis cases show good accumulation of FDG despite the absence of evidence of tumor recurrence.[87]

PET imaging using amino acids as tracers is promising for the detection of malignant tumors in the brain, because the background activity of protein metabolism in the brain is rather low compared to its sugar metabolism. ^{11}C-labeled methionine (C-MET) has been used as a tracer for amino-PET, and for analyzing the metabolism in malignant brain tumors[88,89] as well as for differentiating between radiation necrosis and tumor progression.[89] In addition, ^{18}F-labeled fluoroboronophenylalanine (F-BPA)-PET is very useful for the discrimination of radiation necrosis and tumor progression, as we have described in earlier studies.[90,91] We are currently conducting a nationwide multicenter clinical trial under the rubric of "Intravenous administration of bevacizumab for the treatment of radiation necrosis in the brain with diagnosis based on amino acid PET" as Type 3 Investigational Medical Care System and Advanced Therapy, and has been approved by Japan's Ministry of Health, Labor, and Welfare (MHLW).[92]

Treatments for Radiation Necrosis

I. Surgical treatments

The surgical excision of radiation necrosis had been a gold-standard treatment for symptomatic radiation necrosis, in order to rapidly reduce the increased intracranial pressure.[93] However, as described above, radiation treatment is often applied to surgically inaccessible lesions, and sometimes this surgical intervention worsens the patient's neurological condition, as we described previously.[45] Nonetheless, the indications for the removal of radiation necrosis should be decided carefully and strictly, and potent medical treatment should be developed for use in its stead.

II. Medical treatments other than bevacizumab

Corticosteroids have been used to treat radiation necrosis in the brain for several decades.[94,95] The rationale underlying this steroid usage is that the radiation-induced vascular endothelial damage and resulting breakdown of the blood-brain barrier must be reversed. Some inflammatory responses may also be lessened by corticosteroids. The long-term use of corticosteroids can be expected to cause numerous adverse effects such as hypertension, hyperglycemia, osteoporosis, weight changes, moon face, psychiatric disturbances, and immunosuppression, all of which can severely decrease an individual's quality of life.

As an initial step in the development of radiation necrosis, a hypoxic condition is caused by the damage to the microcirculation near a tumor treated with radiation treatment, as shown in Fig. 1. To improve such microcirculation impairments, anticoagulants and antiplatelets have been used to some effect, but not with satisfactory results.[96] Hyperbaric oxygen treatment has also been used to treat radiation necrosis in the brain to stimulate angiogenesis and the repair of the regional cerebral blood supply compromised by radiation-mediated circulatory injury.[97–99] However, there has been no large-scale study with distinct conclusions. At least one study has reported the use of hyperbaric oxygenation for the prophylaxis of radiation injury

in the treatment of metastatic brain tumors with stereotactic radiosurgery.[100]

III. Medical treatments with bevacizumab

As shown in our surgical specimen and reflected in our hypothesis (Figs. 1, 2), HIF-1α upregulation in the perinecrotic area is an initial step in the development of radiation necrosis in the brain. VEGF overproduction in reactive astrocytes then occurs; this is the most clear-cut cause of leaky and fragile angiogenesis and subsequent cerebral edema in radiation necrosis in the brain, as described above.[42,45] A reasonable strategy to reduce this overexpression of VEGF is the use of the anti-VEGF monoclonal antibody, bevacizumab.

The first report to describe the efficacy of bevacizumab for radiation necrosis was published by Gonzalez et al. in 2007.[101] In that report, bevacizumab was used as an additional chemotherapeutic agent for recurrent malignant gliomas and the authors noted retrospectively that the cases in which bevacizumab was effective seemed to be those that involved radiation necrosis. Several later studies found that bevacizumab is effective as a treatment for radiation necrosis in the brain irrespective of the original histological tumor type (including metastatic brain tumors) and the applied radiation modalities.[102–106] A placebo-controlled randomized trial of bevacizumab was published with class 1 evidence, although the number of patients was limited.[107]

We have also routinely observed the effectiveness of bevacizumab for radiation necrosis, as shown in Fig. 4. However, we also sometimes encounter the aggravation of radiation necrosis after a transient improvement in neuro-imaging and clinical neurological findings (Fig. 4). Almost all of the relevant studies have observed promising effects of bevacizumab, but one review article raised the possibility of adverse effects such as cerebral hemorrhage and thrombo-embolitic complications.[108]

In many cases, however, cerebral radiation necrosis itself has shown a trend of spontaneous hemorrhage around the lesion as a natural course.[45] Moreover, bevacizumab may be used for the prophylaxis of possible radiation necrosis in re-irradiation[109,110] and may improve the clinical results such as the overall survival after re-irradiation itself.[111] In addition to angiogenesis, we hypothesized that there is a significant role of inflammation in the pathogenesis of radiation necrosis, as shown in Fig. 1. In support of this hypothesis, preliminary reports have indicated that anti-TNF antibody may be effective for the treatment of cerebral radiation necrosis.[32,46,47]

Conclusion

Clinicians must bear in mind that radiation treatment carries a risk of radiation-induced injury. Whenever encountering an aggravation of cerebral edema after irradiation for brain tumors or head and neck cancers, it is important to remember that not only tumor progression but also radiation necrosis is possible. At that time, a correct diagnosis and prompt treatment decisions are mandatory to avoid exacerbation of the patient's condition. Re-irradiation should never be applied for possible radiation necrosis. If the lesion

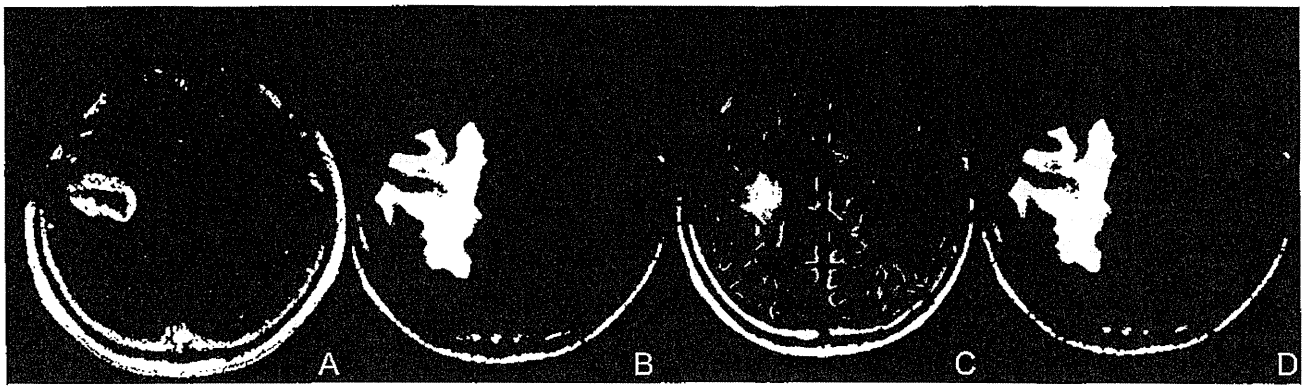

Fig. 4 A representative case of radiation necrosis treated with bevacizumab. The original disease was a metastatic brain tumor from lung cancer. The metastasis was treated with SRS. One year after the SRS, marked enhancement (A) and perilesional edema (B) were recognized on magnetic resonance imaging (MRI). At the time of the MRI, the patient could not walk by himself. After three cycles of bevacizumab treatment 5 mg/kg biweekly, an MRI showed a marked decrease of the edema (C) and he could walk again. Unfortunately, 3 months after the bevacizumab treatment, MRI showed aggravation of the edema (D) with clinical symptom deterioration. Due to financial problems, the patient could not undergo a re-challenge of bevacizumab treatment. A: Gd-enhanced T_1-weighted image. B–D: Fluid-attenuated inversion recovery images. SRS: stereotactic radiosurgery.

can be diagnosed as radiation necrosis, bevacizumab should be considered as a first-line treatment. We are currently trying to obtain the approval for the on-label use of bevacizumab for the treatment of radiation necrosis in Japan from the MHLW.

Conflicts of Interest Disclosure

There is no conflict of interest to disclose for any of the authors.

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