

Chronic expanding hematoma following Gamma Knife irradiation for primary central nervous system lymphoma: illustrative case

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BACKGROUND Chronic expanding hematoma (CEH) is a rare disease characterized by slow expansion, especially reported after Gamma Knife radiosurgery (GKRS) for cerebral arteriovenous malformations. No cases have been reported following treatment for primary central nervous system lymphoma (PCNSL). Vascular endothelial growth factor and vascular endothelial growth factor receptor-1 (VEGFR-1) have been reported to be responsible for CEH induction.

OBSERVATIONS A 56-year-old woman underwent partial tumor removal for PCNSL in the left temporo-occipital lobe at another hospital. One and a half months later, a new lesion was observed, and she underwent GKRS, including the residual lesion. She was treated with multiple chemotherapy regimens including R-MPV (rituximab, methotrexate, procarbazine, vincristine) but relapsed repeatedly and was administered tirabrutinib. Four years after GKRS, the gadolinium-enhanced lesion slowly grew. Tumor recurrence or radiation necrosis was suspected, and surgical removal was performed. The tissue was composed of nonmalignant brain tissue and fibrinized hematoma, which demonstrated strong expression of VEGFR-1 on immunostaining, and the pathological diagnosis was CEH.

LESSONS In this patient, CEH could have resulted from VEGFR-1 expression due to GKRS. For a patient with slow lesion growth following GKRS for PCNSL, surgical removal should be considered, taking into account the possibility of CEH along with recurrence and radiation necrosis.

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KEYWORDS chronic expanding hematoma; primary central nervous system lymphoma; Gamma Knife

Chronic expanding hematoma (CEH) is a rare disease in which the hematoma bleeds repeatedly and tends to slowly expand.¹ CEH arises from vascular diseases such as arteriovenous malformations (AVMs) and cavernous hemangiomas,² especially after Gamma Knife radiosurgery (GKRS) for AVMs, which are often reported as a complication in the chronic phase.³ Except for CEH caused by vascular diseases, most are idiopathic, with only 1 case reported as being caused by a brain tumor following radiotherapy for glioma.⁴ No case has yet been reported following treatment for primary central nervous system lymphoma (PCNSL). Vascular endothelial growth factor (VEGF) and VEGF receptor-1 (VEGFR-1) have been reported to be associated with the development of CEH, and we report their expression levels along with considerations regarding the pathogenesis of CEH.

Illustrative Case

A 56-year-old woman presented with aphasia and vomiting and had a left temporo-occipital lobe tumor (Fig. 1A). She underwent a partial resection at another hospital and was diagnosed with PCNSL, diffuse large B-cell lymphoma (DLBCL). One and a half months later, significant enlargement of the residual tumor was observed (Fig. 1B), and new lesions were found in the right ventricle and left frontal lobe (Fig. 1C and D), so the patient was treated with GKRS (marginal dose 14 Gy/45% isodose/maximum 31.1 Gy, 20 shots, 3 lesions) (Fig. 1E). Seven courses of R-MPV (rituximab, methotrexate, procarbazine, vincristine) were administered, followed by autologous peripheral blood stem cell transplantation with modified etoposide, cytarabine (AraC),

ABBREVIATIONS AraC = cytarabine; AVM = arteriovenous malformation; CEH = chronic expanding hematoma; CSDH = chronic subdural hematoma; DLBCL = diffuse large B-cell lymphoma; FDG = fluorodeoxyglucose; FDOPA = fluorodopa; Gd = gadolinium; GKRS = Gamma Knife radiosurgery; HD-AraC = high-dose AraC; H&E = hematoxylin and eosin; NF-κB = nuclear factor-κB; PCNSL = primary central nervous system lymphoma; PET = positron emission tomography; R-MPV = rituximab, methotrexate, procarbazine, vincristine; VEGF = vascular endothelial growth factor; VEGFR-1 = VEGF receptor-1.

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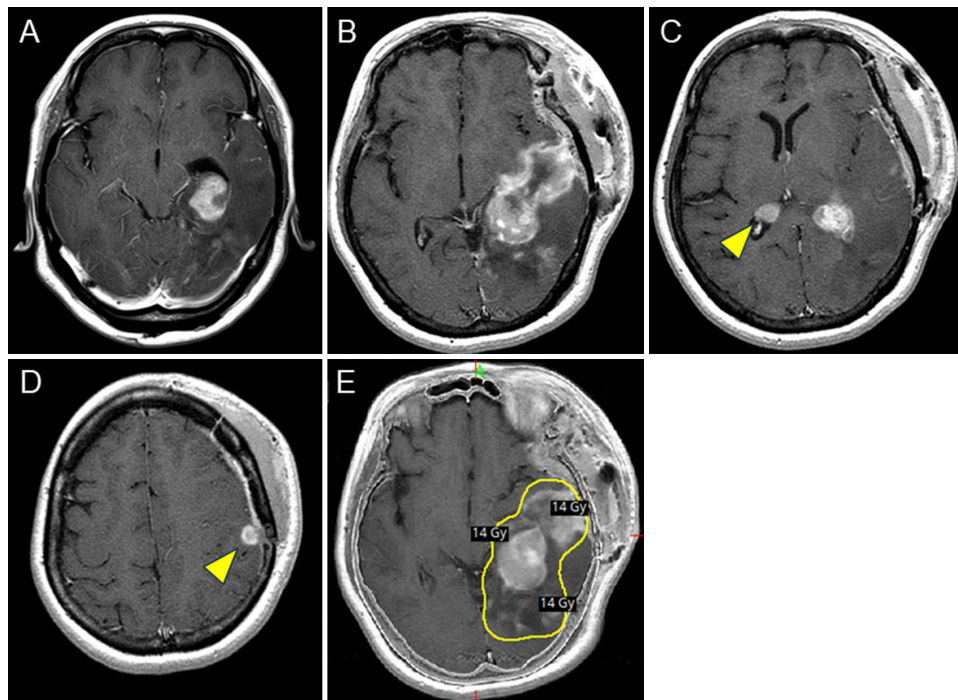


FIG. 1. Gd-enhanced T1-weighted (T1W) MR images from initial diagnosis to first recurrence and Gamma Knife irradiation. **A:** MR image at initial diagnosis. A tumoral lesion is present in the left temporo-occipital lobe. **B–D:** MR image just before GKRS. Reenlargement of the resected area (B) and a new lesion (C and D; arrowheads) appearing within the right ventricle and in the left frontal lobe are observed. **E:** Gamma Knife irradiation. The yellow contour indicates the 45% isodose line (marginal dose of 14 Gy). Residual and new lesions were irradiated.

and melphalan as the conditioning regimen. Two years later, gadolinium (Gd)-enhanced MRI revealed a new lesion around the bilateral lateral ventricles, leading to the diagnosis of recurrence. R-MPV therapy was administered for 3 courses but was changed to high-dose AraC (HD-AraC) therapy due to complications of drug-induced pneumonia caused by methotrexate. The patient was treated with HD-AraC therapy for 3 courses, but because of the mental stress caused by hospitalization, she was switched to outpatient temozolomide treatment, which was administered for 3 courses. However, no effect was observed, and she was referred to our hospital.

At our hospital, the patient was started on tirabrutinib, a Bruton-type tyrosine kinase inhibitor, which was an investigational drug at the time, for recurrent lesions of the thalamus and corpus callosum. During the treatment, there were periods of drug withdrawal due to decreased blood cell counts, but the drug was administered for a total of 4 years. The previously observed Gd-enhanced lesion in the left occipital lobe enlarged very slowly, but not significantly, after the start of tirabrutinib (Fig. 2); therefore, tirabrutinib was discontinued. The lesion showed an internal heterogeneous Gd enhancement effect (Fig. 2D), a finding suspicious for tumor recurrence or radiation necrosis. Since cysts formed inside the lesion and the lesion showed a heterogeneous low signal on T2*-weighted MRI (Fig. 3A) and decreased uptake on both fluorodeoxyglucose positron emission tomography (FDG-PET) and fluorodopa positron emission tomography (FDOPA-PET) (Fig. 3B and C), we considered the possibility of radiation necrosis. The patient presented with cognitive dysfunction, mild disturbance of consciousness, right homonymous hemianopia, mild alexia, and seizure. Because of the progressive enlargement of the lesion, surgical

removal was performed again (Fig. 3D). The lesion was partially resected, and there was no worsening of neurological symptoms after surgery.

Pathological diagnosis revealed an organized hematoma composed of peripheral blood and newly formed blood vessels on hematoxylin and eosin (H&E) staining, with a partial admixture of granulation tissue-like components (Fig. 4A). Mild inflammatory cell infiltration, reactive changes, and necrosis associated with the hematoma were observed within and around the lesion. The necrosis was minimal and macroscopically detectable necrotic tissue, presumed to be caused by treatments such as radiation therapy, was not observed. No tumor component was observed. Based on these findings and the history of slow enlargement, a diagnosis of CEH was made. There was no capsular formation or fibroblast clusters at the border between the normal brain and hematoma (Fig. 4B), which is different from chronic encapsulated expanding hematoma, such as that which occurs after GKRS for AVM. Both lymphoma tissue at the initial surgery and hematoma tissue at the second surgery were positive for VEGF, but there was no significant difference, although quantification was not performed (Fig. 4C and D). The vascular endothelium in the hematoma tissue showed strong expression for VEGFR-1, while no positive cells were observed in the lymphoma tissue (Fig. 4E and F).

Since hematoma resection, the hematoma has not regrown. Although there is no treatment for PCNSL, the patient's condition has remained stable with no recurrence for more than 1 year. Her neurological symptoms have remained unchanged, and she maintains a Karnofsky Performance Status score of 70 and an Eastern Cooperative Oncology Group Performance Status score of 3 and lives at home.

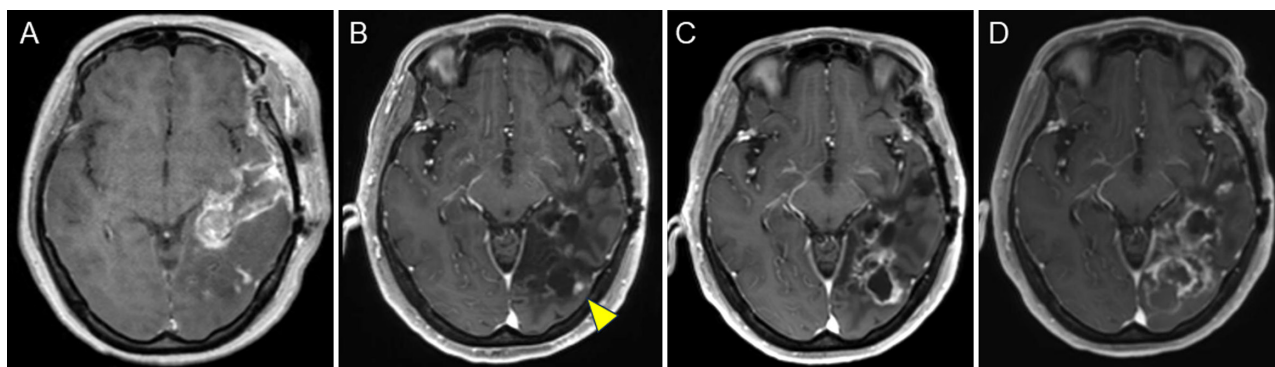


FIG. 2. Gd-enhanced T1W MR images showing longitudinal changes after GKRS. **A:** Immediately after GKRS. **B:** Four years after GKRS. The arrowhead indicates the newly appearing Gd-enhanced lesion. **C:** Four and a half years after GKRS. **D:** Eight years after GKRS. The heterogeneous internal Gd-enhanced lesion in the left occipito-temporal lobe is slowly enlarging.

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

Observations

CEH is a rare disease characterized by slow, progressive hematoma enlargement, particularly reported following GKRS for cerebral AVMs. To date, no case has been reported following treatment for PCNSL. CEH is marked by gradual bleeding over an extended period. Pathologically, the characteristic findings are fibroblast granulation tissue and elevated VEGF expression and associated angiogenesis, which resemble those of chronic subdural hematoma (CSDH).^{2,5} The mechanism of CEH development is not entirely clear. However, in cases of AVMs treated with GKRS, GKRS-induced hypoxia around the lesion has been shown to upregulate VEGF and VEGFR-1, promoting angiogenesis, persistent bleeding, and exudative leakage, leading to chronic hematoma with capsular formation.^{2,3,6,7} CSDH is considered to affect hematoma growth by activating the nuclear factor- κ B (NF- κ B) pathway via VEGF in vascular endothelial cells to form a capsule.^{8,9} In both diseases, increased expression of VEGF and VEGFR-1 and associated capsular formation play an important role in angiogenesis

and vascular permeability. Abou-Al-Shaar et al. reported that CEH after GKRS for AVM had a higher expression of VEGF than in glioblastoma tissue.⁶ The VEGF expression level might be responsible for CEH development following GKRS.

On the other hand, radiation necrosis is tissue necrosis that occurs after radiation therapy and is reported to result from radiation-induced damage to glial cells and blood vessels as well as tissue hypoxia.¹⁰ The pathology is predominantly necrotic brain tissue, with thickened vessel walls and collapsed capillaries.¹⁰ In our case, the absence of apparent necrotic tissue, the predominance of hematoma, the clinical course characterized by gradual enlargement, and the increased expression of VEGFR-1 led to the diagnosis of CEH.

VEGF expression has previously been reported to correlate with malignancy in DLBCL.^{11,12} It is reasonable that VEGF was positive in the pathology at the initial surgery in our case, in which the disease showed early progression after multiple chemotherapy regimens and was assumed to be high grade. The patient underwent extensive Gamma Knife irradiation immediately after the initial surgery, which could have resulted in a high expression of VEGF.

Regarding VEGFR-1, it showed increased expression in the second surgery sample compared with the initial surgery sample, although VEGF expression showed no qualitative difference, suggesting that

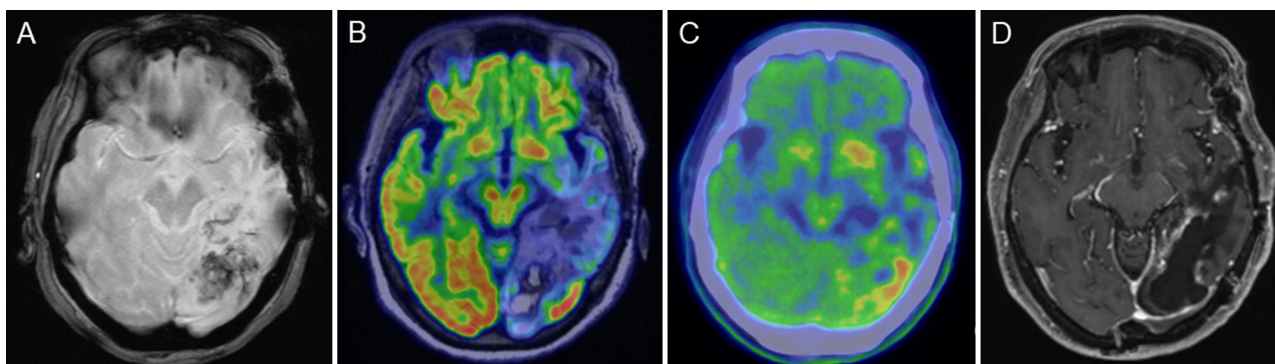


FIG. 3. Gd-enhanced T1W MR images before and after the second surgery. **A:** The enlarged lesion showed heterogeneous hypointensity on T2*-weighted imaging. **B and C:** The enlarged lesion shows decreased internal uptake on FDG-PET (B) and FDOPA-PET (C). The margins of the lesion show high uptake as reactive changes. **D:** MR image immediately after resection of the lesion. The occipital lesion was removed, but the temporal lesion remained.

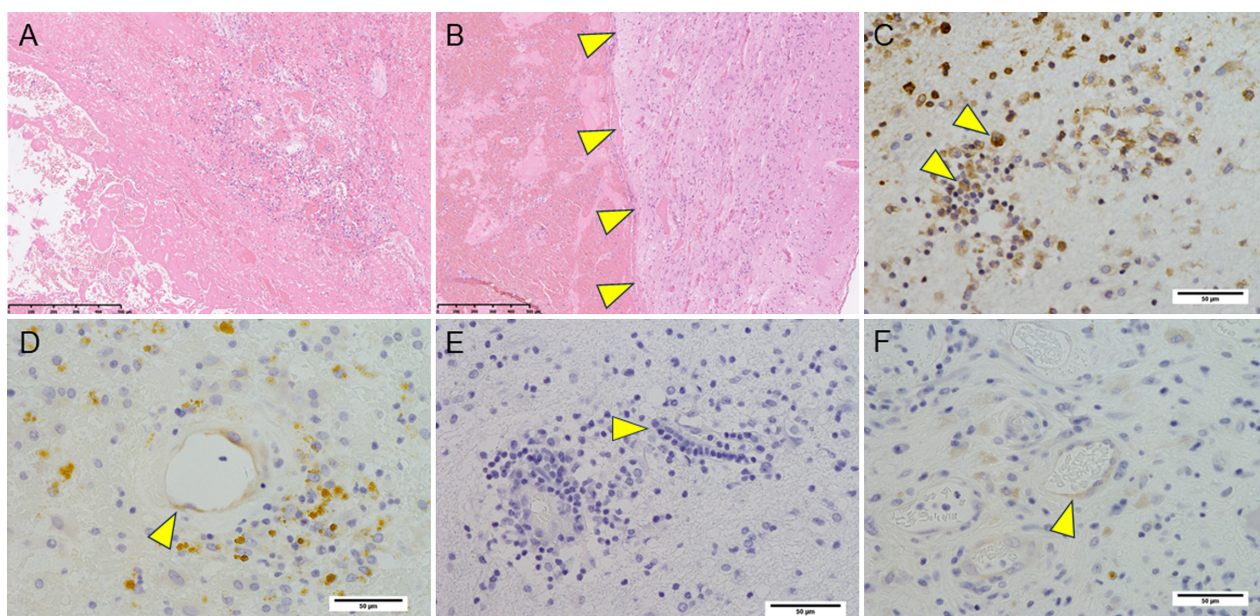


FIG. 4. Pathological images of removed lesions at initial surgery and after GKRS. **A and B:** H&E staining of tissue from the second surgery. A chronic hematoma consisting of peripheral blood and neovascularization, with partial admixture of granulation tissue-like components but no tumor components, was observed (A). No capsule formed between the hematoma and brain parenchyma (B). *Arrowheads* indicate the boundary between the hematoma and brain parenchyma. **C and D:** VEGF immunostaining. Tissue from the initial surgery (C) and after GKRS and tirabrutinib administration (D) similarly showed strong expression of VEGF. The vascular endothelium (*arrowheads*) showed particularly strong staining. **E and F:** VEGFR-1 immunostaining. Tissue from the initial surgery (E) showed no expression of VEGFR-1, while tissue from after GKRS and tirabrutinib administration (F) showed expression, especially in the vascular endothelium (*arrowheads*).

GKRS-induced hypoxia upregulated VEGFR-1 alongside VEGF. VEGFR-1 has been reported to act as a negative regulator of VEGF to control abnormal angiogenesis.¹³ It is possible that GKRS-induced hypoxia could have upregulated VEGFR-1, potentially returning VEGF levels to the initial level via a negative feedback mechanism.

In our case, the capsular formation characteristic of CEH after GKRS for AVM was also not observed. This lack of capsular formation was also caused by a reduction in NF- κ B activity due to the mechanism that reduced the expression of VEGF once it had increased. Furthermore, Oyama et al. reported that VEGF produced by tumor cells weakens NF- κ B activity.¹⁴ This also explains why the CEH in our case did not form a capsule, unlike the CEH that occurs following GKRS for AVM. Based on these findings, it was considered that the major contribution to CEH formation in our case was the increased expression of VEGFR-1.

There is limited experience in using tirabrutinib for PCNSL. In our case, it was administered while the CEH was growing, which might have influenced the occurrence and increase in CEH. However, GKRS has been performed for metastatic brain tumors and other brain tumors, but there are no reports of CEH occurrence. The expression level of VEGF may be the cause, but there was no obvious increase in VEGF in our case either. Factors other than VEGF could have been involved in the occurrence of CEH in our case, and the possibility that the long-term use of tirabrutinib had an influence cannot be excluded. As more cases involving the use of tirabrutinib accumulate in the future, its potential relationship with CEH might become clearer.

In the present case, the preoperative diagnosis of CEH was difficult, so the timing of occurrence and imaging characteristics were also investigated. First, the residual Gd-enhanced lesion in our patient began to slowly enlarge 4 years after GKRS, and the patient

was followed up for approximately 4 years after that because the disease did not clearly progress. CEH following GKRS for AVM has been reported to occur 2–20 years after GKRS, with a wide range.^{2,6} Radiation necrosis often occurs within 1–3 years after irradiation, but it can also occur 10 years later.^{15,16} In our case, it was difficult to distinguish between radiation necrosis and CEH based on the timing of lesion development. Second, on MRI, the Gd-enhanced lesion in our patient contained a cystic component. This finding can also be seen in radiation necrosis,¹⁷ but is considered characteristic of CEH occurring after GKRS for AVM.^{6,18} Third, a hypointense area suggestive of hemosiderin deposition was observed in T2*-weighted images in our case. Although there have been cases of radiation necrosis showing hematoma in pathology,¹⁹ in our case, hypointense areas on T2*-weighted images were found in a widespread area, which was suspicious for a hematoma. Taking these factors into consideration, we could have been considered the likelihood of CEH during the preoperative evaluation in our case.

Despite the surgery in our case being a partial resection, there has been no regrowth of the hematoma for more than 1 year. For CEHs following GKRS for AVMs, removal is recommended for enlarged or symptomatic cases and cyst formation.^{2,18} However, there have also been reports of no significant changes or spontaneous resolution of the hematoma with observation,^{1,20} similar to the natural course of CSDH.^{21,22} There remains a possibility of CEH recurrence from the residual lesion; thus, the patient should be carefully monitored.

Lessons

We report the case of a patient with PCNSL complicated by CEH following GKRS. This is the first report of CEH associated with GKRS in PCNSL. It is most probable that hypoxia in the surrounding tissue

caused by GKRS led to overexpression of VEGFR-1, triggering angiogenesis. The limitation of this report is that we have minimal experience with GKRS for PCNSL.

In patients with PCNSL following GKRS, if slow-growing Gd-enhanced lesions appear during the course of the disease, surgical removal should be considered, keeping in mind the possibility of CEH as well as tumor recurrence and radiation necrosis.

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Author Contributions

Conception and design: Hattori, Terada, Arakawa. Acquisition of data: Hattori Takeuchi, Sano. Analysis and interpretation of data: Hattori, Takeuchi, Sano, Mineharu. Drafting the article: Hattori, Terada. Critically revising the article: Takeuchi, Makino, Sano, Tanji, Mineharu, Arakawa. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Hattori. Statistical analysis: Hattori. Administrative/technical/material support: Hattori, Arakawa. Study supervision: Mineharu, Arakawa.

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