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Pathological Evaluation of Radiation-Induced Vascular Lesions of the Brain: Distinct from *De Novo* Cavernous Hemangioma

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Purpose: We aimed to evaluate the histologic and radiologic findings of vascular lesions after stereotactic radiosurgery (SRS) categorized as radiation-induced cavernous hemangioma (RICH).

Materials and Methods: Among 89 patients who underwent neurosurgery for cavernous hemangioma, eight RICHs from 7 patients and 10 *de novo* CHs from 10 patients were selected for histopathological and radiological comparison.

Results: Histologically, RICHs showed hematoma-like gross appearance. Microscopically, RICH exhibited a hematoma-like area accompanied by proliferation of thin-walled vasculature with fibrin deposits and infiltrating foamy macrophages. In contrast, CHs demonstrated localized malformed vasculature containing fresh and old clotted blood on gross examination. Typically, CHs consisted of thick, ectatic hyalinized vessels lined by endothelium under a light microscope. Magnetic resonance imaging of RICHs revealed some overlapping but distinct features with CHs, including enhancing cystic and solid components with absence or incomplete popcorn-like appearance and partial hemosiderin rims.

Conclusion: Together with histologic and radiologic findings, RICH may result from blood-filled space after tissue destruction by SRS, accompanied with radiation-induced reactive changes rather than vascular malformation. Thus, the term "RICH" would be inappropriate, because it is more likely to be an inactive organizing hematoma rather than proliferation of malformed vasculature.

Key Words: Brain, hemangioma, cavernous, central nervous system, radiosurgery

INTRODUCTION

De novo cavernous hemangioma (CH) is the second most common vascular malformation of the central nervous system, with an incidence of approximately 0.5%.[1] Patients present with headache, neurologic deficits, or seizures. Currently, magnetic resonance imaging (MRI) is the most sensitive and accurate diagnostic tool for *de novo* CH, and typically reveals an enhancing multiloculated cystic lesion with popcorn- or mulberry-like features on both T1- and T2-weighted images, due to clustered capillaries and venules that bleed periodically.[2] Histologically, *de novo* CH is composed of proliferating ectatic, single-endothelial lined abnormal vessels that lack smooth muscle, and absence of intervening brain parenchyma within the lesion is also characteristic. Old hemorrhage and reactive gliosis are frequently found at the periphery of the lesion. Most *de novo* CHs occur sporadically, although some patients have a family history of CH related to mutations in the cerebral cavernous malformation (*CCM*) genes, *CCM*1, *CCM*2, and *CCM*3. So far, these mutations have been most frequently observed in Hispanic-Americans of Mexican descent. Briefly, these gene are thought to be involved in generation of abnormal vessels and affect brain parenchyma surrounding the endothelial cells.[3]

Some sporadic cases of CH have been described as late complications of cerebral radiation.[4,5] Stereotactic radiosurgery (SRS), initially introduced by Leksell,[6] is now widely applied to

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patients with various brain lesions, including primary brain tumors,[7,8] metastatic lesions,[9,10] and vascular malformations.[11,12] Some patients who receive SRS develop a localized vascular, tumor-like lesion at the treatment site, months or even years after treatment.[13] Together with hemorrhage after brain irradiation, these lesions described as a "radiation-induced cavernous hemangioma" (RICH),[14,15] although some authors refer to such lesions as "radiation-induced telangiectasia".[16,17] Similar to *de novo* CHs, RICHs present as enhancing lesions on MRI and are found to be composed of vasculature and hemorrhage upon histological examination. So far, there has been no thorough histologic review of RICHs following SRS in comparison to *de novo* CHs. In the present study, we compared the histological and MRI findings of RICHs following SRS to those of *de novo* CHs.

MATERIALS AND METHODS

Patients

From January 2009 to December 2013, 89 patients received surgical removal of CHs at Severance Hospital. Among them, 7 patients had history of treatment with SRS due to brain tumor or vascular malformation and were diagnosed with CH and/or RICH on follow up MRI. Considering the clinical history of prior SRS, these 7 patients were regarded as RICH patients. Since one of 7 patients received two neurosurgeries for removal of recurrent hemorrhage, which were diagnosed as CHs on MRI, a total of 8 RICHs were included. For comparison, 10 cases of *de novo* CH were selected from amongst 89 patients. This study was approved by the Institutional Review Board of Severance Hospital (4-2014-0449).

Histopathological examination

Sections from formalin-fixed paraffin-embedded tissue were used for Masson trichrome (TRC) staining of collagen and for immunohistochemistry with antibodies against alpha-smooth muscle actin (α-SMA) (1A4, 1:1000, Dako, Glostrup, Denmark) and CD68 (PG-M1, 1:100, Dako). Briefly, 4-μm-thick paraffin sections were deparaffinized and rehydrated by xylene and alcohol solution. Immunohistochemistry was performed using the Ventana Discovery XT automated stainer (Ventana Medical System, Tucson, AZ, USA). Antigen retrieval was performed using CC1 buffer (Cell Conditioning 1; citrate buffer pH 6.0, Ventana Medical System). Appropriate positive and negative controls for immunohistochemistry were included.

In addition to the hematoxylin and eosin-stained sections, immunohistochemical and trichrome stains from all 17 patients were reviewed to examine histological features, assessed by two pathologists (YJC and SHK), using light microscopes. The available gross photographs and gross descriptions from the pathologic reports of RICH and CH cases were also retrieved.

Review of MRI findings

A blinded review of MRI findings for patients with RICH and CH was performed by two radiologists (HJS and JEK). All MRI scans of the RICHs were obtained at the time of diagnosis of brain hemorrhage and were compared with those for the *de novo* CHs.

RESULTS

Patient characteristics

The 7 RICH patients comprised 2 men and 5 women, aged 25–43 years (mean, 35.3 years). The mean latent period from SRS to RICH removal was 11.6 years (range, 5–17 years), and the mean size of the RICH lesions was 3.4 cm (range, 2.9–5.1 cm). Initial diagnoses prior to SRS were pilocytic astrocytoma in 2 patients, arteriovenous malformation in 2 patients, diffuse astrocytoma in 1 patient, glioblastoma in 1 patient, and anaplastic astrocytoma in 1 patient. The clinical characteristics of the patients are summarized in Table 1. These 7 patients had undergone SRS for a brain tumor or vascular malformation from 5 to 17 years prior to neurosurgery for RICH removal. Preoperative diagnoses of RICH were made on the basis of MRI findings considering patient history. The 10 patients with *de novo* CH consisted of 7 men and 3 women, aged 1–52 years (mean, 34.7 years). The mean size of *de novo* CHs was 2.1 cm (range, 0.9–4.0 cm).

Gross and microscopic evaluation

On gross examination, the cut surfaces of RICH lesions exhibit-

Table 1. Clinical Profiles of Patients with Radiation-Induced Cavernous Hemangioma

Case number	Sex	Age (yrs)	Primary lesion	Location	Size (cm)	Latency (yrs)
1	Male	25	Pilocytic astrocytoma	Left thalamus	2.9	13
2	Male	32	Arteriovenous malformation	Right occipital lobe	5.1	11
3	Female	30	Pilocytic astrocytoma	Right frontal lobe	4.3	11
4	Female	34	Arteriovenous malformation	Left parietal lobe	2.7	10
5	Female	35	Diffuse astrocytoma	Midbrain	2.9	11
6	Female	42	Glioblastoma	Right temporal lobe	2.1	5
7*	Female	41	Anaplastic astrocytoma	Left parietal lobe	4.0	15
8*	Female	43	Anaplastic astrocytoma	Left parietal lobe	3.0	17

*Cases 7 and 8 are separate events in the same patient.

ed relatively well-defined, homogenous hematoma-like lesions (Fig. 1A). In contrast, *de novo* CHs showed localized hemorrhage with discernible vascular structures, were filled with clotted fresh blood, and were surrounded by brown hemosiderin-tinged brain parenchyma (Fig. 1B). Microscopically, RICHs showed irregular, partly compressed capillary-sized vascular channels, with capillary proliferation-like area in the center of the lesion (Fig. 1C), whereas *de novo* CHs were composed of thick, well-formed vessels (Fig. 1D). Upon α-SMA staining, the centrally located capillary-like lumens of the RICHs lacked α-SMA expression (Fig. 1E), while endothelial cell-lined lumens of ectatic vessels of *de novo* CHs were well-delineated (Fig. 1F).

Collagen content in vessels differed between RICH and *de novo* CH, which was contrasted by TRC. Ectatic vessel walls of

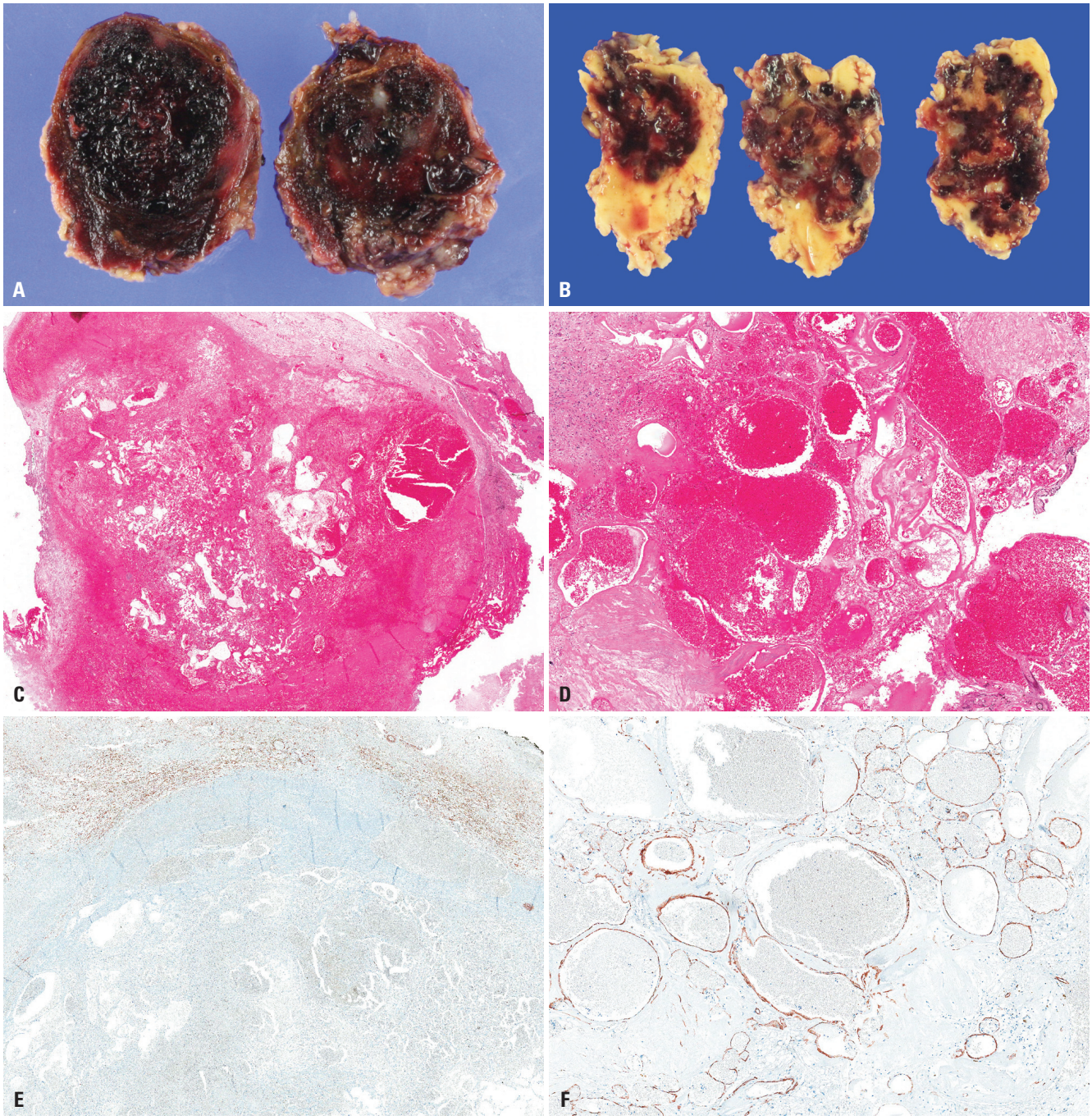

Fig. 1. Gross and microscopic findings of radiation-induced cavernous hemangioma (RICH) following stereotactic radiosurgery and *de novo* cavernous hemangioma (CH). RICH shows a hematoma-like cut surface without grossly identifiable vascular structure (A), while cut surfaces of *de novo* CH show clustered variable sized vessels containing fresh and old hemorrhage, surrounded by hemosiderin-tinged brain parenchyma (B). Microscopically, RICH shows hematoma like-area without recognizable vasculature (C), whereas CH consists of clusters of vascular lumens lined by endothelial cells (D). With α-SMA immunohistochemical staining, well-formed vasculature is not discernable in RICH (E), whereas endothelial lined lumens in CH are well-delineated (F).

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RICH lesions were thin and less hyalinized, compared to the thick, hyalinized walls of CH (Fig. 2A-D). With CD68 staining, RICH showed infiltration of foamy macrophages into vessel walls (Fig. 2E), whereas only scattered macrophages, located in old hemorrhage and outside of vessel walls, were found in *de novo* CH (Fig. 2F). Among the RICH cases, there was no identifiable residual tumor or accompanying *de novo* CH.

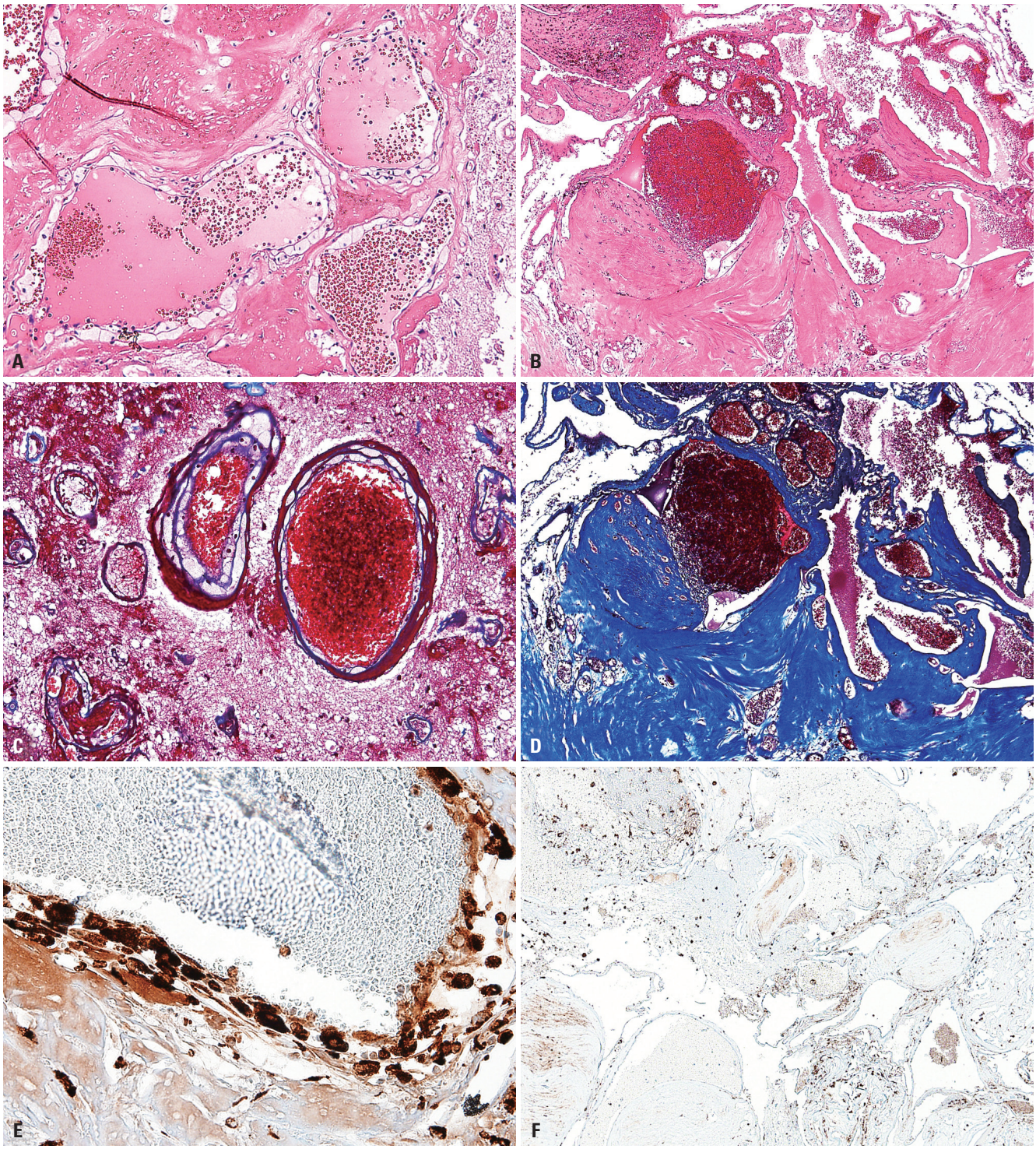

Fig. 2. Radiation-induced cavernous hemangioma (RICH) shows thin-walled vessels with fibrin and infiltrating foamy macrophages in the vessel walls (A). On the contrary, cavernous hemangioma (CH) consists of thick walled ectatic vessels sharing a common wall (B). This difference is further highlighted by trichrome staining, in which RICH lacks hyalinization in vessel walls (C) and CH shows prominent hyalinization (D). CD68 staining underscores the collection of foamy macrophages splitting the vessel walls in RICH (E). In CH, only a few macrophages are scattered in areas of old hemorrhage (F).

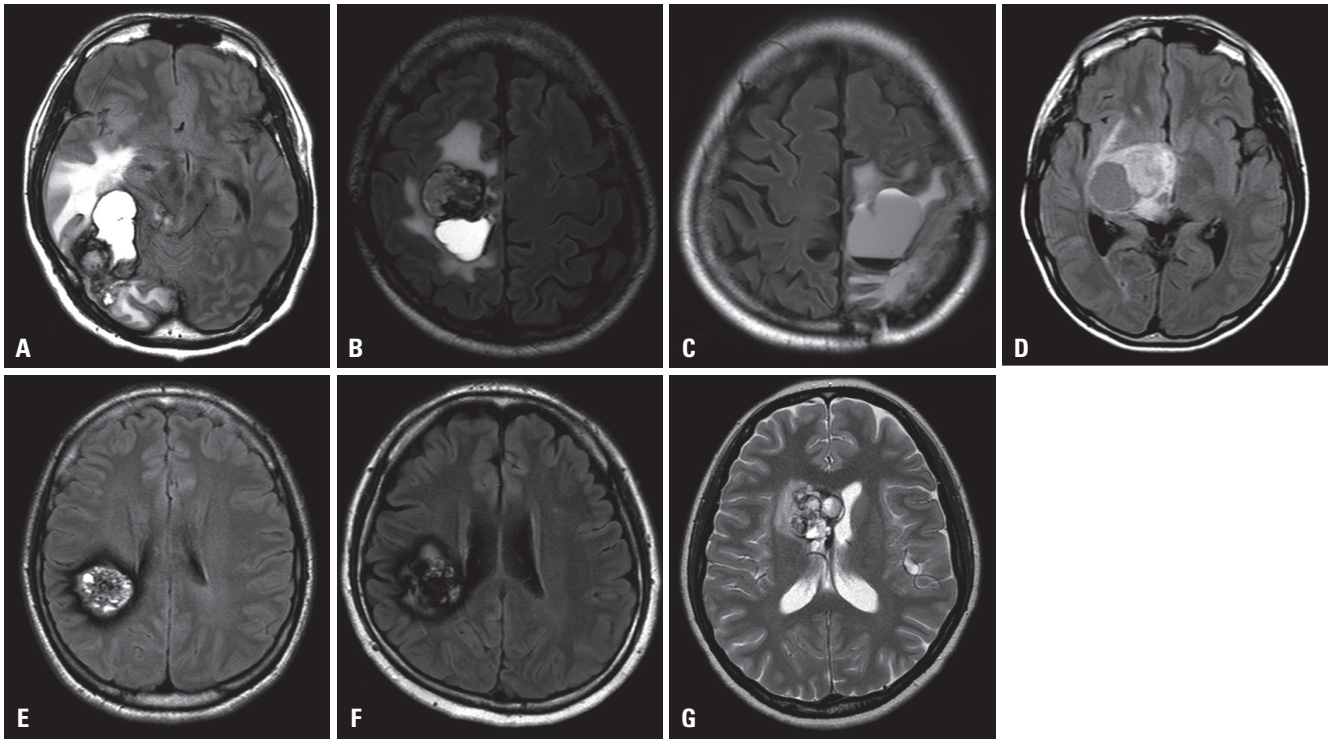

Fig. 3. (A-D) Radiological comparison of radiation-induced cavernous hemangioma (RICH) and *de novo* cavernous hemangioma (CH). Although a popcorn-like appearance and partial hemosiderin rim in RICH overlap with CH, other atypical findings such as an unilocular cystic area with some solid component and prominent perilesional edema are distinguishing features of RICH. (E, F, and G) A popcorn-like appearance, complete hemosiderin rim, and less prominent perilesional edema are common findings of *de novo* CH.

Radiologic findings

By adjunct comparison with MRI findings, RICHs showed some distinct and overlapping features with *de novo* CHs. All RICHs showed enhancing cystic and solid components on a T2-weighted image with perilesional edema. Six out of 8 RICHs had a uniloculated cyst rather than a multiloculated cyst, which is a common finding in *de novo* CH. Half of RICHs had no popcorn-like appearance, while the other half showed an incomplete popcorn-like appearance accompanied by only occasional, partial hemosiderin rims (Fig. 3A-D). Nevertheless, all 10 *de novo* CHs exhibited a classic popcorn-like appearance with a complete hemosiderin rim on T2-weighted sequences and mild or absence of perilesional edema (Fig. 3E, F, and G).

DISCUSSION

RICH has been studied in children with leukemia as a late complication of brain irradiation.[15,18,19] In patients who underwent cranial irradiation during childhood for the treatment and prevention of hematologic malignancies, such as acute lymphoblastic leukemia, cerebral hemorrhage can develop after several years.[18] Both CH and telangiectasia have been reported as possible complications of brain irradiation, and the terms have been used to describe vascular lesions.[4,18,20] There have been studies about the relationship between brain irradiation during childhood and development of RICH.[20,21] Heckl, et al.[15] concluded that the younger the patient was at the time of radiation treatment, the more likely a hemorrhagic event was to develop. In adults, a few RICHs following radiotherapy to treat arteriovenous malformation or a tumor have been reported,[22,23] and the dose of radiation seems to be associated with the risk of developing RICH.[4] Regarding the development of RICH, two models have been proposed: one model suggests that RICH is a *de novo* response to the radiation. Another model suggests the possibility of bleeding from a preexisting occult CH.[19] In a previous study of the role of structural proteins and angiogenic factors in CH, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor were highly expressed in CH.[24] Since radiation may induce deterioration of the brain blood barrier, hypoxia and subsequent release of VEGF may follow,[25] and elevation of VEGF levels could play a role in the development of RICH.

Ionizing radiation and SRS are now widely used to treat a variety of brain lesions, from tumors to vascular malformations.[26,27] However, radiation induces variable histologic changes in the brain parenchyma, including edema, as an early effect, and spongionecrosis, reactive gliosis, and telangiectasia, as late effects.[28,29] Fibrinoid necrosis, hyaline fibrous degeneration, perivascular macrophage collection, telangiectasia, and hemorrhage are results of vascular alteration by radiation.[30-33] As a late complication of whole brain irradiation and SRS, cerebral hemorrhage has been grouped as RICHs[34,35] or radiation-induced

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telangiectasia.[16,17] Diagnoses thereof are made based on MRI findings rather than histologic examination.[23,36,37] Unlike ionizing radiation, SRS emits a much higher dose of radiation to a small target area, leading to the shrinkage of the target lesion,[38-40] which in turn results in a small cavitary lesion in the center of the focal area. We hypothesized that RICH may originate from this cavitary lesion rather than malformation of vessels. After tissue destruction, this newly-made small cavity would be filled with blood. Spillage of fibrin would then inhibit further extension of the hemorrhage, and finally, a stabilized hematoma would be made. In support of our hypothesis, the locations of RICHs were identical to the sites of SRS, where prior tumors or vascular malformations existed. The proliferation of thin-walled vasculature and macrophage collection in RICHs are more likely to be radiation-related changes, and greatly different from *de novo* CH.

Although RICHs have been diagnosed with MRI, radiologic findings of RICHs differed from *de novo* CHs. While all *de novo* CHs in current study were typical multiloculated lesions with a popcorn-like appearance and a complete hemosiderin rim, none of the RICHs satisfied these features. Instead, most RICHs showed mixed intensity with an enhancing cystic and/or solid component and an incomplete hemosiderin rim, findings that would be insufficient for a diagnosis of *de novo* CH.

In terms of patient treatment, *de novo* CH warrants immediate treatment through surgical removal, because of the risk of intracranial hemorrhage. However, the treatment algorithm for RICH is not well established. Several studies have shown that a sizable proportion of patients with a RICH present with a seizure due to intracranial hemorrhage,[5,21] although some authors have suggested that RICH tends to more often be asymptomatic and have a relatively low risk of intracranial hemorrhage.[15,16] Although surgical intervention is required to remove *de novo* CH and/or RICH, surgery itself involves the risk of a neurologic deficit. We hypothesized that, since RICH is an inactive hematoma-like lesion, it may follow a more asymptomatic and safe course than *de novo* CHs, which harbor abnormal vessels bearing shear stress from circulating blood flow. However, the natural course of RICH has yet to be established, and a more precise study with a larger cohort is needed.

In summary, we reviewed hemorrhagic lesions following SRS that have been referred to as RICH. We found that these lesions are distinct from *de novo* CH in regards to their histologic and radiologic features. Since RICH is a rare condition and a small number of cases were included in current study, well-established radiologic and histologic features should be investigated. Further validation with a larger cohort accompanied with molecular studies, such as *CCM* gene mutation analysis, would help to elucidate the pathogenesis of RICH and its clinical implications. In conclusion, we suggest that RICH following SRS is more likely to be an inactive organizing hematoma rather than to involve the proliferation of malformed vasculature. Accordingly, the term "radiation-induced cavernous hemangioma" is inappropriate to describe this lesion, and we carefully suggest the term "radiation-induced organizing hematoma."

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REFERENCES

1. Del Curling O Jr, Kelly DL Jr, Elster AD, Craven TE. An analysis of the natural history of cavernous angiomas. J Neurosurg 1991;75:702-8.
2. Hegde AN, Mohan S, Lim CC. CNS cavernous haemangioma: "popcorn" in the brain and spinal cord. Clin Radiol 2012;67:380-8.
3. Mindea SA, Yang BP, Shenkar R, Bendok B, Batjer HH, Awad IA. Cerebral cavernous malformations: clinical insights from genetic studies. Neurosurg Focus 2006;21:e1.
4. Koike T, Yanagimachi N, Ishiguro H, Yabe H, Yabe M, Morimoto T, et al. High incidence of radiation-induced cavernous hemangioma in long-term survivors who underwent hematopoietic stem cell transplantation with radiation therapy during childhood or adolescence. Biol Blood Marrow Transplant 2012;18:1090-8.
5. Nimjee SM, Powers CJ, Bulsara KR. Review of the literature on de novo formation of cavernous malformations of the central nervous system after radiation therapy. Neurosurg Focus 2006;21:e4.
6. Leksell L. The stereotaxic method and radiosurgery of the brain. Acta Chir Scand 1951;102:316-9.
7. Salvetti DJ, Nagaraja TG, Levy C, Xu Z, Sheehan J. Gamma Knife surgery for the treatment of patients with asymptomatic meningiomas. J Neurosurg 2013;119:487-93.
8. Yianni J, Rowe J, Khandanpour N, Nagy G, Hoggard N, Radatz M, et al. Stereotactic radiosurgery for pineal tumours. Br J Neurosurg 2012;26:361-6.
9. Xu Z, Elsharkawy M, Schlesinger D, Sheehan J. Gamma knife radiosurgery for resectable brain metastasis. World Neurosurg 2013;80:351-8.
10. Salvetti DJ, Nagaraja TG, McNeill IT, Xu Z, Sheehan J. Gamma Knife surgery for the treatment of 5 to 15 metastases to the brain: clinical article. J Neurosurg 2013;118:1250-7.
11. Friedman WA. Stereotactic radiosurgery of intracranial arteriovenous malformations. Neurosurg Clin N Am 2013;24:561-74.
12. Bradac O, Charvat F, Benes V. Treatment for brain arteriovenous malformation in the 1998-2011 period and review of the literature. Acta Neurochir (Wien) 2013;155:199-209.
13. Matsumoto H, Takeda T, Kohno K, Yamaguchi Y, Kohno K, Takechi A, et al. Delayed hemorrhage from completely obliterated arteriovenous malformation after gamma knife radiosurgery. Neurol Med Chir (Tokyo) 2006;46:186-90.
14. Keezer MR, Del Maestro R. Radiation-induced cavernous hemangiomas: case report and literature review. Can J Neurol Sci 2009;36:303-10.
15. Heckl S, Aschoff A, Kunze S. Radiation-induced cavernous hemangiomas of the brain: a late effect predominantly in children. Cancer 2002;94:3285-91.
16. Koike S, Aida N, Hata M, Fujita K, Ozawa Y, Inoue T. Asymptomatic radiation-induced telangiectasia in children after cranial irra-

diation: frequency, latency, and dose relation. Radiology 2004;230:93-9.
17. Gaensler EH, Dillon WP, Edwards MS, Larson DA, Rosenau W, Wilson CB. Radiation-induced telangiectasia in the brain simulates cryptic vascular malformations at MR imaging. Radiology 1994;193:629-36.
18. Humpl T, Brühl K, Bohl J, Schwarz M, Stoeter P, Gutjahr P. Cerebral haemorrhage in long-term survivors of childhood acute lymphoblastic leukaemia. Eur J Pediatr 1997;156:367-70.
19. Larson JJ, Ball WS, Bove KE, Crone KR, Tew JM Jr. Formation of intracerebral cavernous malformations after radiation treatment for central nervous system neoplasia in children. J Neurosurg 1998;88:51-6.
20. Baumgartner JE, Ater JL, Ha CS, Kuttesch JF, Leeds NE, Fuller GN, et al. Pathologically proven cavernous angiomas of the brain following radiation therapy for pediatric brain tumors. Pediatr Neurosurg 2003;39:201-7.
21. Jain R, Robertson PL, Gandhi D, Gujar SK, Muraszko KM, Gebarski S. Radiation-induced cavernomas of the brain. AJNR Am J Neuroradiol 2005;26:1158-62.
22. Furuse M, Miyatake SI, Kuroiwa T. Cavernous malformation after radiation therapy for astrocytoma in adult patients: report of 2 cases. Acta Neurochir (Wien) 2005;147:1097-101.
23. Sasagawa Y, Akai T, Itou S, Iizuka H. Gamma knife radiosurgery-induced cavernous hemangioma: case report. Neurosurgery 2009;64:E1006-7.
24. Kiliç T, Pamir MN, Küllü S, Eren F, Ozek MM, Black PM. Expression of structural proteins and angiogenic factors in cerebrovascular anomalies. Neurosurgery 2000;46:1179-91.
25. Tsao MN, Li YQ, Lu G, Xu Y, Wong CS. Upregulation of vascular endothelial growth factor is associated with radiation-induced blood-spinal cord barrier breakdown. J Neuropathol Exp Neurol 1999;58:1051-60.
26. Freeman CR, Souhami L, Caron JL, Villemure JG, Olivier A, Montes J, et al. Stereotactic external beam irradiation in previously untreated brain tumors in children and adolescents. Med Pediatr Oncol 1994;22:173-80.
27. El Ahmadieh TY, Aoun SG, Bendok BR, Batjer HH. Management of brainstem cavernous malformations. Curr Treat Options Cardiovasc Med 2012;14:237-51.
28. Valk PE, Dillon WP. Radiation injury of the brain. AJNR Am J Neuroradiol 1991;12:45-62.
29. Martins AN, Johnston JS, Henry JM, Stoffel TJ, Di Chiro G. Delayed radiation necrosis of the brain. J Neurosurg 1977;47:336-45.
30. Schiffer D, Giordana MT, Soffietti R, Tarenzi L, Milani R, Vasario E, et al. Radio- and chemotherapy of malignant gliomas. Pathological changes in the normal nervous tissue. Acta Neurochir (Wien) 1981;58:37-58.
31. Reinhold HS, Hopewell JW. Late changes in the architecture of blood vessels of the rat brain after irradiation. Br J Radiol 1980;53:693-6.
32. Rottenberg DA, Chernik NL, Deck MD, Ellis F, Posner JB. Cerebral necrosis following radiotherapy of extracranial neoplasms. Ann Neurol 1977;1:339-57.
33. Lampert PW, Davis RL. Delayed effects of radiation on the human central nervous system; "Early" and "Late" delayed reactions. Neurology 1964;14:912-7.
34. Park YS, Kim SH, Chang JH, Chang JW, Park YG. Radiosurgery for radiosurgery-induced cavernous malformation. World Neurosurg 2011;75:94-8.
35. Vinchon M, Leblond P, Caron S, Delestret I, Baroncini M, Coche B. Radiation-induced tumors in children irradiated for brain tumor: a longitudinal study. Childs Nerv Syst 2011;27:445-53.
36. Faraci M, Morana G, Bagnasco F, Barra S, Polo P, Hanau G, et al. Magnetic resonance imaging in childhood leukemia survivors treated with cranial radiotherapy: a cross sectional, single center study. Pediatr Blood Cancer 2011;57:240-6.
37. Duhem R, Vinchon M, Leblond P, Soto-Ares G, Dhellemmes P. Cavernous malformations after cerebral irradiation during childhood: report of nine cases. Childs Nerv Syst 2005;21:922-5.
38. Tung GA, Noren G, Rogg JM, Jackson IM. MR imaging of pituitary adenomas after gamma knife stereotactic radiosurgery. AJR Am J Roentgenol 2001;177:919-24.
39. Chernov MF, Ono Y, Abe K, Usukura M, Hayashi M, Izawa M, et al. Differentiation of tumor progression and radiation-induced effects after intracranial radiosurgery. Acta Neurochir Suppl 2013;116:193-210.
40. Sharpton SR, Oermann EK, Moore DT, Schreiber E, Hoffman R, Morris DE, et al. The volumetric response of brain metastases after stereotactic radiosurgery and its post-treatment implications. Neurosurgery 2014;74:9-15.

http://dx.doi.org/10.3349/ymj.2015.56.6.1714