JOURNAL OF NEUROSURGERY:
Case Lessons

J Neurosurg Case Lessons 8(23): CASE24570, 2024
DOI: 10.3171/CASE24570

Cerebral cavernous malformation with prolonged postoperative paralysis due to perilesional inflammation: illustrative case

Soichi Inai, MD,[1] Noritaka Sano, MD, PhD,[1] Yasuhide Takeuchi, MD, PhD,[2] Yasuhide Makino, MD, PhD,[1] Etsuko Yamamoto Hattori, MD, PhD,[1] Shigeki Takada, MD, PhD,[1] Masahiro Tanji, MD, PhD,[1] Yohei Mineharu, MD, PhD,[1] and Yoshiki Arakawa, MD, PhD[1]

[1]Department of Neurosurgery, Kyoto University Graduate School of Medicine, Kyoto, Japan; and [2]Department of Diagnostic Pathology, Kyoto University Hospital, Kyoto, Japan

BACKGROUND Postoperative symptom exacerbation after resection of cerebral cavernous malformations (CCMs) is usually due to surgical damage to the eloquent areas or venous outflow obstruction from injury to a developmental venous anomaly (DVA).

OBSERVATIONS A 21-year-old right-handed female presented with headache, right limb weakness, and aphasia. Magnetic resonance imaging (MRI) revealed a 3.5-cm CCM with significant perilesional edema in the middle frontal gyrus. Despite medical treatment, her weakness worsened, necessitating emergency resection. Imaging revealed no DVA or venous obstructions. Histopathological examination revealed marked neutrophil infiltration, indicating noninfectious inflammation. One week postoperatively, MRI revealed increased edema around the resection site. Although the aphasia improved, paralysis (manual muscle testing grade 3) persisted, prompting betamethasone administration. The symptoms rapidly improved over 10 days, and the patient was discharged symptom free on day 20 with no recurrence thereafter.

LESSONS Patients with prolonged postoperative deficits after CCM resection can experience noninfectious inflammation. Anti-inflammatory treatments such as corticosteroids may be necessary in similar cases with poor recovery from edema and symptoms.

https://thejns.org/doi/abs/10.3171/CASE24570

KEYWORDS cavernous malformation; inflammation; corticosteroids

Cerebral cavernous malformations (CCMs), also known as "cavernous angiomas," are low-flow vascular malformations of the central nervous system characterized by clusters of dilated sinusoidal channels that sometimes result in intracranial hemorrhage, seizures, and neurological deficits.[1] The surgical indications include persistent or progressive neurological symptoms and CCM hemorrhage. However, the resection of CCMs located in eloquent or deep regions carries a higher risk of postoperative symptom exacerbation than the resection of lesions in noneloquent areas. Therefore, the indications for surgery should be carefully considered.[2–4]

Recent studies revealed that inflammation plays an essential role in CCM pathogenesis, involving the upregulation of proinflammatory cytokines, leading to enhanced leukocyte recruitment and repeated rupture of the lesion.[5,6] Inflammatory cellular infiltration has also been associated with aggressive behavior in CCMs with a developmental venous anomaly (DVA).[7]

In this case, we encountered a patient whose CCM-associated inflammation led to extensive perifocal edema, resulting in the acute exacerbation of pre- and postoperative symptoms. We believe that this case is worth reporting as it provides valuable insights for appropriately managing similar cases.

Illustrative Case

A 21-year-old right-handed female with no family history of CCM or significant medical history presented with headache, right upper- and lower-limb muscle weakness (manual muscle testing [MMT] level 4), and aphasia. Initial magnetic resonance imaging (MRI) performed at a local hospital suggested intracerebral bleeding, leading to a referral to our hospital. Upon arrival, MRI revealed a typical "popcorn" appearance of a solitary CCM (35 × 33 × 30 mm) in the subcortical region of the middle frontal gyrus with massive edema extending as far as the precentral gyrus (Fig. 1A—E). Blood tests revealed slightly elevated levels of white blood cells (10.44×10^9/L), neutrophils (9.04×10^9/L), and D-dimer (1.1 μg/mL), but no other significant abnormalities were observed.

Initially, thrombosis of the DVA associated with CCM or impairment of the surrounding venous drainage was suspected to cause

ABBREVIATIONS CCM = cerebral cavernous malformation; CT = computed tomography; DVA = developmental venous anomaly; MMT = manual muscle testing; MRI = magnetic resonance imaging; SMA = supplementary motor area; SWI = susceptibility-weighted imaging.

INCLUDE WHEN CITING Published December 2, 2024; DOI: 10.3171/CASE24570.
SUBMITTED August 28, 2024. **ACCEPTED** September 25, 2024.

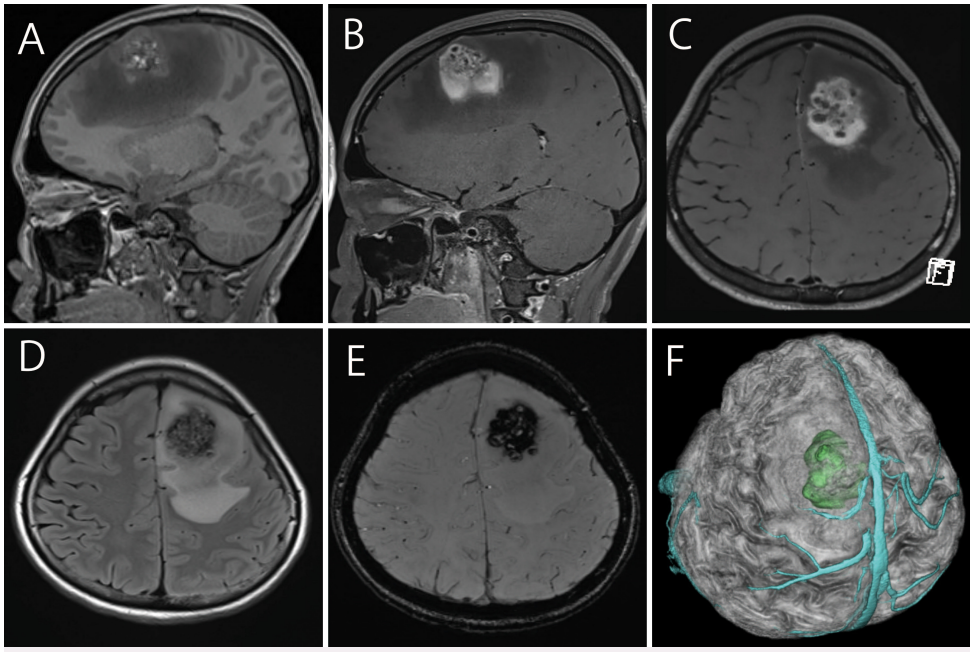

FIG. 1. A: Sagittal T1-weighted MRI showing scattered high-intensity spots, suggesting the presence of a minor hemorrhage at different time intervals. **B and C:** Sagittal and axial gadolinium-enhanced T1-weighted images showing perilesional enhancement, indicating disruption of the blood-brain barrier, signifying the presence of inflammation and edema. **D:** Axial fluid-attenuated inversion recovery image showing perifocal edema. **E:** SWI showing the typical popcorn-like appearance without occult DVA. **F:** Three-dimensional image reconstructed using fused contrast-enhanced CT venography and contrast-enhanced MRI, showing no major venous occlusion.

the massive perifocal edema. However, contrast-enhanced computed tomography (CT) venography and MRI with susceptibility-weighted imaging (SWI) revealed no obvious venous abnormalities (Fig. 1E). Despite medical treatment with intravenous osmotic diuretics (10% glycerol, 400 mL per day), her right limb weakness rapidly worsened to an MMT score of 2 over several days, prompting emergency resection.

The surgery was performed without any technical issues. Initially, a left frontal craniotomy was performed. After a wide dural incision, a 2-cm incision was made in the cerebral cortex directly above the CCM. The lesion was resected en bloc (Fig. 2A and B). Intraoperative findings revealed no obvious DVA in the surrounding area or occluded veins. However, significant edema in the surrounding cerebral cortex was observed. Immediately after surgery, paralysis in the right upper and lower limbs worsened to MMT levels of 1. Considering the impact of surgical invasion on the supplementary motor area (SMA), intravenous osmotic diuretics were continued.

Although gradual improvement was observed, right upper- and lower-limb paralysis at MMT level 3 persisted. Histopathological examination revealed marked neutrophil infiltration within the malformations, and the neutrophils had spread to the surrounding cerebral white matter (Fig. 2C–E). To exclude infectious diseases, Periodic acid-Schiff, Grocott, and Gram staining were performed; however, no evident pathogenic microorganisms were identified. Postoperative contrast-enhanced MRI confirmed that perifocal edema had deteriorated; however, no new occlusions of the major surrounding veins or venous sinuses occurred (Fig. 3A–D). Considering the pathological and diagnostic imaging results, betamethasone (8 mg) was initiated for 3 days. Symptoms improved rapidly over 10 days during tapering off the steroid, and both edema and midline shift improved dramatically (Fig. 3E and F). She was discharged home symptom free on postoperative day 20, with no recurrence of symptoms after that, and the perifocal edema significantly improved by 3 months postoperatively (Fig. 3G and H).

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

Observations

Here, we present a case of CCM with prolonged postoperative paralysis due to perilesional inflammation. To the best of our knowledge, this is the first reported case in which inflammation extended around the CCM and the symptoms worsened even after resection.

Surgical indications for CCMs include persistent or progressive neurological symptoms and repeated hemorrhages.[2,8] While many reports indicate a significant improvement in prognosis due to surgery,[9,10] a few studies have pointed out that CCM excision is associated with worse outcomes than conservative management, including an increased risk of symptomatic intracranial hemorrhage and new focal neurological deficits.[11] These findings suggest that the indications for surgery should be determined carefully, considering the patient's overall condition, the size of the lesion, and whether it is located in an eloquent or deep area. There is an ongoing debate regarding the risks associated with the surgical management of DVAs. Generally, DVAs are involved in normal venous drainage, and incidental resection

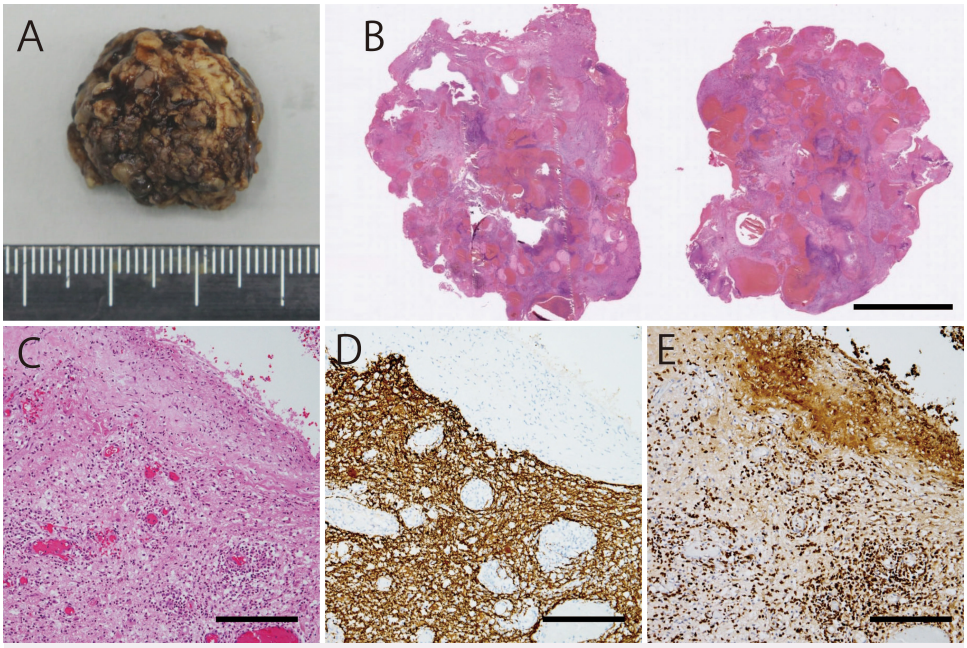

FIG. 2. A: Photograph showing a typical popcorn appearance. **B:** Hematoxylin and eosin staining revealing closely packed, thin-walled, dilated, abnormal vascular channels without intervening brain parenchyma. Bar = 5 mm. **C–E:** Tissue surrounding the cavernous malformation, including the adjacent brain tissue. Bar = 200 µm. Hematoxylin and eosin staining revealed significant infiltration of inflammatory cells within the tissue (C). Areas with a high density of inflammatory cells were positive for glial fibrillary acidic protein, indicating that they were part of the brain tissue (D). The majority of infiltrating cells were myeloperoxidase-positive, suggesting that they are neutrophils (E).

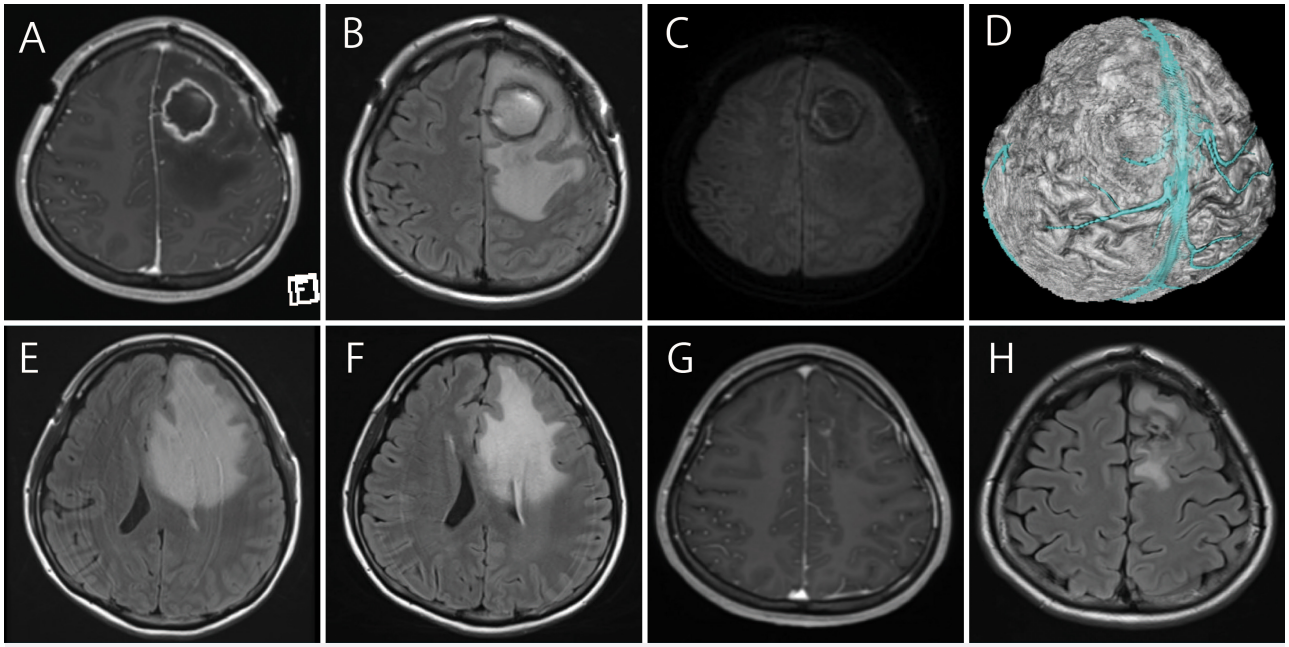

FIG. 3. Six days postoperatively, an axial gadolinium-enhanced T1-weighted image (**A**) showed perilesional enhancement, and an axial fluid-attenuated inversion recovery image (**B**) showed posteriorly enlarged perifocal edema compared with panel D. There was no new cerebral infarction around the lesion on diffusion-weighted imaging (**C**) and no obvious major venous occlusion (**D**). The midline shift and edema improved from postoperative day 6 (**E**) to day 13 (**F**). Three months postoperatively, perilesional contrast enhancement (**G**) and edema on the axial fluid-attenuated inversion recovery (**H**) images had diminished significantly.

or occlusion during surgery is expected to cause cerebral edema. However, some reports indicate that no significant issues arise from incidental resection,[12] and the complications are usually not severe if they occur.[13] Nonetheless, severe complications can occur in some cases; thus, preservation of the DVAs is recommended whenever possible.[13]

In the present case, the potential causes of postoperative symptom deterioration included surgical damage to the SMA, occlusion of an occult DVA, and occlusion of the superior sagittal sinus or its major branches. However, the possibility of both is unlikely for several reasons. The lesion was primarily located in the middle frontal gyrus, and postoperative MRI did not reveal any new infarctions or contusions in the SMA region. Therefore, direct damage might not be the primary cause of postoperative deterioration, while perilesional edema extending to the SMA might have some effect. Preoperative SWI, contrast-enhanced T1-weighted imaging, and contrast-enhanced CT venography did not reveal any DVAs associated with the CCM, and no newly occluded major veins were observed on pre- or postoperative imaging.

Recent studies have revealed the significant role of inflammation in the pathogenesis of CCM. Inflammatory mechanisms, including oxidative stress and immune responses, contribute to CCM formation, growth, and hemorrhage.[6,14] In addition, the interaction between the CCM endothelium, astrocytes, and immune cells plays a crucial role in lesion growth and immunothrombosis.[15] Among these inflammatory cells, the recruitment of neutrophils, as well as the deposition of neutrophil extracellular traps at neuroinflammatory sites, plays the most important role in the development of CCMs.[6] Neutrophil extracellular traps are composed of deoxyribonucleic acid, histones, and antimicrobial proteins released by neutrophils for killing pathogens, but their excessive formation can contribute to inflammation, vascular permeability, and subsequent bleeding. Macrophages and microglia also play a role in breaking down of red blood cells after hemorrhage and releasing proinflammatory mediators such as interleukin-1β and interleukin-6.[1] In the present case, numerous hemorrhages were observed within the CCM, and extensive necrosis and infiltration of numerous neutrophils were observed within the vascular lumen, with the infiltration of neutrophils extending into the surrounding brain tissue. Although similar reports were not found in our literature review, there was a case report of severe edema occurring around the CCM following Gamma Knife treatment, in which extensive necrosis within the hemangioma was observed.[16] Contrast enhancement over a wide area surrounding the hemangioma on contrast-enhanced T1-weighted images, along with extensive edema, was similar to that observed in our case. Therefore, severe inflammation caused by necrosis within the CCM, repeated microhemorrhages, and thrombosis can lead to significant edema.

Perilesional edema on noncontrast T1-weighted images is considered a characteristic finding in CCM;[17] however, in our case, a markedly extensive low signal area was observed, along with widespread contrast enhancement. These findings suggest the presence of an intense inflammatory reaction causing localized disruption of the blood-brain barrier. Another possible explanation for this postoperative edema is an allergy to oxidized cellulose in the removal cavity, which is used as a hemostatic agent.[18] However, considering the extensive inflammatory findings observed preoperatively, assuming that inflammation persisted postoperatively seems more plausible. As the symptoms were exacerbated by edema due to severe inflammation, we believe that the corticosteroids were highly effective.

Lessons

Inflammation is associated with the progression and recurrent hemorrhage associated with CCM. When perilesional edema does not improve after resection and infection or venous outflow obstruction is ruled out, prolonged inflammation should be considered. Therefore, prompt corticosteroid treatment should be considered in these patients.

Acknowledgments

This work was supported by a JSPS KAKENHI Grant-in-Aid for Early-Career Scientists (no. 23K15667, N.S.).

References

1. Li Y, Srinath A, Alcazar-Felix RJ, et al. Inflammatory mechanisms in a neurovascular disease: cerebral cavernous malformation. *Brain Sci*. 2023;13(9):1336.
2. Kearns KN, Chen CJ, Tvrdik P, Park MS, Kalani MYS. Outcomes of surgery for brainstem cavernous malformations a systematic review. *Stroke*. 2019;50(10):2964-2966.
3. Akers A, Al-Shahi SR, Awad IA, et al. Synopsis of guidelines for the clinical management of cerebral cavernous malformations: consensus recommendations based on systematic literature review by the angioma alliance scientific advisory board clinical experts panel. *Clin Neurosurg*. 2017;80(5):665-680.
4. Porter PJ, Willinsky RA, Harper W, Wallace MC. Cerebral cavernous malformations: natural history and prognosis after clinical deterioration with or without hemorrhage. *J Neurosurg*. 1997;87(2): 190-197.
5. Mouchtouris N, Jabbour PM, Starke RM, et al. Biology of cerebral arteriovenous malformations with a focus on inflammation. *J Cereb Blood Flow Metab*. 2015;35(2):167-175.
6. Yau ACY, Globisch MA, Onyeogaziri FC, et al. Inflammation and neutrophil extracellular traps in cerebral cavernous malformation. *Cell Mol Life Sci*. 2022;79(4):206.
7. de Souza JM, Aiex CA, Silva Canedo NH, Marques SA, Blanco Martinez AM. Intraaxial and extraaxial cavernous malformation with venous linkage: immune cellular inflammation associated with aggressiveness. *World Neurosurg*. 2019;131:87-89.
8. Sandalcioglu IE, Wiedemayer H, Secer S, Asgari S, Stolke D. Surgical removal of brain stem cavernous malformations: surgical indications, technical considerations, and results. *J Neurol Neurosurg Psychiatry*. 2002;72(3):351-355.
9. Gross BA, Batjer HH, Awad IA, Bendok BR, Du R. Brainstem cavernous malformations: 1390 surgical cases from the literature. *World Neurosurg*. 2013;80(1-2):89-93.
10. Chang EF, Gabriel RA, Potts MB, Berger MS, Lawton MT. Supratentorial cavernous malformations in eloquent and deep locations: surgical approaches and outcomes: clinical article. *J Neurosurg*. 2011;114(3):814-827.
11. Moultrie F, Horne MA, Josephson CB, et al. Outcome after surgical or conservative management of cerebral cavernous malformations. *Neruology*. 2014;83(7):582-589.
12. Tantongtip D, Spetzger U, Arnold S, von Schilling A, Kiriyanthan G. How relevant is occlusion of associated developmental venous anomaly in cerebral cavernoma surgery? A clinical and radiographic comparison study. *J Neurol Surg A Cent Eur Neurosurg*. 2015;77(2):111-117.
13. Zhang P, Liu L, Cao Y, Wang S, Zhao J. Cerebellar cavernous malformations with and without associated developmental venous anomalies. *BMC Neurol*. 2013;13:134.
14. Tu T, Peng Z, Ren J, Zhang H. Cerebral cavernous malformation: immune and inflammatory perspectives. *Front Immunol*. 2022; 13:922281.

15. Lai CC, Nelsen B, Frias-Anaya E, et al. Neuroinflammation plays a critical role in cerebral cavernous malformation disease. *Circ Res*. 2022;131(11):909-925.
16. Takenaka N, Imanishi T, Sasaki H, et al. Delayed radiation necrosis with extensive brain edema after gamma knife radiosurgery for multiple cerebral cavernous malformations--case report. *Neurol Med Chir (Tokyo)*. 2003;43(8):391-395.
17. Alturki IA, Alluhidan TA, Alturki AA, Alzahrani FS, Alluwaymi NA. Hyperintense perilesional edema on T1-weighted imaging in cavernoma: a case report. *Cureus*. 2024;16(1):e51454.
18. Franceschini G. Use of oxidized regenerated cellulose as a hemostatic agent in neurosurgery: appraisals and recommendations to prevent postoperative complications and facilitate follow-up. *Surg Technol Int.* 2021;38:481-485.

Disclosures

Dr. Mineharu reported an endowed course by Omron Healthcare Co. Ltd. outside the submitted work. Dr. Arakawa reported grants from Philips, Otsuka, Chugai, Nihon Medi-Physics, Daiichi Sankyo, Stryker, Eisai, Japan Blood Products Organization, Ono Pharmaceutical, Taiho Pharma, Sumitomo Dainippon Pharma, Astellas Pharma, Incyte Biosciences, and Servier; and personal fees from Nippon Kayaku, Novocure, UCB Japan, Ono Pharmaceutical, Brainlab, Merck, Chugai, Eisai, Daiichi Sankyo, Carl Zeiss, Nihon Medi-Physics, and Stryker outside the submitted work.

Author Contributions

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

Correspondence

Noritaka Sano: Kyoto University Graduate School of Medicine, Kyoto, Japan. n_sano@kuhp.kyoto-u.ac.jp.