 doi: 10.2176/jns-nmc.2024-0215

NMC Case Report Journal 12, 97-101, 2025

Amyloid β-related Angiitis Presenting with Subarachnoid Hemorrhage Diagnosed by Brain Biopsy: A Case Report

Motoki ISHIDA,[1] Naoki SHIMOYA,[2] Hiromi SHIBATA,[1]
Takayuki OHNO,[1] Takashi IWATA,[1] Atsuhito TAISHAKU,[1]
Kentaro YAMADA,[2] Shingo INAGUMA,[3] and Noritaka AIHARA[1]

[1]*Department of Neurosurgery, Nagoya City University East Medical Center, Nagoya, Aichi, Japan*
[2]*Department of Neurology, Nagoya City University East Medical Center, Nagoya, Aichi, Japan*
[3]*Department of Pathology, Nagoya City University East Medical Center, Nagoya, Aichi, Japan*

Abstract

Cerebral amyloid angiopathy is a vascular disorder characterized by amyloid β deposition in leptomeningeal and cortical blood vessels. Rarely, amyloid β accumulation induces inflammatory responses, classified as cerebral amyloid angiopathy-related inflammation or amyloid β-related angiitis, with the latter being extremely rare. We report a case of a 74-year-old woman presenting with visual field disturbance, occipital pain, speech impairment, agraphia, and acalculia. Imaging revealed subarachnoid hemorrhage without an identifiable source on cerebral angiography. Magnetic resonance imaging demonstrated abnormal enhancement in the dura and pia mater of the left temporal and parietal lobes. Brain biopsy confirmed amyloid β-related angiitis, showing histopathological findings of amyloid deposition with granulomatous inflammation. Steroid pulse therapy led to marked clinical and radiological improvement. This case highlights the importance of considering amyloid β-related angiitis in the differential diagnosis of angiographically negative subarachnoid hemorrhage. Early recognition and immunosuppressive therapy are essential to reduce neurological deficits, with brain biopsy providing a definitive diagnosis.

Keywords: Aβ-related angiitis, unknown SAH, brain biopsy

Introduction

Cerebral amyloid angiopathy (CAA) is a condition characterized by amyloid β (Aβ) protein deposition in subcortical or meningeal blood vessels, predominantly affecting elderly individuals.[1,2] CAA is typically a non-inflammatory, age-related disorder associated with cerebral hemorrhage, infarcts, leukoencephalopathy, and dementia. However, in rare cases, Aβ deposition triggers an inflammatory response, which can be classified into CAA-related inflammation (CAA-RI) and Aβ-related angiitis (ABRA). CAA-RI and ABRA represent distinct pathological entities with no known correlation in their clinical manifestations. CAA-RI features inflammatory cell infiltration around Aβ-laden blood vessels without vasculitis. In contrast, ABRA is characterized by Aβ deposition with adjacent granulomatous inflammation, including granuloma formation and necrosis within the affected vasculature.[3,4]

ABRA is an extremely rare vasculitis, most commonly observed in elderly patients presenting with cognitive dysfunction and stroke.[2] A 2014 study by Danve et al.[5] reviewed 94 cases of ABRA, reporting symptoms such as cognitive decline, microbleeds, and transient cerebral ischemia. Notably, no cases in the study presented with subarachnoid hemorrhage (SAH). This absence highlights a significant gap in the literature regarding ABRA as a potential cause of angiographically negative SAH.

This case report addresses this gap by describing an instance of ABRA presenting with SAH. It emphasizes the utility of brain biopsy for definitive diagnosis and highlights the role of immunosuppressive therapy in improving clinical outcomes. Through this report, we aim to enhance

Received September 2, 2024; Accepted January 2, 2025

awareness of ABRA as a differential diagnosis in unexplained SAH and provide insights for early identification and management.

Case Report

A 73-year-old woman presented with a headache and visual field disturbance and was referred to our hospital. Neurological examination revealed impairments in speech comprehension and word production, along with acalculia, agraphia, and right homonymous hemianopia. Cranial computed tomography (CT) imaging demonstrated faint high-density lesions in the cerebral sulci of the left parietal and occipital lobes, suggestive of SAH (Fig. 1). Brain magnetic resonance imaging (MRI) showed high signal intensity in the left temporal, parietal, and occipital lobes on diffusion-weighted imaging (Fig. 2A). Fluid-attenuated inversion recovery imaging revealed corresponding areas of high signal intensity, while susceptibility-weighted imaging demonstrated low signal consistent with the CT findings (Fig. 2B and C). Magnetic resonance angiography, CT angiography, and cerebral angiography were performed but failed to identify a clear source of bleeding. Cerebrospinal fluid analysis revealed xanthochromia, a slight increase in mononuclear cell count, and increased protein levels, confirming SAH and excluding infectious causes such as encephalitis or meningitis.

The right homonymous hemianopia and language impairments were attributed to symptomatic epilepsy, and the patient was started on the anti-epileptic drug (AED) levetiracetam at 1000 mg/day. While her visual field deficit improved following AED administration, language impairment, acalculia, and agraphia showed minimal improvement. A follow-up MRI on the second day of hospitalization demonstrated abnormal contrast enhancement in the dura and pia mater, correlating with the site of the SAH (Fig. 3).

To establish a definitive diagnosis, a brain biopsy was performed using a neuronavigation-guided mini craniotomy. A cortical sample was obtained from the region displaying leptomeningeal contrast enhancement on MRI. Hematoxylin and eosin staining revealed vascular connective tissue changes, including intimal thickening, luminal narrowing, neutrophil infiltration, and fibrinoid necrosis in small to medium-sized blood vessels. Associated ischemic degeneration of the brain tissue was also observed (Fig. 4 A). Amyloid deposition was confirmed on blood vessel walls through direct fast scarlet staining, which appeared red under standard light and displayed apple-green birefringence under polarized light (Fig. 4B and C). There were no pathological findings suggestive of infection, granulomas, or malignancy. Based on these findings, a diagnosis of Aβ-related vasculitis was confirmed.

Steroid pulse therapy was initiated, starting with 1000 mg of methylprednisolone daily for 3 days, followed by

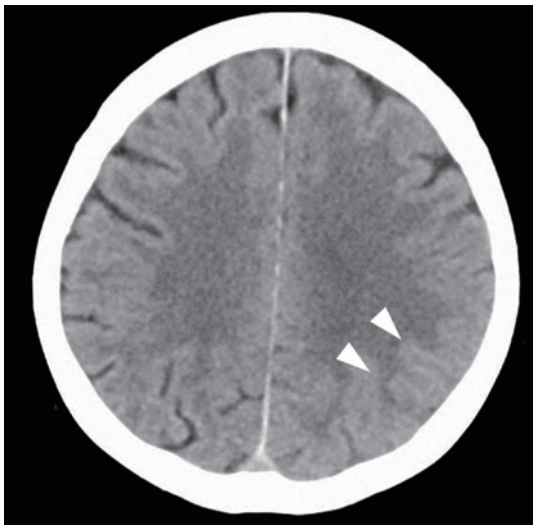

Fig. 1 CT scan on admission. The image shows faint high-density lesions (arrowheads) in the cerebral sulcus of the left parietal and occipital lobes, suggesting a subarachnoid hemorrhage.
CT: computed tomography

maintenance therapy with 40 mg/day with gradual dose tapering. Biweekly follow-up MRIs done post-biopsy demonstrated progressive resolution of abnormal contrast enhancement in the pia and dura mater along the cerebral sulci.

The patient exhibited gradual improvement in language function, acalculia, agraphia, and overall cognitive abilities 2 weeks following the biopsy. She was discharged 48 days post-biopsy with a modified Rankin Scale score of 2. Since discharge, no symptom recurrence has been observed, and her oral steroid dose has been gradually reduced. She is currently maintained on 4 mg/day of methylprednisolone as an outpatient.

Discussion

CAA is a small vessel disease involving amyloid deposition in the blood vessels, leading to risks such as intracerebral hemorrhage (ICH) and SAH. Among patients with CAA, the annual incidence rate of symptomatic ICH is 19%, compared with 7% in those without CAA. Effective hypertension management is critical for preventing such events, and caution is needed when prescribing antithrombotic medications.[1,6-8)]

In certain cases, an inflammatory reaction occurs associated with Aβ deposition, which can be classified as CAA-RI or ABRA. These inflammatory variants of CAA share overlapping clinical presentations but are quite distinct from non-inflammatory CAA. Inflammatory CAA more commonly presents with acute or subacute cognitive or functional decline, neurological deficits, or seizures. While cerebral hemorrhage is uncommon in inflammatory CAA,

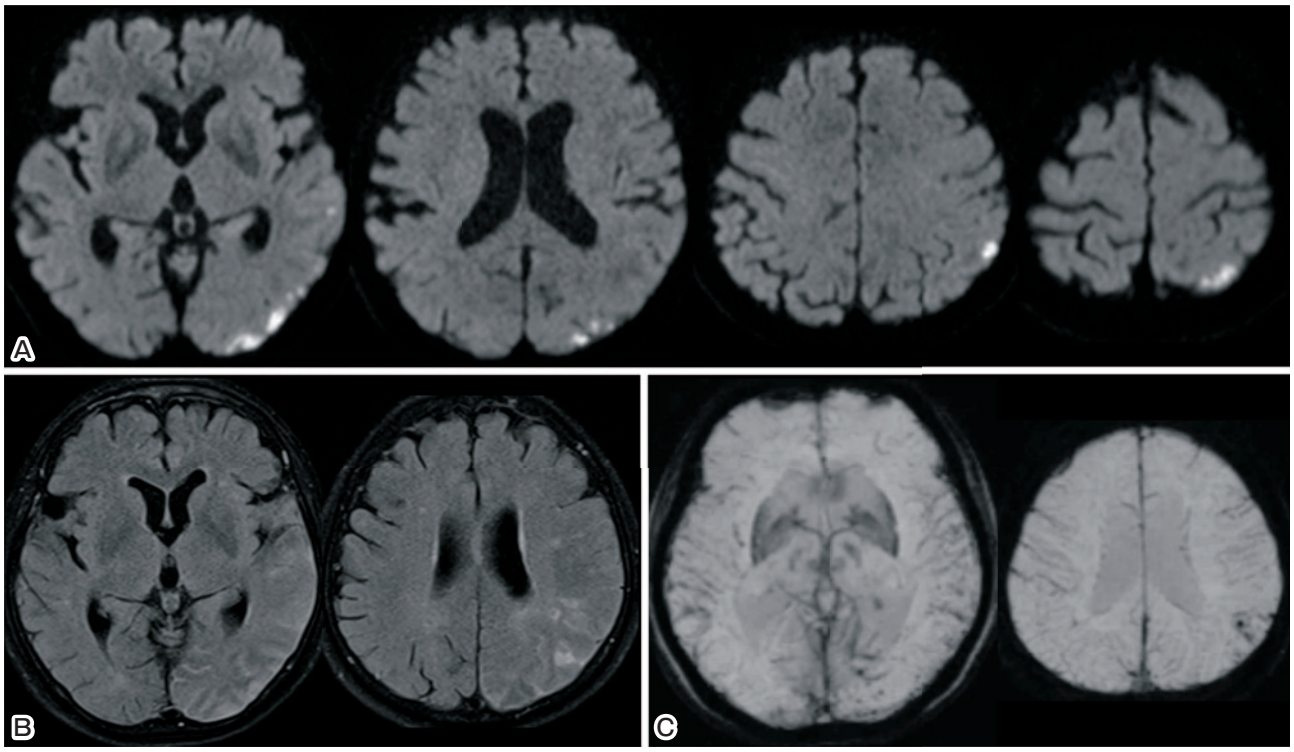

Fig. 2 MRI on admission. A: DWI shows high signal intensity in the left temporal, parietal, and occipital lobes. B: FLAIR imaging reveals high signal intensity in the same regions. C: SWI shows low signal intensity in areas corresponding to the high-density lesions observed in the CT scan.
CT: computed tomography; DWI: diffusion-weighted imaging; FLAIR: fluid-attenuated inversion recovery; MRI: magnetic resonance imaging; SWI: susceptibility-weighted imaging

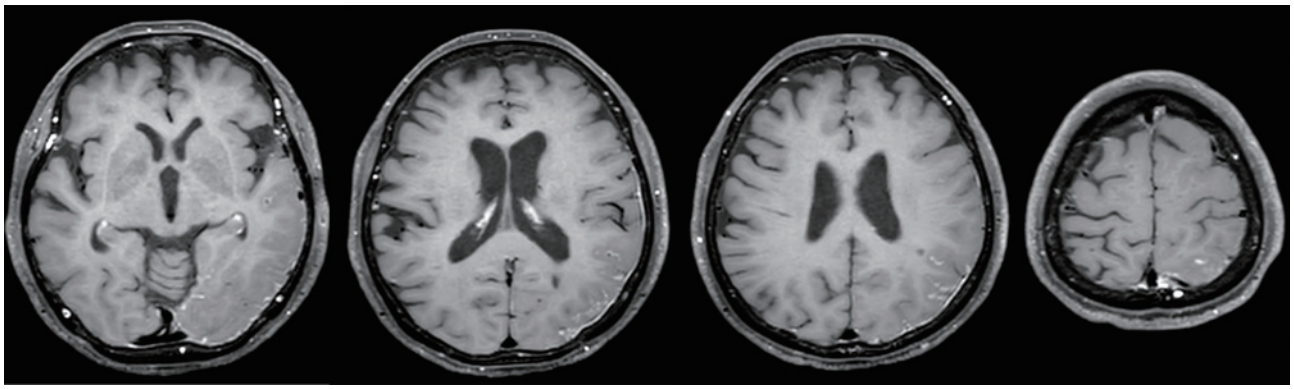

Fig. 3 Contrast-enhanced MRI on day 2 of hospitalization. Abnormal contrast enhancement is observed in the dura and pia mater, consistent with the site of subarachnoid hemorrhage. Enhancement of both the pia-subarachnoid and dura-arachnoid patterns is observed.
MRI: magnetic resonance imaging

it can occur. Compared to non-inflammatory CAA, inflammatory CAA is also associated with a significantly younger age at onset (approximately 7 years younger) and exhibits more extensive white matter abnormalities on imaging, with a predominantly lobar distribution.[9]

ABRA, a rare inflammatory subtype of CAA recognized in 2005, involved transmural or intramural inflammation of amyloid-laden blood vessels with surrounding microglia and macrophages. It typically presents at a mean age of 67, with symptoms such as altered mental status (75%), headache (32%), and seizures (32%).[4,10-13]

In our patient's case, granulomatous changes with vascular wall destruction were observed pathologically, leading to a diagnosis of ABRA. This represents a very rare in-

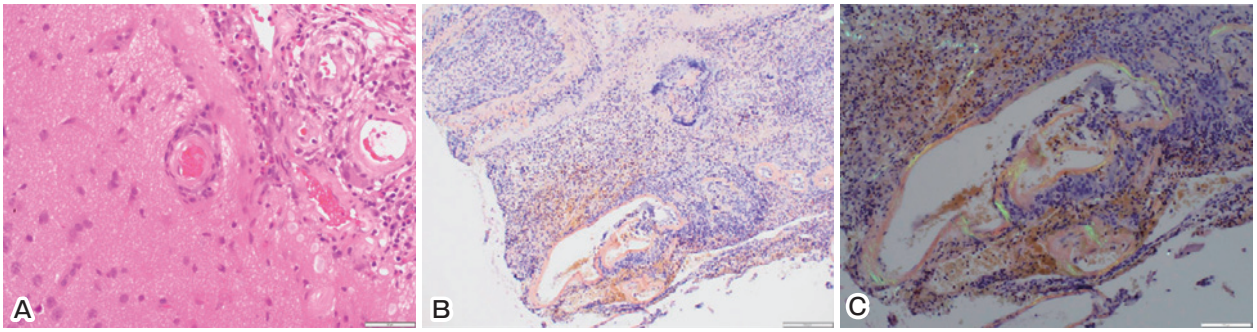

Fig. 4 Histopathology of cortical tissue sample. A: HE staining (original magnification ×40) of brain tissue containing vascular structures reveals intimal thickening, narrowing of the lumen, neutrophil infiltration, and fibrinoid necrosis in small to medium-sized blood vessels. Degeneration of brain tissue due to ischemia and inflammation spreading to veins with giant cells are also noted. B: Direct fast scarlet (DFS) staining (original magnification ×10) shows red-stained amyloid deposits in blood vessel walls. C: Under polarized light (original magnification ×20), green birefringence is observed using DFS staining, indicating amyloid deposits in blood vessel walls.
HE: hematoxylin and eosin

stance of ABRA presenting with SAH. Inflammatory CAA typically presents with symptoms such as headache, cognitive impairment, focal neurological deficits, and occasionally epileptic seizures or encephalopathy.[14,15] Common radiological findings include parenchymal or leptomeningeal gadolinium enhancement, cortical superficial siderosis, and lobar hemorrhage. The primary differential diagnoses to exclude are primary angiitis of the central nervous system (PACNS) and tumors, particularly primary central nervous system lymphoma (PCNSL).[12,16]

The Boston Criteria are widely utilized in evaluating patients for CAA, incorporating clinical, pathological, and radiographic parameters to assess its likelihood. Although brain biopsy is often considered the gold standard for definitive diagnosis, it is an invasive procedure associated with complications in approximately 18% of cases, including fever, neurological deficits, and brain abscesses.[17] Consequently, brain biopsy should be reserved for cases with compelling clinical symptoms and imaging findings consistent with the Boston Criteria while weighing the risks and benefits of this invasive approach.

PACNS is defined as a vasculitis confined to the CNS, unassociated with systemic illness, and confirmed through histopathological or angiographic evidence. PACNS typically presents with a gradual onset of headache, mental status alterations (e.g., confusion, disorientation, or dementia), and focal neurological deficits, including hemiparesis, aphasia, amnesia, visual disturbances, and cranial nerve palsies. Unlike CAA or ABRA, PACNS primarily affects younger stroke patients without conventional cerebrovascular risk factors. While the clinical features are highly variable, PACNS may present with transient ischemic attacks, large cerebral infarcts, multi-infarct states, SAH, or intraparenchymal hemorrhage.[18-20]

PCNSL is another critical differential diagnosis, characterized by its malignant and rapidly progressive course. Focal neurological deficits occur in approximately 70% of patients, with imaging typically demonstrating uniform contrast enhancement on CT and MRI. However, atypical presentations, including hemorrhage, calcification, cystic changes, or necrosis, may occasionally be observed.[21,22] Given the nonspecific clinical and neuroradiological features of PCNSL, histopathological confirmation is essential for accurate diagnosis. While timely initiation of immunosuppressive treatment is crucial for managing PCNSL, avoiding unnecessary immunosuppressant use is paramount to minimizing potential harm.[23]

Conclusion

We report a case in which ABRA was definitively diagnosed by brain biopsy in a patient with SAH of unknown origin, with symptom improvement following early steroid treatment.

In summary, CAA is a potential differential diagnosis for unexplained SAH, and brain biopsy may aid in establishing a definitive diagnosis.

Informed Consent

Informed consent for publication was obtained from the patient.

Conflicts of Interest Disclosure

All authors have no conflict of interest. The authors, who are members of the Japan Neurosurgical Society, have submitted the self-reported Conflicts of Interest Disclosure Statement Forms online.

References

1) Ii Y, Tomimoto H. Recent advances in cerebral amyloid angiopa-

thy. Neurotherapeutics. 2022;39(3):187-91. doi: 10.1007/s13311-022-01147-4
2) Taniguchi Y, Kitamura T, Inoue H, et al. Amyloid β related angiitis without marked leukoencephalopathy. Rinsho Shinkeigaku. 2019;59(12):814-7. doi: 10.5692/clinicalneurol.cn-001278
3) Eng JA, Frosch MP, Choi K, et al. Clinical manifestations of cerebral amyloid angiopathy-related inflammation. Ann Neurol. 2004;55(2):250-6. doi: 10.1002/ana.10810
4) Scolding NJ, Joseph F, Kirby PA, et al. Aβ-related angiitis: primary angiitis of the central nervous system associated with cerebral amyloid angiopathy. Brain. 2005;128(3):500-15. doi: 10.1093/brain/awh379
5) Danve A, Grafe M, Deodhar A. Amyloid beta-related angiitis: a case report and comprehensive review of the literature of 94 cases. Semin Arthritis Rheum. 2014;44(1):86-92. doi: 10.1016/j.semarthrit.2013.12.007
6) Wilson D, Hostettler IC, Ambler G, et al. Convexity subarachnoid haemorrhage has a high risk of intracerebral haemorrhage in suspected cerebral amyloid angiopathy. J Neurol. 2017;264(4):664-73. doi: 10.1007/s00415-017-8398-y
7) Hostettler IC, Wilson D, Fiebelkorn CA, et al. Risk of intracranial haemorrhage and ischaemic stroke after convexity subarachnoid haemorrhage in cerebral amyloid angiopathy: international individual patient data pooled analysis. J Neurol. 2022;269(3):1427-38. doi: 10.1007/s00415-021-10706-3
8) Block F, Dafotakis M. Cerebral amyloid angiopathy in stroke medicine. Dtsch Ärztebl Int. 2017;114(3):37-42. doi: 10.3238/arztebl.2017.0037
9) Nouh A, Borys E, Gierut AK, et al. Amyloid-beta related angiitis of the central nervous system: case report and topic review. Front Neurol. 2014;5:13. doi: 10.3389/fneur.2014.00013
10) Ekkert A, Šaulytė M, Jatužis D. Inflammatory disorders of the central nervous system vessels: narrative review. Medicina (Kaunas). 2022;58(10):1446. doi: 10.3390/medicina58101446
11) Wu JJ, Yao M, Ni J. Cerebral amyloid angiopathy-related inflammation: current status and future implications. Chin Med J (Engl). 2021;134(6):646-54. doi: 10.1097/CM9.0000000000001427
12) Salvarani C, Morris JM, Giannini C, et al. Imaging findings of cerebral amyloid angiopathy, Aβ-related angiitis (ABRA), and cerebral amyloid angiopathy-related inflammation: a single-institution 25-year experience. Medicine (Baltimore). 2016;95(20):e3613. doi: 10.1097/MD.0000000000003613
13) Tanner JA, Richie MB, Cadwell CR, et al. Amyloid-β related angiitis presenting as eosinophilic meningitis: a case report. BMC Neurol. 2022;22(1):116. doi: 10.1186/s12883-022-02638-w
14) Antolini L, DiFrancesco JC, Zedde M, et al. Spontaneous ARIA-like events in cerebral amyloid angiopathy-related inflammation: a multicenter prospective longitudinal cohort study. Neurology. 2021;97(18):e1809-22. doi: 10.1212/WNL.0000000000012750
15) Martín-Jiménez P, Sánchez-Tornero M, Llamas-Velasco S, et al. Cerebral amyloid angiopathy-related inflammation: clinical features and treatment response in a case series. Neurologia (Engl Ed). 2023;38(8):550-9. doi: 10.1016/j.nrl.2020.12.008.
16) Ronsin S, Deiana G, Geraldo AF, et al. Pseudotumoral presentation of cerebral amyloid angiopathy-related inflammation. Neurology. 2016;86(10):912-9. doi: 10.1212/WNL.0000000000002444
17) de Boysson H, Zuber M, Naggara O, et al. Primary angiitis of the central nervous system: description of the first fifty-two adults enrolled in the French cohort of patients with primary vasculitis of the central nervous system. Arthritis Rheumatol. 2014;66(5):1315-26. doi: 10.1002/art.38340
18) Calabrese LH, Mallek JA. Primary angiitis of the central nervous system: report of 8 new cases, review of the literature, and proposal for diagnostic criteria. Medicine (Baltimore). 1988;67(1):20-39. doi: 10.1097/00005792-198701000-00002
19) Calabrese LH, Furlan AJ, Gragg LA, et al. Primary angiitis of the central nervous system: diagnostic criteria and clinical approach. Cleve Clin J Med. 1992;59(3):293-306. doi: 10.3949/ccjm.59.3.293
20) Salvarani C, Brown RD Jr, Calamia KT, et al. Primary central nervous system vasculitis: analysis of 101 patients. Ann Neurol. 2007;62(5):442-51. doi: 10.1002/ana.21226
21) Morell AA, Shah AH, Cavallo C, et al. Diagnosis of primary central nervous system lymphoma: a systematic review of the utility of CSF screening and the role of early brain biopsy. Neurooncol Pract. 2019;6(6):415-23. doi: 10.1093/nop/npz015
22) Lin X, Khan IRA, Seet YHC, et al. Atypical radiological findings of primary central nervous system lymphoma. Neuroradiology. 2020;62(6):669-76. doi: 10.1007/s00234-020-02377-0
23) Chwalisz BK. Cerebral amyloid angiopathy and related inflammatory disorders. J Neurol Sci. 2021;424:117425. doi: 10.1016/j.jns.2021.117425

Corresponding author: Noritaka Aihara, MD.
Department of Neurosurgery, Nagoya City University East Medical Center, 1-2-23 Wakamizu, Chikusa-ku, Nagoya, Aichi 464-8547, Japan.
e-mail: aihara@med.nagoya-cu.ac.jp