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Case Report

Cerebral amyloid-β-related angiitis without cerebral microbleeds in a patient with subarachnoid hemorrhage

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ABSTRACT

Amyloid-β-related angiitis (ABRA), a subtype of cerebral amyloid angiopathy (CAA), is vasculitis occurring in relation to amyloid-β (Aβ) deposition in the walls of intracranial blood vessels. ABRA is presumed to be caused by some immune response to the deposited Aβ. An 81-year-old man on oral anticoagulant therapy complained of headache, nausea, and difficulty with standing after a head injury. Head computed tomography revealed subcortical bleeding in the right temporoparietal lobe, and 3 days after admission, magnetic resonance imaging (MRI) showed subarachnoid hemorrhage (SAH) around the hematoma. Cerebral microbleeds, a characteristic of CAA, were not detected on MRI. On worsening of his symptoms, intracranial brain biopsy and hematoma removal were performed. Intraoperative rapid diagnosis with a frozen section suspected vasculitis, which enabled the prompt initiation of steroid therapy. He was pathologically diagnosed with ABRA (granulomatous angiitis) using a formalin-fixed paraffin-embedded section. Vasculitis was prominent around blood vessels in the pia matter covering the cerebrum. In this case, the inflammatory cells seemed to appear via the subarachnoid space following cerebral hemorrhage and SAH. ABRA seemed to be developed by intracranial hemorrhage in this case.
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1. Introduction

Cerebral amyloid angiopathy (CAA) is a cerebral microvascular lesion that results from progressive amyloid-β (Aβ) deposition in the small- to medium-sized intracranial vascular walls and makes blood vessels vulnerable, causing subcortical bleeding in the elderly population [1]. CAA is radiologically characterized by cerebral microbleeds, which show spotty low signals on T2*-weighted imaging of the cerebral cortex [2]. CAA is sometimes accompanied by infiltration of inflammatory cells such as macrophages and rarely exhibits Aβ-related angiitis (ABRA). A patient with ABRA clinically presents with various symptoms, e.g., disturbance of consciousness, acute to subacute cognitive impairment, headaches, focal neurologic deficits, seizures, and hallucinations [3]. ABRA is presumed to be caused by some immune response to the deposited Aβ, and it responds well to steroid therapy [4]. Here, we present a patient with ABRA diagnosed by brain biopsy wherein it was difficult to diagnose the condition based on the clinical course and radiological findings owing to the lack of cerebral microbleeds.

2. Case report

An 81-year-old man on direct oral anticoagulant (DOAC) therapy (dabigatran; 220 mg/day) for atrial fibrillation (AF) presented to our hospital. He had no past history of hypertension and/or cerebrovascular disease. He suddenly felt anacatesthesia and lightheaded while walking and hit the left side of his face against a utility pole a day before the first visit to our hospital. On returning home after the incident, he complained of headache, nausea, and difficulty with standing. Because the symptoms persisted on the next day, he visited our hospital. His vital signs were as follows: body temperature, 38.3°C and blood pressure, 166/88 mmHg. The neurologic findings showed dysarthria, left spatial neglect, and mild sensory disturbance in the left half of the body. No sign of meningeal irritation was observed. Laboratory data showed no increased inflammatory

Abbreviations: Aβ, amyloid-β; ABRA, amyloid-β-related angiitis; ANCA, antineutrophil cytoplasmic antibody; AF, atrial fibrillation; CAA, cerebral amyloid angiopathy; CT, computed tomography; DOAC, direct oral anticoagulant; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; PACNS, primary angiitis of the central nervous system; SAH, subarachnoid hemorrhage.

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reaction: white blood cell counts, 5800 cells/μl (normal: 3100–9500 cells/μl) and C-reactive protein, <0.3 mg/dl (normal: <0.3 mg/dl). Head computed tomography (CT) revealed subcortical bleeding in the right temporoparietal lobe (Fig. 1A). Clinical and radiological examination revealed cerebral cortex bleeding with DOAC administration, and the patient was initially conservatively treated with an antihypertensive agent (Azilsartan). However, his headache worsened, and magnetic resonance imaging (MRI) showed subarachnoid hemorrhage (SAH) around the hematoma at 3 days after admission (Fig. 1B). Cerebrospinal fluid investigation by lumbar puncture was notable for mild lymphocytic pleocytosis with 38 cells/mm^3 (normal: ≤5/mm^3), immunoglobulin G levels of 53.8 mg/dl (normal: ≤0.73 mg/dl), and elevated protein level of 487 mg/dl (normal: ≤45 mg/dl). In serological studies, autoantibodies, including antinuclear antibody and anti-neutrophil cytoplasmic antibody (ANCA), and anti-viral antibodies, including antibodies against herpes simplex virus and cytomegalovirus, were within normal limits. A metastatic cerebral tumor was not suspected because there were no primary tumors detected on whole body CT. On conducting head CT, the low-density area expanded to the white matter of the right occipital lobe. Contrast-enhanced MRI showed enhancement in the cerebral surface but not in the right occipital white matter lesion (Fig. 1C, D). T2*-weighted images on MRI did not reveal spotty low signals, which are known as microbleeds and characterize CAAs, in the cortex. Accurate clinical and radiological diagnosis was difficult; differential diagnosis covered diverse conditions including tumor, infection, and inflammation. Surgical open brain biopsy and hematoma removal were performed.

Intraoperative rapid diagnosis was performed using a frozen section of the collected specimen. Granulomatous inflammation accompanied by multinucleated giant cells was observed in the pia matter encephali covering cerebrum (Fig. 2A), in which it was particularly remarkable around the blood vessels (Fig. 2B), although some vessels with eosinophilic wall were not accompanied by granulomatous inflammation despite segmented-leukocytes infiltration into the pia mater (Fig. 2C). We suspected this lesion to be meningitis and vasculitis. After intraoperative diagnosis, specimens were collected for histological analysis using formalin-fixed paraffin-embedded sections.

The obtained cerebral biopsy specimens were pathologically examined. Histologically, granulomatous inflammation with foreign body macrophage-like multinucleated giant cells was prominent around blood vessels in the pia mater covering the cerebrum (Fig. 3A). The granulomatous inflammation destroyed the blood vessel wall, indicating granulomatous vasculitis (Fig. 3B, C). Eosinophilic amorphous materials were deposited on the vessel walls, not only on the inflamed vascular walls but also on the uninflamed ones (Fig. 3A, B). Eosinophilic amorphous deposits were stained pale orange by direct fast scarlet staining (Fig. 4A) and showed apple-green birefringence by polarization (Fig. 4B). Immunohistochemically, the deposits were positive for amyloid P component and Aβ (Fig. 4C). The patient was then diagnosed with ABRA. While amyloid deposition was universally present in vascular walls, the associated vasculitis was limited to a subset of afflicted vessels. Vasculitis was almost entirely found in the pia mater, and it was scarcely observed in the vasculatures in the cerebrum. White matter was hardly collected; most of the brain tissue was gray matter, in which senile plaques were clearly visible, especially with Aβ immunostaining (Fig. 3A and 4C). Mild astrocytosis and satellitosis were also observed. Extravasation of erythrocytes in the Virchow–Robin space was not observed.

Because vasculitis was suspected by intraoperative diagnosis using a frozen section, corticosteroid therapy with prednisolone (50 mg/day) was administered. Because the final pathological diagnosis suggested ABRA, administration of prednisolone was continued. His neurological findings, such as dysarthria, left spatial neglect, and mild sensory disturbance of the left half of the body, gradually recovered. The patient was transferred to a rehabilitation hospital during the recovery phase with continued administration of prednisolone (15 mg/day). Thirty-eight days after discharge, however, neurological symptoms got worse, and he was readmitted to our hospital requiring adjustments in pharmacotherapy. After 161 days of hospitalization, he was again rehabilitated with prednisolone administration (15 mg/day).

3. Discussion

Here we presented a case of ABRA, with definitive diagnosis by intracranial brain biopsy, despite the difficulty in clinicoradiological diagnosis because of the lack of microbleeds, which are the characteristic findings of CAAs, with spotty low signals in the cortex on T2*-weighted

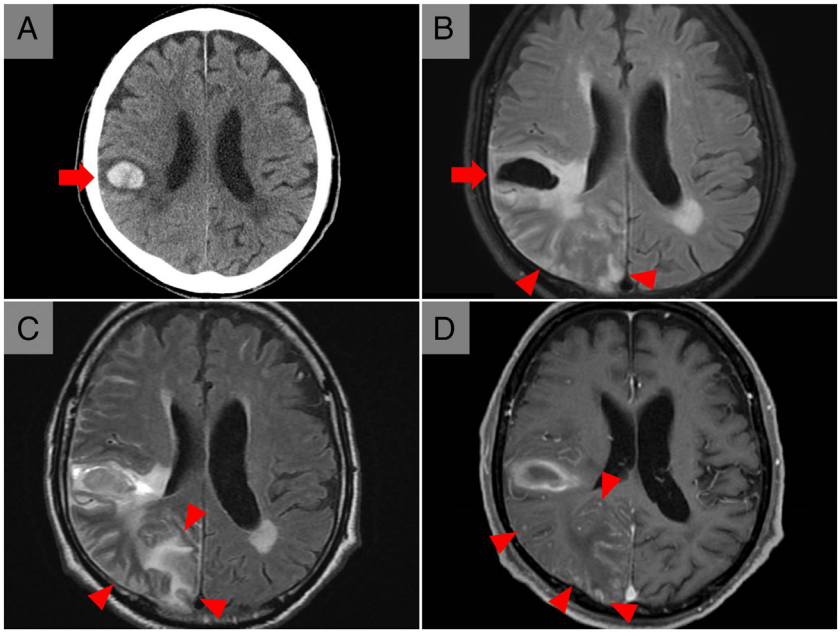

Fig. 1. Radiological images. (A) First day of hospitalization: CT reveal subcortical bleeding in the right temporoparietal lobe (arrow). (B) Three days after admission, FLAIR image on MRI shows hematoma in the right temporoparietal lobe cortex (arrow) and shows areas of increased signals in the sulci (arrowheads). (C) Nine days after admission, FLAIR image shows expansion of the occipital high-signal areas, indicating white matter lesion (arrowheads). (D) No enhancement in the occipital white matter lesion is observed on contrast-enhanced MRI; however, dot-like contrasted lesions are found, especially along the brain surface (arrowheads).

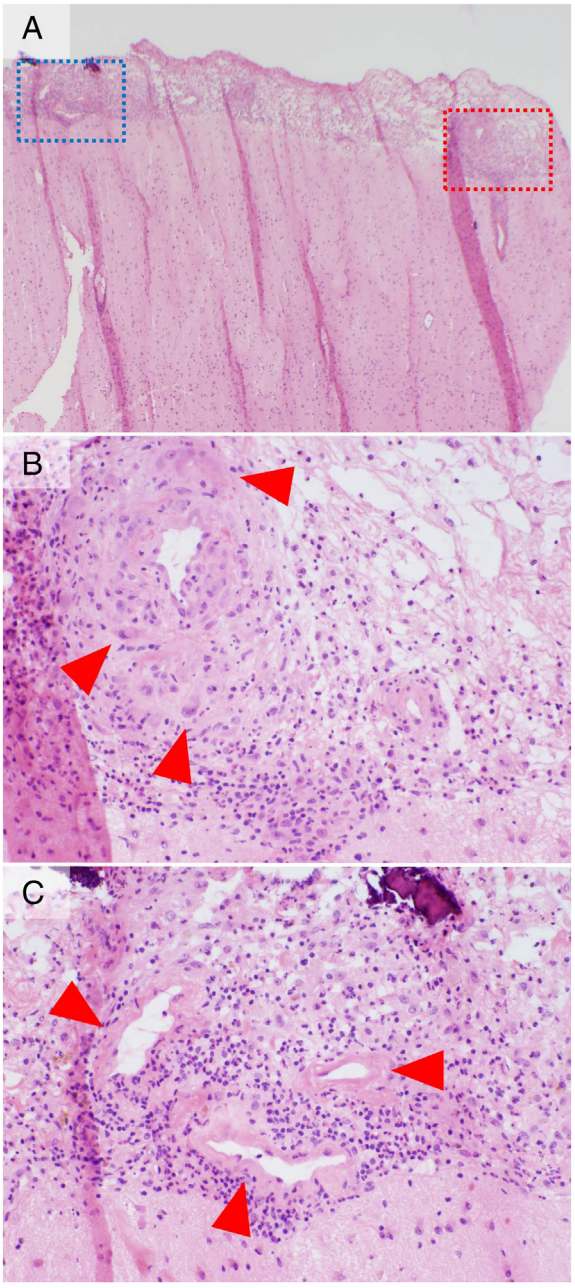

Fig. 2. Frozen-section intraoperative rapid diagnosis (A–C: hematoxylin–eosin staining). (A) Granulomatous inflammation is observed in the pia mater encephali covering the cerebrum (an area surrounded by red dotted line indicates an area of B, and an area surrounded by blue dotted line indicates that of C). (B) Granulomatous inflammation is particularly remarkable around the blood vessels (arrowheads). (C) Some vessels with eosinophilic walls are not affected by granulomatous inflammation despite segmented leukocytes being infiltrated into the pia mater (arrowheads).

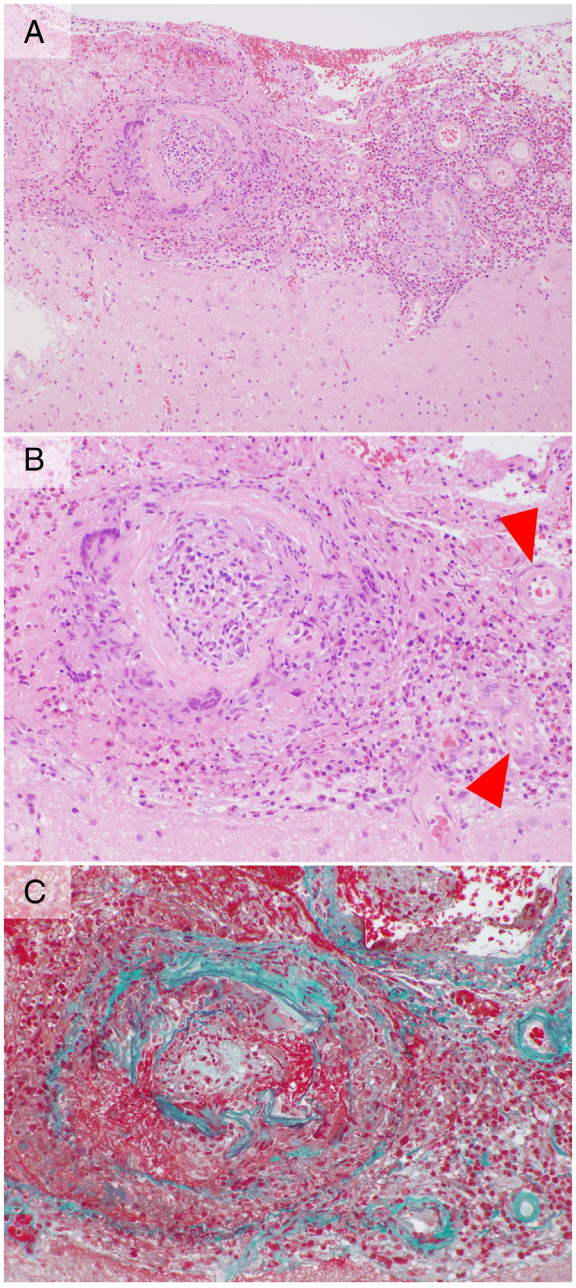

Fig. 3. Histological analysis of the brain biopsy specimen of a formalin-fixed paraffin-embedded tissue (A, B: hematoxylin–eosin staining; C: Elastica-Masson staining). (A) Inflammatory cells infiltrate into the pia mater covering the cerebrum, and granulomatous inflammation is also observed around some blood vessels in the pia mater. (B) Granulomatous inflammation is found around the blood vessels, although some vessels with eosinophilic wall are not accompanied by inflammation (arrowheads). (C) Granulomatous inflammation destroyed the vascular wall.

imaging. The patient was primarily diagnosed with cerebral subcortical bleeding and was on DOAC therapy and showed SAH. However, elevation of protein levels in the cerebrospinal fluid, MRI findings of expansion of white matter lesion predominantly in occipital lobe, and restricted enhancement in brain surface were unexplainable only with cerebral cortex bleeding under DOAC administration and SAH. This prompted us to conduct a surgical open brain biopsy, leading to definitive diagnosis.

Primary angiitis of the central nervous system (PACNS), including ABPA, is vasculitis occurring only in blood vessels of the central nervous system without systemic vasculitis, causing symptoms such as headache, paralysis, and higher brain dysfunction [5,6]. Because PACNS shows various findings on MRI, such as bilateral multiple cerebral infarction, cerebral parenchymal or meningeal contrast enhancement, cerebral hemorrhage, tumor-like occupied lesion, and nonspecific high signal in fluid-attenuated inversion recovery (FLAIR) image [6,7], it is challenging to correctly diagnose it radiologically. Histologically, it is classified as granulomatous vasculitis, lymphocytic vasculitis, and necrotizing vasculitis [7]. In contrast, CAA is a degenerative vascular disorder that is caused by Aβ deposition on the vascular walls of the intracranium. CAA causes not only cerebral hemorrhage but also cerebral infarction, white matter encephalopathy, transient neurological symptoms, and CAA-related inflammation [6]. Although it is very rare, central nervous system vasculitis can develop in association with CAA, known as ABRA, which pathologically shows granulomatous vasculitis

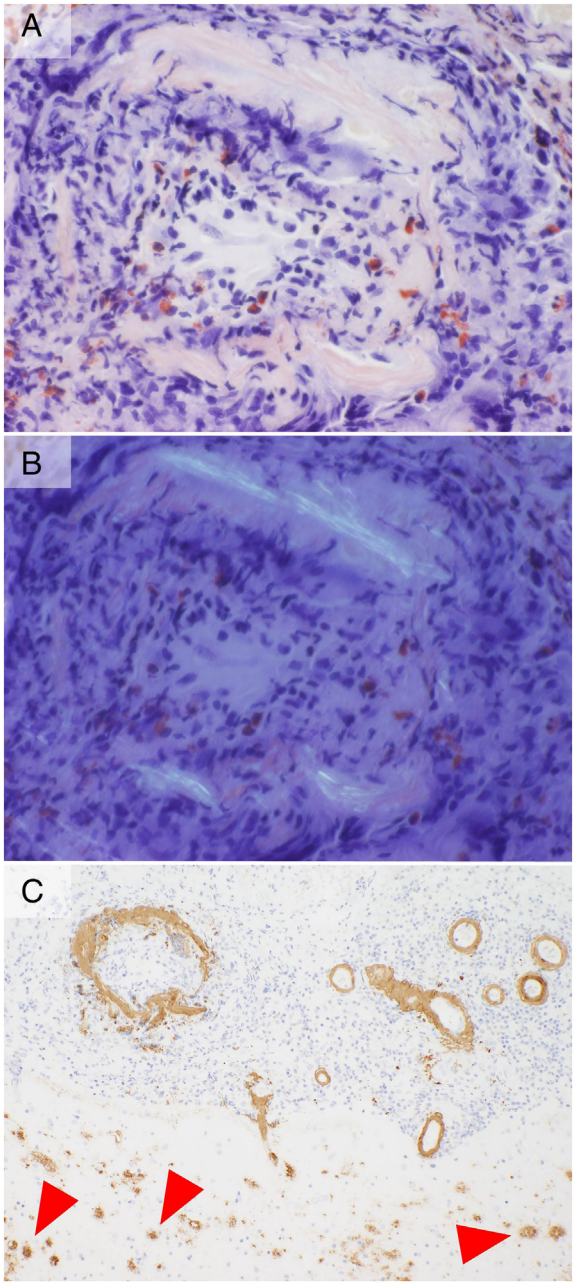

Fig. 4. Investigation of the amyloid deposition. (A) Eosinophilic amorphous deposits are stained pale orange by direct fast scarlet (DFS) staining. (B) DFS-stained deposits show apple-green birefringence by polarization. (C) These deposits to vascular walls show positivity for amyloid-β immunostaining. Senile plaques are also seen (arrowheads).

[6,9]. However, these symptoms and radiological imaging are nonspecific, and noninvasive definitive diagnosis is challenging. Brain biopsy is rarely performed for the diagnosis of non-neoplastic neurological diseases; however, it is essential for the correct diagnosis of PACNS, including ABRA, and also helps exclude other diseases, such as infections, malignancies, and other syndromes [8]. In this case, granulomatous inflammation accompanied by multinucleated giant cells around the blood vessel was observed on intraoperative diagnosis using a frozen section, by which we could suspect vasculitis. Thus, we could achieve early induction of steroid therapy.

The utility of intraoperative diagnosis of surgical open brain biopsy specimen for the diagnosis of ABRA is never studied and remains unclear. In this study, vasculitis was suspected by intraoperative diagnosis, which contributed to early treatment. However, it was difficult to confirm ABRA by intraoperative diagnosis alone. On a retrospective review of the specimen, we suspected an acidophilic vascular wall, as observed in CAA. However, if we suspect all such vessels to be CAA, the false-positive rate may increase. There is no fundamental difference in the treatment of PACNS and ABRA during the early postoperative period [3,6]. Pathologists are responsible for suspecting vasculitis during intraoperative diagnosis in such cases.

Our patient was diagnosed with ABRA because it pathologically shows granulomatous vasculitis accompanied by Aβ deposition on the vascular wall, although microbleeds, reflecting hemosiderin deposition, and punctiform low signal regions distributed in the cortex were not observed. The patient was primarily admitted to the hospital with cerebral hemorrhage accompanied by head trauma and was on DOAC administration for AF. Considering the floating feeling and lightheadedness just before the head injury, the possibility of CAA could not be denied; however, other CAA symptoms were unclear. Based on these points, we suspected CAA without CAA-related microhemorrhage.

The pathogenesis of CAA includes the deposition of Aβ caused by the failure of Aβ excretion through the vessel wall, and that of ABRA includes the induction of inflammation accompanying the deposition of Aβ in the vascular wall as an immunological mechanism [3]. In this case, a blood–brain barrier failure was suspected as a result of cerebral hemorrhage, making it possible for the inflammatory cells to move out to the subarachnoid space, leading to the development of vasculitis. In addition, Aβ deposition was widely observed in the brain and meninges, while almost all of vasculitis was found in blood vessels within the pia mater of the brain surface. The distribution of vasculitis seems to be explainable by the fact that the inflammatory cells moved into the subarachnoid space accompanying traumatic subarachnoid hemorrhage. ABRA is commonly found in the occipital lobe [10], in conformity with the fact that inflammatory cells after bleeding tend to gather in the posterior region of intracranium in the supine position. In contrast, because all ABRA patients showing microbleeds do not show vasculitis despite the microhemorrhage, it is insufficient to explain the pathogenesis of ABRA only by the movement of the inflammatory cells after bleeding. On the other hand, Aβ tends to involve the superficial and leptomeningeal vessels in occipital to temporal lobe [3,11]. Distribution of Aβ deposition also seemed to be related to that of the affected vessels in ABRA. In the future, studies including a higher number of patients with subclinical CAA and ABRA focusing on the mechanisms such as the immunological state are expected.

In summary, we have presented a case of ABRA, which was suspected to be vasculitis after intraoperative rapid diagnosis using a biopsy specimen of the brain surface, leading to the early induction of steroid therapy. Microbleeds were not detected by T2*-weighted imaging in this case, presumably because of the early detection of ABRA as a subtype of CAA as the patient was admitted for a head injury and was on DOAC therapy. ABRA seemed to be developed by intracranial hemorrhage in this case.

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Declaration of conflicting interests

The authors declare no potential conflicts of interests with respect to the research, authorship, and/or publication of this article.

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