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Title: Amyloid-β related angiitis: a report of two cases with unusual presentations

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Abstract

Amyloid-β related angiitis (ABRA) is a rare complication of cerebral amyloid angiopathy in which amyloid-β (Aβ) deposition in the leptomeningeal and cortical vessels is associated with vasculitis characterized by transmural lymphohistiocytic, often granulomatous, inflammation. Patients usually present with acute to subacute cognitive dysfunction, headaches, and focal neurologic deficits. We report two cases of ABRA with unusual clinical presentations, including one case with fatal cerebral edema leading to herniation and Duret hemorrhages, and another associated with both lobar and deep parenchymal hemorrhages with intraventricular extension as well as hypercoagulability. Both showed extensive vascular Aβ deposition associated with granulomatous angiitis and foreign-body type multinucleated giant cells. One of our cases demonstrates the likely effects of ABRA on impairment of fluid regulation leading to severe cerebral edema, which is an uncommon manifestation of ABRA, and may be a result of impaired blood-brain barrier function or malfunction of the neurovascular unit.

1. Introduction

Cerebral amyloid angiopathy (CAA) is a cerebral microvascular lesion which most commonly results from progressive amyloid-β (Aβ) deposition in the walls of small- to medium-sized blood vessels, preferentially within the cortex and leptomeninges [1,2]. CAA is reported to occur in approximately 20-40% of the non-demented elderly population, with increased prevalence with age, and is strongly associated with dementia. CAA is seen to some degree in the majority of patients with Alzheimer disease [3]. Accounting for approximately 15% of ICH in the elderly, CAA is a significant cause of intracerebral hemorrhage (ICH), and is also associated with ischemic lesions [1,4,5]. In severe CAA there is often development of CAA-associated microangiopathies such as "lumen within a lumen" appearance, inflammation, vascular scarring, fibrinoid necrosis, and microaneurysm formation, the latter two associated with ICH [1].

Amyloid β-related angiitis (ABRA) is an extreme form of CAA-associated inflammation in which amyloid laden vessels demonstrate true vasculitis with transmural, often granulomatous inflammation, and damage of the vessel wall [1]. Rather than dementia and intracerebral hemorrhage, which are common presentations of CAA, ABRA occurs in a small subset of CAA patients who typically present with altered mental status, acute to subacute cognitive decline, behavioral changes, headaches, focal neurological deficits, seizures, or hallucinations [6–8]. ABRA patients typically present at a younger age, with a mean age of 67, compared to CAA (mean age 76 years), but older than patients with primary angiitis of the central nervous system (PACNS) with a mean age of 45 years [6]. PACNS is a rare idiopathic vasculitis restricted to the brain and spinal cord which can have histologic features similar to ABRA except without Aβ deposition [6]

The majority of patients with ABRA have abnormal but nonspecific cerebrospinal fluid (CSF) findings, most often with mild increases in protein and pleocytosis, mostly commonly lymphocytic [6,7]. A variety of imaging findings have been found in ABRA including white matter changes, sometimes with mass-like

abnormalities, macro- and microhemorrhages, ischemic changes, leukoencephalopathy and leptomeningeal contrast enhancement [9,10]. Herein we review two unusual presentations of ABRA including one patient who progressed to fatal cerebral edema, which has not previously been reported to our knowledge.

2. Case reports

2.1. Case 1

A 71-year old female with a prior history of quadriplegia due to severe spinal stenosis, osteoarthritis and hypertension presented with one week of headaches and generalized weakness, and one day of altered mental status. She was found to be lethargic with an elevated blood pressure of 191/104 mmHg. Non-contrast head computed tomography (CT) demonstrated bilateral, asymmetric cerebral edema in the frontal and temporal lobes (Fig. 1A). She was admitted to the intensive care unit (ICU) with a working diagnosis of hypertensive encephalopathy, infectious encephalitis or acute disseminated encephalomyelitis (ADEM). Treatment was started with antihypertensive agents and empiric antibiotics and antivirals including vancomycin, ceftriaxone and acyclovir, with the addition of intravenous dexamethasone. Attempted lumbar puncture was unsuccessful.

Magnetic resonance imaging (MRI) demonstrated right greater than left-sided T2/FLAIR subcortical hyperintensities consistent with vasogenic edema (Fig. 1B), along with foci of cortical microhemorrhages on susceptibility weighted imaging (Fig. 1C). Dexamethasone was replaced with high dose intravenous (IV) solumedrol. On hospital day three, the patient rapidly deteriorated, requiring intubation with an emergent head CT demonstrating diffuse cerebral edema. She expired shortly thereafter.

At autopsy, limited to the brain, the 1530-gram brain showed severe cerebral edema with moderate sulcal effacement and suggestion of right transtentorial herniation, evaluation limited by the friability of the tissue, and cerebellar tonsillar herniation with Duret hemorrhages in the pons (Fig. 2A). Microscopic

examination demonstrated many leptomeningeal and cortical vessels with severe CAA, with eosinophilic, congophilic material in their walls (Fig. 2F) that was immunopositive for amyloid-β40 (Aβ40) (Fig. 2E) and Aβ42, some demonstrating a "lumen within a lumen" appearance and fibrinoid necrosis of their walls. Many amyloid laden vessels showed associated granulomatous perivascular and transmural inflammation (Fig. 3C) with lymphocytes, histiocytes, and foreign-body type multinucleated giant cells (Fig. 3D). In the pons, there was acute hemorrhage and scattered hemosiderin laden macrophages as well as amyloid laden vessels and focal perivascular lymphocytic inflammation (Fig. 2B). Occasional cortical vessels were surrounded by hemosiderin-laden macrophages, suggestive of old microhemorrhages, in correlation with imaging findings. Microinfarcts were noted in the right frontal, temporal and parietal cortices. There was no evidence of significant amyloid plaques or neurofibrillary tangles, as demonstrated by Aβ or phospho-tau immunohistochemistry, to suggest changes of early Alzheimer disease. Immunohistochemistry was performed with the following antibodies: Aβ42 (EMD Millipore, rabbit polyclonal, AB5078P), Aβ40 (EMD Millipore, rabbit polyclonal, AB5074P), and phospho-tau (Thermo Fisher, mouse monoclonal, AT8).

2.2. Case 2

A 65-year old man with a history of arthritis and remote history of atrial fibrillation presented to an outside hospital with a several week history of throbbing, bitemporal and retro-orbital headaches. He also complained of mild cognitive slowing, behavioral changes, and difficulty with coordination and spatial recognition, sustaining a fall resulting in rib fractures. CSF obtained by lumbar puncture was notable only for mild pleocytosis of 9 red blood cells and 20 white blood cells (lymphocyte predominant)/mm3 and elevated protein of 82 mg/dL, with a normal glucose of 54 mg/dL and negative cytology and cultures. MRI showed slight diffusion restriction and mild T2/FLAIR hyperintensity in the right parietal lobe (Fig. 1D) compatible with infarct, so he was placed on the anti-platelet agent clopidogrel. Several days after discharge, the patient was admitted for bilateral pulmonary emboli and was subsequently placed on the factor Xa inhibitor rivaroxaban. However, a few days later he developed severe headaches. Non-contrast

CT demonstrated multifocal intracerebral hemorrhages involving the left orbitofrontal region and right caudate head with intraventricular extension (Fig. 1E). He was transferred to the ICU where anticoagulation was discontinued and an inferior vena cava (IVC) filter placed. Although he was also placed on empiric antibiotics for possible brain abscess, extensive work up for infectious and metastatic disease including total-body positron emission tomography (PET) scanning was negative. Cardiac monitoring showed no arrhythmias and multiple transthoracic echocardiograms were largely unremarkable. Cerebral angiogram demonstrated focal vasculopathy in the area of the right parietal lesion but no vascular malformation or imaging findings suggestive of vasculitis. MRI demonstrated gyriform enhancement on post-contrast T1-weighted images consistent with subacute infarct enhancement (Fig. 1F).

A brain biopsy, measuring 1.7 cm in greatest dimension, of the lesional area in the right parietal lobe demonstrated fibrous thickening of the leptomeninges with marked perivascular and transmural granulomatous inflammation with lymphocytes, epithelioid histiocytes, scattered plasma cells, and many multinucleated giant cells centered in the leptomeningeal vessels (Fig. 3A) but also involving vessels of the superficial cortex. Many vessels demonstrated partial to complete obliteration of their lumens and mural eosinophilic hyalinized material positive for Congo red and demonstrating yellow-green birefringence on polarization microscopy (Fig. 3B) as well as immunoreactivity for Aβ40 (Fig. 3E). The adjacent brain tissue showed focal necrosis and marked gliosis with gemistocytic astrocytes. No emboli were identified. Gomori methenamine silver, periodic acid Schiff, Ziehl-Neelsen, and Gram stains were all negative for microorganisms. Some giant cells and histiocytes demonstrated Aβ40 immunoreactivity in their cytoplasm suggestive of ingestion of Aβ40 (Fig. 3F). CD68 highlighted the prominent histiocytic infiltrate and giant cells. The lymphocytic infiltrate was composed predominantly of CD4-positive T-lymphocytes (Fig. 3C) as compared to CD8-positive T-lymphocytes (Fig. 3D). Scattered CD20-positive B-lymphocytes were also present. Immunohistochemistry was performed with the same antibodies as in the first case with the following additional antibodies: CD4 (Cell Marque, rabbit monoclonal, SP35), CD8

(Dako, mouse monoclonal, C8/144B), CD20 (Dako, mouse monoclonal, L26), and CD68 (Dako, mouse monoclonal, PG-M1).

The patient's post-operative course was complicated by recurrent pulmonary emboli despite the presence of the IVC filter, which required right pulmonary artery thrombectomy, as well as subsequent thrombectomy and replacement of his IVC filter. He had no prior personal or family history of blood clots. Extensive hypercoagulability workup was negative, including testing for: dilute Russell viper venom time; cardiolipin and beta-2-glycoprotein antibodies; antithrombin III, protein C, and protein S activity; activated protein C; prothrombin G20210A variant; and complete blood count. Serologic work up including antineutrophil cytoplasmic antibodies (ANCA), rheumatoid factor, and cyclic citrulline antibodies was also negative. After a course of IV solumedrol and cyclophosphamide, he was administered cyclophosphamide every three weeks. Several months after the biopsy, the IVC was removed, and he was placed on low dose heparin. At that time he still had intermittent headaches and bilateral upper extremity tremors but with minimal residual deficits from the intracranial hemorrhage.

3. Discussion

Histopathologically, ABRA is characterized by angiodestructive perivascular and transmural, commonly granulomatous, inflammation of amyloid-laden leptomeningeal and cortical vessels, usually in a background of severe CAA, as in our cases [6]. The infiltrate consists of lymphocytes, predominantly CD4-positive T-cells, epithelioid histiocytes, and often multinucleated giant cells [6,10]. The brain parenchyma can demonstrate activated microglia, gliosis and rarefaction of the white matter. The amyloid can be found within the cytoplasm of multinucleated giant cells on immunohistochemistry for Aβ, as seen in our second patient, and as non-membrane bound collections of amyloid on electron microscopy, suggestive of amyloid phagocytosis [10].

A wide spectrum of imaging findings can be seen in ABRA, including T2-weighted white matter hyperintensities with signal characteristics suggestive of vasogenic edema, microbleeds, and leptomeningeal enhancement [9]. Recently proposed clinicoradiological criteria for the diagnosis of CAA-related inflammation (CAA-ri) have demonstrated that white matter hyperintensities extending to the immediately subcortical white matter, especially if asymmetric, along with cortico-subcortical hemorrhagic lesions are highly specific for CAA-ri [8,11]. In the more recent study, CAA-ri was defined as the presence of mural lymphocytes or perivascular histiocytes, not associated with hemosiderin, in amyloid-laden vessels [11]. These imaging findings are similar to those seen in a subset of patients receiving Aβ immunotherapies, termed amyloid-related imaging abnormalities (ARIA) which encompass signal changes suggestive of vasogenic edema and sulcal effusion as well as hemosiderin deposits from microhemorrhages and cortical superficial siderosis [12]. If we apply the new clinicoradiological criteria to our cases, the first patient would have fulfilled the criteria for probable CAA-ri, but less likely our second patient, underlying the importance of pathologic examination in atypical presentations. Moreover, there has been a report of anaplastic astrocytoma found on biopsy in a patient who met criteria for probable CAA-ri [13].

Although imaging findings suggestive of vasogenic edema are often seen in both ABRA and ARIA, no pathologic correlates have been reported [13]. To our knowledge, our first patient is the first ABRA case of unusually prominent cerebral edema leading to Duret hemorrhages, herniation and death, which is an unexpectedly rapid evolution of ABRA. Hemorrhage or large infarcts that could have accounted for the edema were absent despite the wide distribution of angiitis. Only old microinfarcts and microhemorrhages not in association with inflamed vessels were identified, consistent with the association of CAA with ischemic lesions [1]. The milder inflammation in the first patient compared to the second is likely due to immunosuppressive therapy (the treatment for ADEM, the presumed diagnosis), and ABRA as well as PACNS [8]. Advanced disease at time of presentation and extent of involvement may have been a contributing factor in the failure of therapy in our first patient as the majority of patients with ABRA are

responsive to treatment with immunosuppression [7]. In case series of clinically or biopsy-proven ABRA, approximately 70-80% of treated patients showed at least a partial response to treatment such as high dose corticosteroids, with or without the addition of additional immunosuppressive agents such as cyclophosphamide and methotrexate [4,8]. Removal of what were thought to be mass lesions on imaging has also resulted in clinical improvement [6]. Moreover, it has been shown that mortality is lower in patients with ABRA compared to non-inflammatory CAA even after adjusting for age [7].

The pathogenesis of ABRA is unclear but may involve autoimmunity to Aβ [14,15]. Aβ is commonly detected within the cytoplasm of macrophages and multinucleated giant cells suggesting phagocytosis [6,10,15]. The cerebrospinal concentrations of anti-Aβ autoantibodies have been shown to be elevated during the acute phase of ABRA and decrease in the remission phase [14]. Melzer et al. have demonstrated major histocompatibility complex (MHC) class II-expressing histiocytes in close proximity to CD4-positive T-lymphocytes in ABRA [15]. Although the association with true vasculitis is unclear, perivascular inflammation of amyloid-laden vessels has been associated with the APOE ε4/ε4 genotype [15]. Intriguingly, ARIA is also associated with the APOE ε4 allele [12]. Furthermore, not only imaging but histological findings in ABRA are similar to those seen in a subset of patients who developed meningoencephalitis after receiving Aβ immunotherapy, with decreased parenchymal amyloid deposition but severe CAA and meningeal and perivascular inflammation [6]. The severe edema seen in our first case may be due to vascular leakage associated with "attempted" Aβ removal [12].

Although ABRA patients present less often with ICH compared to CAA [7,9], CAA is postulated to be a significant contributor to anticoagulation related ICH [3]. Anticoagulant therapy is likely to have contributed to the multifocal ICH in our second patient. CAA tends to cause lobar ICH, and the basal ganglia is an unusual location for CAA or CAA-related hemorrhage [1]. Despite an extensive work up, the etiology for hypercoagulability in our second patient was unclear. ANCA-associated vasculitis, vasculitides associated with predominantly IgG autoantibodies against cytoplasmic components of

neutrophils, are associated with a hypercoagulable state [16], but there have been no reported association of hypercoagulability with CAA or ABRA, both of which are restricted to the brain [6]. Moreover, the two phenomena may be unrelated, and his hypercoagulability may simply be attributed to trauma, hospitalization leading to immobility, and major surgery, all known to increase risk for thromboembolic events.

In summary, our cases expand the clinicopathologic spectrum of ABRA. One study has demonstrated a trend toward a longer time from symptom onset to diagnosis compared to non-inflammatory CAA, underlying the difficulties in the diagnosis of ABRA [7]. Prompt diagnosis is of paramount importance given its response to immunosuppressive treatment. Although CAA is prevalent in the elderly population, ABRA is rare and only a subset of those who received Aβ immunotherapy have developed meningoencephalitis or ARIA [4,12]. Given the similarities between these patient groups, further studies on susceptibility to ABRA may also help shed light on the risk factors and mechanisms of side effects of Aβ immunotherapy, several currently undergoing clinical trials.

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Figure Legends

Fig. 1 Case 1. A, Axial non-contrast computed tomography (CT) demonstrating severe asymmetric cerebral edema in bilateral frontal and temporal lobes. B, Axial magnetic resonance imaging showing right greater than left T2/fluid attenuation inversion recovery (FLAIR)-subcortical hyperintensities (arrows), consistent with vasogenic edema, along with foci of cortical microhemorrhages on coronal susceptibility weighted imaging (arrows, C). Case 2. D, Mild right parietal hyperintensity (arrow) with lack of significant underlying white matter involvement on axial FLAIR imaging. E, Axial non-contrast CT demonstrating intraparenchymal hemorrhages in the left orbitofrontal region and right caudate head with intraventricular extension (arrows). F, Subsequent coronal post-contrast T1-weighted multiplanar reconstructed MR image showing gyriform enhancement (arrow) in the right parietal region.

Fig. 2 Case 1. A, The pons shows Duret hemorrhages (arrows) (20x) and scattered hemosiderin laden macrophages as well as focal perivascular chronic inflammation (arrows) (B, 40x). C, Perivascular and transmural granulomatous inflammation of the cortical arterioles (200x) with foreign-body type multinucleated giant cells (arrows) (D, 400x). E, Severe cerebral amyloid angiopathy with "lumen within a lumen" appearance (arrow) on Aβ40 immunohistochemistry (100x). Note the relative paucity of Aβ40-immunoreactive senile plaques (arrowhead), which was also noted on Aβ42-immunostained sections (not shown). Lymphohistiocytic inflammation and fragmentation of amyloid laden vessels are seen on Congo red stain (F, 200x).

Fig. 3 Case 2. A, Meningeal vessels with florid perivascular and transmural granulomatous inflammation with foreign-body type multinucleated giant cells, with vessels showing luminal thrombosis and containing hyalinized eosinophilic material in their walls (arrow) (100x) that demonstrates yellow-green birefringence on polarization when stained with Congo red (B, 400x). C, Immunohistochemistry demonstrates that the lymphocytic infiltrate is predominantly composed of CD4-positive T-lymphocytes (100x) although scattered CD8-positive T-lymphocytes are also present (D, 100x). E, Cortical vessel, immunoreactive for Aβ40, infiltrated by epithelioid histiocytes with disruption of the vessel wall (arrow) (400x). F, Multinucleated giant cells containing cytoplasmic Aβ40 (arrow) (200x).
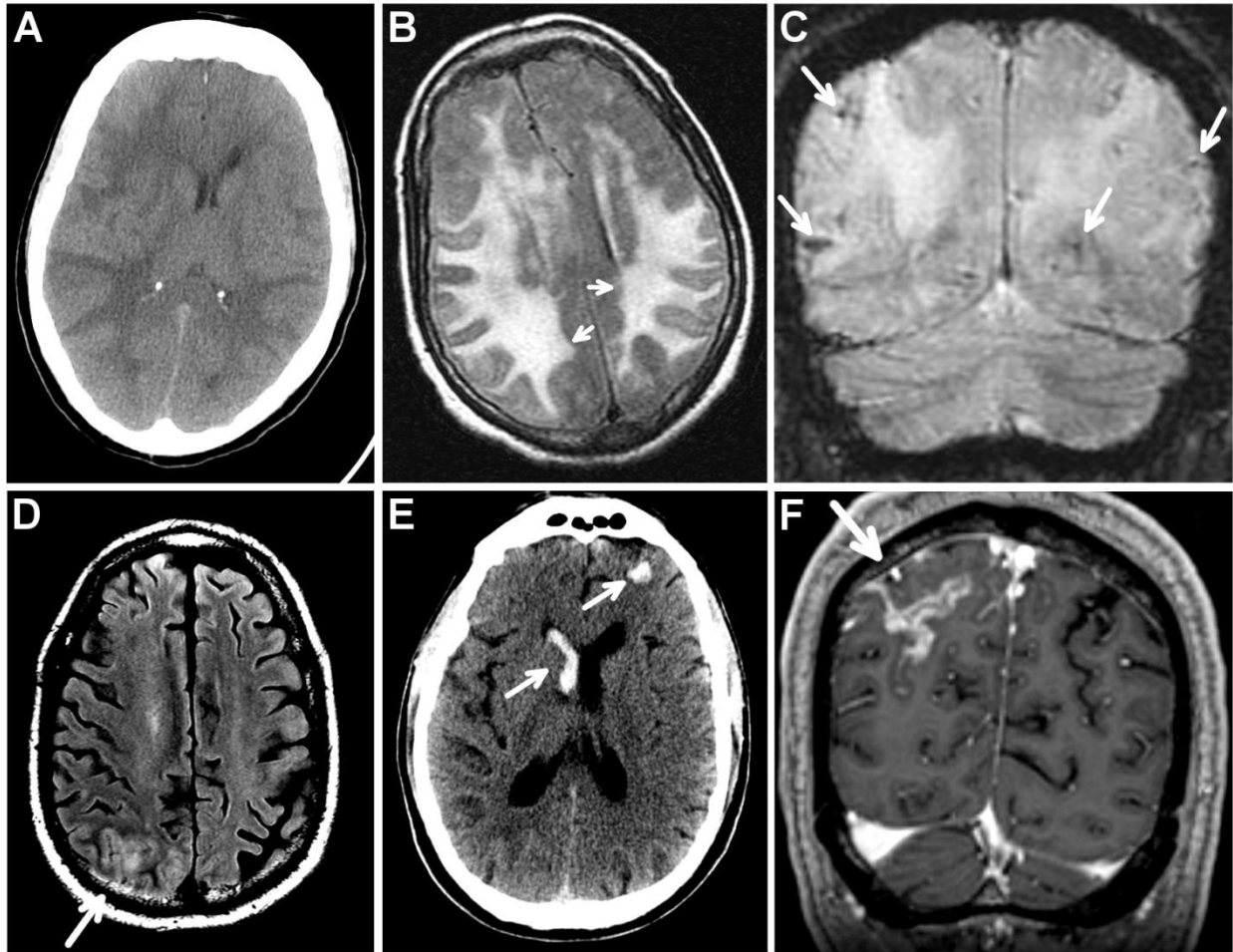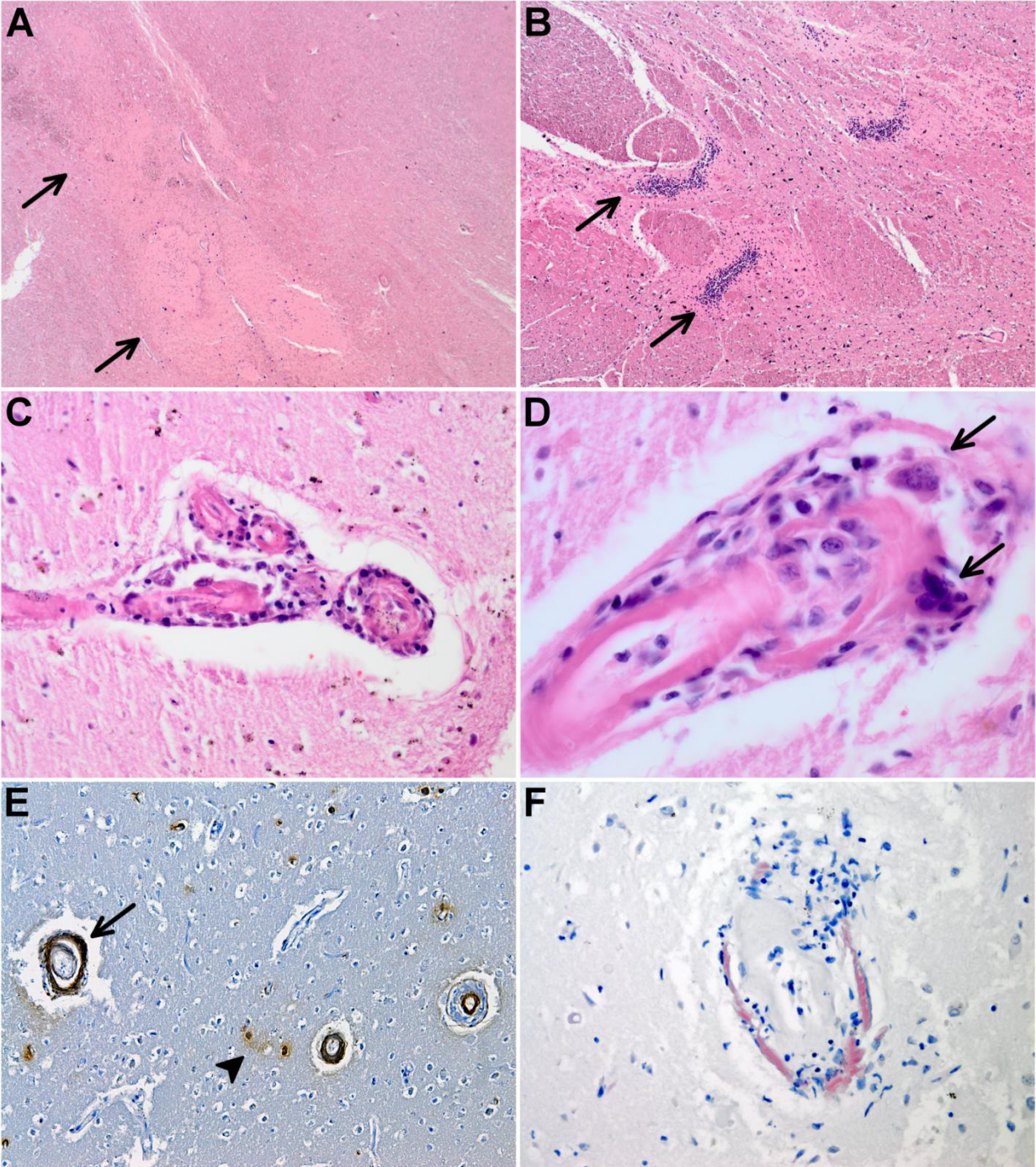
Fig. 1

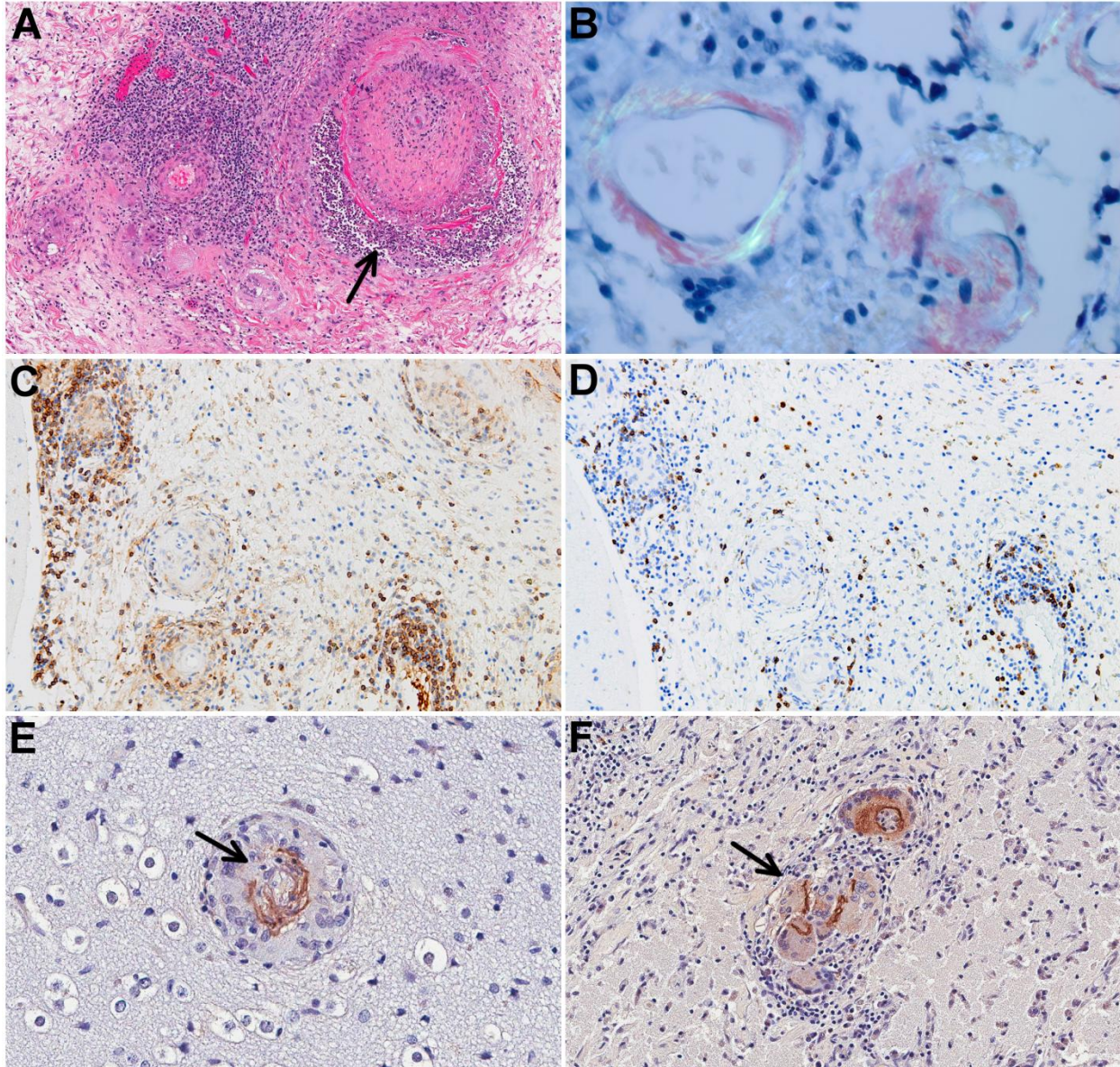**Fig. 2**

Fig. 3