Atypical Arteritis in Internal Carotid Arteries: A Novel Concept of Isolated Internal Carotid Arteritis

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ABSTRACT

We presented a 38-year-old woman suffering from acute cerebral infarction due to arteritis limited to bilateral internal carotid arteries without a condition of giant cell arteritis or granulomatosis with polyangitis. Our case is unprecedented and characterized by a young woman with wall enhancement in the internal carotid arteries on contrast-enhanced magnetic resonance imaging (MRI), therapeutic effects of steroids, and positive status for human leucocyte antigen-B39, -B51 and -DR4. These disease characteristics were not in accordance with existing diagnostic criteria of vasculitis, such as Takayasu's arteritis, giant cell arteritis, granulomatosis with polyangiitis, and Behcet's disease. We suggested consideration of a novel "isolated internal carotid arteritis" disease concept.

Key words arteritis; carotid artery; internal; magnetic resonance imaging; vasculitis

Here, we report a case of arteritis that was limited to the internal carotid artery (ICA), presenting a challenge to existing disease concepts. The first International Chapel Hill Consensus Conference on the Nomenclature of Systemic Vasculitides (CHCC) proposed names and definitions for the most common forms of vasculitis in 1994, and these were then revised at the second International CHCC in 2012.[1] Although atypical cases exist, no cases of arteritis limited to the ICA have been reported. The present case suffered repeated strokes within a short period, and contrast-enhanced magnetic resonance imaging (MRI) revealed wall enhancement in bilateral ICAs. Subsequent administration of prednisolone and antithrombotic therapy successfully ameliorated the clinical conditions.

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Abbreviations: ACA, anterior cerebral artery; CCA, common carotid artery; CHCC, Chapel Hill Consensus Conference; CT, computed tomography; ESR, erythrocyte sedimentation rates; GCA, giant cell arteritis; GPA, granulomatosis with polyangiitis; HLA, human leucocyte antigen; ICA, internal carotid artery; IMP-SPECT, iodoamphetamine single photon emission computed tomography; LV-GCA, large-vessel giant cell arteritis; MCA, middle cerebral artery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PR3-ANCA, proteinase 3-antineutrophil cytoplasmic antibody; STA, superficial temporal artery; TA, temporal arteritis; TAK, Takayasu's arteritis

PATIENT REPORT

A 38-year-old woman presented with pain in the extremities and fluctuating left-sided weakness in the beginning of August 2011. At the end of August, she presented with right-sided weakness and was admitted to our hospital. She had no past medical history and was not taking any prescription medications. Family history pertaining to her mother revealed high blood pressure and pertaining to her father revealed depression. Her blood pressure was 154/108mmHg and her body temperature was 37.2 °C. Physical examinations revealed tenderness in both arms, although no arterial bruits or prominent temporal arteries were evident. Neurological examinations showed impaired consciousness (Glasgow Coma Score, E3V4M6), left hemispatial neglect, ocular deviation to the right, left supranuclear facial palsy, dysarthria and breathy voice, left flaccid hemiplegia, right mild hemiparesis, left deep and mild superficial hypoesthesia with dysesthesia of the left side of the body, hyperactive tendon reflexes in the right upper and lower limbs, and a right Babinski's sign. Urine testing yielded normal results, whereas laboratory data revealed elevated leukocyte counts (9800 cells/μL), erythrocyte sedimentation rates (ESR; 45 mm/h), C-reactive protein levels (0.32 mg/dl) and CH50 titers (50 U/mL). Tests of blood coagulation and fibrinolysis yielded normal results. However, serotyping of human leucocyte antigen (HLA) class I and II revealed that the patient was positive for A2, A24, B39, B51, DR4 and DR11, and tests for serum autoantibodies, including cytoplasmic and perinuclear anti-neutrophil cytoplasmic antibodies, were all negative. Levels of vitamins, amino acids, alpha-galactosidase, tumor markers, and markers of infection, including tuberculosis, were all normal. Cerebrospinal fluid testing also revealed normal results.

Onset at a young age and absence of risk factors indicated the presence of an uncommon cause of stroke. On admission, magnetic resonance angiography (MRA;

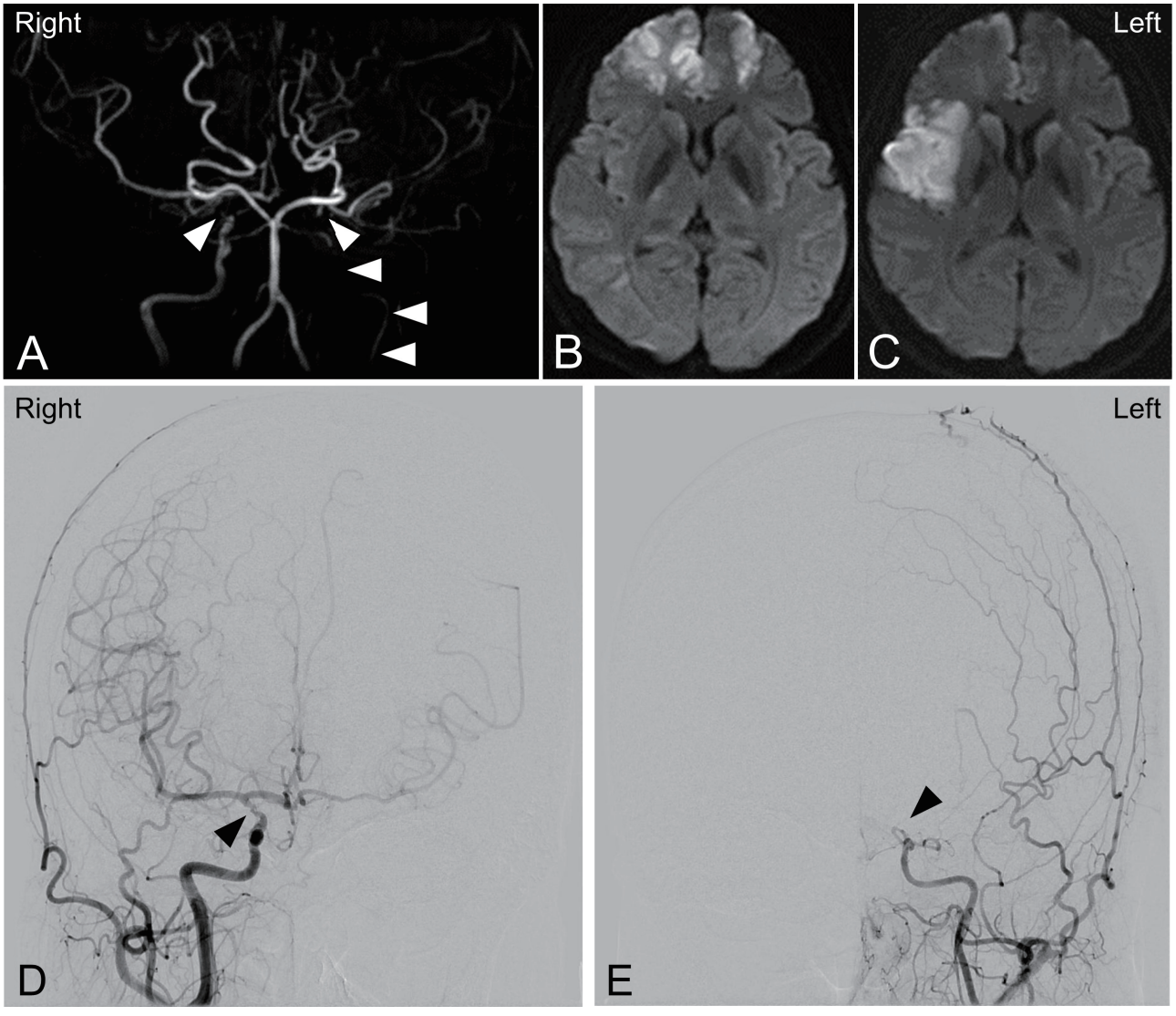

Fig. 1. Magnetic resonance imaging, magnetic resonance angiography, and digital subtraction angiography.
A) MRA on admission showed multiple stenosis and distal occlusion (arrows) in the left ICA, severe stenosis (arrows) in the distal right ICA, and bilateral signal loss in the ACA and MCA.
B) Diffusion-weighted MRI on admission showed acute ischemic infarcts in bilateral frontal lobes.
C) Diffusion-weighted MRI on day 17 of hospitalization showed recurrent infarcts in the right frontal and temporal lobes and left corona radiata.
D) Right CCA angiography of the cervical portion on day 15 of hospitalization showed severe stenosis (arrow) of the supraclinoid segment and multiple arterial wall irregularities in the right ICA, cross-flow into the left ACA and MCA via the anterior communicating artery, and no abnormality in the branches of the right external carotid artery.
E) Left CCA angiography of the cervical portion on day 15 of hospitalization showed a diffusely thin left ICA with multiple arterial wall irregularities, and occlusion (arrow) just distal to the ophthalmic artery origin. No abnormalities indicated Moyamoya disease, fibromuscular dysplasia, dissection, or intracranial arteritis, and no abnormalities were evident in the branches of the left external carotid artery.
ACA, anterior cerebral artery; CCA, common carotid artery; ICA, internal carotid artery; MCA, middle cerebral artery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.

Fig. 1A) showed occlusion of the left ICA and severe stenosis of the right ICA. Moreover, MRI (Fig. 1B) demonstrated acute ischemic infarcts in bilateral frontal lobes, and carotid ultrasonography showed the absence of macaroni signs in bilateral common carotid arteries (CCAs), reducing end-diastolic velocity in the left CCA, thickening of the wall to the right ICA, and complete absence of color-flow signals of the cervical portion in the left ICA. The anti-coagulant argatroban and the neuroprotective agent edaravone were administered to improve the levels

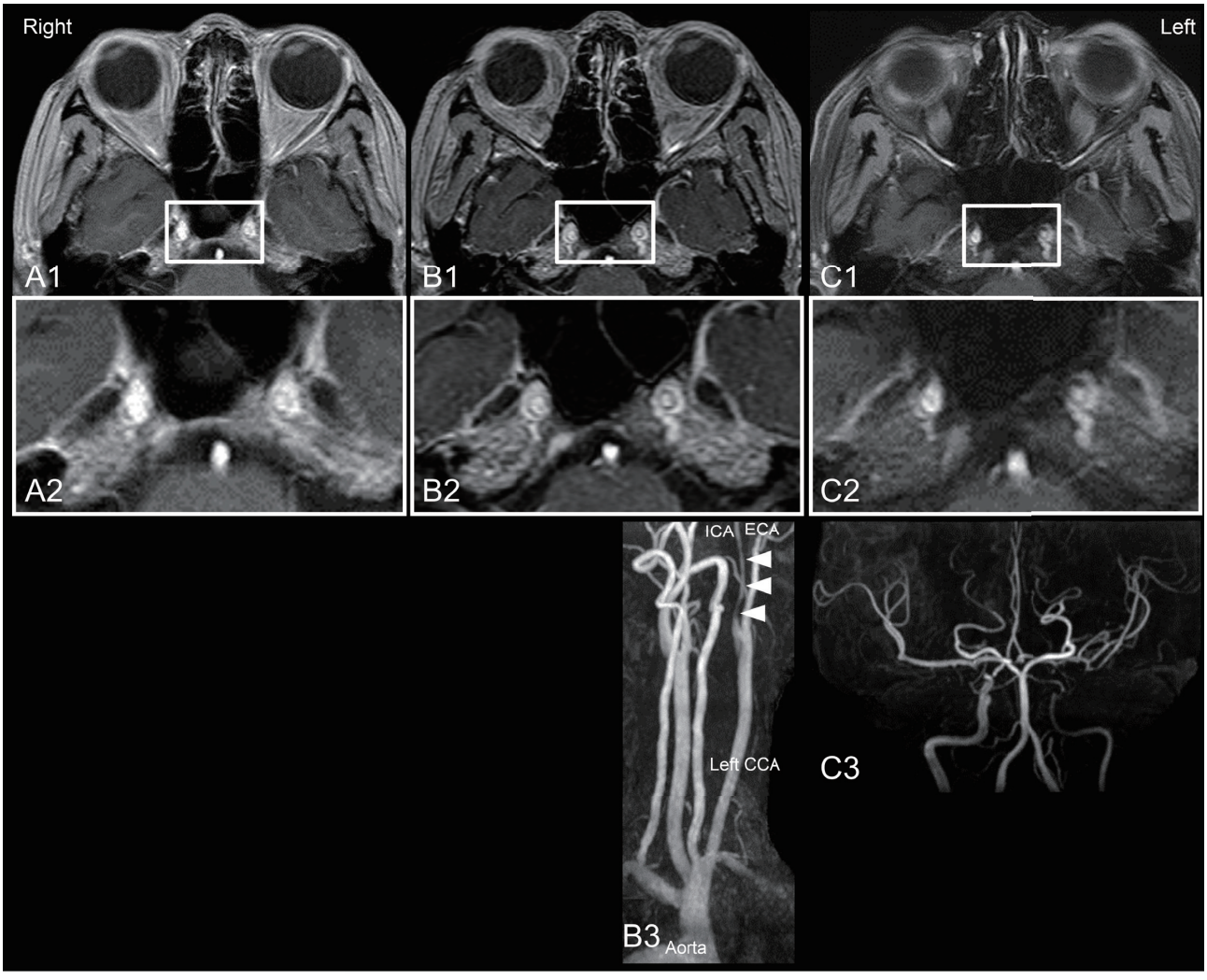

Fig. 2. Contrast-enhanced T1-weighted MRI.
A1, A2), admission; **B1, B2, B3**), day 23 of hospitalization; **C1, C2, C3**), at the time of discharge after prednisolone treatment.
A1) Retrospective contrast-enhanced T1-weighted MRI showed wall enhancement as in B1. **A2**) Magnified view of A1.
B1) Contrast-enhanced T1-weighted MRI showed wall enhancement in bilateral ICAs and bilateral wall thickening in the ICA and distal CCA. **B2**) Magnified view of B1. **B3**) Cervical MRA showed stenosis (arrows) in the left ICA.
C1) Contrast-enhanced T1-weighted MRI showed persistent wall enhancement in bilateral ICAs. **C2**) Magnified view of C1. **C3**) MRA showed bilateral improvements of signal intensity in the ACA and MCA.
ACA, anterior cerebral artery; CCA, common carotid artery; ECA, external carotid artery; ICA, internal carotid artery; MCA, middle cerebral artery; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.

of consciousness and ameliorate the right hemiparesis. Subsequent N-isopropyl-p-(^{123}I) iodoamphetamine single photon emission computed tomography (^{123}I-IMP SPECT) showed hypoperfusion in the territory of the bilateral anterior and middle cerebral arteries, with left dominance.

On the 5th day of hospitalization, progressive right hemiparesis occurred and brain computed tomography (CT) showed hemorrhagic infarction in the left anterior lobe. Hence, argatroban was discontinued and the patient's condition was stabilized. Cerebral angiography on the 15th day of hospitalization (Figs. 1D and E) revealed left ICA occlusion and no abnormalities in branches of external carotid arteries. No indicators of Moyamoya disease, fibromuscular dysplasia, dissection or intracranial arteritis were observed. Although cilostazol therapy (200 mg/day, BID) was initiated to prevent recurrent stroke, the patient showed low fever, impaired consciousness and progression of bilateral hemiparesis. MRI showed recurrent infarcts in the right frontal and

temporal lobes and left corona radiata suggesting embolic infarction on the 17th day of hospitalization (Fig. 1C). Impaired consciousness and right hemiparesis improved after resuming argatroban and edaravone, although the patient presented with gradually increasing fever, tenderness of bilateral carotid arteries, bilateral headache, odynophagia, arthralgia and an elevated erythrocyte sedimentation rate (ESR) (97 mm/h) on the 22nd day of hospitalization. Contrast-enhanced MRI and MRA (Figs. 2B1–B3) revealed wall enhancement in bilateral ICAs and wall thickening in bilateral ICAs and distal CCAs, warranting diagnosis of arteritis. Positron emission tomography–computed tomography, 3-dimensional CT angiography, and sonography showed no abnormal lesions in arterial or venous systems. Moreover, a superficial temporal artery (STA) biopsy showed only slight intimal thickening without inflammation, with no evidence of giant cell arteritis (GCA). Ophthalmologic and dermatologic consultation detected no abnormalities such as fundus abnormalities, uveitis, temporal artery distention, oral aphtha and skin lesions., implying particular immunological diseases including Behcet's disease. Although symptoms stabilized with argatroban therapy during the acute stage, stroke recurred following discontinuation of this treatment and initiation of cilostazol therapy. Hence, arteritis was the suspected cause of stroke recurrences, and oral prednisolone therapy (0.6 mg/kg body weight/day, 30 mg/day) was administered on the 36th day of hospitalization according to the guidelines for GCA and Takayasu's arteritis (TAK). Heparin infusions (10,000 U/day) were then initiated and the dose was adjusted based on activated partial thromboplastin times. Subsequently, fever, body tenderness and inflammatory markers were improved after three weeks, and the dose of prednisolone was gradually increased by 2.5-mg increments from 5 mg/week to 20 mg/day, and was then further tapered by 2.5-mg increments every three weeks to 10 mg/day. Follow-up MRA showed improved signal intensity in bilateral anterior cerebral arteries (ACAs) and middle cerebral arteries (MCAs), whereas contrast-enhanced MRI demonstrated persistent wall enhancement in bilateral ICAs. The patient showed neurological symptoms, such as moria, emotional incontinence, grasp reflex, right hemiparesis and left hemiplegia, and was transferred to a rehabilitation center at 15 weeks after administration. Contrast-enhanced MRI at six months after onset revealed persistent wall enhancement in bilateral ICAs. However, no stroke recurrence has been identified with continuing to take small doses of prednisolone (less than 10 mg/day) during four years of follow-up.

DISCUSSION

The present patient experience indicates that arteritis can be limited to the ICA. In addition, the patient was: i) a young woman; ii) had wall enhancements in contrast-enhanced MRI; iii) responded to steroid therapy and iv) was positive for the serotypes HLA-B39, -B51 and -DR4.

In contrast with exiting disease concepts, arteritis was caused by autoimmune disease in the present case, according to contrast-enhanced MRI findings and the efficacy of steroid therapy. Moreover, although we did not observe symptoms or organ involvements, autoantibodies indicated autoimmune disease such as systemic lupus erythematosus and medium- or small-vessel vasculitis, and the lesion was primarily located in bilateral ICAs. Based on these findings, we suspected TAK or GCA, both of which are types of large-vessel vasculitis or Behçet's disease, which induces lesions in large–small arteries. We also considered tuberculosis because a tuberculosis patient reportedly developed infectious vasculitis with a primary lesion in the ICA.[2] However, tuberculosis was not evident in the present case.

Cerebral infarction is an accepted diagnostic marker of TAK.[3] Although intracranial artery lesions are rare complications, the presence of such lesions has been observed previously using angiography, and in biopsies.[4, 5] However, to the best of our knowledge, no reports have described TAK cases with primary lesions at the ICA, and no reported TAK cases presented with aortic lesions after follow-up surveillance of ICA lesions that developed during the early stages of disease. The present patient was a young woman and exhibited symptoms that were suggestive of TAK, including bilateral blood pressure differences and the presence of HLA-B39. However, the absence of lesions in the aorta or at the proximal region of the first branch precluded diagnosis of TAK.

Numerous reports describe GCA primarily at the ICA.[6–14] Although onset at a young age is extremely rare, pathologically demonstrated GCA has been reported in patients of more than 50 years of age.[15–17] However, STA biopsy examinations can produce false-negative diagnoses, and even after identification of negative biopsies on one side, only 3 to 10% of biopsies on the contralateral side reportedly result in positive findings.[18]

Atypical presentations of GCA have been reported in previous case studies, and the present observations, including histology of the primary lesion site, symptomatic headaches, augmented ESR and the presence of HLA-DR4, are indicative of GCA. However, the present case was not diagnosed with GCA according to diagnostic criteria, because onset occurred at a young age and no temporal artery anomalies or artery biopsy abnormalities were observed.

Table 1. Reported cases of non-infectious arteritis predominantly affecting the ICA, without involvement of intracranial arteries (except ICA and vertebral artery), aortas or proximal aortic branches

Authors (Reference number)	Year	Age (years) / Sex	Diagnosis	Antibody	Stenosis/ Occlusion	Modality	Pathology	Treatment	Prognosis /Prevention
Wilkinson 1 (8)	1972	74/ Male	GCA	ND	Bil. ICA, Bil. VA	Autopsy	Biopsy STA (+), Autopsy	PSL	Died on the day of admission/ND
Wilkinson 2 (8)	1972	80/ Male	GCA	ND	Bil. ICA, Bil. VA	Autopsy	Biopsy STA (+), Autopsy	PSL	Died 6 days after admission/ ND
Wilkinson 3 (8)	1972	79/ Male	GCA	ND	Bil. ICA, Bil. VA	Autopsy	Biopsy STA (+), Autopsy	PSL	Died/ND
Wilkinson 4 (8)	1972	75/ Male	GCA	ND	Bil. ICA, Bil. VA	Autopsy	Autopsy STA (+)	PSL	Died 6 days after admission/ND
Cull (6)	1979	46/ Female	GCA	Negative	Rt. ICA	Angiography	Biopsy STA (+)	PSL	Alive/PSL
Howard (9)	1984	65/ Female	GCA	Negative	Bil. ICA	Autopsy	Autopsy ICA (+)	Unknown	Died 33 days after admission/ND
Bogousslavsky (10)	1985	60/ Male	GCA	ND	Bil. ICA	Autopsy	Autopsy ICA (+)	Dexamethasone	Died 12 days after admission/ND
Vincent (7)	1986	60/ Female	GCA	ND	Bil. ICA	Angiography	Biopsy STA (+)	PSL, Aspirin	Alive 3 Y later/PSL
Gonzalez (11)	1998	65/ Female	GCA	aCL Ab	Lt. ICA	Angiography	Biopsy STA (+)	PSL, Aspirin	Alive 5 Y later/Aspirin
Thielen (12)	1998	69/ Female	GCA	Antinuclear Ab	Bil. ICA, Lt. VA	Angiography	Biopsy STA (+)	Steroid	Alive 15M later/ND
Noguchi (23)	1999	76/ Female	GCA	Negative	Bil. ICA, Bil. ECA	Angiography	Biopsy STA (+)	Steroid, AP, AC	Alive 2 Y later/ PSL, AP
Takekawa (24)	2008	56/ Male	GCA	ND	Bil. ICA	Angiography	Unknown	PSL	Improvement of MRA findings/ND
Solans-Laque (13)	2008	90/ Male	GCA	ND	Lt. ICA	US/CTA/ MRA	Biopsy STA (+)	mPSL, PSL, AP, AC	Alive 40 M later/ PSL, AP
Lu-Emerson1 (14)	2010	64/ Female	GCA	ND	Bil. ICA, Bil. VA	Angiography	Biopsy STA (+), Autopsy	Steroid, Aspirin, CPA, Rituximab	Stepwise decline and died 2 Y later/ ND
Lu-Emerson 2 (14)	2010	65/ Male	GCA	ND	Bil. ICA, Bil. VA	Angiography	Biopsy STA (+)	AP, intraarterial stent placement , Steroid, CPA	Stepwise decline and died 7 M later/ ND
Logar (21)	1994	32/ Female	GPA	PR3-ANCA	Bil. ICA	Angiography	Biopsy Kidney (+)	mPSL, PSL, CPA	Improvement of laboratory Findings/ND
Schmidt (22)	2001	37/ Male	GPA	PR3-ANCA	Lt. ICA	US, MRA, Angiography	Biopsy Kidney (+)	PSL, CPA, Aspirin	Improvement of laboratory findings/ ND
Present case		38/ Female	Undetermined	Negative	Bil. ICA	US, MRA, Angiography	Biopsy STA (–)	AP, AC, PSL	Alive 3 Y later/ PSL, AP

Autopsy (+)" or "Biopsy (+)" indicates the presence of pathological findings which support the diagnosis: giant cell, granulomas or others. Ab, antibody; AC, anti-coagulant drug; aCL, anticardiolipin; AP, anti-platelet drug; Bil, bilateral; CPA, cyclophosphamide; CTA, computed tomography angiography; ECA, external carotid artery; GCA, giant cell arteritis; GPA, granulomatosis with polyangiitis; ICA, internal carotid artery; Lt, left; M, months; mPSL, methylprednisolone; MRA, magnetic resonance angiography; ND, no description; PR3-ANCA, proteinase 3-antineutrophil cytoplasmic antibody; PSL, prednisolone; Rt, right; STA, superficial temporal artery; US, ultrasonography; VA, vertebral artery; W, weeks; Y, years.

Clinical hallmarks of GCA, including the presentation of vasculitis of the temporal artery and the intracranial artery (cranial GCA), and arteritis of the aorta or first branch [large-vessel GCA (LV-GCA)], have been specified as clinical presentations of classical temporal arteritis (TA).[19] Moreover, LV-GCA is observed in 10 to 15% of all GCA cases, and reportedly presents as lesions in the aorta, carotid arteries and subclavian arteries in the absence of TA in biopsies. In addition, both GCA and TAK are characterized by histopathological formations of granulomatous lesions, and TAK and LV-GCA exhibit similarities in affected vessel morphology, histopathology and clinical symptoms, suggesting inclusion within the same disease spectrum.[20] However, although temporal artery biopsy resulted in negative findings in the present case, the clinical spectrum for the affected vessel did not coincide with that of LV-GCA.

Lesions of any size can occur in Behçet's disease and predominantly affect veins rather than arteries. Typically, vasculo-Behçet's disease occurs several years after the onset of Behçet's disease. The present patient was HLA-B51-positive and the affected vessel was somewhat consistent with Behçet's disease. However, because whole-body symptoms of Behçet's disease and vein lesions were not observed, Behçet's disease was considered unlikely. The present patient was diagnosed with a form of non-infectious vasculitis with atypical clinical presentation, and after consideration of large-vessel vasculitis diseases TAK and GCA, Behçet's disease criteria were examined. However, the present patient conditions were not sufficiently consistent with any of these diseases, and the patient was diagnosed as having a type of vasculitis with primary lesions in the ICA that was on the disease spectrum of TAK and GCA, but with different clinical presentation.

In comparison with the 17 previously reported cases of ICA arteritis,[6–14, 21, 22] distinguishing characteristics of the present female case included relative youth, wall enhancement on contrast-enhanced MRI, therapeutic effects of steroids and the presence of HLA serotypes (HLA-B39, -B51 and -DR4) (Table 1). Fifteen of these cases were diagnosed with GCA[6–14] and the remaining 2 cases had granulomatosis with polyangiitis (GPA).[21, 22] Although these two GPA cases had onset at a young age, renal lesions and proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA) expression were not consistent with the present case. Another previous case described a patient with autoimmune disease who developed ICA lesions[25]; however, the distributions of vascular lesions were dissimilar to those in the present case. Thus, none of the 17 cases presented the clinical characteristics that were consistent with the present case.

The relative youth and gender of the present case was nearly in accordance with one GCA case[6] and one GPA case.[21] However, wall enhancement on contrast-enhanced MRI was not described for any of the previously reported 17 cases, despite its correlation with serum markers of disease activity, and its utility for assessments of mural inflammation in GCA and TAK.[26–28] Although enhanced MRI facilitates primary diagnosis of TA, a recent study suggested that assessments of wall enhancement are limited indicators of disease activity in long-term follow-up of TA.[29] In agreement, contrast-enhanced T1-weighted MRI assessments of the ICA were of diagnostic value in the present case, with wall enhancement on admission not only from a retrospective viewpoint (Figs. 2A1 and A2) but also after symptoms and inflammatory markers were improved by prednisolone therapy (Figs. 2C1 and C2). Hence, persistent vessel wall enhancement may not always indicate increased disease activity.

Steroids, immunosuppressants or antithrombotic agents are common as acute and preventive therapy for clinical vasculitis,[6–14, 21, 22] and are used in combination for cases with favorable prognoses. Combined prednisolone and antithrombotic treatments were successful as acute therapy in the present case, and subsequent low-dose prednisolone and antiplatelet therapy prevented further strokes. Hence, combination immune and antithrombotic therapy should be considered for arteritis involving cervical and cerebral arteries.

Finally, onset of vasculitis has been associated with environmental and genetic factors and various correlations between vasculitis and HLA alleles have been elucidated. Specifically, TAK is reportedly associated with HLA-B52 (B*5201) and -B39 (B*3902),[30] whereas Behçet's disease is associated with HLA-B51 (B*5101),[31] GCA is associated with HLA-DR4 (DRB1*04), cranial GCA is associated with DRB1*0401, and large-vessel GCA is associated with DRB1*0404.[19] In the present case, the HLA serotypes HLA-B39, -B51 and -DR4 were identified without HLA allele typing, unprecedentedly suggesting Behçet's disease, TAK and GCA, respectively. In contrast, no HLA serotypes or alleles were reported in the aforementioned 17 cases.[6–14, 21, 22] Thus, further accumulations of HLA typing in similar cases are required to evaluate these associations.

In summary, the present case was distinguished from previous cases by relative youth and contrast-enhanced MRI and HLA characteristics.

Here we report a rare evidence of arteritis limited to ICA in an unprecedented case of a young woman with wall enhancement on contrast-enhanced MRI, therapeutic effects of steroids, and HLA serotypes HLA-B39,

-B51 and -DR4. These disease characteristics were not in accordance with existing diagnostic criteria, warranting consideration of a novel "isolated internal carotid arteritis" disease concept.

The authors declare no conflict of interest.

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