Efficacy of Carotid Endarterectomy for Mild (<50%) Symptomatic Carotid Stenosis with Unstable Plaque

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BACKGROUND: **Carotid endarterectomy (CEA) is known to reduce stroke risk in patients with symptomatic, moderate to severe carotid stenosis but has no apparent impact in patients with symptomatic, mild (less than 50%) carotid stenosis. However, recent development of noninvasive imaging modalities has shown that a certain subgroup of patients are at high risk for further ischemic events despite antiplatelet therapy. This study, therefore, aimed to clarify the patients' clinical features and explore the impact of CEA for them.**

METHODS: **This prospective cohort study included 74 patients who underwent CEA for symptomatic carotid stenosis between April 2012 and December 2016. Of these, 16 (22%) had mild (less than 50%) carotid stenosis. Their demographic, radiologic, intraoperative, and pathologic findings were precisely analyzed, and their outcome after CEA was examined for 38.5 ± 13.3 months.**

RESULTS: **Of these 16 patients, 12 had already been treated with antiplatelets against previous ischemic cerebrovascular or coronary artery diseases. Plaque magnetic resonance imaging revealed that all patients had vulnerable plaque, including lipid-rich plaque (n = 6) and intraplaque hemorrhage (n = 10). Intraoperative observations confirmed this. Histologic analysis revealed that inflammatory cells and fragile angiogenesis were widely found in the specimens. Only 1 patient experienced transient (less than 30 days) neurologic deficit after CEA, and none of them repeated cerebrovascular events during the follow-up period.**

CONCLUSIONS: **It is not rare the patients who are at high risk for subsequent ischemic events because of vulnerable plaque despite mild (less than 50%) carotid stenosis. Magnetic resonance imaging is quite useful to noninvasively detect such vulnerable plaque. CEA is a promising procedure to treat these patients.**

INTRODUCTION

The degree of carotid stenosis is well known to estimate the risk of recurrence of cerebrovascular events and helps to determine therapeutic strategies for patients with carotid stenosis.[1,2] Large multicenter randomized controlled trials, such as the North American Symptomatic Carotid Endarterectomy Trial[2] and European Carotid Surgery Trial,[1] have confirmed that carotid endarterectomy (CEA) significantly reduces the risk of subsequent stroke when compared with medical treatment in symptomatic patients with moderate to severe stenosis. However, it has not been proven that the procedure has apparent benefits to those with symptomatic mild (less than 50%) stenosis.

Recent developments of noninvasive plaque imaging, such as magnetic resonance imaging (MRI) and ^{18}F-fluorodeoxyglucose

Key words
- Carotid endarterectomy
- Carotid stenosis
- Mild stenosis
- MRI
- Unstable plaque

Abbreviations and Acronyms
3D: 3-Dimensional
AHA: American Heart Association
CAS: Carotid artery stenting
CEA: Carotid endarterectomy
IPH: Intraplaque hemorrhage
MRI: Magnetic resonance imaging
TIA: Transient ischemic attack
TOF: Time-of-flight

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positron emission tomography, have increased our understandings on high-risk plaque with vulnerable components and/or aggressive inflammation.[3-5] There is increasing evidence that the inflamed, unstable carotid plaque readily causes amaurosis fugax, transient ischemic attack (TIA), or ischemic stroke through plaque rupture and induces artery-to-artery embolism regardless of the degree of stenosis.[6] Furthermore, recent studies have also suggested that a certain subgroup of patients with mild carotid stenosis tend to repeat TIA and ischemic stroke despite best medical treatments, including antiplatelets.[7] These observations strongly suggest that not only should stenosis degree but also plaque component be taken into consideration when determining treatment strategies for patients with carotid stenosis. Namely, it may shift from stenosis degree era to plaque vulnerability era. Indeed, Brinjikji et al.[8] speculated that the identification of intraplaque hemorrhage (IPH) on MRI in patients with mild carotid stenosis is a risk factor for failure of medical therapy and that such patients may fair better with CEA.

Until now, however, the impact of CEA on symptomatic patients with mild (less than 50%) carotid stenosis is poorly understood even in this plaque vulnerability era. Previously reported data are too small to determine it. This study, therefore, aimed to clarify clinical features in patients with repeat TIA and/or ischemic stroke because of mild (less than 50%) carotid stenosis and assess the impact of CEA on their prognosis.

PATIENTS AND METHODS

Patients

This study is a prospective nonrandomized case series. We searched the database from our prospective cohort study on carotid stenosis that included 172 patients who underwent CEA or carotid artery stenting (CAS) for symptomatic or asymptomatic carotid stenosis between April 2012 and December 2016 at our institution.[9] The database included 86 symptomatic patients and 86 asymptomatic ones. All symptomatic patients experienced amaurosis fugax, retinal artery occlusion, TIA, or ischemic stroke in the ipsilateral carotid artery territory within 6 months before admission. According to the degree of stenosis, all patients were categorized into 3 groups: mild (less than 50%), moderate (50%–69%), and severe (70% or more). This study precisely analyzed the demographic data, medical records, radiologic findings, operative findings, histopathologic findings, and postoperative results in patients who underwent CEA for mild (less than 50%) carotid stenosis. The patients with carotid dissection or radiation-induced angiopathy were excluded.

Radiologic Examinations

Stenosis Degree. The degree of carotid stenosis was determined according to the North American Symptomatic Carotid Endarterectomy Trial criteria on 3-dimensional (3D) computed tomography angiography (GCA9300 [Toshiba, Tokyo, Japan]).[2] Mild stenosis was defined as less than 50% stenosis. The detailed method has been previously reported.[10]

MRI Plaque Imaging. The plaque component was evaluated using a 1.5-Telsa MRI scanner (Magnetom Vision [Siemens, Erlangen, Germany]). To characterize the plaque component, the long-axis and axial images of the carotid artery were obtained from the 3D gradient-echo sequence by targeting the area with the highest degree of stenosis. In addition, 3D time-of-flight (TOF) magnetic resonance angiography was also acquired through both carotid bifurcations in the axial plane. The following imaging sequences were used: 3D TOF imaging with field of view, 220 mm/87.5%; repetition time, 23 milliseconds; and echo time, 7.00 milliseconds; and T1-weighted imaging with field of view, 200 mm/100%; repetition time, 500 milliseconds; and echo time, 11 milliseconds. Slice thickness was 1.2 mm for 3D TOF and 4 mm for T1-weighted images. The plaque components were defined according to the following criteria: when the plaque displayed a signal intensity that was more than 200% of that for muscle at any place or section in the plaque, the plaque was categorized as having a hyperintense signal. The plaque was considered fibrous when the signal intensity was isointense on both T1-weighted and TOF images. When the signal intensity was high on T1-weighted images, but isointense on TOF images, the plaque was categorized as lipid-rich. When the signal intensity was high on both T1-weighted and TOF images, the plaque was considered as having IPH. IPH and lipid-rich plaque was designated as vulnerable plaque, whereas fibrous plaque was considered stable, as reported previously.[11] All plaque was assigned a grade of I–VIII according to the modified American Heart Association (AHA) plaque grading system for MRI based on previous studies.[12,13]

Treatment Strategy

All 16 patients with symptomatic, mild (less than 50%) carotid stenosis underwent CEA because of recurrent TIA or ischemic stroke despite prior antiplatelet therapy or were considered at high risk of further ischemic stroke because of vulnerable plaque on MRI.

All patients were medically treated in the acute stage. The therapeutic goals of medical treatments included controlling hypertension, hyperlipidemia, and diabetes mellitus. We confirmed hypertension was under control in all patients to decide indication of CEA. Statins were preferentially administered to patients with hyperlipidemia. Coronary 3D computed tomography angiography or coronary angiography was performed to evaluate the perioperative risk of myocardial infarction in all 16 patients.

CEA

Experienced and certified neurosurgeons (D. K., N. A., and S. K.) performed all CEA surgeries. Antiplatelet therapy was continued through perioperative periods. All surgical procedures were performed under general anesthesia, using routine intraoperative near-infrared spectroscopy to continuously measure cerebral oxygenation status through surgery to detect critical cerebral ischemia.[14,15] Routine internal shunting was performed on all 16 patients regardless of the findings on near-infrared spectroscopy. Under a surgical microscope, the plaque was carefully removed, and the carotid artery was sutured with a primary closure technique. Patients were carefully monitored in the recovery room for 24 hours or until blood pressure and neurologic status were judged as stable.[16]

During surgery, the component of plaque was examined, and the surface of plaque was precisely observed to identify the cause of cerebrovascular events such as erosion and surface disruption. The surface disruption was defined as the presence of cap rupture and/or ulcer formation.

Follow-Up

After surgery, the postoperative course was carefully observed. Adverse perioperative events within 30 days after surgery included any stroke, myocardial infarction, TIA, amaurosis fugax, or death. To detect postoperative hyperperfusion, Technetium-99m hexamethylpropylene amineoxime single photon emission computed tomography was performed to qualitatively determine cerebral blood flow just after surgery and at 2 and 7 days postsurgery. Hyperperfusion was defined as cerebral blood flow in the ipsilateral hemisphere elevated to a higher level than in the contralateral hemisphere. To identify fresh cerebral infarct, diffusion-weighted MRI was performed within 3 days before and after CEA. The modified Rankin Scale was measured just before and at 30 days post-CEA. Minor and major stroke were defined as new neurologic deficits that completely resolved within 30 days and at or after 30 days post-CEA, respectively. All patients were followed-up at our outpatient clinics monthly during the first 6 months after surgery and then every 6 or 12 months thereafter. Brain MRI and neck-to-brain magnetic resonance angiography were performed every 6 or 12 months during follow-up periods to detect new brain lesions and/or restenosis.

Histopathology

After CEA, the carotid plaque was fixed in 4% formaldehyde, the carotid plaque was embedded in paraffin, and 4-μm-thick axial slices were prepared. The section with the largest plaque burden was classified as the culprit lesion and subjected to subsequent staining. The deparaffinized sections were processed for antigen retrieval for 2 minutes in a pressure pot. Hematoxylin-Eosin-stained sections were evaluated for IPH screening. Immunohistochemical analysis was used to identify the marker of vulnerable plaque. The expression levels of M1 macrophage markers, including CD11c, were confirmed by immunohistology.[17,18] The expression level of hypoxia cells markers to identify vulnerable plaque, including HIF-1α antibody, was confirmed by immunohistology.[19] The expression level of intraplaque neovessel markers, including CD31, was also confirmed by immunohistology.[20-23] Briefly, each section was treated with the primary antibody against CD11c (rabbit monoclonal, 1:50 dilution; ab52632 [Abcam, Tokyo, Japan]), HIF-1α (mouse monoclonal, 1:200 dilution; GT10211 [Funakoshi, Tokyo, Japan]), or CD31 (mouse monoclonal, 1:200 dilution; TLD-3A12 [Funakoshi]) for 40 minutes at 24°C and then treated with the Envision polymer of DAKO EnVision+Kit (DAKO Cytomation, Denmark) for 60 minutes. The DAB Chromogen of the DAB Substitute Kit (DAKO Cytomation) was applied for 3–4 minutes, and hematoxylin was used for counterstaining. The carotid plaque was divided into 4 lesions (shoulder, bottom, core, and interface-to-media region) as described previously.[24] Shoulder regions were defined as tissue adjacent to the outer border of the lipid core down to the vessel lumen. The count of positive cells and microvessels was performed in the shoulder region. The CD11c-, HIF-1α–, and CD31-positive cells were counted in each region using the cell counter tool of ImageJ software (National Institutes of Health, Maryland, USA). The counts of cells positive for each antigen were performed by 2 certified neurosurgeons (D. K. and S. K.). In cases where the observers disagreed, results were discussed by 2 neurosurgeons and a consensus was reached.

RESULTS

According to the findings on 3D computed tomography angiography and plaque MRI, 74 of 86 symptomatic patients underwent CEA in this study. These 74 patients were divided into 3 groups according to the degree of carotid stenosis: mild (less than 50%; n = 16), moderate (50%–69%; n = 12), and severe (70% or more; n = 46). Therefore, the mild stenosis group occupied 21.6% of symptomatic patients who underwent CEA. None of the symptomatic patients with mild carotid stenosis underwent CAS (Figure 1).

All 16 patients who underwent CEA for symptomatic, mild (less than 50%) carotid stenosis were men. Their mean age was 72.8 ± 6.3 years with a range of 63–84 years. Clinical diagnosis included TIA in 2 patients, ischemic stroke in 13 patients, and amaurosis fugax in 1 patient. Comorbidities included hypertension (n = 11; 68.8%), hyperlipidemia (n = 8; 50%), and diabetes mellitus (n = 6; 37.5%). A history of coronary artery diseases and cerebrovascular events was observed in 5 (31.3%) and 7 patients (43.8%), respectively. None of them had a history of atrial fibrillation. Of these 16 patients, 12 (75.0%) had already been treated with antiplatelet agents prior to the present events for ipsilateral ischemic stroke in 1 patient, ipsilateral retinal artery occlusion in 3 patients, contralateral ischemic stroke in 3 patients, and coronary artery disease in 5 patients. Antiplatelet agents included aspirin (100 mg/d) in 4 patients, clopidogrel (75 mg/d) in 6 patients, and/or cilostazol (200 mg/d) in 4 patients. Dual or triple antiplatelets were given in 4 patients. Therefore, prior antiplatelet therapy could not prevent ischemic events caused by mild carotid stenosis. The other 4 patients (25.0%) had no history of antiplatelet therapy but underwent CEA because they had vulnerable plaque on MRI (see Table 1). The clinical data are shown in Table 1.

Radiologic Findings

Of 16 lesions, 10 were located on the right side and 6 on the left side. The mean degree of stenosis was 37.2% ± 10.6%, ranging from 15% to 49%.

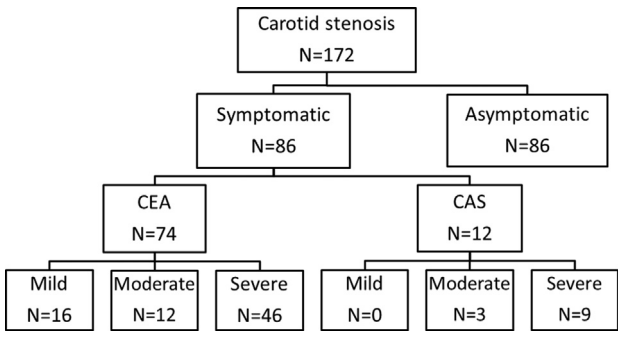

Figure 1. The data in this study were extracted from our prospective cohort study on carotid stenosis that included a total of 172 patients who underwent carotid endarterectomy or carotid artery stenting for symptomatic or asymptomatic carotid stenosis. There were 86 patients with symptomatic carotid stenosis. The mild stenosis group occupied 21.6% of symptomatic patients who underwent carotid endarterectomy. CAS, carotid artery stenting; CEA, carotid endarterectomy.

Table 1. Summary of Clinical Features in 16 Patients with Symptomatic, Mild (less than 50%) Stenosis of the Ipsilateral Carotid Artery

Patient Number	Age (Years)	Sex	Diagnosis	Side	Stenosis (%)	Plaque MRI (AHA)	History	Prior Antiplatelet Therapy	Surgical Complications	30-Day Results	Follow-Up (Months)
1	63	Male	Ischemic stroke	L	48	IPH (VI)	Ipsilateral retinal artery occlusion	Yes	None	Unchanged	59
2	66	Male	Ischemic stroke	R	34	IPH (VI)	Myocardial infarction	Yes	None	Unchanged	48
3	78	Male	Ischemic stroke	R	40	Lipid rich (VI)	Unstable angina	Yes	None	Unchanged	33
4	76	Male	TIA	L	49	Lipid rich (VI)	None	No	None	Unchanged	36
5	66	Male	Ischemic stroke	L	47	IPH (VI)	Contralateral ischemic stroke	Yes	None	Unchanged	38
6	76	Male	Ischemic stroke	L	20	IPH (VI)	Contralateral ischemic stroke	Yes	None	Unchanged	41
7	77	Male	Ischemic stroke	R	20	IPH (VI)	Unstable angina	Yes	None	Unchanged	26
8	79	Male	Ischemic stroke	R	35	Lipid rich (VI)	None	No	Hemiparesis	Unchanged	22
9	65	Male	Ischemic stroke	R	46	Lipid rich (VI)	Ipsilateral retinal artery occlusion	Yes	None	Unchanged	26
10	66	Male	Ischemic stroke	R	44	IPH (VI)	Unstable angina	Yes	None	Unchanged	28
11	74	Male	Retinal artery occlusion	R	37	Lipid rich (VI)	Ipsilateral retinal artery occlusion	Yes	None	Unchanged	17
12	65	Male	Ischemic stroke	R	42	IPH (VI)	None	No	None	Unchanged	25
13	75	Male	Ischemic stroke	L	34	IPH (VI)	Contralateral ischemic stroke	Yes	None	Unchanged	17
14	75	Male	TIA	R	15	IPH (VI)	Ipsilateral ischemic stroke	Yes	None	Unchanged	15
15	84	Male	Ischemic stroke	L	40	IPH (VI)	Myocardial infarction	Yes	None	Unchanged	13
16	70	Male	Retinal artery occlusion	R	44	Lipid rich (VI)	None	No	None	Unchanged	12

MRI, magnetic resonance imaging; L, left; IPH, intraplaque hemorrhage; R, right; TIA, transient ischemic attack; AHA, American Heart Association classfication.

Plaque MRI was performed to characterize the component of carotid plaque in all 16 patients. T1-weighted imaging demonstrated high-intensity plaque in all 16 patients. TOF images showed isointensity plaque in 6 patients and high-intensity plaque in 10 patients. Therefore, all 16 patients with mild carotid stenosis were considered to have vulnerable plaque, including lipid-rich plaque in 6 patients and IPH in 10 patients. In contrast, plaque MRI revealed 50 patients with high-intensity plaque and 8 patients with isointensity plaque on T1-weighted imaging. On TOF magnetic resonance angiography, 27 patients had high-intensity plaque and 31 had isointensity plaque. Therefore, patients with moderate to severe carotid stenosis had fibrous plaque in 8 patients, lipid-rich plaque in 23 patients, and IPH in 27 patients. The plaque components did not significantly differ between the 2 groups ($P = 0.24$). All plaque was classified into AHA type VI according to modified AHA classification for MRI. The radiologic data are summarized in Table 1.

Intraoperative Findings

All 16 patients with mild carotid stenosis successfully underwent CEA at 24.8 ± 16.6 days after the last cerebrovascular events. Intraoperative observations revealed that plaque had a large necrotic core or IPH in all 16 patients. The surface of the plaque was disrupted and developed an ulceration or fibrous cap in all patients. In detail, the ulcer formation was found in 14 of 16 patients (93.8%), and the cup rupture was found in 12 of 16 patients (75.0%) as culprit lesions. Illustrative cases are precisely presented in Figures 2–5.

Surgical Results

Of 16 patients, 1 (6.3%) developed transient hemiparesis contralateral to the operated carotid artery with positive diffusion-weighted MRI findings, but completely recovered within 30 days after CEA. However, postoperative course was uneventful and no positive diffusion-weighted lesions were detected in the other 15

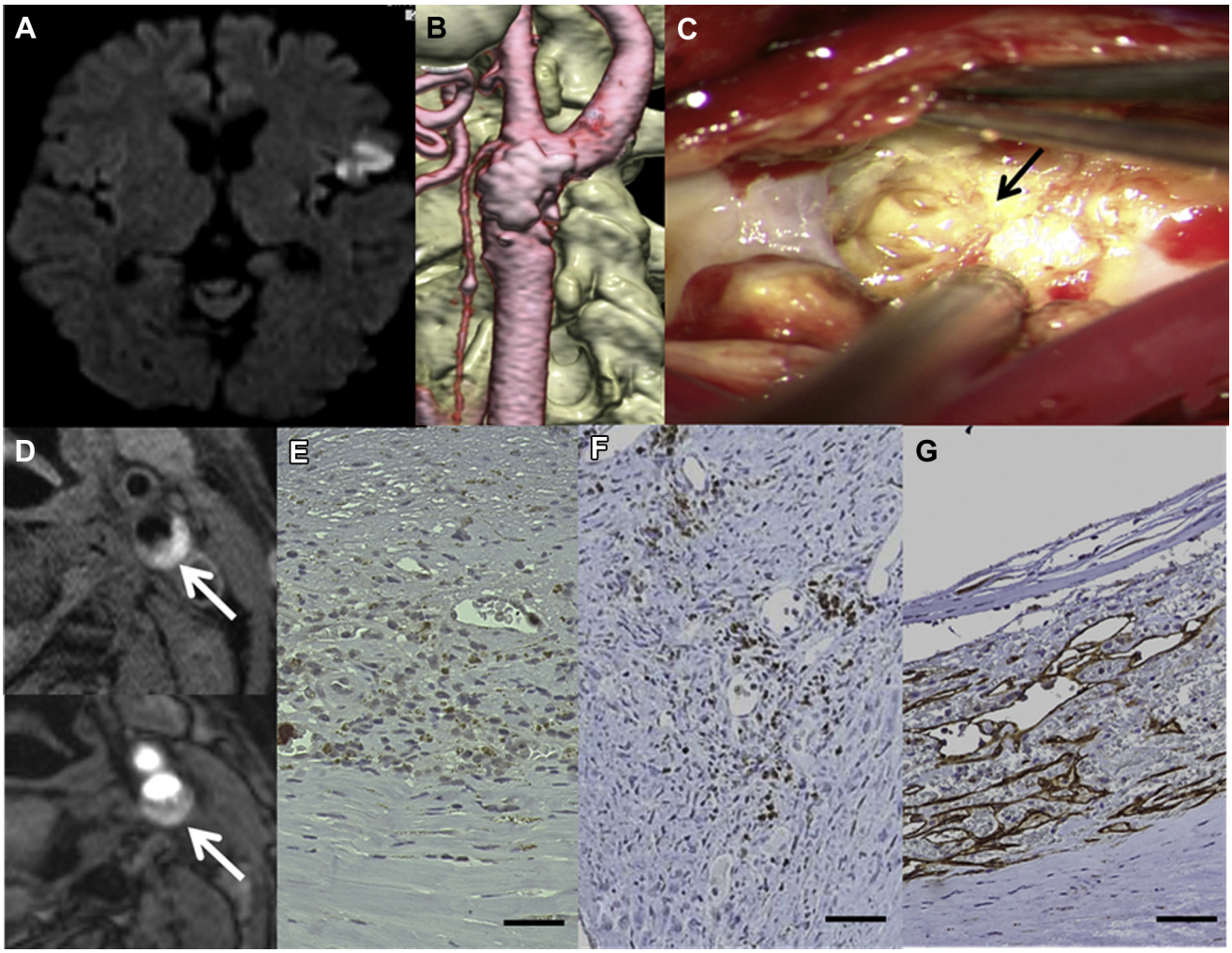

Figure 2. A 63-year-old man was treated with antiplatelet therapy for left retinal artery occlusion. However, he reported repeat transient monocular blindness on the left side and was referred to our hospital. Diffusion-weighted magnetic resonance imaging (MRI) showed fresh cerebral infarction in the left frontal lobe (**A**). Three-dimensional computed tomography angiography demonstrated mild (48%) stenosis of the left internal carotid artery (**B**). Intraoperative findings included an ulceration (*arrow*) and surface disruption of plaque (**C**). Plaque (*arrow*) MRI revealed high-intensity plaque on both T1-weighted imaging and time-of-flight imaging, strongly suggesting the existence of intraplaque hemorrhage (**D**). Photomicrographs of immunohistochemistry against CD11c (**E**), HIF-1α (**F**), and CD31 (**G**) show that the CD11c- and HIF-1α–positive cells and CD31-positive neovessels were densely distributed in the shoulder of the plaque. Scale bar, 50 μm.

patients (93.7%). Neurologic function was maintained at 30 days post-CEA in all 16 patients. Myocardial infarction, cranial nerve dysfunction, hyperperfusion syndrome, or wound hematoma did not occur during perioperative periods (Table 1).

Histologic Analysis

Immunohistochemistry revealed that the CD11c- and HIF-1α–positive cells were densely distributed in the shoulder region of plaque in all 16 patients. Therefore, the plaque was characterized by an abnormally increased concentration of M1 macrophages and hypoxia-state cells (Figures 2–5). Furthermore, the CD31-positive vessels were also widely distributed in the same area of them, which suggested widespread angiogenesis in the plaque (Figures 2–5).

Outcome

All 16 patients survived and were followed-up at the outpatient clinic during a mean period of 38.5 ± 13.3 months. None of them experienced further cerebrovascular events. Follow-up magnetic resonance angiography detected no restenosis.

DISCUSSION

The principal findings reported here are that clinical application of plaque MRI detected 16 symptomatic patients who required CEA for mild (less than 50%) carotid stenosis. This occupied around 20% of all symptomatic patients who underwent CEA in this study. They would most likely be treated medically, if only the degree of stenosis was used to make a decision about their therapeutic strategy according to previous randomized controlled

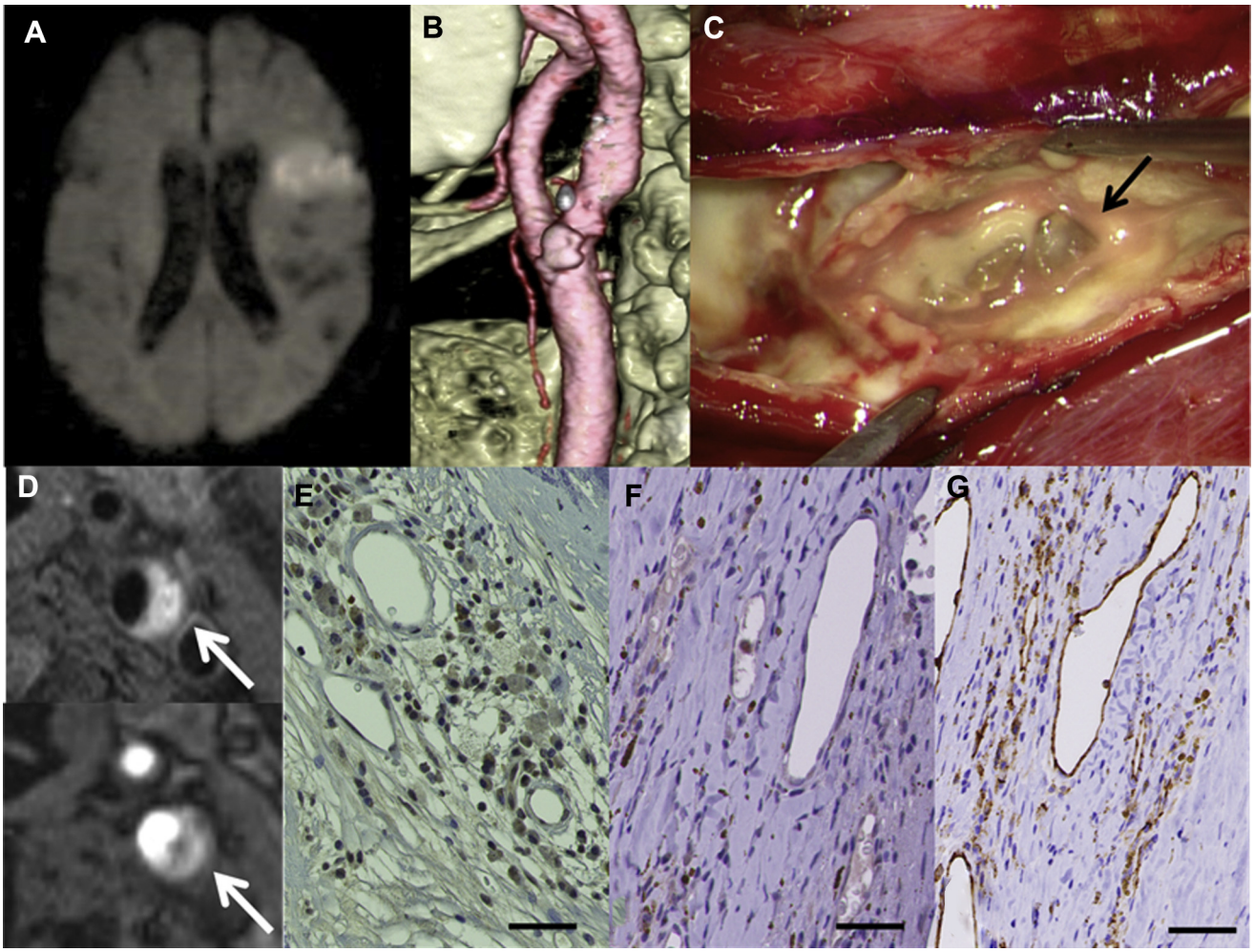

Figure 3. A 76-year-old man was treated with antiplatelet therapy for ischemic stroke on the right side. However, he presented with motor aphasia and was referred to our hospital. Diffusion-weighted magnetic resonance imaging (MRI) showed fresh cerebral infarction in the left frontal lobe (**A**). Three-dimensional computed tomography angiography demonstrated mild (20%) stenosis of the left internal carotid artery (**B**). Intraoperative findings included an ulcer (*arrow*) formation and surface disruption of plaque (**C**). Plaque (*arrow*) MRI revealed high-intensity plaque on both T1-weighted imaging and time-of-flight imaging (**D**). Photomicrographs of immunohistochemistry against CD11c (**E**), HIF-1α (**F**), and CD31 (**G**) show that the CD11c- and HIF-1α–positive cells and CD31-positive neovessels were densely distributed in the shoulder of the plaque. Scale bar, 50 μm.

trials.[2] More importantly, 12 of these 16 patients presented with cerebrovascular events in the territory of the ipsilateral carotid artery despite prior antiplatelet therapy. Previously, medical treatments have often been selected for patients with symptomatic, mild carotid stenosis according to the current standard-of-care guidelines. However, there is increasing evidence to suggest the limitation of medical treatment when they have vulnerable plaque.[7,25,26] For example, Altaf et al.[25] reported that 4 of 22 patients (18%) with symptomatic, mild carotid stenosis (30%–49%) experienced recurrent TIA or stroke despite medical treatment with antiplatelet drugs during a prospective 2-year follow-up period. MRI detected the presence of IPH in all 4 patients, suggesting that the plaque with IPH was high risk for the recurrence of cerebrovascular events, regardless of the degree of stenosis and use of antiplatelet therapy. Yoshida et al.[26] also reported that symptomatic, mild carotid stenosis with vulnerable plaque was significantly associated with high rates of stroke recurrence (46.0% per patient-year) and concluded that mild carotid stenosis with vulnerable plaque would be refractory even to aggressive medical treatment. Karlsson et al.[7] followed-up patients with symptomatic, mild (20%–49%) carotid stenosis for 3 years and reported that their cumulative incidence of recurrent ipsilateral stroke was 7.4%. The value was significantly higher than that in patients with asymptomatic, equal-degree carotid stenosis (hazard ratio, 5.5; 95% confidence interval, 1.8–17.1; $P = 0.003$).[7] Considering these findings, together with our results, it is most likely that noninvasive medical treatment may reduce the risk of subsequent cerebrovascular events in most patients with

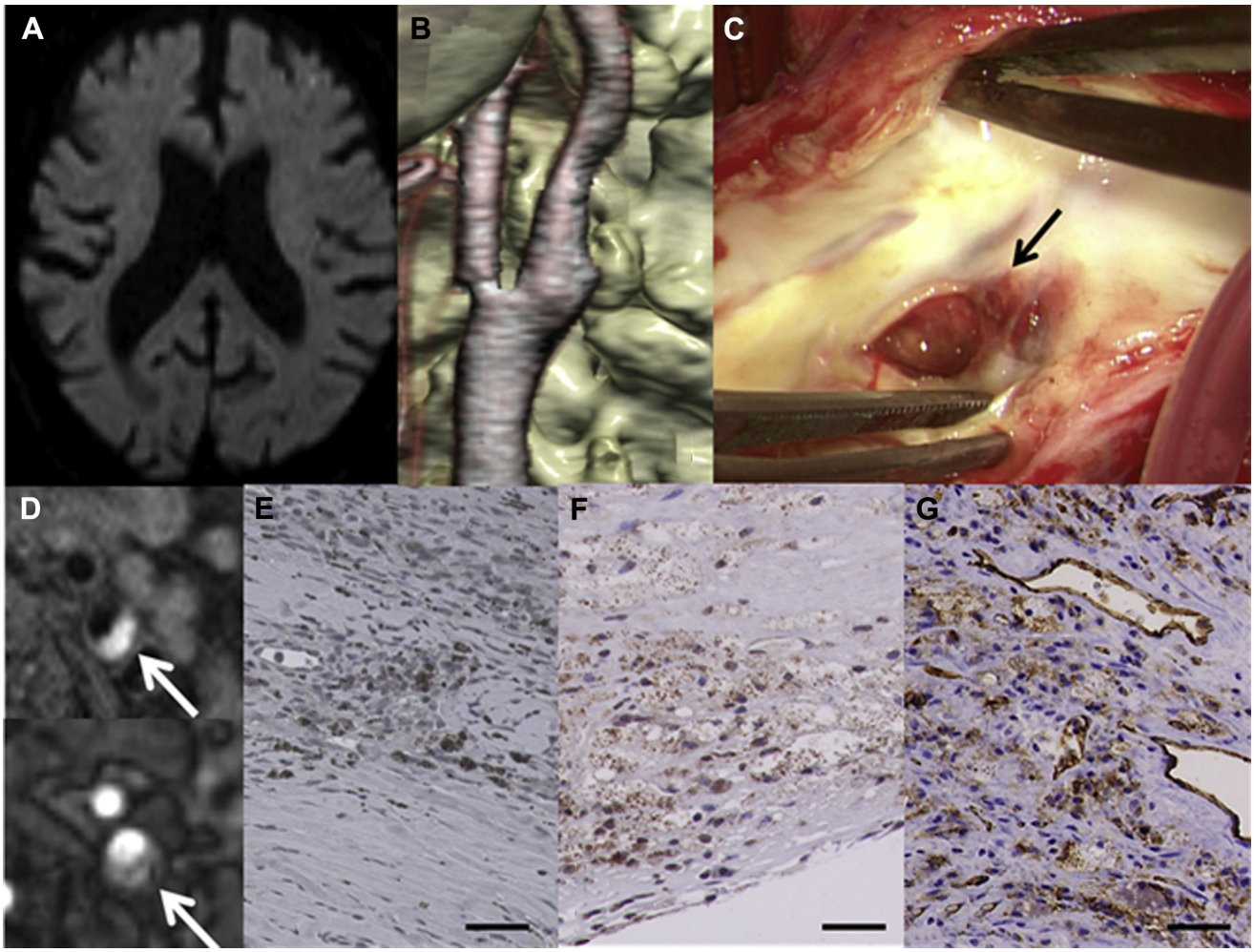

Figure 4. A 75-year-old man was treated with antiplatelet therapy for ischemic stroke on the right side. However, he presented with right mild hemiparesis and was referred to our hospital. Diffusion-weighted magnetic resonance imaging (MRI) showed small, fresh cerebral infarction in the left frontal lobe (**A**). Three-dimensional computed tomography angiography demonstrated mild (34%) stenosis of the left internal carotid artery (**B**). Intraoperative findings included an ulcer (*arrow*) formation and surface disruption of plaque (**C**). Plaque (*arrow*) MRI revealed high-intensity plaque on both T1-weighted imaging and time-of-flight imaging (**D**). Photomicrographs of immunohistochemistry against CD11c (**E**), HIF-1α (**F**), and CD31 (**G**) showed that the CD11c- and HIF-1α—positive cells and CD31-positive neovessels were densely distributed in the shoulder of the plaque. Scale bar, 50 μm.

symptomatic, mild carotid stenosis, but its efficacy is largely limited in a certain subgroup of them when they have high-risk vulnerable plaque. Therefore, it is quite important to detect the vulnerable plaque accurately and noninvasively.[11,27]

CEA was indicated to 16 patients because they had sustained a recurrent stroke or were diagnosed as having vulnerable plaque on MRI despite mild carotid stenosis. All of them had high-intensity plaque on T1-weighted imaging. In addition, 10 of 16 patients (62.5%) had high-intensity plaque on TOF, which strongly suggested IPH. The other 6 patients had isointensity plaque on TOF, indicating lipid-rich plaque with necrotic core. No fibrous plaque was observed in the patients. This strongly suggests that all cerebrovascular events occurred through artery-to-artery embolism.[11] Therefore, all 16 patients with mild carotid stenosis had vulnerable plaque on MRI. Intraoperative observations support this. Therefore, all operated plaque had surface disruption and/or ulcer formation. Immunohistochemistry revealed that the CD11c- (M1 macrophage) and HIF-1α— (hypoxia) positive cells, both of which are known as markers for vulnerable plaque, were densely distributed in the shoulder region of the plaque. Intraplaque microvessels, which are known to play a key role in causing IPH, were also densely presented in the same region. A previous report suggested macrophage polarization from M2 subtype to M1 subtype lead to hyperinflammation and hypoxic

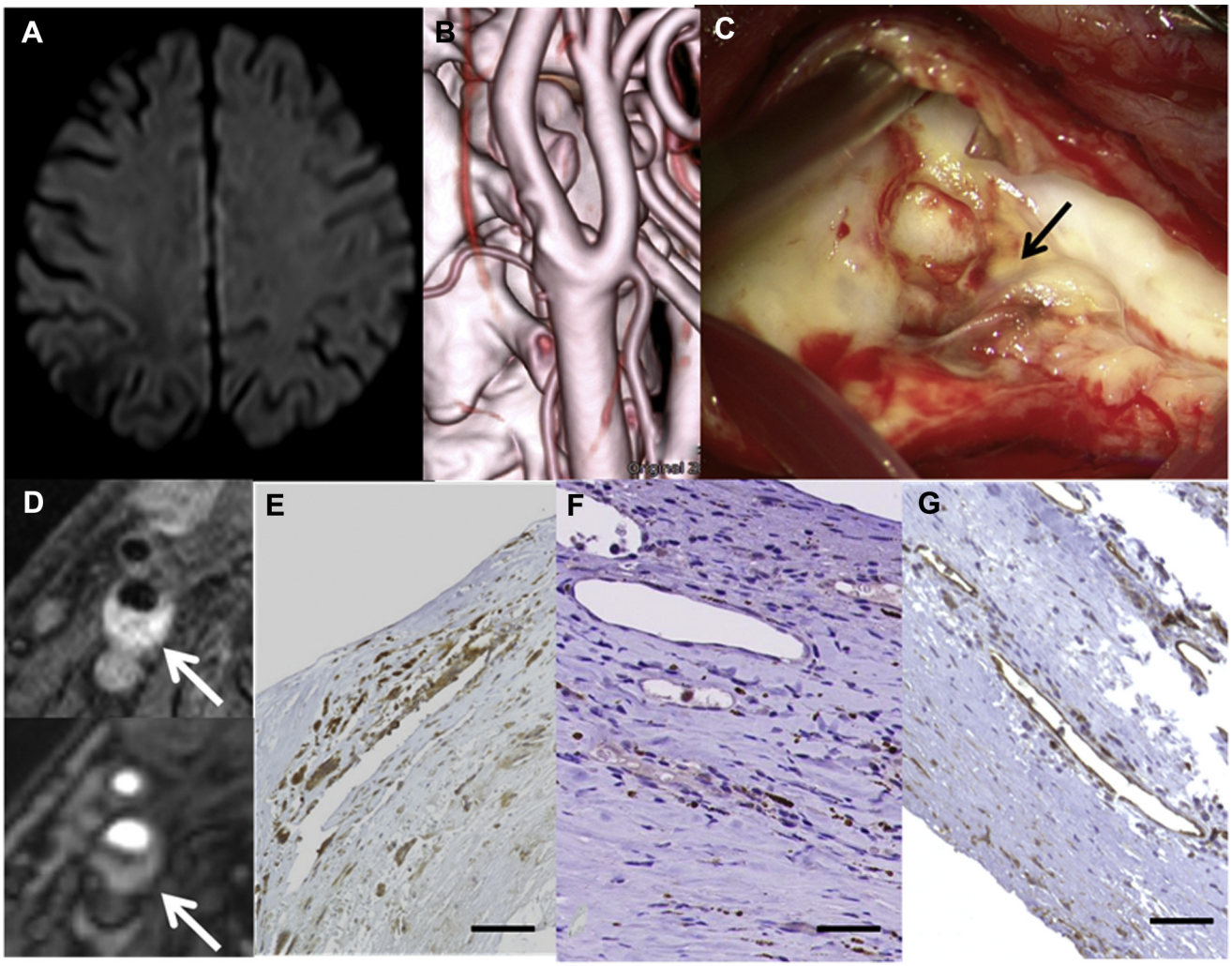

Figure 5. A 70-year-old man had a repeat episode of transient monocular blindness on the right side and was referred to our hospital. Diffusion-weighted magnetic resonance imaging (MRI) showed no cerebral infarction (**A**). Three-dimensional computed tomography angiography demonstrated mild (44%) stenosis of the right internal carotid artery (**B**). Intraoperative findings included an ulcer (*arrow*) formation and surface disruption of plaque (**C**). Plaque (*arrow*) MRI revealed high-intensity plaque on T1-weighted imaging and isointensity plaque on time-of-flight imaging, suggesting lipid-rich plaque (**D**). Photomicrographs of immunohistochemistry against CD11c (**E**), HIF-1α (**F**), and CD31 (**G**) show that the CD11c- and HIF-1α–positive cells and CD31-positive neovessels were densely distributed in the shoulder of the plaque. Scale bar, 50 μm.

state in plaque.[28] These states are prone to production of angiogenic factors, such as vascular endothelial growth factor, which lead to neovessels formation (CD31).[29]

These results strongly suggest that the present protocol of MRI can highly identify vulnerable plaque at quite high risk for subsequent cerebrovascular events in patients with symptomatic, mild carotid stenosis. In fact, the protocol used in this study has been confirmed to most sensitively detect vulnerable plaque.[30,31] Although our data are case series in a limited cohort, the results correlate very well with recent opinion that plaque vulnerability is essential to evaluate high-risk carotid stenosis and determine the necessity of CEA.[8] As previously mentioned, the degree of stenosis is known as a major independent variable in predicting the risk of further stroke.[4,8,32] Plaque morphology may be an alternative factor to determine it. Therefore, using multivariate analysis, Hokari et al.[33] reported that the irregular shape of the carotid lumen was the most powerful variable to predict symptomatic lesions in 30%–69% ICA stenosis. The present results may further provide us contemporary knowledge that the plaque component should be added as the third important factor to determine the outcome in patients with symptomatic, mild (less than 50%) carotid stenosis to the degree of stenosis and plaque morphology.

This study demonstrates that CEA is an effective strategy to prevent future cerebrovascular events for patients with symptomatic, mild carotid stenosis. There was no mortality in this study.

No patients experienced any further cerebrovascular events during a mean follow-up period of 38.5 ± 13.3 months. Only 1 patient (6.3%) developed transient hemiparesis contralateral to the operated carotid artery, but completely resolved within 30 days after CEA. The complication rate in this study was slightly higher than recommendation of the guidelines (less than 6%) for revascularization in symptomatic cases. Further studies with larger cohorts would be warranted to evaluate the clinical significance and safety of CEA on the outcome in patients with symptomatic, mild carotid stenosis.

Finally, there are some limitations in this study. This study is based on a single-center experience for 5 years; therefore, the sample size (n = 16) is rather small to establish a novel treatment guideline for patients with symptomatic, mild carotid stenosis in the plaque vulnerability era. CEA was the only procedure performed and mentioned in this study, whereas CAS is a less invasive method and might be appropriate. Similarly, there is no comparative cohort treated with consistent antiplatelet treatment or CAS. Therefore, we are now conducting a multicenter prospective cohort study in Japan to evaluate the outcome and optimal therapeutic strategy in patients with symptomatic, mild carotid stenosis, called the Mild, but Unstable Stenosis of Internal Carotid Artery Study (number 000023635), which began in January 2017. The study enrolls patients who experienced TIA, ischemic stroke, or retinal artery diseases ipsilateral to mild (less than 50%) carotid stenosis. Demographic, clinical, and radiologic data are being pooled. The patients are medically treated and, if necessary, they undergo CEA or CAS. All cohorts are strictly followed-up for 2 years. The final results will be reported in 2022. The results of the study are expected to provide valuable information to establish the therapeutic strategy for these patients. In addition, the interval between cerebrovascular events and CEA was not strictly determined in each patient; however, this was a prospective study. For the results, the value widely varied (24.8 ± 16.6 days). The optimal timing of CEA should be determined in the near future because plaque was vulnerable and at very high risk for subsequent stroke despite the mild degree of stenosis.

CONCLUSIONS

It is not rare the patients who are at high risk for subsequent ischemic events because of vulnerable plaque despite mild (less than 50%) carotid stenosis. MRI is quite useful to noninvasively detect such vulnerable plaque. CEA may be one procedure to treat this. Further studies with larger cohorts would be warranted to establish a novel treatment guideline for the patients in the plaque vulnerability era, but not in the stenosis degree era.

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