

The Detection of Carotid Plaque Rupture Caused by Intra-plaque Hemorrhage by Serial High-resolution MRI ~a case report

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A running title: plaque rupture and intra-plaque hemorrhage

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Abstract

Background: Plaque rupture is believed to be a critical event that leads to thromboembolic complications in atherosclerotic carotid artery disease. Intra-plaque hemorrhage can also cause fibrous cap disruption, and may be related to the progression of atherosclerosis. However, the mechanism that leads to fibrous cap disruption is not well defined, and there have been few reports in the literature that carotid plaque rupture could be clearly visualized by serial high-resolution MRI.

Case Description: We describe a case of a 79-year old man who presented with minor ischemic stroke. On diffusion weighted image, new multiple embolic spots were detected. Plaque rupture caused by intra-plaque hemorrhage could be clearly detected by serial high-resolution MRI of the cervical carotid artery. The patient underwent carotid endarterectomy, and an atheromatous plaque was extracted intact for histological analysis. In the histological section corresponding to the MRI slices, plaque rupture caused by intra-plaque hemorrhage was demonstrated.

Conclusions: This case represents a valuable example of artery-to-artery embolisms from a carotid plaque rupture secondary to intra-plaque hemorrhage. High-resolution MRI may have important applications in natural history studies and in clinical trials of carotid plaques.

Key words: carotid plaque rupture, high-resolution MRI, intra-plaque hemorrhage

Recently, it has been well demonstrated that atherosclerotic carotid plaque composition, rather than the degree of arterial stenosis, appears to be a critical determinant of both risk of carotid rupture and subsequent thrombogenicity [9, 10]. In particular, plaque rupture is believed to play an important role in acute ischemic events [4, 6, 7, 19]. Carr et al reported that the prevalence of plaque rupture was significantly higher among patients with ischemic stroke history [4]. Intra-plaque hemorrhage is also commonly observed in atherosclerotic carotid plaques, and some can cause fibrous cap disruption. Some investigators have suggested that intra-plaque hemorrhage may be caused by fragile neovasculature, and have founded that intra-plaque hemorrhage may produce a stimulus for the progression of atherosclerosis [13, 18].

The mechanisms of plaque rupture are not well understood: therefore, non-invasive imaging modality is needed that can serially examine the morphological and compositional characteristics of the lesions. High-resolution MRI is a useful non-invasive tool for serial studies of atherosclerotic lesions. A number of studies have demonstrated that MRI can be used to identify morphological and compositional features of atherosclerotic plaque both *in vivo* and *in vitro* [3, 8, 12, 21]. However, there have been few reports in the literature that carotid plaque rupture caused by intra-plaque hemorrhage could be clearly visualized by serial MRI studies [5, 11, 20, 22].

We describe an interesting case of carotid plaque rupture caused by intra-plaque hemorrhage detected by serial high-resolution MRI studies. These MRI studies corresponded with later histologic findings of carotid plaque rupture.

Case Report

A 77-year-old, right-handed man presented to an outside hospital after experiencing transient speech disturbance with no other clinical symptoms. Eight years before the onset of neurological symptoms, he was treated with coronary bypass graft (CABG) for

unstable angina pectoris. Although an acute cerebral infarction was not identified on MRI, radiology did demonstrate severe right cervical internal carotid artery stenosis by MR angiography (MRA). He was transferred to our institution for further diagnostic evaluation. Conventional intra-arterial angiography confirmed a 70% stenosis based on North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria. In the high-resolution MRI study of the carotid arteries, the plaque demonstrated high signal intensity on T1-weighted image (T1WI), and it was considered to be lipid-rich.

The patient had been followed in a clinical research study because he selected conservative therapy, and was continuously treated with anti-coagulant and anti-platelet agents. He had no other neurological complaints. Two years after the first onset, however, he presented with mild speech disturbance and memory disturbance again. A follow-up intracranial MRI demonstrated new multiple embolic spots in the right cerebral hemisphere on diffusion weighted image (DWI). Cardiac embolism was excluded due to the almost normal chest radiograph, electrocardiogram, and ultrasonic cardiogram. Laboratory findings were within normal limits. Conventional intra-arterial angiography confirmed a 75% stenosis based on NASCET criteria. Cerebrovascular reserve, as demonstrated by acetazolamide challenge in a ¹²³I-IMP-SPECT study was sufficient for maintenance. An obvious local signal change in the anterior arterial wall was detected in a serial high-resolution MRI study. The local area revealed slightly

high signal intensity on T1WI, low intensity on proton density weighted image (PDWI), high intensity on 2-dimensional time-of flight (2D-TOF), and low intensity on T2WI. This finding was suggestive of intra-plaque hemorrhage. Moreover, on the next distal slice of T2WI, the lesion's features were suggestive of a ruptured plaque showing discontinuity of the fibrous cap. These findings were compatible with artery-to-artery embolisms from a carotid plaque rupture caused by intra-plaque hemorrhage. After informed consent was obtained, the patient underwent carotid endarterectomy (CEA) on 28th November 2005, and the atheromatous plaque was excised intact and retrieved for histological analysis. In the corresponding hematoxylin and eosin (H&E) stained histological slice, intra-plaque hemorrhage corresponding to the previously described signal changes on MRI was confirmed. The lesion was consistent with an advanced complicated plaque (the American Heart Association classification; type VI). Moreover, the plaque's fibrous cap revealed partial discontinuity, which suggested incomplete healing subsequent to plaque rupture. Postoperatively, the patient suffered from mild swallowing difficulty, but gradually recovered. He continues to be followed on a clinical research study protocol.

Discussion

Cervical carotid disease is the primary cause of ischemic stroke and primarily caused by atherosclerosis, which is a chronic disease characterized by the accumulation of lipids and fibrous tissue within the arterial wall [17]. Traditionally, the severity of

arterial stenosis has been used to identify high-risk carotid plaques. However, it has been demonstrated that mild-to-moderate coronary artery stenosis may lead to acute myocardial infarction, and recently, it has been well established that the risk of an acute event mediated by rupture is predicated on the plaque component rather than the degree of luminal narrowing [1, 9, 10].

Plaque rupture, that is, the disruption of the fibrous cap that overlies the thrombogenic subendothelial necrotic core, is believed to be an important event that leads to acute ischemic events, such as stroke and transient ischemic attack [4, 6, 7, 19]. However, some plaques may rupture silently without causing symptoms [5, 14]. Previous reports suggested the presence of a fibrous cap that is thinned or ruptured was the critical feature in the vulnerable atherosclerotic plaques [4, 6, 7, 19]. Falk founded that almost all acute coronary events are precipitated by plaque rupture [7], and Carr noted plaque rupture in 74% of plaques in symptomatic lesions compared with 32% of plaques from asymptomatic ones [4]. Yuan et al. reported that patients with ruptured caps were 23 times more likely to have had a recent TIA or stroke compared with patients with thick fibrous caps [22]. Although it is suggested that factors contributing to plaque rupture include not only unfavorable plaque morphologies such as a thin fibrous cap and extensive lipid pool with intra-plaque hemorrhage, but also the degree of inflammation within the plaque and biomechanical stresses on the plaque as a result of blood flow [16], the mechanisms that lead to fibrous cap disruption are not well defined. This lack of understanding is due in part to the lack of an animal model of plaque rupture and thus we are restricted to autopsy tissue or histological studies of plaques excised at the time of surgery.

Intra-plaque hemorrhage is also commonly observed in atherosclerotic carotid plaques and considered by some to be caused by rupture of fragile neovasculature, which lacks the support by smooth muscle cells and experiences focal discontinuity of

the endothelial lining [13, 18, 19]. In our studies, we sometimes observe extensive neovasculature surrounding intra-plaque hemorrhage. But we also observe no neovasculature surrounding hemorrhage, which may be suggested that microvessels have completely destroyed as well as not a trace remains of neovasculature. Intra-plaque hemorrhage can frequently cause fibrous cap disruption. Kolodgie et al found that immature microvessel-related intra-plaque hemorrhage has been associated with lipid core expansion through the accumulation of free cholesterol and phospholipids from erythrocyte membranes, and this hemorrhage may stimulate atherogenic activity by being a source of free cholesterol and macrophage activation [13]. Repeated intra-plaque hemorrhage may be a marker for plaque instability and may be a predisposing factor toward a more rapid progression of atherosclerosis.

The healing process after plaque rupture is also believed to be an important mechanism of plaque instability that leads to ischemic events [2, 14]. Healed ruptures in the coronary arteries are readily detected microscopically by identification of breaks in the fibrous cap surrounded by a repair reaction [15]. It is speculated that repeated plaque rupture and thrombosis can incite plaque progression in the absence of clinical ischemic events [2, 14]. Therefore, an understanding of the process by which these ruptures heal is of critical clinical importance. Although there are some limitations about extrapolating carotid research from the results of coronary research, our case described here may provide clues to this healing process following plaque rupture.

As mentioned above, the mechanisms of plaque rupture are not well understood: therefore a non-invasive imaging modality is needed that can serially examine the morphological and compositional characteristics of the lesions to monitor the effects of therapeutic interventions for stabilization on the plaque composition. High-resolution MRI is a promising non-invasive tool for characterizing atherosclerotic carotid plaque composition and provides excellent contrasted images of the arterial wall [3, 8, 12, 21].

It is possible not only to visualize plaque components (lipids and fibrosis) but also to detect fibrous cap disruption or intra-plaque hemorrhage by using a multisequence algorithm. Hatsukami et al. reported that high-resolution MRI is capable of distinguishing intact, thick fibrous caps from thin or ruptured caps in human carotid plaques with good sensitivity and specificity [11]. They demonstrated that thick fibrous caps appear as a juxtaluminal band of low signal in time-of-flight (TOF) MR images, but that in thin or ruptured fibrous caps, this band is absent and there is a region of hyperintense signal adjacent to the lumen. In the case described here, the definitive fibrous cap disruption was demonstrated on T2WI and intra-plaque hemorrhage was demonstrated on serial multisequence images. These changes were verified histologically. The ability of high-resolution MR to visualize the state of fibrous cap has been reported; however, there are few reports describing discovery by serial MRI examination of carotid plaque rupture secondary to intra-plaque hemorrhage [5, 11, 20, 22]. Therefore the present case is an excellent example for understanding the mechanism of atherosclerotic carotid plaque rupture.

In conclusion, this patient represents a valuable example of artery-to-artery embolisms from a carotid plaque rupture caused by intra-plaque hemorrhage. This rupture was clearly visualized by high-resolution MRI and demonstrated histologically. MRI may have important applications in natural history studies and in clinical trials of carotid artery plaques. The elucidation of the mechanism of atherosclerotic carotid plaque rupture is expected by the further research, which may include combination of morphologic plaque imaging and functional plaque imaging using various contrast agents.

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Figure legends

Fig.1- High-resolution MR images of right internal carotid artery performed in April 2003

A: Carotid plaque is demonstrated as high signal intensity on T1WI.

B: On PDWI, carotid plaque reveals iso-intensity.

C: On two-dimensional TOF (2D-TOF) image, arterial wall does not reveal high signal change.

Fig.2-

A: Right carotid angiogram performed in 2005 reveals internal carotid artery stenosis (75% stenosis based on NASCET criteria) including common and external carotid stenosis.

B,C,D,E: On DWI, multiple high signal spots (arrows) are demonstrated on the right cerebral hemisphere (parietal lobe, temporal lobe, caudate nucleus, frontal lobe).

Fig.3- High-resolution MR images of right internal carotid artery in November 2005

A: Carotid plaque is demonstrated as high signal intensity with a slightly low signal change on the anterior arterial wall on T1WI.

B: A distinctive low signal change on the anterior arterial wall is demonstrated on PDWI.

C: A high signal change on the anterior arterial wall is demonstrated on 2D-TOF image, which is suggestive of intra-plaque hemorrhage.

D: On contrast-T1WI, the area with a local signal change is enhanced by gadolinium agent.

E: A low signal change on the anterior arterial wall is demonstrated on T2WI.

F: A discontinuity of fibrous cap with a low signal change on the anterior arterial wall is clearly demonstrated on the next distal slice of T2WI.

Fig 4 – Histological evaluation of carotid plaque corresponding to the MRI slice

A: Carotid plaque reveals advanced atherosclerotic lesion. (H&E stain, American Heart Association classification; type VI) *; lumen

B: Intra-plaque hemorrhage is demonstrated on the anterior arterial wall. (H&E stain 100×, scale bar; 50µm)

C: A partial discontinuity of the fibrous cap is demonstrated, which suggested incomplete healing subsequent to plaque rupture. (arrow, Azan stain 50×, scale bar; 500µm) *; lumen

Table-1: The high-resolution MRI protocol (Signa, GE Medical System, USA)

T1WI; T1-weighted imaging, T2WI; T2-weighted imaging, PDWI; proton-density weighted imaging, 2D-TOF; two-dimensional time-of-flight imaging, TR; repetition time, TE; echo time

| | |
|------------------|--|
| T1WI | 2-dimensional fast-spin echo (FSE), TR/TE = 800/11 ms, echo train length (ETL) = 4, slice thickness 2.5 ~ 3.0 mm, fat suppression |
| T2WI/PDWI | FSE, black-blood (double-inversion recovery) technique, TR = 2 heart beats (1400 ~ 2000 ms, depending on heart rate), TE = 80 ms for T2WI and 20 ms for PDWI, ETL = 16, slice thickness 2.5 ~ 3.0 mm, fat suppression |
| 2D-TOF | TR/TE = 50/4.2 ms, flip angle 45 degrees, field-of-view = 13 cm, matrix size 256 x 128, slice thickness 2.5 ~ 3.0 mm, fat suppression |

Table 1

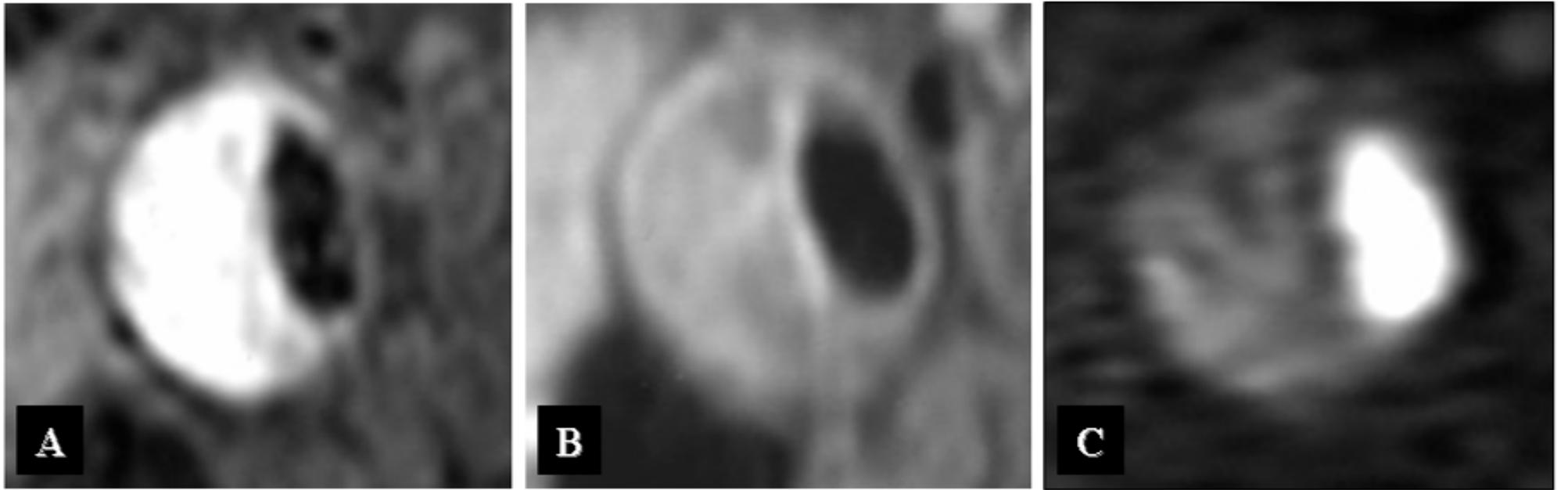


Figure-1

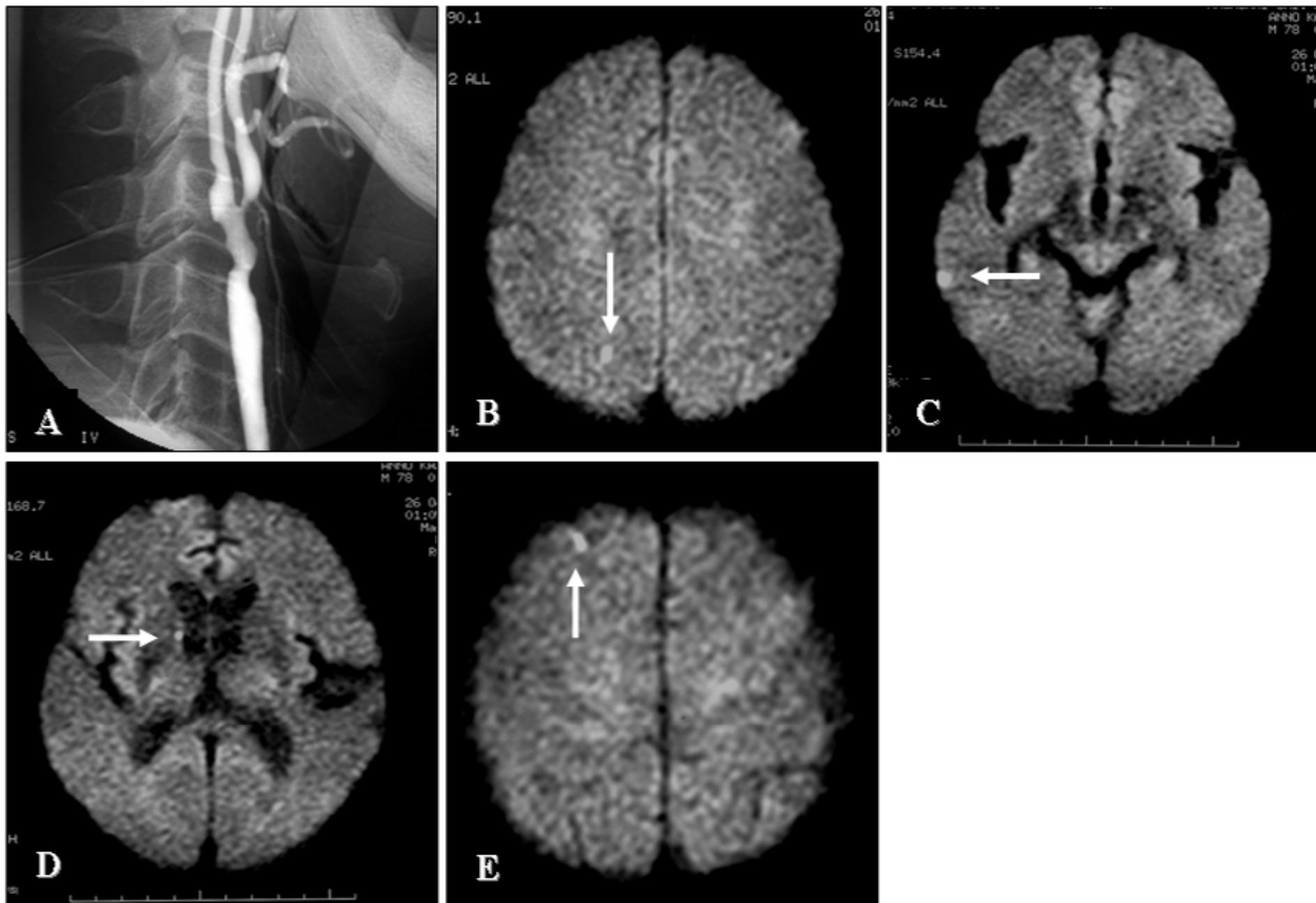


Figure-2

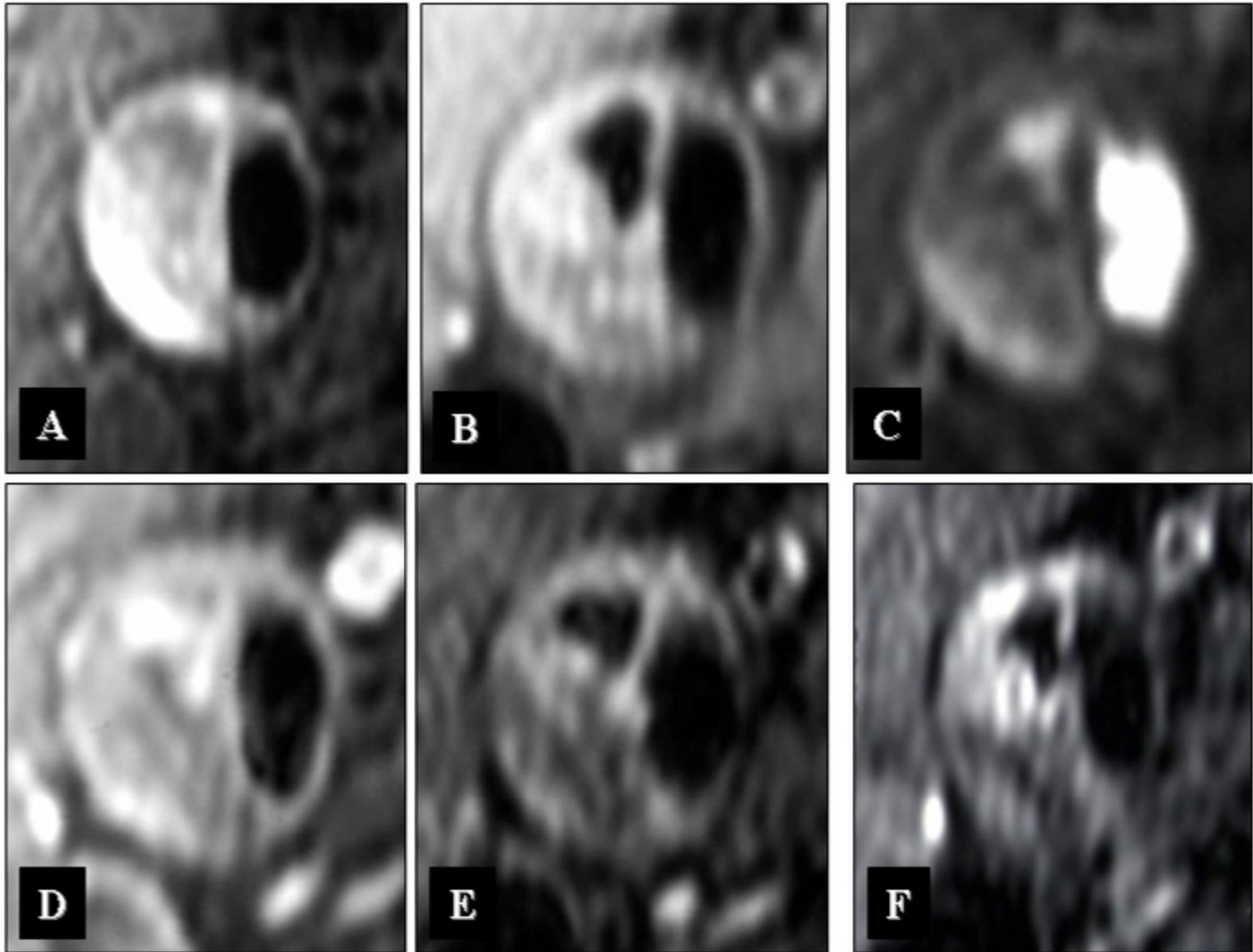


Figure-3

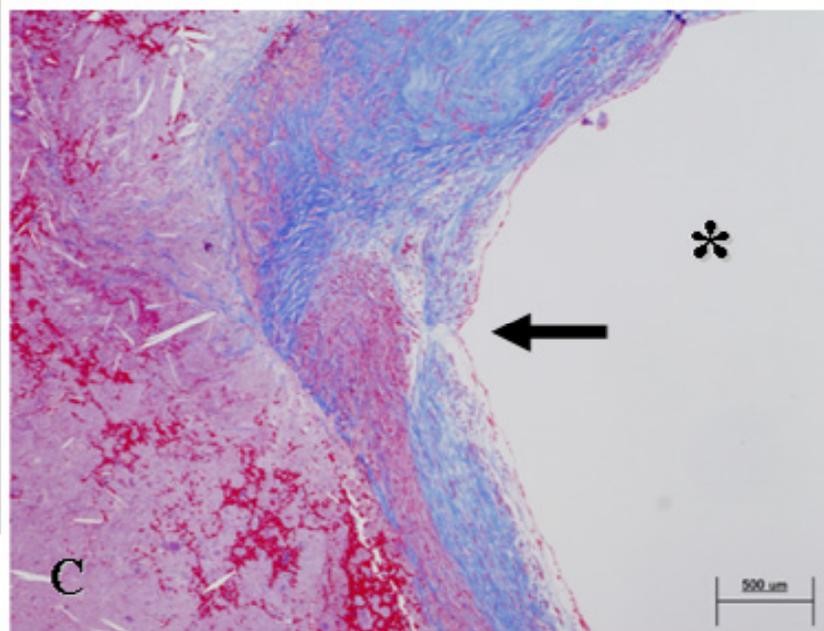
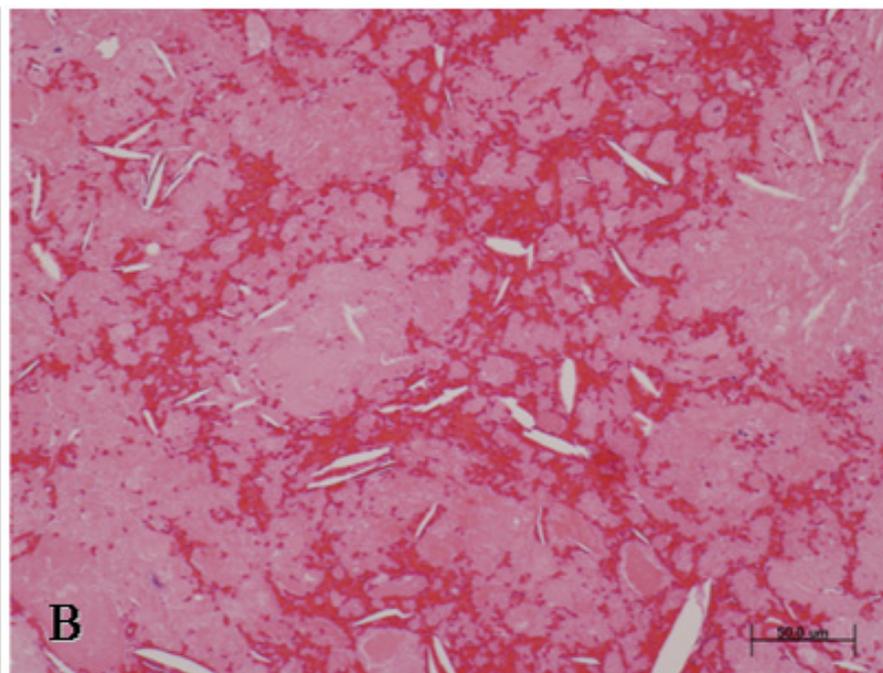
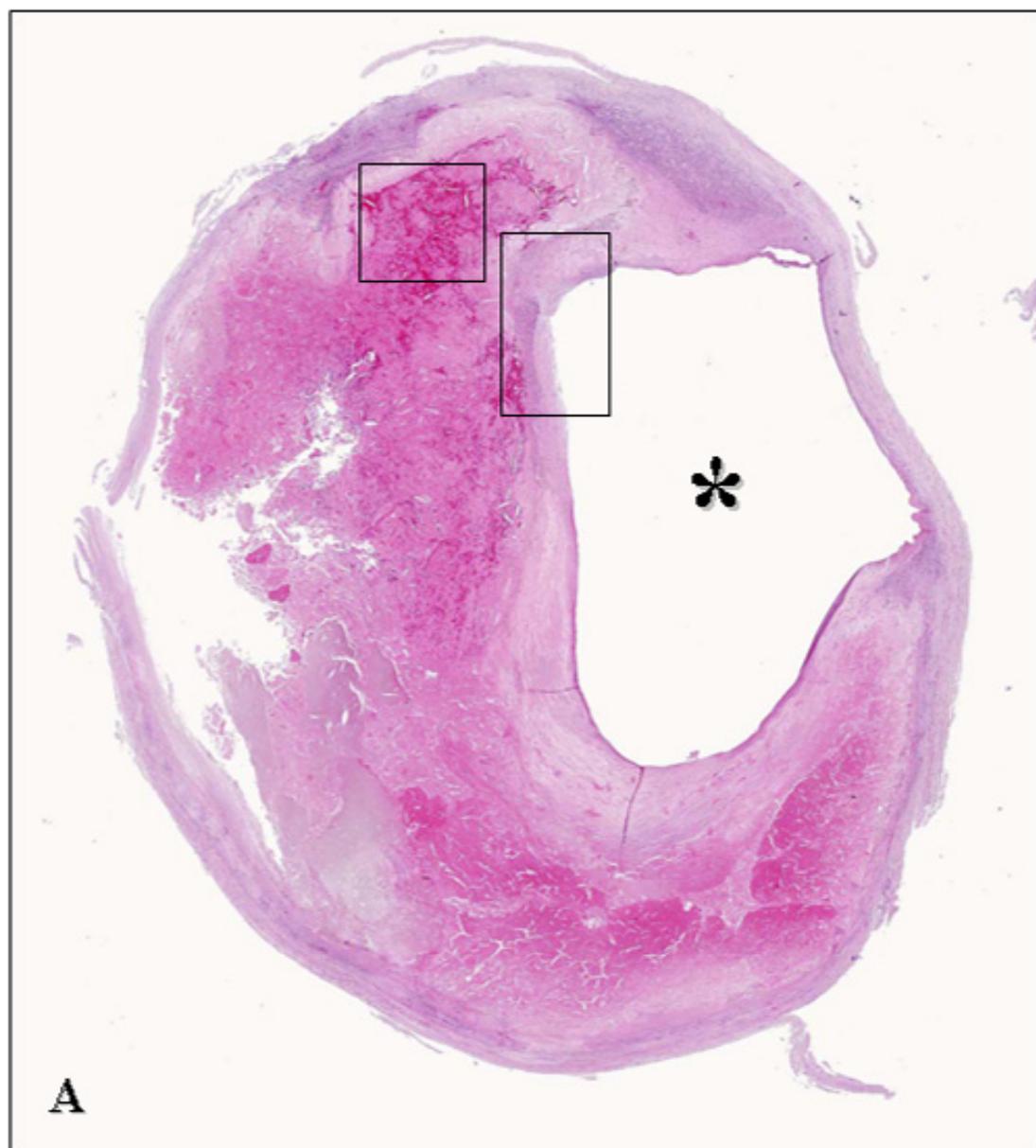


Figure-4