Clinical Evaluation of High-Resolution MRI Combined With DWI In Identifying Vulnerable Carotid Plaque

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Research Article

Keywords: high resolution MRI, diffusion weighted imaging, vulnerable plaque, apparent diffusion coefficient, inflammatory markers

Posted Date: June 23rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-596735/v1

Version of Record: A version of this preprint was published at The Neurologist on March 29th, 2022. See the published version at https://doi.org/10.1097/NRL.0000000000000432.

Abstract

Objective: High-resolution magnetic resonance imaging (HR-MRI) combined with diffusion weighted imaging (DWI) is used to identify Vulnerable plaques (VP) and their characteristic components, and apparent diffusion coefficient (ADC) correlation analysis with serum inflammatory markers to assess plaque vulnerability.

Methods: Into eligible 60 patients, including vulnerable plaques group (VP group) of 29 cases and the non-vulnerable plaques group (N group) of 31 cases, measure the two groups of the average ADC, serum levels of inflammatory markers [high-sensitivity C-reactive protein (hs-CRP), myeloperoxidase (MPO) and erythrocyte sedimentation rate (ESR)], compared the VP plaque characteristics of different components and the level of blood vessel walls of ADC, assessment of patients with serum levels of inflammatory markers plaques ADC average correlation.

Results: The results showed that the ADC mean value of the plaques in the VP group was significantly lower than that in the N group, and the levels of hs-CRP and MPO were correlated with the ADC mean value of the plaques.

Conclusion: The ADC value of plaque measured by HR-MRI combined with DWI sequence can quantify the identification of vulnerable plaque and its characteristic components, reflect the inflammation of plaque to a certain extent, and thus prevent and treat stroke and other adverse outcomes more effectively.

Introduction

Carotid atherosclerotic plaque is one of the main causes of ischemic stroke[1]. Plaque stenosis is not the only factor leading to ischemic stroke. Previous studies have shown that plaque composition and vulnerability are more closely related to it[2]. Inflammation is considered to be an important factor involved in the development, progression and rupture of atherosclerotic plaques, leading to thrombosis[3]. Effective identification of active plaque inflammation is a key link for accurate identification of vulnerable plaques. In recent years, HR-MRI of intracranial arteries has been proved to have higher reproducibility and clinical significance, and is an important technique for in vivo evaluation of intracranial arterial walls and plaques [4, 5]. For extracranial plaques, carotid ultrasound and CTA are more dependent. Ultrasound, CTA and DSA are not sensitive to inflammation. Although PET-CT can reflect inflammation through uptake rate, it is expensive and has potential radiation damage to patients. In arthritis studies, MRI combine with DWI can show early changes in inflammation [6, 7]. HR-MRI has been shown to be a sensitive tool for morphological identification of atherosclerotic plaques, compatible with histology [8].

Skinner *et al* confirmed that HR-MRI combined with DWI or SWI functional imaging had higher spatial resolution and tissue component recognition for carotid artery vulnerable plaques[9–11]. DWI is the only non-invasive imaging examination method that can detect molecular diffusion movement in vivo. It can accurately distinguish plaque components from normal vascular wall tissues by showing microscopic pathological changes reflecting the degree of molecular diffusion movement restriction and combining

with quantifiable ADC. However, there are few studies on this topic at present. Therefore, correlation analysis was conducted between serum inflammatory markers and imaging parameters in this study to explore the value of DWI in evaluating vulnerable carotid plaques.

Materials And Methods

Patients. Between September 2018 and March 2020, 60 patients in the Department of Neurology China-Japan Union Hospital of Jilin University were selected, including 43 males and 17 females, aged between 39 and 80 years. The present study was approved by the Ethics Committee of China-Japan Union hospital of Jilin University (approval no.2020010812; Changchun, China). Patients who participated in this research had complete clinical data. Signed informed consents were obtained from the patients and/or the guardians.

Inclusion and exclusion criteria. Inclusion criteria: i) the age of the patient fell within the range 18–80 years; ii) Carotid plaque had been identified by carotid ultrasound; iii) Patients have completed the baseline data examination; and iv) the patients and their families were willing to sign informed consent forms. *Exclusion criteria*: i) the patient has a serious life-threatening disease; ii) patients could not perform the examinations applied in this study, such as: metal prostheses or pacemaker implantation in vivo; claustrophobia; psychiatric disorders; drug and alcohol abuse; convulsions; iii) HR-MRI image quality score was ≤ 2, and subsequent image data analysis cannot be performed; iv) patients who have received intravenous thrombolysis and interventional therapy;and v) patients with chronic inflammation were excluded.

Study groups. According to the American College of Cardiology's modified the American Heart Association (AHA) classification standard for MRI, the plaque signal performance on high-resolution MRI was reviewed and divided into vulnerable plaque group (VP group, n = 29) and non-vulnerable plaque group (N group, n = 31) [12]. Through the signal characteristics of each series □, □ and □ plaque into the VP group, the rest of the type into N groups.

Collection of image data

Cervical vascular examination. Mindray DC-8 color Doppler ultrasound imaging instrument (Mindray Medical International Limited) was used with the probe frequency of 9Hz to scan the bilateral carotid arteries and vertebral arteries respectively, and the presence of carotid artery plaque was detected according to color Doppler flow imaging and echo characteristics.

Carotid HR-MRI examination.

Scanning was performed using a German Siemens (model Skyra) 3.0T superconducting magnetic resonance scanner, and axial imaging was performed using a head-neck combined 20-channel coil and a carotid artery dedicated 4-channel coil. The carotid artery bifurcation as shown in the MRA reconstructed automatically by three-dimensional time-of-flight (3D-TOF) was taken as the center to scan the upper and

lower 3cm of the carotid artery bifurcation. In this study, the signals of adjacent muscle tissues were used as iso-signals to compare the signal levels of carotid artery plaques in different sequences of HR-MRI. HR-MRI + DWI sequence and main parameters: carotid artery 3D-TOF scan [time of echo (TE), 4 ms; time of repetition (TR), 29 ms; field of View (FOV), 180 mm], T1WI-TRA (TE, 9.2 ms, TR, 800 ms, FOV, 180 mm. TR,1300 ms). DWI (TE,88/155 ms; TR,3300 ms; FOV, 242 mm). The B value of DWI sequence is 50 s/mm^2 and 600 s/mm^2, and the voxel size is 1.2 mm×1.2 mm×3.0 mm.

Image post-processing. Image quality of all sequences of plaque HR-MRI and DWI was evaluated by two experienced physicians according to the HR-MRI quality rating criteria, which divided image quality from low to high into 1 to 4, excluding images with score ≤ 2[13]. The AHA plaque typing method was followed, which was based on the modified plaque classification standard for nuclear magnetics in which plaque types I-II, III, VII and VIII are classified as stable plaque (N group), and plaque types IV-V and VI are categorized as vulnerable plaque (VP group)[6, 14]. The main observation targets were lipid core (LC), fibrous cap (FC), calcification and intraplaque hemorrhage (IPH) of plaque.

With Siemens post-processing workstation, the DWI sequence ADC diagram is reconstructed. With the measurement tool of DICOM browser RadiAnt DICOM Viewer 5.5.0, the ADC average of all the plaques and their characteristic components is independently measured. Determination of ADC mean value of plaque components: i) In conventional HR-MRI sequence images, the area of signal change of target components (normal vessel wall, LC, FC and IPH) was manually designated as the Region of Interest (ROI); ii) Manually copy the ROI of the target component into the ADC diagram at the corresponding level; iii) Measure ADC values of three times of target ROI at each level and take the average value. When two or more plaques are present in the same patient, the average value of each plaque is measured according to the above method and then taken as the average ADC value of the plaque of the patient. The ADC values of image quality and ROI above were analyzed by two radiologists with 15 and 13 years of experience in a blind way, and consensus was reached through discussion in case of disagreement.

Test method. Serum levels of inflammatory markers hs-CRP, MPO and ESR were measured in all subjects. The hs-CRP was determined by antu A2000 automatic immune analyzer, and the reagent was used by the hypersensitive C-reactive protein (hs-CRP) detection kit (magnetic particle chemiluminescence). MPO was determined using the human MPO assay kit (enzyme-linked immunoassay). The ESR was determined by Westergren method.

Statistical analysis. The obtained research data were statistically analyzed using SPSS software version 25.0 (IBM Corp.), and comparisons between the data groups were performed by using the $\chi 2$ test. Bland-Altman method was used to evaluate the consistency of ADC mean values of plaques. Multiple comparisons were performed using single-factor ANOVA and LSD test. The correlation between serum inflammatory markers (hs-CPR, MPO and ESR) and the mean value of plaque ADC was analyzed by Pearson correlation analysis.

Results

Comparison of baseline data: The number of cases with carotid plaque in VP group and N group were statistically analyzed. The general baseline data and risk factors of arterial plaque formation, including gender, age, smoking and alcohol history, hypertension history, diabetes history, coronary heart disease history, TG, CHOL, LDL, HDL, Hcy levels, were not significantly different.

ADC comparisons between different groups. The ADC of the overall plaque and the characteristic components of the vascular wall and vulnerable plaque measured by the two doctors were 1.3% and 3.2%, respectively, that were outside the consistency limit. Therefore, the ADC average values measured by the two physicians are consistent. Mean ADC results of each characteristic component of the vascular wall and plaque were performed using ANOVA. Homogeneity of variance test was as follows: P = 0.146 (P > 0.05), namely, homogeneity of variance of ADC mean values of vessel wall, lipid core, fibrous cap and IPH. ANOVA univariate analysis showed that P = 0.00 (P < 0.05), there were statistically significant differences in ADC values between the vascular wall, lipid core, fibrous cap, and IPH as a whole. Multiple comparisons of LSD test showed that P = 0.00 (P < 0.05; shown in Table 1). The mean value of ADC values in VP group and N group was (1.71 ± 0.21 vs. 1.87 ± 0.18×10^{-3} mm^2/s; P = 0.005). The serum levels of inflammatory markers (hs-CRP, MPO and ESR) in the VP group were higher than that in the N group (shown in Table 2). The levels of hs-CRP in the VP group and the N group were (3.96 ± 2.12 vs. 2.63 ± 1.96 mg/dL; P = 0.015). The MPO level of VP group and N group was (75.52 ± 45.10 vs. 53.49 ± 35.19 mg/dL. P = 0.038). The level of ESR in VP group and N group was (17.70 ± 9.31 vs. 14.35 ± 8.16 mg/dL; P = 0.145). Pearson correlation analysis showed that serum inflammatory markers (hs-CRP, MPO and ESR) were correlated with plaque ADC value (shown in Table 3).

Table 1
ADC mean results of each characteristic component of vascular wall and plaque

Project	Vascular wall (n = 78)	LC (n = 34)	IPH (n = 10)	FC (n = 34)
The average ADC (x 10^{-3} mm^2/s)	1.36 ± 0.21	0.57 ± 0.16	1.05 ± 0.13	1.67 ± 0.28
The ADC mean values of vessel wall, LC, and IPH were statistically significant.				
Mean ADC results of each characteristic component of the vascular wall and plaque were performed using ANOVA. Homogeneity of variance test was as follows: P = 0.146 (P > 0.05), namely, homogeneity of variance of ADC mean values of vessel wall, lipid core, fibrous cap and IPH.				

Table 2
Comparison of ADC mean results and serum inflammatory markers

Project	The VP group	N group	P values
The average ADC (x 10^{-3} mm^2/s)	1.71 ± 0.21	1.87 ± 0.18 × 10^{-3}	0.005
hs - CRP (mg/dl)	3.96 ± 2.12	2.63 ± 1.96	0.015
MPO (mg/dl)	75.52 ± 45.10	53.49 ± 35.19	0.038
ESR (mg/dl)	17.70 ± 9.31	14.35 ± 8.16	0.145
Patients with VP group and N group the average ADC, hs-CRP, MPO level have obvious difference (P < 0.05). There was no significant difference in ESR between the VP group and the N group (P > 0.05).			

Table 3
Correlation analysis between serum inflammatory markers and ADC mean value

Project		The hs - CRP (n = 60)	MPO (n = 60)	The ESR (n = 60)
The average ADC (n = 60)	R value	0.784	0.613	0.002
	P values	0.00**	0.00**	0.988
The serum hs-CRP level was negatively correlated with the mean value of plaque ADC (r=-0.784, P < 0.05), and the serum MPO level was negatively correlated with the mean plaque ADC value (r=-0.613, P < 0.05). There was no significant correlation between serum ESR level and mean ADC value of plaque (P > 0.05).				

Comparison plaque characteristics and images between cervical vascular ultrasound and the DWI sequences of HR-MRI: The assessment of vulnerable plaques by cervical vascular ultrasound and ADC maps of HR-MRI combined with DWI is consistent. The size of the posterior wall plaque of the common carotid artery biforked was 0.97×0.24 cm, ADC was high signal (shown in Fig. 1), the ADC mean value of each component was 1.79×10^{-3} mm^2/s, hs-CRP was 0.55 mg/dl, MPO was 18.14 mg/dl and ESR was 6 mg/dl. A mixed echo plaque was observed in the left carotid sinus to the anterior wall of the initial segment of the internal carotid artery, with a size of about 2.2×0.30 cm. ADC was iso-signal (shown in Fig. 2). The ADC mean value of each component was 1.62×10^{-3} mm^2/s, hs-CRP 2.79 mg/dl, MPO 65.49 mg/dl and ESR 8 mg/dl. Calcium spots were observed on the anterior wall of the carotid sinus, with a size of 1.2×0.25 cm. ADC was low signal (shown in Fig. 3). The ADC mean value of each component was 1.51×10^{-3} mm^2/s, hs-CRP 1.29 mg/dl, MPO171.7 mg/dl and ESR 6 mg/dl. HR-MRI combined with DWI can clearly show the characteristic components of vessel wall and plaque (lipid core, fibrous cap and IPH), and can be quantitatively identified by measuring ADC value. The higher the ADC value, the lower the level of serum inflammatory markers. HR-MRI is more effective in identifying vulnerable plaques and has obvious advantages compared with ultrasonography (shown in Fig. 1–3).

Discussion

Many previous studies have contributed to the degree of stenosis of arteries and plaque morphology, however, the occurrence of adverse outcome events such as cerebral infarction or TIA does not depend entirely on the volume of carotid plaque or the degree of carotid stenosis. Carotid vulnerable plaques are present in 20% of cerebrovascular patients with carotid stenosis rate less than 50%[15], and in 6–8% of patients with cerebrovascular disease without carotid stenosis[16].Therefore, accurate identification of vulnerable plaques and their compositional characteristics can better prevent the occurrence of adverse outcome events such as cerebral infarction or TIA.

On the basis of previous studies that applied HR MRI based DWI sequences to identify inflammatory lesions in other diseases, this study examined the association between ADC values of HR MRI based DWI sequences and plaque related inflammatory markers to identify changes in plaque active inflammation [17, 18]. The consistency of ADC values of plaques and their characteristic component ROI measured by the two physicians was analyzed using Bland-Altman method, which is the basis for quantitative analysis of imaging information to identify lesions, and is consistent with the conclusions of previous studies on quantitative identification of lesions using HR-MRI combined with DWI sequence[19, 20]. HR-MRI combined with quantifiable functional imaging has improved the deficiencies of traditional MRI in the identification of micro-lesion structures. HR-MRI showed that ADC values of the characteristic components of vulnerable plaques (vascular wall, lipid, FC, and IPH) were statistically different (shown in Table 1). In the DWI sequence of MRI, the weighted sum of quantized MRI signals from inside and outside the cells was performed, and the results were expressed as ADC. ADC can deduce the microenvironment of cells by measuring the limitation of different microstructures on the diffusion of water molecules[21]. This study found increased serum inflammatory markers (hs-CRP, MPO) in response to active plaque inflammation in a subset of plaques not defined as VP by conventional HR-MRI sequences and a correlation between serum hs-CRP, MPO and ADC values (shown in Fig. 1–3), which may provide new insights into the noninvasive diagnosis of VP.

The VP group had higher levels of serum inflammatory markers (hs-CRP, MPO) than the N group, the VP group had lower mean ADC values than the N group, and the levels of serum inflammatory markers (hs-CRP, MPO) were inversely correlated with the ADC values of the plaques, whereas hs-CRP, MPO were serum markers reflecting active inflammation of the plaques. Therefore, the ADC values could be applied to reflect the inflammation of the plaques, and complement the application of conventional HR-MRI for assessment of plaque vulnerability.

It is also demonstrated that hs-CRP and MPO participate in inflammatory response and are closely related to the formation of vulnerable cervical plaques. Although some evidence[22] has shown that ESR has a certain diagnostic effect on unstable plaques, in this study, there was no significant difference between the VP group and the N group, indicating that the diagnosis of ESR on vulnerable plaques remains to be explored.

The present study has certain limitations. Firstly, although motion detection technology was added in this study to improve the accuracy of ADC images, data bias caused by image resolution and motion pseudo-error cannot be excluded. Secondly, the sample size of the present case was small, and there may be a certain bias associated with some of the conclusions. Finally, the lack of a gold standard of pathology as a verification tool in this study is a limitation of current research.

Conclusion

The DWI sequence and its ADC of HR-MRI can be used to evaluate the carotid artery vulnerable plaques and their characteristic components in a convenient and non-invasive manner, reflecting that plaque active inflammation is superior to other imaging examinations and has unique advantages in the prevention and treatment of ischemic stroke.

Abbreviations

High-resolution magnetic resonance imaging (HR-MRI); diffusion weighted imaging (DWI); Vulnerable plaques (VP); apparent diffusion coefficient (ADC); non-vulnerable plaques group (N group); high-sensitivity C-reactive protein (hs-CRP), myeloperoxidase (MPO) ; erythrocyte sedimentation rate (ESR).

Declarations

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of China-Japan Union hospital of Jilin University (approval no.2020010812; Changchun, China).

Consent for publication

We’re in complete agreement.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

None.

Funding

Funding was received from the Jilin Province Science and Technology Project (grant no. 20190303163SF). Funding agencies provide financial support.

Authors' contributions

Xinyi Wang interpreted and analyzed the data. Jing Li wrote the manuscript, analyzed the data and designed the study. Xin Wang and Jialu Gao performed statistical analysis and data analysis. Hongyan Jing collected the ultrasound and MRI data of the patients, and acquired and interpreted data. Ying Xing reviewed the article and designed the study. All authors read and approved the final manuscript.

Acknowledgements

The authors would like to thank the teachers of department of neurology and department of radiology, the China-Japan Union Hospital of Jilin University.

Statement of Ethics

The current study comply with internationally accepted standards for research practice and reporting. The current study was approved by the Ethics Committee of China-Japan Union hospital of Jilin University (approval no. 2020010812). Patients who participated in this research had complete clinical data. Signed informed consents were obtained from the patients and/or the guardians.

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Figures

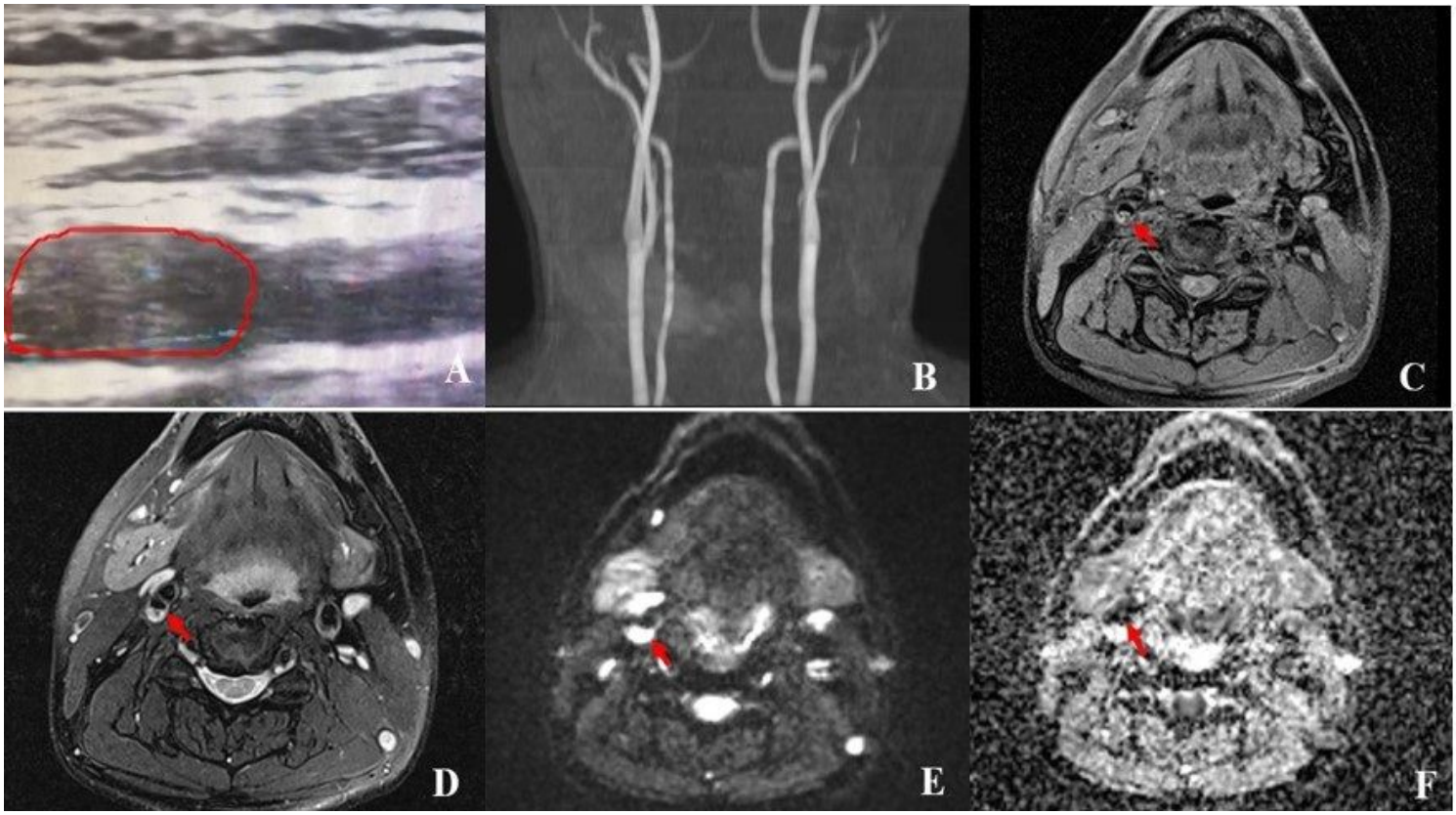

Figure 1

Imaging findings with IPH. A: cervical vascular ultrasound, B: MRA, C: T1, D: T2, E: ADC, F: DWI.

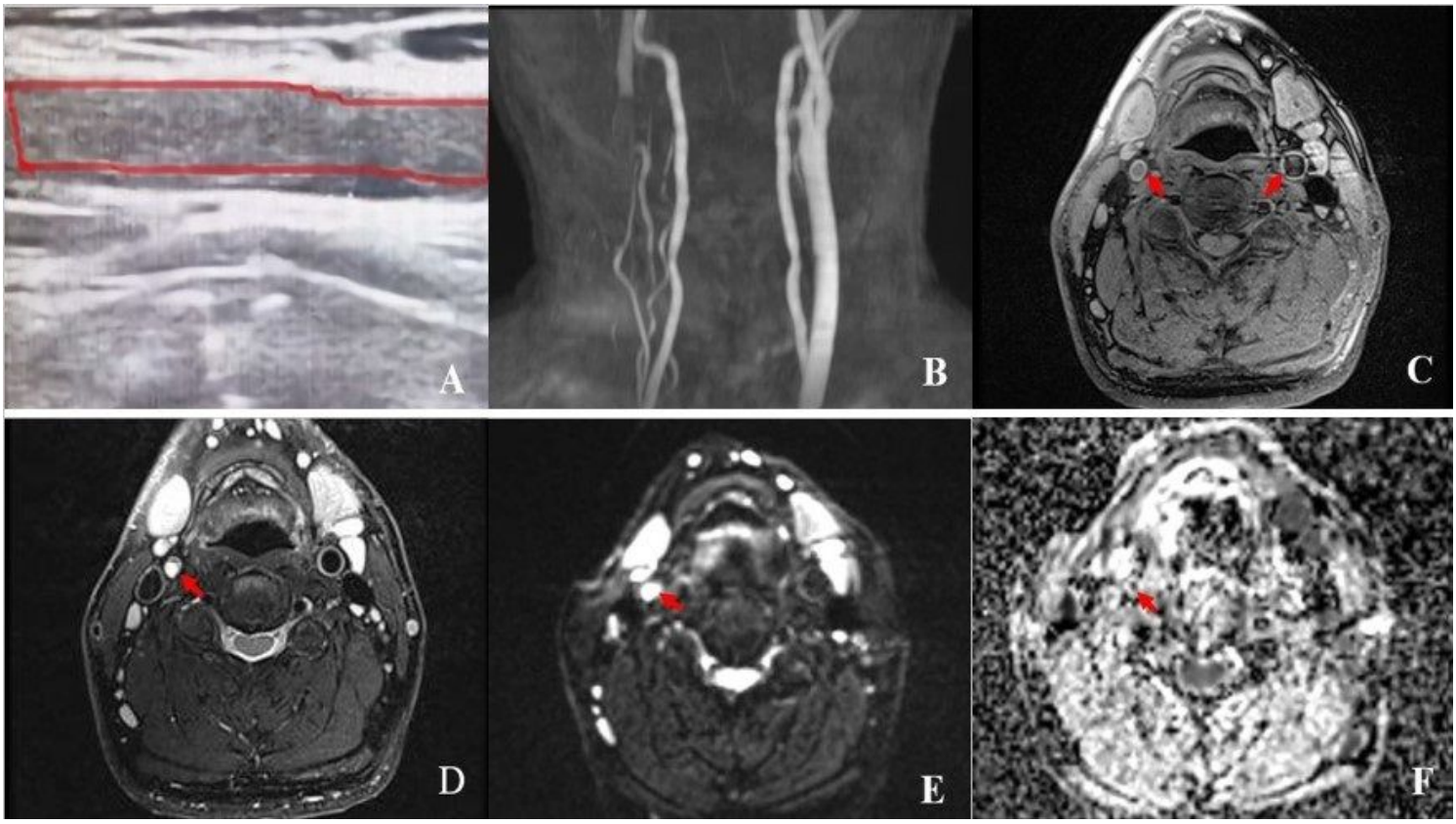

Figure 2

Imaging findings of plaques with thrombosis. A: cervical vascular ultrasound, B: MRA, C: T1, D: T2, E: ADC, F: DWI.

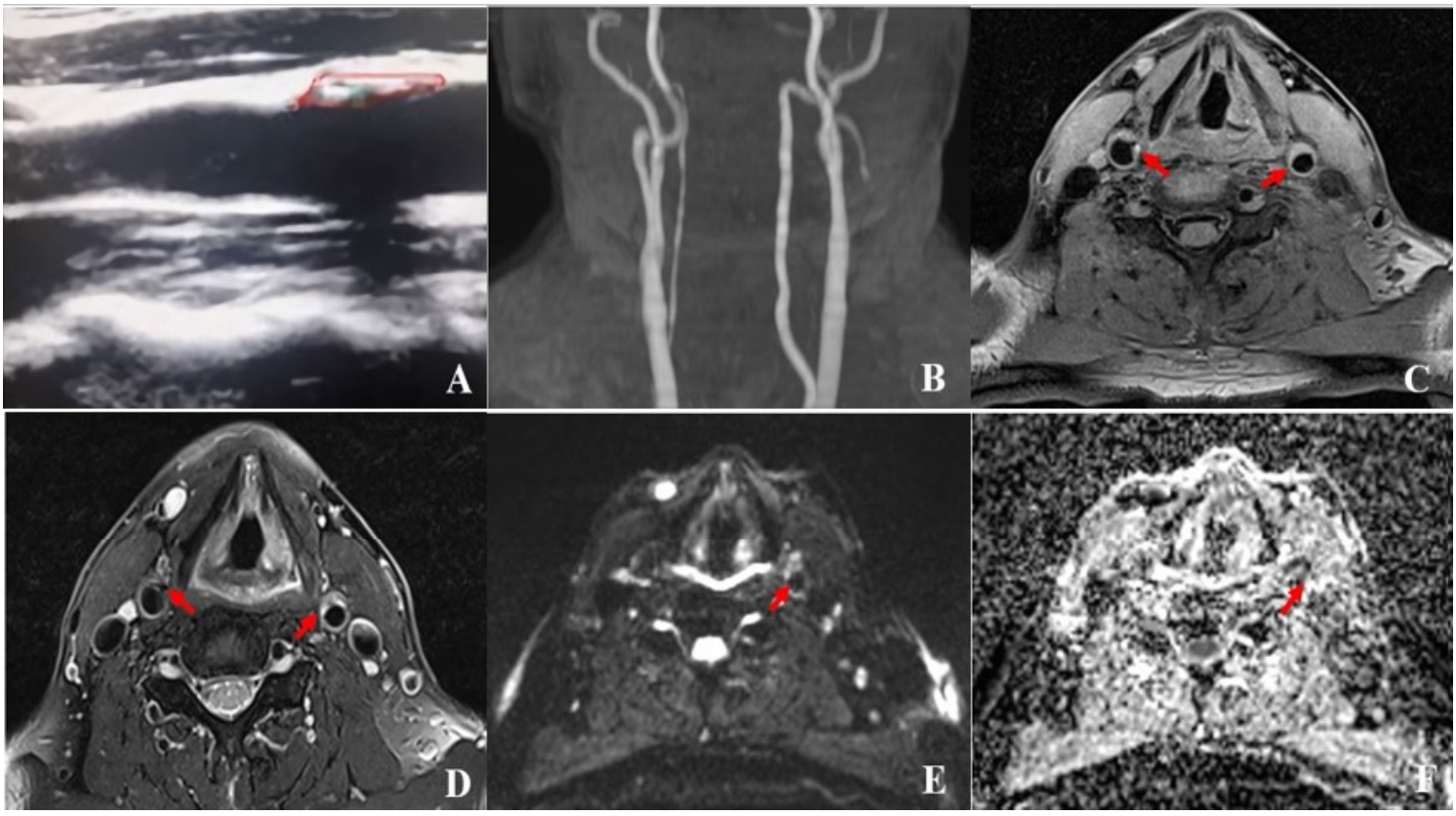

Figure 3

Imaging findings of plaques with fibrous tissue wrapping. A: cervical vascular ultrasound, B: MRA, C: T1, D: T2, E: ADC, F: DWI.