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**A novel ultrasound finding for the diagnosis of giant cell arteritis: Comparison  
with temporal artery biopsy findings**

**Running title:** A novel ultrasound finding for the diagnosis of giant cell arteritis

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## **Abstract**

Hypoechoic halo is a typical ultrasound finding in giant cell arteritis (GCA), but it may be a false positive due to arteriosclerosis. Therefore, we focused on the segmental distribution of GCA lesions, defined the luminal irregularity in long-axis images as the string of beads sign, and examined its diagnostic ability. As a result, the C-statistic of hypoechoic halo and string of beads sign was better than that of hypoechoic halo alone (1.00 vs 0.89). Based on the above, the diagnostic ability of GCA can be improved by adding the string of beads sign to the conventional hypoechoic halo.

**KEY WORDS:** giant cell arteritis, ultrasound, temporal artery, hypoechoic halo

## **1 INTRODUCTION**

Giant cell arteritis (GCA) is a type of granulomatous arteritis classified as a large vessel vasculitis that often presents with swelling and tenderness in the temporal artery, making it a diagnostic target. Blindness is a serious complication of GCA and early diagnosis is extremely important [1]. The American College of Rheumatology [2] classification criteria used to diagnose GCA do not require a temporal artery biopsy (TAB) for histological diagnosis, but histological evidence of vasculitis is desirable for definitive diagnosis. However, GCA is characterized by segmental lesions, and TAB requires the excision of arteries of a certain length, which is highly invasive. In recent years, non-invasive ultrasound (US) has gained attention as an adjunctive diagnostic modality for GCA. Hypoechoic halo [3,4] is a well-known US finding in GCA, but it has been reported that it may be a false-positive finding in atherosclerosis [5]. The aim of this study was to focus on the segmental presence of GCA lesions and to investigate whether the ability to diagnose GCA would be improved by capturing the characteristics of these lesions using US. This will be investigated by comparing US and TAB.

## **2 MATERIAL AND METHODS**

### **2.1 Study subjects**

The study population consisted of 16 patients who underwent US examination and TAB to diagnose or exclude GCA at Hokkaido University Hospital between 2006 and 2022.

They included 8 males and 8 females, and their ages ranged from 43 to 86 years.

All subjects agreed to participate in this study, and informed consent was obtained through an opt-out website. Those who refused were excluded, and the study protocol was approved by the Research Ethics Committee of Hokkaido University Hospital.

### **2.2 TAB examinations**

The presence or absence of intimal thickening, internal elastic lamina destruction, adventitial fibrosis, inflammatory cell infiltration, multinucleated giant cells, and calcification was determined in the temporal artery tissue specimen (Fig. 1). The diagnosis of GCA was made when multinucleated giant cells were observed [6].

### **2.3 US examinations**

US examinations were performed using a high-frequency linear probe (14-24MHz) equipped with LOGIQ E9/10 (GE Healthcare, Milwaukee, WI, USA), Aplio XG/500/i800 (Canon Medical Systems, Otawara, Japan), and HI VISION Avius (FUJIFILM Healthcare, Tokyo, Japan) by 7 sonographers, of whom 3 to 39 years of experience.

The US findings of the main trunk, frontal branch and parietal branch of both temporal arteries were interpreted by two readers: a sonographer with 14 years of experience in US examinations and a novice with no practical experience. We evaluated the presence or absence of hypoechoic halo (defined as a hypoechoic ring  $\geq 0.34$  mm thick, separating the surrounding tissue from the arterial lumen, seen in the short-axis image) [7], and stenosis/occlusion as previously reported findings of GCA [8]. We redefined the irregular bead-like caliber (string of beads sign) in the arterial lumen on the newly focused long-axis image and evaluated its presence or absence (Fig. 2). If the above-mentioned US findings were observed in at least one of the six interpreted temporal arteries, it was determined that the findings were considered positive.

## **2.4 Statistical analyses**

Continuous data were expressed as mean  $\pm$  standard deviation. Student's t-test was used to compare continuous variables between the two groups. Categorical variables were presented as numbers (%) and compared using chi-squared test or Fisher exact test, as appropriate. Receiver operating characteristic curve analysis was performed to evaluate the diagnostic performance of GCA. For inter-reader reliability purposes, each US parameter was evaluated by the concordance rate, which is the value at which the scores of each item in the inter-reader assessment agree and calculated using the kappa coefficient ( $\kappa$ ). All statistical analyses were performed using JMP Pro 16.1.0 (SAS Institute Inc., Cary, NC, USA), and statistical significance was set at a P-value  $< 0.05$ .

## **3 RESULTS**

Based on histological evidence, 3 of 16 cases were diagnosed as GCA.

### **3.1 Baseline clinical characteristics**

There were no items that showed significant differences between the GCA and non-GCA groups (Table 1). However, the GCA group tended to be older, had a higher proportion of females, and had a higher erythrocyte sedimentation rate. There were also no significant differences in the interval between US and TAB, or in cases of steroid treatment prior to US or TAB.

### **3.2 Comparison of TAB with US findings**

Hypoechoic halo was observed in 6 cases (Table 2). The rates of inflammatory cell infiltration and multinucleated giant cells were significantly higher in the hypoechoic halo positive group than in the negative group (83% vs 0%,  $p=0.001$ , 50% vs 0%,  $P=0.036$ ), and GCA and more cases were diagnosed (50% vs 0%,  $P=0.036$ ). There were no significant differences in the TAB findings of stenosis/occlusion (2 cases). The string of beads sign was observed in 5 cases (Table 3). In the string of beads sign positive group, the rate of multinucleated giant cells was significantly higher (60% vs 0%,  $P=0.018$ ) and more cases were diagnosed as GCA (60% vs 0%,  $P=0.018$ ).

### **3.3 Diagnostic performance of GCA with US findings**

The diagnostic performance of GCA with hypoechoic halo was C-statistic 0.89, sensitivity 100%, specificity 77%, and accuracy 81%. The diagnostic performance of GCA with positive hypoechoic halo and positive string of beads sign had a C-statistic of 1.00 and a sensitivity/specificity/accuracy rate of 100%, which was better than hypoechoic halo alone (Fig. 3).

### **3.4 Inter-reader reliability for US findings**

Inter-reader agreement was 93% (75/81 branches) for hypoechoic halo, and 98% (61/62 branches) for stenosis/occlusion. and 97% (58/60 branches) for the string of beads sign, with  $\kappa$  value of 0.66, 0.85 and 0.73 respectively, all of which were good.

## **4 DISCUSSION**

In this study, we compared US findings with TAB findings and clarified the following.

(1) Hypoechoic halo, which has been shown to be useful in the diagnosis of GCA [9], histologically reflected inflammatory cell infiltration and the appearance of

multinucleated giant cells. (2) The presence or absence of temporal artery stenosis/occlusion [8], a finding associated with GCA, was not associated with TAB findings. (3) The newly defined string of beads sign, inspired by the segmental nature of GCA lesions, was useful in diagnosing GCA.

In 1995, Schmidt et al reported in the Lancet that hypoechoic halo was useful in the diagnosis of GCA [3]. Since then, evidence for hypoechoic halo has accumulated and is now included in guidelines [9]. However, the definition is still ambiguous in the literature, such as "thickening of the blood vessel wall" [9] and "circumferential low-intensity thickening around blood vessels" [8]. The reason for this is that US cannot differentiate between the intima, media and adventitia of blood vessels, making it difficult to distinguish whether the hypoechoic halo is vessel wall' or 'perivascular' thickening. In this study, hypoechoic halo was histologically associated with inflammatory cell infiltration and the appearance of multinucleated giant cells but was not associated with findings in the intima or adventitia, suggesting that it may primarily reflect inflammation in the media.

The newly proposed string of beads sign in this study is histologically associated with

the appearance of multinucleated giant cells, and its evaluation in addition to hypoechoic halo improved the diagnostic ability of GCA. Previously, hypoechoic halo was considered a low sensitivity finding, with reports of 17-40% [10,11], but in this study the sensitivity of hypoechoic halo was 100%. The reason for this is the improvement in the spatial resolution of US diagnostic equipment in recent years [12].

On the other hand, the positive predictive value of hypoechoic halo in this study was low at 50%. It has been reported that hypoechoic halo may give a false positive result due to thickening from the intima to the media caused by atherosclerosis [5]. The low positive predictive value of hypoechoic halo in this study was thought to be mainly due to this atherosclerosis. Therefore, it was thought that by adding the string of beads sign as a finding reflecting segmental GCA lesions, it was thought that false positives for hypoechoic halo could be reduced.

Inter-reader reliability for US findings was reported to be 91.3% for hypoechoic halo and 87.5-100% for stenosis/occlusion [9], which is consistent with the results of this study (93% and 98%, respectively). That for the string of beads sign was as high as 97% and was considered to be a highly reproducible index.

The limitations of this study are that the number of cases was small and that some of the branches of the temporal artery were missing on the US scan, so it was not possible to compare the US and TAB results at the same site. Here are some things we couldn't do. In addition, the temporal artery stenosis/occlusion [8] traditionally associated with GCA was not associated with TAB findings. This is because the number of cases in which this was observed was extremely small, and the results may have been affected by type II error. In the future, prospective observational studies are needed to clarify the mechanism of the formation of the string of beads sign and its usefulness in the diagnosis and follow-up of GCA.

## **5 CONCLUSION**

The diagnostic performance of GCA may be improved by evaluating the hypoechoic halo with the addition of the string of beads sign.

## **CONFLICT OF INTEREST STATEMENT**

Yusuke Kudo, Karin Hara, Michito Murayama, Sanae Kaga, Satomi Omotehara,

Takahito Iwai, Utano Tomaru, Yoshihiro Matsuno, and Akihiro Ishizu do not have any relationship that could lead to a conflict of interest.

Masaru Kato has received research grants from AbbVie, Actelion, GlaxoSmithKline, Janssen, Nippon Shinyaku and Novartis and speaking fees from Astellas, Boehringer, Eisai, Eli Lilly, Janssen, Mitsubishi Tanabe and Pfizer.

#### **DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

#### **ETHICS STATEMENT**

This study protocol was approved by the Research Ethics Committee of Hokkaido University Hospital (No. 022-0088) and conducted in accordance with the Declaration of Helsinki.

## **PATIENT CONSENT STATEMENT**

All patients agreed to participate in this study, and informed consent was obtained through an opt-out website. Those who refused were excluded

## REFERENCES

1. Ponte C, Martins-Martinho J, Luqmani RA. Diagnosis of giant cell arteritis. *Rheumatology (Oxford)*. 2020; 59(Suppl 3): iii5-iii16.
2. Hunder GG, Bloch DA, Michel BA, et al. The American College of Rheumatology 1990 criteria for the classification of giant cell arteritis. *Arthritis Rheum*. 1990; 33: 1122-8,.
3. Schmidt WA, Kraft HE, Volker L, et al. Colour Doppler sonography to diagnose temporal arteritis. *Lancet*. 1995; 345: 866.
4. Schmidt WA, Kraft HE, Vorpahl K, et al. Color duplex ultrasonography in the diagnosis of temporal arteritis. *N Engl J Med*. 1997; 337: 1336-42.
5. De Miguel E, Beltran LM, Monjo I, et al. Atherosclerosis as a potential pitfall in the diagnosis of giant cell arteritis. *Rheumatology (Oxford)*. 2018; 57: 318-21.
6. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. *Lancet*. 2008; 372: 234-45.
7. Schafer VS, Juche A, Ramiro S, et al. Ultrasound cut-off values for intima-media thickness of temporal, facial and axillary arteries in giant cell arteritis. *Rheumatology*

(Oxford). 2017; 56: 1479-83.

8. Schmidt WA. Doppler sonography in rheumatology. *Best Pract Res Clin Rheumatol*. 2004; 18: 827-46.
9. Chrysidis S, Duftner C, Dejaco C, et al. Definitions and reliability assessment of elementary ultrasound lesions in giant cell arteritis: a study from the OMERACT Large Vessel Vasculitis Ultrasound Working Group. *RMD Open*. 2018; 4: e000598.
10. Maldini C, Depinay-Dhellemmes C, Tra TT, et al. Limited value of temporal artery ultrasonography examinations for diagnosis of giant cell arteritis: analysis of 77 subjects. *J Rheumatol*. 2010; 37: 2326-30.
11. Salvarani C, Silingardi M, Ghirarduzzi A, et al. Is duplex ultrasonography useful for the diagnosis of giant-cell arteritis? *Ann Intern Med*. 2002; 137: 232-8.
12. Noumegni SR, Hoffmann C, Jousse-Joulin S, et al. Comparison of 18- and 22-MHz probes for the ultrasonographic diagnosis of giant cell arteritis. *J Clin Ultrasound*. 2021; 49: 546-53.

## **FIGURE LEGENDS**

**FIGURE 1** Typical TAB findings of GCA are shown. **a:** Intimal thickening, internal elastic lamina destruction (arrow), adventitial fibrosis; **b:** Inflammatory cell infiltration consisting mainly of lymphocytes; **c:** Multinucleated giant cells (arrow); **d:** Calcification (arrow). **a:** Modified Goldner's Masson trichrome stain; **b, c, d:** Hematoxylin and eosin stain.

**FIGURE 2** US findings of GCA are shown. **a:** Hypoechoic halo. A Doppler short-axis scan shows hypoechoic ring, separating the surrounding tissue from the arterial lumen (arrow); **b:** Stenosis. A Doppler long-axis scan shows narrowing of the arterial lumen (arrow) /Occlusion. Absence of Doppler signal (arrowhead); **c:** The string of beads sign. A Doppler long-axis scan shows irregular bead-like caliber in the arterial lumen.

**FIGURE 3** Receiver operating characteristic curves showing the C-statistic for

**hypoechoic halo alone and hypoechoic halo with the string of beads sign for the diagnosis of GCA.**

## TABLES

TABLE 1 Baseline clinical characteristics

|                                                                                                    | GCA<br>n = 3 | non-GCA<br>n = 13 | P-value |
|----------------------------------------------------------------------------------------------------|--------------|-------------------|---------|
| Age (years)                                                                                        | 75±9         | 66±11             | 0.102   |
| Male/Female                                                                                        | 0/3          | 8/5               | 0.200   |
| clinical presentation n (%)                                                                        |              |                   |         |
| headache                                                                                           | 2 (67)       | 4 (31)            | 0.518   |
| abnormal temporal artery on physical examination<br>(swelling or tenderness, or diminished pulses) | 2 (67)       | 4 (31)            | 0.518   |
| jaw claudication                                                                                   | 2 (67)       | 5 (38)            | 0.550   |
| vision disorder                                                                                    | 0 (0)        | 2 (15)            | 1.000   |
| laboratory values                                                                                  |              |                   |         |
| ESR (mm/h)                                                                                         | 90±14        | 64±33             | 0.112   |
| CRP (mg/dL)                                                                                        | 6.77±3.17    | 7.32±5.11         | 0.568   |
| Lc ( $\times 10^3/\mu\text{L}$ )                                                                   | 7.5±1.7      | 9.1±3.9           | 0.743   |
| Hb (g/dL)                                                                                          | 10.4±1.8     | 11.0±2.1          | 0.670   |
| Tc ( $\times 10^3/\mu\text{L}$ )                                                                   | 427±119      | 366±174           | 0.288   |
| days between US and biopsy (days)                                                                  | 7±3          | 12±16             | 0.594   |
| on steroids before US n (%)                                                                        | 1 (33)       | 1 (8)             | 0.350   |
| on steroids before biopsy n (%)                                                                    | 1 (33)       | 5 (38)            | 0.786   |

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; Lc, leucocytes; Hb, hemoglobin; Tc, thrombocytes

**TABLE 2** Comparison of TAB findings with hypoechoic halo

|                                      | hypoechoic halo (+)<br>n = 6 | hypoechoic halo (-)<br>n = 10 | P-value |
|--------------------------------------|------------------------------|-------------------------------|---------|
| intimal thickening n (%)             | 6 (100)                      | 10 (100)                      | NA      |
| internal elastic lamina tear n (%)   | 6 (100)                      | 10 (100)                      | NA      |
| adventitial fibrosis n (%)           | 6 (100)                      | 10 (100)                      | NA      |
| inflammatory cell infiltration n (%) | 5 (83)                       | 0 (0)                         | 0.001   |
| multinucleated giant cells n (%)     | 3 (50)                       | 0 (0)                         | 0.036   |
| calcification n (%)                  | 1 (17)                       | 3 (30)                        | 0.885   |
| GCA n (%)                            | 3 (50)                       | 0 (0)                         | 0.036   |

GCA, giant cell arteritis; NA, not applicable

**TABLE 3** Comparison of TAB findings with string of beads sign

|                                      | string of beads sign (+)<br>n = 5 | string of beads sign (-)<br>n = 11 | P-value |
|--------------------------------------|-----------------------------------|------------------------------------|---------|
| intimal thickening n (%)             | 5 (100)                           | 10 (91)                            | NA      |
| internal elastic lamina tear n (%)   | 5 (100)                           | 10 (91)                            | NA      |
| adventitial fibrosis n (%)           | 5 (100)                           | 10 (91)                            | NA      |
| inflammatory cell infiltration n (%) | 3 (60)                            | 2 (18)                             | 0.245   |
| multinucleated giant cells n (%)     | 3 (60)                            | 0 (0)                              | 0.018   |
| calcification n (%)                  | 0 (0)                             | 3 (27)                             | 0.245   |
| GCA n (%)                            | 3 (60)                            | 0 (0)                              | 0.018   |

GCA, giant cell arteritis; NA, not applicable

Fig.1

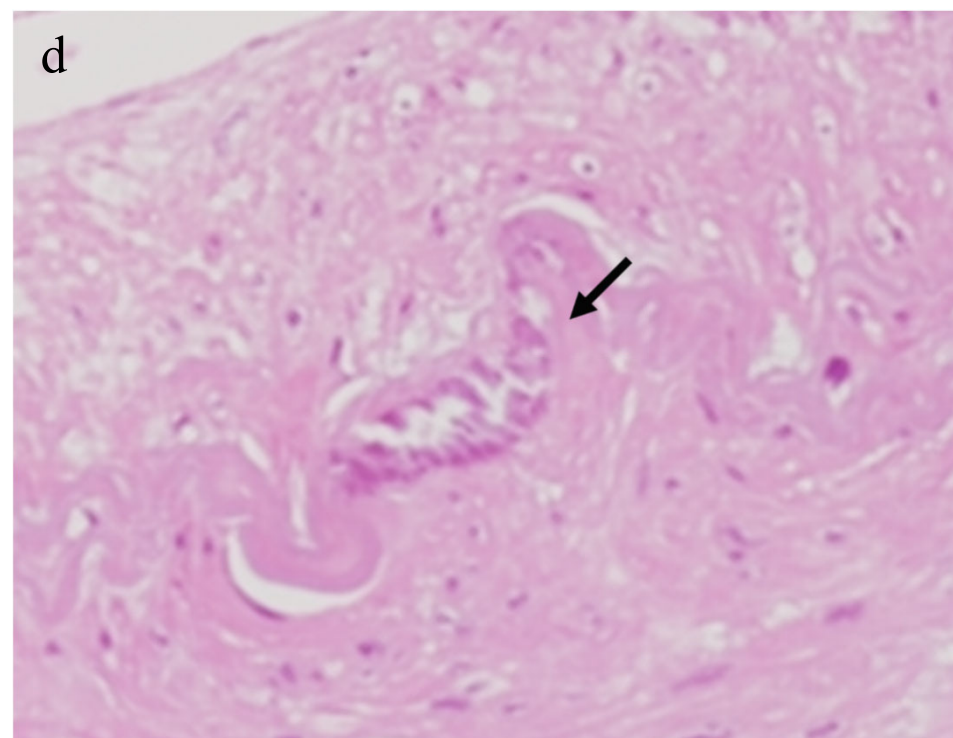
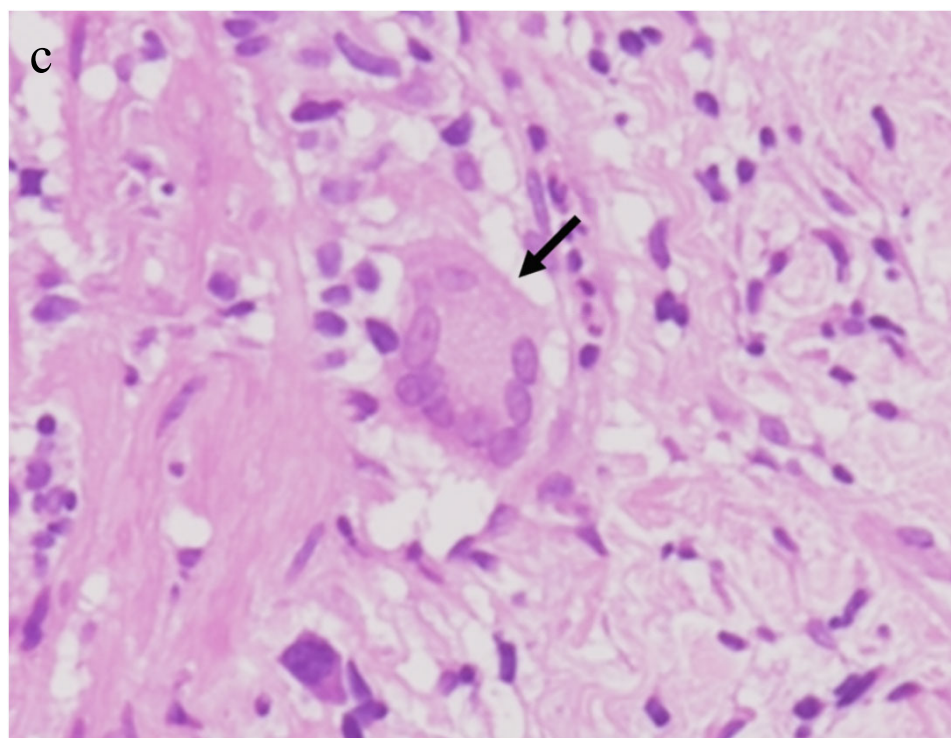
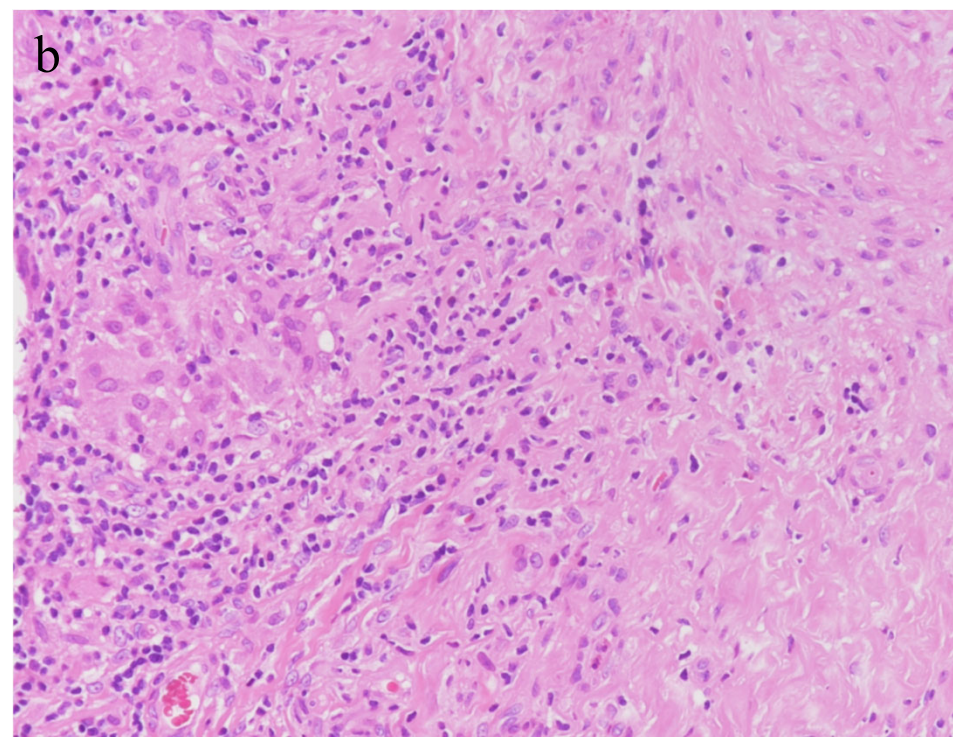
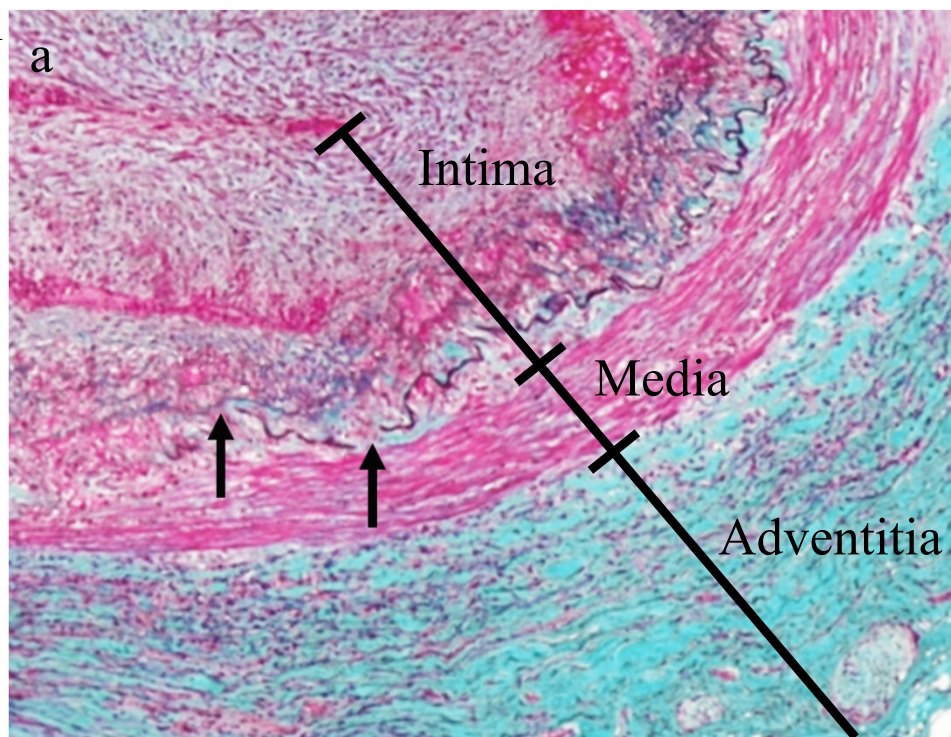


Fig.2

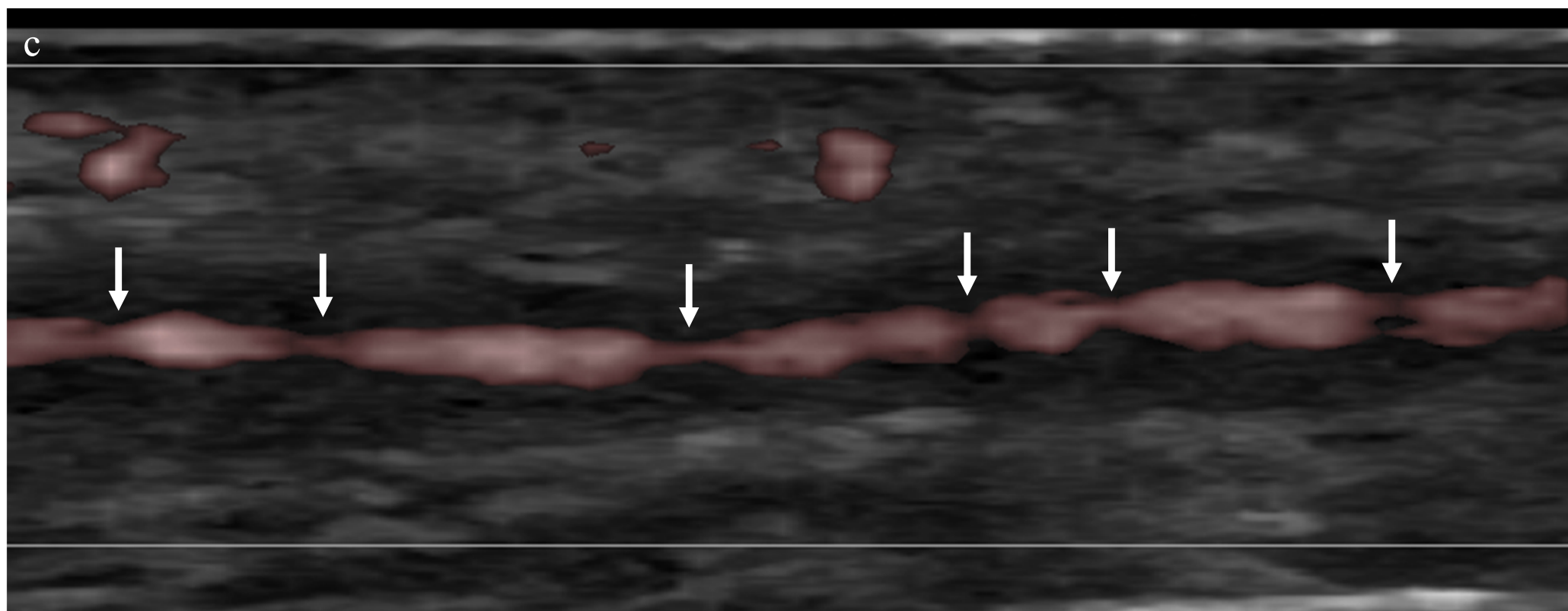
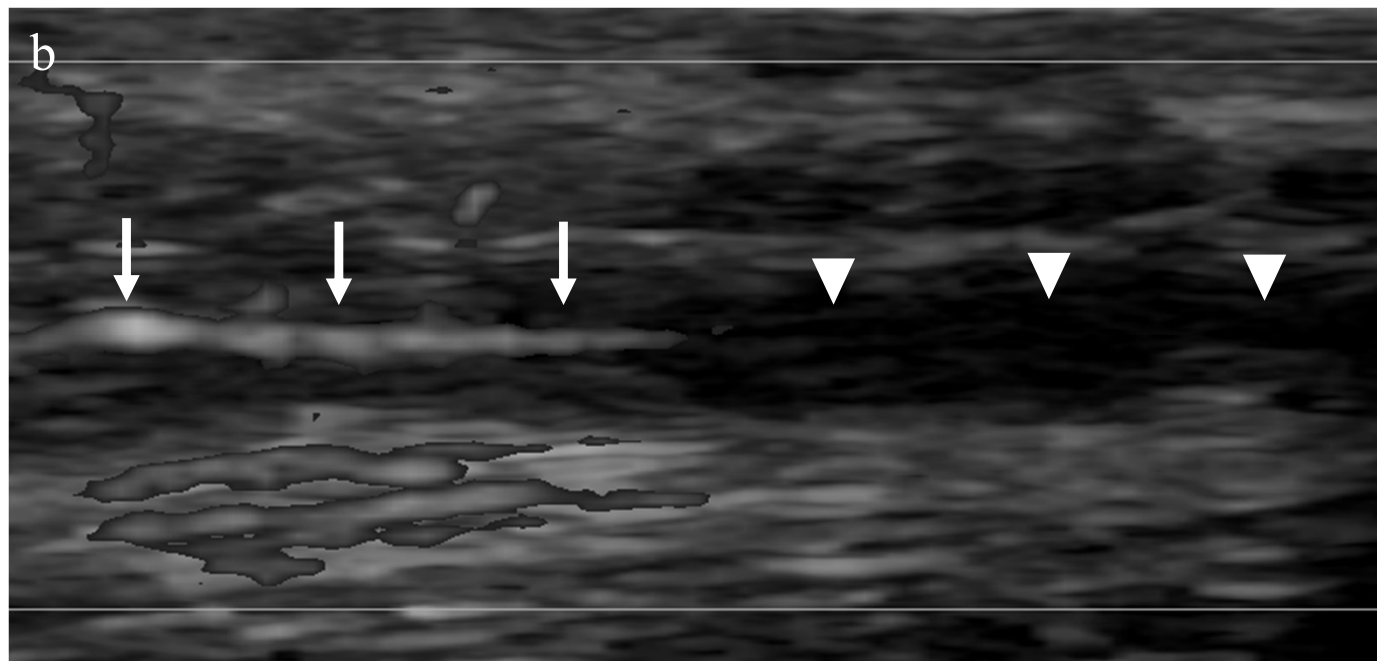
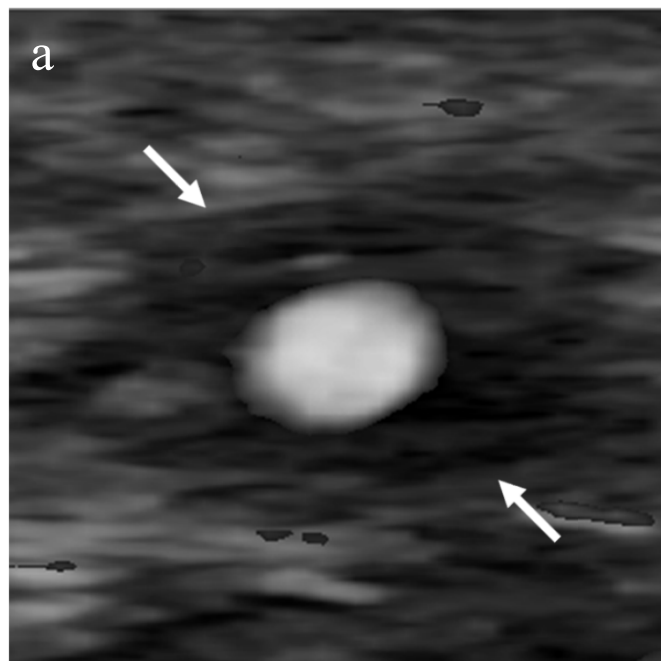


Fig.3

