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Ultrasound appearances and histological correlation of native arteriovenous fistula stenoses – A retrospective case series

Kate Steiner | Sivaramakrishnan Ramanarayanan | Matthew Metcalfe | Praveen Jeevaratnum | Sadasivam Selvakumar | Ashish Narula

East and North Herts NHST U.K., The Lister Hospital Stevenage, Corey's Mill Lane, Hertfordshire, UK

Correspondence
Kate Steiner, East and North Herts NHST U.K., The Lister Hospital Stevenage, Corey's Mill Lane, Hertfordshire SG4 4AB, UK.
Email: kate.steiner@nhs.net

Abstract

The pathophysiology of haemodialysis arteriovenous fistulae (AVF) stenoses is not fully understood. The aim of this study was to perform histology assessment of stenoses in native AVF and compare and correlate the findings between ultrasound and histology. Intimal medial thickness (IMT) was measured on ultrasound where there was measurable neointimal hyperplasia at the site of stenosis and percentage intimal thickening calculated. Ultrasound findings were then compared with histology analysis of AVF stenoses in nine patients. In this small sample, different sonographic appearances and histology were demonstrated. Ultrasound demonstrated stenoses with neointimal hyperplasia and those with no measurable neointimal hyperplasia. Percentage intimal thickening was between 0% and 100%. The histology of the de novo stenoses (where no previous radiological or surgical procedure was performed) demonstrated stenoses with neointimal hyperplasia, no neointimal hyperplasia and neointimal hyperplasia and fibrosis. The histology findings after percutaneous angioplasty (PTA) demonstrated stenoses with neointimal hyperplasia and fibrosis and a stenosis with an acute inflammatory reaction. The findings in this small sample demonstrated that AVF stenoses are not a uniform group as demonstrated by different sonographic and corresponding appearances at histology. Ultrasound appearances of neointimal hyperplasia appear to correlate with neointimal hyperplasia on histology. These findings warrant further investigation and may have implications for treatment strategies.

1 | INTRODUCTION

Failure of maturation of native autologous arteriovenous fistulae (AVFs), fistula thrombosis and dialysis access dysfunction are most often caused by arteriovenous (AV) access stenosis.[1] The pathophysiology of AVF stenosis and mechanisms of restenosis are not yet fully understood.

Venous neointimal hyperplasia is a recognised cause of vascular access stenosis and fistula failure.[2] Failure of fistula maturation and early fistula failure have been shown to be due to both neointimal hyperplasia and adverse adventitial remodelling or a failure of venous dilatation resulting in AVF stenosis.[2]

Ultrasound is a non-invasive, readily available diagnostic tool used in the assessment of AVF dysfunction and failure of fistula maturation. Doppler ultrasound has a high sensitivity and specificity in the diagnosis of vascular access stenosis.[3,4] The technique, in the hands of an experienced operator, has high accuracy and reproducibility in detecting more than 90% of significant stenosis.[4] Ultrasound can also be used to assess neointimal hyperplasia by measuring intimal-medial thickness (IMT) at the site of a stenosis.[5] Carotid intima-media thickness (CIMT) measurements are made

within the common carotid artery (CCA), bulb and internal carotid artery using high-frequency ultrasound and may be used to predict cardiovascular risk.[6] B-mode measurements of intimal and medial thickness of the CCA have been correlated with histology analysis and found to be accurate.[7] CIMT is defined as a low-level echo-grey band which does not project into the vessel lumen.[8] We have taken the same definition and measured IMT within native AVF stenoses. The aim was to perform radiology–pathology correlation between the ultrasound and histology findings in a small series to determine whether this warrants further investigation.

2 | METHODS

Nine resection specimens obtained during surgical revision of AVF venous stenotic lesions at the Lister Hospital, East and North Hertfordshire NHS trust were collected and sent for histology analysis which was performed by a single consultant histopathologist who had no access to the ultrasound findings at the time of histology assessment. Specimens were collected over a 24-month period and were obtained during surgery, which was performed for dialysis access dysfunction or AVF thrombosis. When surgery was performed electively for dialysis access dysfunction, patients were discussed prior to treatment at a multidisciplinary team meeting attended by nephrologists, vascular surgeons, interventional radiologists and a vascular access nurse specialist. To ensure that the specimen of venous stenosis sent for histology was the same segment from where sonographic measurements were taken, pre-operative marking on the skin using surgical skin markers was performed after verbal consent.

Specimens were collected and fixed in 10% formalin and cut at three locations; at the proximal end, distal end and middle of the specimen. Five-micrometre-thickness sections were taken and stained with Haematoxylin and Eosin (H&E) and Elastic van gieson (EVG). Neointimal hyperplasia, medial thickening, presence or absence of fibrosis and significant inflammation were recorded.

Ultrasound examinations were performed as per standard of care. Patients were referred for investigation of dialysis access dysfunction. Patients were scanned in a sitting position in a vascular ultrasound room using either a GE (General Electric Healthcare, Little Chalfont, Buckinghamshire, UK) Logic E7 and a 12 MHz probe or GE Logic E9 and a 15 MHz probe. All images were recorded on the radiology picture archiving and communication system (PACS). The ultrasound examinations were performed by a consultant vascular radiologist and a vascular sonographer. IMT, outer to outer wall vessel diameter and luminal diameter were measured (Figure 1).

Measurements of luminal diameter and vessel wall diameter were used to calculate the percentage of the lumen occupied by IMT using the formula:

$$(\text{Outer to outer wall vessel wall diameter} - \text{Luminal diameter}) \div \text{Outer to outer wall vessel diameter} \times 100 = \%\text{IMT}$$

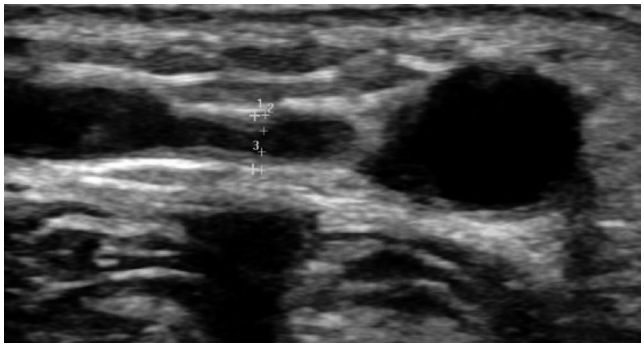

FIGURE 1 B-mode ultrasound image of a juxta-anastomotic stenosis of a radiocephalic fistula. Measurements of IMT, outer to outer vein diameter and luminal diameter are shown

Histological examination of resected AVF stenotic lesions is part of standard of care in our centre and samples were analysed retrospectively. Consent was obtained for retention of the specimen excised for histology analysis and research purposes. The principles of the Declaration of Helsinki have been followed. This small series has led to a larger prospective study; the AV SONOPATH study which has Health Research Authority and local ethical approval (Integrated Research Application System Project ID: 254077). This study will overcome some of the drawbacks of this case series as it will be a prospective study and the protocol will ensures there is no significant gap between ultrasound examination and surgery.

3 | RESULTS

The mean patent age was 61.5 ± 20 years (range 27–84 years). The majority of patients were men (6/9). The mean age of AVF at the time of the surgical intervention was 16.9 months (range 1–33 months). There were a variety of causes of renal failure and comorbidities. Two patients had diabetes mellitus, two hypertension, three ischaemic heart disease, one patient had lupus nephritis and one patient IgA nephropathy. Percentage intimal thickness was between 0% and 100%. In two patients there was no measurable neointimal hyperplasia and therefore 0% intimal thickness was recorded. One patient had complete occlusion of the vein and 100% intimal thickness was recorded. IMT measurements were between 0 and 2.6 mm. Six of the stenoses were de novo lesions with no previous intervention to the stenosis, three of the stenoses had been treated by percutaneous transluminal angioplasty (PTA) prior to surgical resection. The histology findings and DUS findings are summarised in Table 1.

All six patients who had demonstrable neointimal hyperplasia on ultrasound had neointimal hyperplasia on histology as shown in Figure 2.

For three of these patients, there were long time intervals of between 182 and 396 days between the ultrasound and surgical resection.

TABLE 1 Summary of Doppler and histology findings of patients with AVF stenosis and their AVF characteristics such as location, type of AVF and age of AVF

Patient	Age of AVF (months)	Fistula Type	Stenosis Location	% IMT on U/S	Histology findings	Indication for surgical repair	Interval between histology and U/S (days)	Interventions to index lesion between U/S and Histology
1	24	BCF	Cephalic venous outflow	58	Neointimal hyperplasia	Low flow and cannulation segment stenosis	51	0
2	16	RCF	Juxta-anastomotic	47	Neointimal hyperplasia and fibrosis	Poor maturation of AVF	306	1 PTA
3	18	RCF	Juxta-anastomotic	0	Modest medial thickening, no significant neointimal hyperplasia	Clotted AVF	87	0
4	27	BVT	Basilic venous outflow	71	Neointimal hyperplasia and fibrosis	Clotted AVF	396	1 PTA
5	1	BVT	Basilic vein "swing" point	0	Normal venous anatomy, no neointimal hyperplasia	Poor maturation	11	0
6	33	BCF	Juxta-anastomotic	65	Neointimal hyperplasia and aggressive acute inflammatory reaction	Clotted AVF	182	1 PTA DCB
7	6	RCF	Juxta-anastomotic	57	Neointimal hyperplasia	Poor maturation	0	0
8	18	RCF	Juxta-anastomotic	100	Neointimal hyperplasia and fibrosis resulting in complete occlusion	Clotted AVF	2	0
9	9	RCF	Juxta-anastomotic	39	Neointimal hyperplasia and fibrosis almost complete occlusion	Poor maturation	65	0

Patients 3 & 5 who did not have measurable IMT on ultrasound did not have significant neointimal hyperplasia on histology as shown in Figure 3.

There were two de novo lesions with neointimal hyperplasia and fibrosis (patients 8 and 9). One with complete occlusion of the lumen secondary to neointimal hyperplasia and fibrosis with no thrombus.

Patients 2, 4 & 6 had had a percutaneous transluminal angioplasty (PTA) to the stenosis before resection. In two patients, neointimal hyperplasia and fibrosis were seen on histology (Figure 4).

The histology specimen for patient 6 was acquired 182 days after a PTA procedure using a drug-coated balloon (DCB) which demonstrated neointimal hyperplasia and an aggressive acute inflammatory reaction.

4 | DISCUSSION

Radiology–pathology correlation is essential to understanding pathology seen on imaging and understanding the pathology which is being treated when performing dialysis access interventions. In a small sample, there were heterogeneous appearances of dialysis access stenoses on histology and ultrasound. IMT can be measured during ultrasound assessment of AVF stenosis in the similar way to how it is measured in the carotid arteries and where seen in this small sample appeared to correlate with neointimal hyperplasia at histology. One of the limitations of this series is that in three of the samples there were long time intervals between the ultrasound and surgical resection of between 182 and 396 days and PTA was performed between the initial ultrasound and surgical resection. This will be addressed by the AV SONOPATH Study.

We are not the first group to describe different appearances of AVF stenosis on ultrasound. Yamamoto et al in 2012 described three different types of AVF stenosis of arteriovenous grafts based on ultrasound appearances; a neointimal proliferation type, a vascular constriction type and a mixed type.[5] This group demonstrated higher primary patency rates at 6, 12, 18 and 24 months where bare metal stent placement was used to treat the vascular constriction type of stenosis (100, 92.3, 84.6 and 75% respectively) compared with bare metal stent placement used to treat the neointimal proliferation type

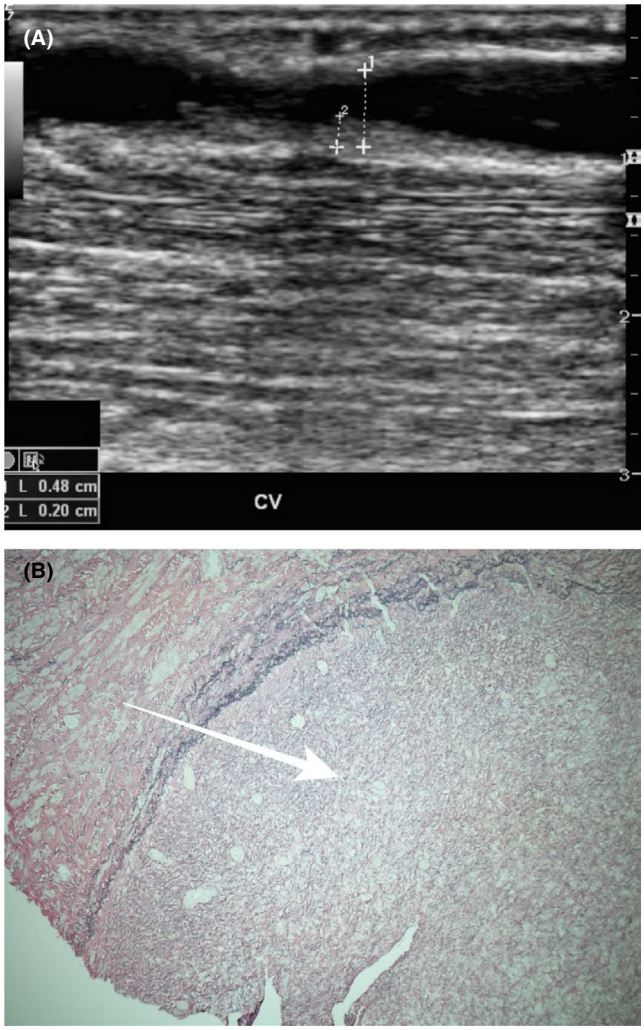

FIGURE 2 Patient 1 B-mode ultrasound image and Histology specimen demonstrating venous neointimal hyperplasia. (A) B-mode ultrasound image of a cephalic venous outflow stenosis; IMT and vein diameter have been measured. (B) H&E stain of the same lesion demonstrating neointimal hyperplasia (white arrow)

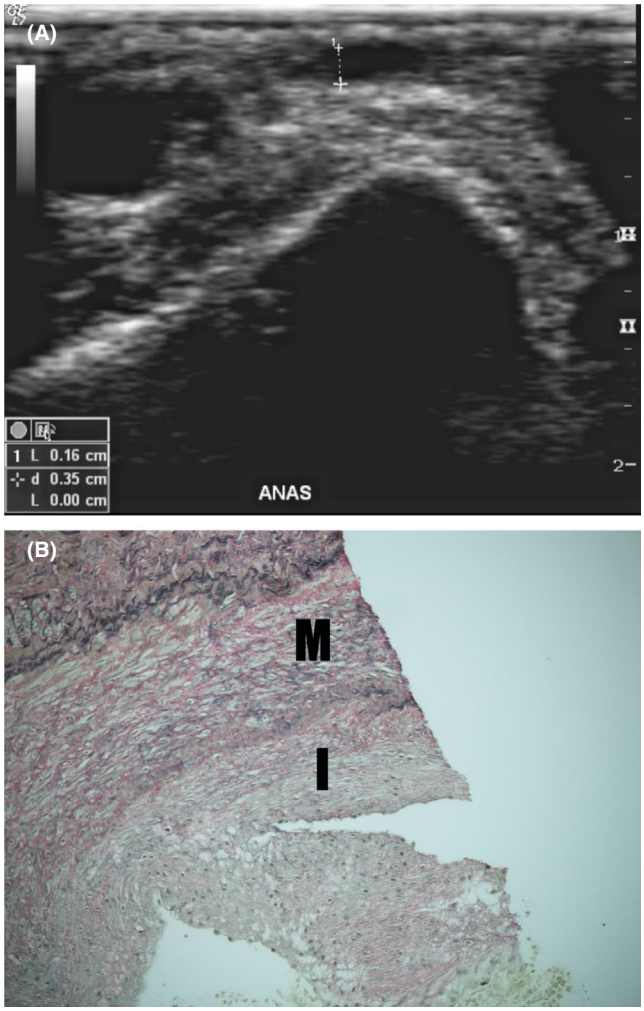

FIGURE 3 Patient 3 B-mode ultrasound image and histology specimen of a juxta-anastomotic stenosis with no neointimal hyperplasia. (A) B-mode U/S image demonstrating a juxta-anastomotic stenosis with no measurable IMT, vessel diameter has been measured. (B) H&E stain demonstrating no significant neointimal hyperplasia, there is modest medial thickening (I = intima, M = media)

(66.7, 33.3, 33.3 and 25.0%) or the mixed type (90.5, 52.4, 38.1 and 27.2%). Suemitsu et al in 2017 described three types of stenosis based on ultrasound appearances; an intimal hyperplasia type, a shrinking type and a valve type. They reported that a shrinking lumen morphology had a negative impact on primary patency at 6 months following percutaneous angioplasty (HR 2.05, 95% CI 1.25–3.36, $p = 0.005$) and a venous valve type stenosis had a positive impact on primary patency (HR 0.19, 95% CI 0.04–0.79, $p = 0.023$).[9] Both these studies suggest that the type of AVF stenosis assessed on ultrasound may affect patency rates after treatment.

We have demonstrated different types of AVF stenosis on ultrasound and histology. Within the de novo lesions – stenosis with neointimal hyperplasia; stenosis with no intimal hyperplasia and stenosis/occlusion with intimal hyperplasia and fibrosis.

Fibrosis was seen in addition to neointimal hyperplasia in two specimens post-PTA and an acute inflammatory reaction was seen after PTA using a drug-coated balloon (DCB).

Increased cell proliferation in re-stenotic lesions after PTA has previously been described.[10] The heterogenous histopathological findings might be due to a difference in underlying pathophysiology which needs further investigation at a molecular and genetic level and correlation with clinical and demographic factors. Unravelling the pathophysiology may also lead to development of novel interventions and targeted use of available interventions for different types of stenosis.

The majority of the specimens are juxta-anastomotic vein. A larger prospective study is needed to draw any firm conclusions. The AV SONOPATH study is currently recruiting at our institution which aims to confirm ultrasound findings of intimal medial thickening that correlate with venous neointimal hyperplasia on histology and define the different types of AVF stenosis based on ultrasound and histology assessment. The findings from this study may provide data to inform future studies where interventions could be targeted based

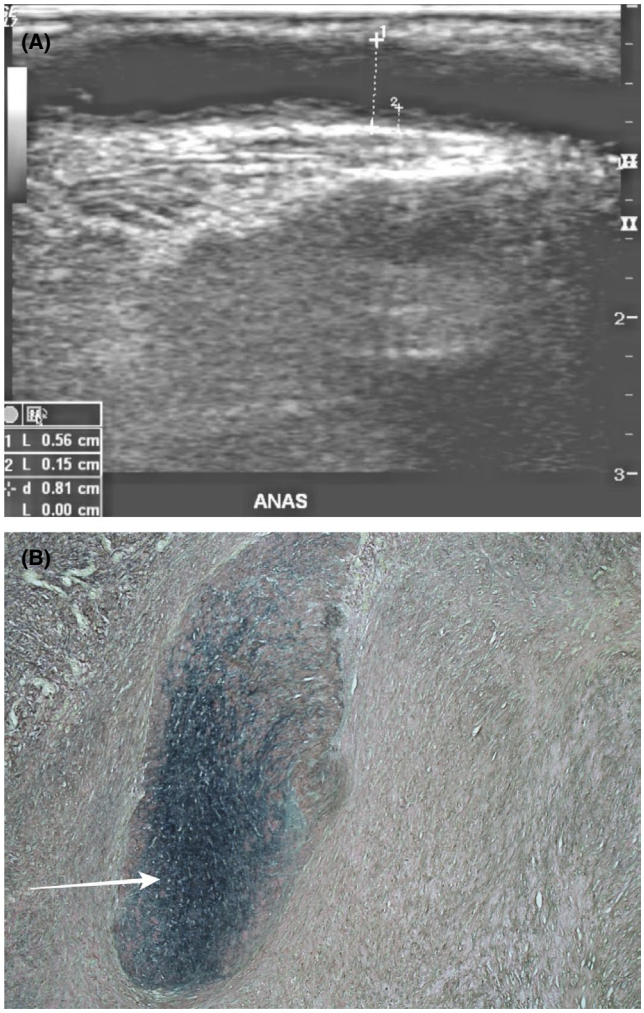

FIGURE 4 Patient 2 B-mode ultrasound image and histology specimen of a juxta-anastomotic stenosis with neointimal hyperplasia and fibrosis post-PTA. (A) B-mode ultrasound image demonstrating a juxta anastomotic stenosis pre-PTA, IMT has been measured. (B) Recurrent stenosis post-PTA; EVG stain demonstrating marked neointimal proliferation with fibrosis. The region of fibrosis is stained blue (white arrow)

on sonographic appearance of the stenotic lesions, for example, using drug paclitaxel-coated balloons for lesions with significant neointimal hyperplasia. Studies like this may be the definitive proof-of-concept that different morphologic types of stenotic lesions (based on B-mode ultrasound appearances) benefit from different approaches to treatment. This case series, although small and retrospective, represents the first attempt to confirm the correlation between sonographic findings and histological findings among native AVF stenotic lesions.

5 | CONCLUSION

The histology findings in this small number of specimens have demonstrated that AVF stenoses within autologous native AVFs are a heterogeneous group. In particular, de novo lesions with neointimal hyperplasia and with no neointimal hyperplasia have been demonstrated. This is a small series, the results are not generalisable.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

ORCID

Sivaramakrishnan Ramanarayanan https://orcid.org/0000-0003-4238-122X

REFERENCES

1. MacRae JM, Dipchand C, Oliver M, et al. Arteriovenous Access Failure, Stenosis, and Thrombosis. *Can J Kidney Health Dis [Internet]*. 2016;3:https://doi.org/10.1177/2054358116669126
2. Roy-Chaudhury P, Sukhatme V, Cheung A. Hemodialysis vascular access dysfunction: a cellular and molecular viewpoint. *J Am Soc Nephrol JASN*. 2006;17(4):1112-1127.
3. Chandra A, Dimascio D, Gruenewald S, Nankivell B, Allen R, Swinnen J. Colour duplex ultrasound accurately identifies focal stenoses in dysfunctional autogenous arteriovenous fistulae. *Nephrol Carlton Vic*. 2010;15(3):300-306.
4. Doelman C, Duijm LEM, Liem YS, et al. Stenosis detection in failing hemodialysis access fistulas and grafts: comparison of color Doppler ultrasonography, contrastenhanced magnetic resonance angiography, and digital subtraction angiography. *J Vasc Surg*. 2005;42(4):739-746.
5. Yamamoto Y, Nakamura J, Nakayama Y, Hino H, Kobayashi H, Sugiura T. Relationship between the outcomes of stent placement and the properties of arteriovenous graft outflow vein stenotic lesions. *J Vasc Access*. 2012;13(4):426-431.
6. Greenland P, Alpert J, Beller G, et al. ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/ American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2010;56:e50-103.
7. Pignoli P, Tremoli E, Poli A, Oreste P, Paoletti R. Intimal plus medial thickness of the arterial wall: a direct measure with ultrasound imaging. *Circulation*. 1986;74:1399-1406.
8. Benedetto F, Mallamaci F, Tripepi G, Zoccalo C. Prognostic value of ultrasonographic measurement of carotid intima media thickness in dialysis patients. *J Am Soc Nephrology*. 2001;12:2458-2464.
9. Suemitsu K, Shiraki T, Lida O, et al. Impact of lesion morphology on durability after angioplasty of failed arteriovenous fistulas in dialysis patients. *Journal of endovascular therapy* https://doi.org/10.1177/1526602817748316
10. Chang C-J, Ko P-J, Hsu L-A, et al. Highly increased cell proliferation activity in the restenotic hemodialysis vascular access after percutaneous transluminal angioplasty: implication in prevention of restenosis. *Am J Kidney Dis*. 2004;43(1):74-84.

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