Ultrasound Evaluation in AV Access Lesions

Kate Steiner, MBBS, FRCR, shares insights from a recent case series on the ultrasound appearances of native arteriovenous fistula stenoses and their histologic correlation.

In your article in *Seminars in Dialysis*, you and colleagues presented a small case series where histologic assessments of stenoses in native arteriovenous fistulas (AVFs) were compared with ultrasound findings.[1] Can you explain the big-picture benefits of studying the radiology-pathology correlation in the case series? What were your goals when initiating this series and your main takeaways upon completion?

Radiology-pathology correlation is essential to understanding the pathology seen on imaging. It goes beyond the anatomy of dialysis access stenosis and helps us understand what is being treated when performing dialysis access interventions. Treatment options were more limited in the past, but there are more options now, such as drug-coated balloons (DCBs) and stent grafts. When considering these more costly options, the ideal location in the access circuit and for which lesions and which patients to use them are not yet fully understood. Understanding the pathology that causes AVF stenosis could help develop strategies for treatment based on lesion location and type.

Multiple repeat endovascular interventions are necessary for some patients to maintain functional patency of AV access. However, it is my experience that there are patients who respond better to endovascular intervention and have longer time intervals between treatments. The pathology of the lesions being treated may play a part in determining which patients will respond well to plain balloon angioplasty and who will benefit from a DCB, stent graft, or surgery.

The main goal was to perform radiology-pathology correlation between ultrasound and histologic findings in a small series to determine whether further investigation was warranted and, if so, to inform the design of a larger trial. When performing Doppler ultrasound examinations of AV access, we noticed significant differences in the appearances of stenotic lesions. Most notable was the presence or absence of intimal medial thickening (IMT), which appeared similar to the IMT seen when scanning carotid arteries. To confirm we were seeing IMT on ultrasound, correlation with histology was necessary.

The main takeaways on completion of the study were (1) AV access stenoses were not all the same and (2) different appearances were demonstrated on ultrasound and histology. In this small sample, the ultrasound findings of IMT appear to correlate with neointimal hyperplasia seen on histology. This suggests it is possible to assess neointimal hyperplasia in AV access stenosis using B-mode ultrasound.

Most patients included had stenosis at the juxta-anastomotic vein (with a few in other locations), and the indication for surgical repair varied. How did the different locations and indications affect what was found on histology and ultrasound and their correlation?

In this small series, there does not appear to be any correlation between the type of lesion seen on histology and the clinical indications for surgical repair. There were three patients with immature AVFs who had stenoses that were surgically excised. Histology was different for each patient. One had neointimal hyperplasia, a second had neointimal hyperplasia and fibrosis, and a third had normal venous anatomy with no neointimal hyperplasia.

When comparing the de novo lesions with lesions after percutaneous transluminal angioplasty (PTA), there were some interesting findings. Fibrosis was seen in addition to neointimal hyperplasia in two specimens post-PTA, and neointimal hyperplasia and an aggressive inflammatory reaction were seen in the third. This raises the possibility that PTA results in endothelial and intimal injury, which then results in an acute inflammatory reaction that may progress to fibrosis. If this finding is confirmed by further study, it would provide further evidence that we should be treating symptomatic hemodynamically significant lesions only and leaving asymptomatic lesions alone.

In one de novo lesion, fibrosis and neointimal hyperplasia were seen, demonstrating that fibrosis can occur in the absence of vessel injury associated with PTA. The stenoses

with no neointimal hyperplasia were all de novo lesions. It would be interesting to observe these lesions after PTA to see if they then develop neointimal hyperplasia.

What is the significance of the amount of time between ultrasound and surgical resection, and how did that affect your evaluation?

The time interval between ultrasound and histology meant that there was potential for the lesions to develop over time, and the ultrasound may have not matched the histologic findings. In the time between the ultrasound and histology, stenoses may have progressed in severity and the degree of intimal hyperplasia may have significantly worsened. For the lesions where no intimal hyperplasia was seen, the longest time interval between ultrasound and histology was 87 days, and the ultrasound and histologic findings correlated.

To accurately correlate histologic and ultrasound findings by measuring IMT on ultrasound and correlating that with measurement of neointimal hyperplasia on histology, the ultrasound scan should be as close as possible to the surgical resection date. In the AV SONOPATH study, the limit is 4 weeks.

Along with the long intervals between ultrasound and surgical resection for three patients, what other limitations did you encounter in this series?

The sample size was the main limitation of this study, as only nine specimens were examined. The majority of the specimens were of the juxta-anastomotic vein, so we need a wider distribution of specimens to examine the findings in the cephalic and basilic venous outflow. Only native autologous AVFs were studied; there were no specimens from AV grafts (AVGs) or the venous outflow tract of an AVG. Although other studies have examined the histology of graft vein anastomotic lesions, it would be interesting to compare those histologic findings with ultrasound. Stenotic lesions at the graft vein anastomosis are a well-recognized cause of AVG dysfunction and thrombosis.

There was a PTA procedure performed between the ultrasound and surgical resection in three cases. This was a significant limitation, as there was an intervention to the lesion after the ultrasound. In these three cases, ultrasound and histology both demonstrated neointimal hyperplasia.

It was discussed that the heterogeneity in the histopathologic findings could be due to a difference in underlying pathophysiology. Can you further hypothesize what this difference might be? What are the molecular/genetic and clinical/demographic aspects at play?

The main differences seen in the histologic findings were the presence or absence of neointimal hyperplasia and the presence or absence of fibrosis.

Roy-Chaudhury et al explained that the final determinant of a mature AVF is the luminal cross-sectional area. There may be a combination of both vascular constriction and the development of neointimal hyperplasia, resulting in a significant venous inflow stenosis.[2]

Venous neointimal hyperplasia is caused by upstream and downstream events. Upstream events are those initial events that result in endothelial injury—endothelial damage at the time of surgery, angioplasty, and repeated needle puncture, for example. Downstream events result from endothelial injury caused by the upstream event(s). A release of a series of mediators leads to smooth muscle cell and fibroblast migration to the intima and cellular proliferation.[2] Where there is turbulence and increased wall shear stress, this can cause endothelial activation and neointimal hyperplasia.

The findings in our small series support that there are types of stenoses with neointimal hyperplasia as the primary pathology and types without intimal hyperplasia with perhaps adverse vascular remodeling as the primary pathology. Ischemia of the vessel wall due to stripping of the vasa vasorum during surgery can lead to the development of fibrosis and vascular constriction.

Neointimal hyperplasia results from cellular proliferation. The other histologic findings were fibrosis, no intimal hyperplasia (possible adverse vascular remodeling), and an inflammatory response. It therefore may follow that genetic and demographic variants that affect cellular proliferation, inflammation, vascular remodeling, and fibrosis are at play. These are not yet fully understood, but a better understanding may lead to treatments that are specific to each patient based on demographic factors, comorbidities, lesion location and type, and possibly biochemical markers in the future.

What are the specific research goals of the currently recruiting AV SONOPATH study that was introduced in the paper? How will it differ from this case series?

The primary objective of the AV SONOPATH study is to confirm whether ultrasound findings of IMT correlate with venous neointimal hyperplasia seen on histology of AVF stenoses. The secondary objective is to define the different types of AVF stenosis based on ultrasound and histologic assessment.

For each stenosis, measurements of IMT on ultrasound will be compared with measurements of neointimal hyperplasia on histology. Other histologic findings will be included, such as the presence or absence of inflammation and fibrosis. In this prospective observational study,

chronic kidney disease patients (predialysis or undergoing dialysis) who present with acute or chronic AV access dysfunction (AVF stenosis or thrombosis) and are referred for surgical intervention will be screened for eligibility.

Ultrasound evaluation must be within 4 weeks of the surgery, with no interventions to the target lesion between the ultrasound assessment and resection, thus addressing some of the limitations of our small series. This is a larger study that includes a wider variety of lesion locations within the venous outflow that are amenable to surgery.

In your case series, it was demonstrated that AVF stenoses are not a uniform group. If these findings are corroborated in further research and larger studies, what implications would it have on the dialysis landscape and treatment strategies?

Further characterization of AV access stenosis into different types based on B-mode ultrasound assessment, validated by histologic findings, could potentially change how we treat dialysis access stenosis. Clinical trials examining the response of different stenosis types to different treatment strategies would be the next step, in my opinion. For lesions where there is significant neointimal hyperplasia, which is known to be secondary to cellular migration and proliferation, it is reasonable to test the hypothesis that antiproliferative therapy may be more effective than plain balloon angioplasty. Currently, clinical trials that examine proof of concept of a new therapy in the treatment of AV access stenosis may be using the therapy to treat different pathologies that could respond differently, thus affecting results. Trials or registries with subgroups based on stenosis type could examine the efficacy of a treatment modality on different types of stenosis.

In our paper, we referenced two studies describing different types of AV access stenosis and examined their response to treatment. In 2018, Suemitsu et al described three types of stenosis based on B-mode ultrasound appearance: an intimal hyperplasia type, a shrinking lumen type, and a valve type. They reported that the shrinking lumen morphology had a negative impact on primary patency on multivariate analysis 6 months after PTA (hazard ratio [HR], 2.05; 95% CI, 1.25-3.36, $P = .005$). The venous valve type stenosis had a positive impact on primary patency (HR, 0.19; 95% CI, 0.04-0.79; $P = .023$).[3] In 2012, Yamamoto et al described three different types of AVF stenosis involving the AVG vein outflow based on ultrasound appearance: a neointimal proliferation type, a vascular constriction type, and a mixed type.[4] This group demonstrated higher primary patency rates at 6, 12, 18, and 24 months when bare-metal stent (BMS) placement was used to treat the vascular constriction type of stenosis (100%, 92.3%, 84.6%, and 75%, respectively) compared with BMS placement used to treat the neointimal proliferation type.

Larger trials using an agreed reproducible method of characterizing stenosis type based on B-mode ultrasound appearance would take this work further.

With respect to potentially applying these findings in real-world settings, what do you feel are the potential barriers that would need to be overcome in the widespread utility of ultrasound evaluation?

The potential barriers to widespread utility are training and availability of ultrasound. Training can be addressed by education. Any individual who can perform ultrasound assessment of AV access can easily be trained in recognizing and measuring IMT. Most endovascular specialists will perform B-mode ultrasound assessment of AV access prior to intervention to plan access and treatment. They can be trained to recognize IMT on ultrasound. High-frequency probes are not needed. In my experience, IMT can be identified using a reasonable-quality mobile ultrasound with a probe anywhere between 9 to 15 MHz. Most mobile ultrasound machines in interventional radiology suites and operating theaters used for vascular access will have a suitable probe. Ultrasound is often a useful adjunct to fluoroscopy during AV access intervention because it reduces exposure to ionizing radiation. Ultrasound-guided fistuloplasty may also be performed. ■

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