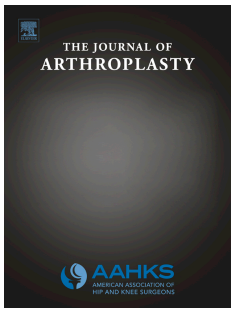

Ultrasound-guided periprosthetic biopsy in failed total hip arthroplasty: a novel approach to test infection in patients with dry joint

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Ultrasound-guided periprosthetic biopsy in failed total hip arthroplasty: a novel approach to test infection in patients with dry joint

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Ultrasound-guided periprosthetic biopsy in failed total hip arthroplasty: a novel approach to test infection in patients with dry joint

Abstract

Background: To diagnose periprosthetic joint infection (PJI) preoperatively, ultrasound-guided joint aspiration (US-JA) may not be performed when effusion is minimal or absent. We aimed to report and investigate the diagnostic performance of ultrasound-guided periprosthetic biopsy (US-PB) of synovial tissue to obtain joint samples in patients without fluid around the implants.

Methods: One-hundred nine patients (55 males; mean age: 68±13 years) with failed total hip arthroplasty (THA) who underwent revision surgery performed pre-operative US-JA or US-PB to rule out PJI.

Results: Sixty-nine out of 109 patients had joint effusion and underwent US-JA, while the remaining 40 with dry joint required US-PB. Thirty-five out of 109 patients (32.1%) had PJI, while 74/109 (67.9%) had aseptic THA failure. No immediate complications were observed in both groups. Technical success of US-PB was 100%, as the procedure was carried on as planned in all cases. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of US-JA were 52.2%, 97.8%, 92.3%, 80.3%, and 82.6%, while for US-PB they were 41.7%, 100%, 100%, 80%, and 82.5%, respectively, with no significant difference (P=0.779). Using the final diagnosis as reference standard, we observed a moderate agreement with both US-JA (k=0.56) and US-PB (k=0.50).

Conclusion: We present a novel US-guided technique to biopsy periprosthetic synovial tissue of failed THA to rule out PJI. We found similar diagnostic performance as compared to traditional US-JA. This supports future larger studies on this procedure that might be applied in patients without joint effusion. [i]

Keywords: Hip; prosthesis; infection; joint aspiration; biopsy; ultrasound; dry tap.

[i] **Abbreviations**: THA: total hip arthroplasty, US-JA: ultrasound-guided joint aspiration, US-PB: ultrasound-guided periprosthetic biopsy, PJI: periprosthetic joint infection, PPV: positive predictive value, NPV: negative predictive value, AAOS: American Academy of Orthopaedic Surgeons, IDSA: Infectious Diseases Society of America.

Introduction

Total hip arthroplasty (THA) failure may be related to aseptic or septic complications, with periprosthetic joint infection (PJI) accounting up to 20% of failed implants subjected to revision surgery [1]. The diagnosis of PJI is reached combining clinical findings, imaging, tests on peripheral blood, and joint aspiration (JA), cultures and histological evaluation of intraoperative tissue samples [2–4]. In this regard, several criteria and scores have been proposed [5]. However, diagnosis of THA infection may be challenging. Clinical manifestations vary according to several factors, and the most commonly reported symptom is pain (79-100% of PJIs) [6], which is a frequent manifestation of non-infected THA failure as well. Specific clinical features of PJI are considered swelling, erythema, fever, and sinus tracts [7]. However, the diagnostic odds of swelling and erythema is still unknown, fever is mostly observed in hematogenous PJI, and sinus tracts are mostly absent [6]. As a matter of fact, blood tests have limited accuracy, given that C-reactive protein, erythrocyte sedimentation rate, and leukocyte count have limited specificity in the diagnosis of PJI [2]. Imaging examinations are routinely used for pre-operative evaluation of painful THA. Interestingly, some papers have recently reported promising results of pre-operative MRI for early detecting PJI in patients with THA failure [8–10]. Indeed, MRI is excellent for evaluating peri-articular soft tissues, particularly to assess muscles and tendons status and to detect collections and sinus tracts; however, despite the use of metal artifact reduction sequences protocol, substantial susceptibility artifacts occasionally decrease image quality of MRI scans [9]. Anyway, JA still remains an essential step for pre-operative detection of PJI in septic THA, including the importance of the identification of the microorganism before surgery or antimicrobial intervention to select a tailored therapy. JA is considered a valuable procedure, being of paramount importance in the comprehensive diagnostic work-up of patients with painful THA. It is performed selectively for diagnosis of PJI and specimens are interpreted on the basis of the results of the culture as well as the white cell count [11]. Nevertheless, accuracy of a single JA for PJI is around 60-70% [6]. Further, when periprosthetic fluid is abundant, JA is easy to perform and is used to obtain samples

for bacterial cultures. Conversely, when fluid is scarce or absent, sampling may be impossible even using imaging guidance, with high risk of dry tap, which may occur up to 46% of cases, particularly in the hip [12–14]. In this setting, recent studies have suggested saline solution lavage and re-aspiration for culture analysis as an alternative option in patients with dry tap [13,15]. However, the clinical value of this procedure is controversial, as some authors advise against this procedure due to concerns for false positive results related to skin contaminants or the possibility of inhibiting bacterial growth [15,16]. Hence, caution is recommended when injecting saline in patients with a dry tap. Further, a diagnostic threshold for post-lavage synovial fluid white blood cells count to diagnose PJI has not been established. In our study, we describe and investigate the diagnostic performance of a novel biopsy technique specifically designed to obtain joint samples in patients without fluid around the implants.

Materials and Methods

Our Institutional Review Board approved this retrospective study. Patients signed a written consent for anonymized data use for research purposes at the time of the interventional procedure, that was considered by the Institutional Review Board as informed consent for this study. Our database, including laboratory and surgical data, was anonymized according to the General Data Protection Regulation for Research Hospitals.

Study population

This retrospective study is concerned with the evaluation of patients with failed THA managed at our Institution between June 2017 and January 2020. In this study, failed THAs were considered those in which mechanical factors (wear, aseptic loosening, instability), biological factors (infection, reaction to debris) or pain, alone or in combination, determined an indication for revision. We enrolled patients with the following inclusion criteria: (i) patients admitted to our Radiology department to perform a pre-operative ultrasound-guided hip JA (US-JA) or ultrasound-guided periprosthetic biopsy (US-PB) of synovial tissue; (ii) availability of results of the microbiological tests; (iii) final diagnosis of infected or non-infected failed THA; and (iv) availability of pre-operative pelvis MRI performed with a metal artifact reduction sequence protocol [17], which is performed by patients admitted to our Department for revision surgery. We excluded patients with suspect of PJI of other joints (e.g. knee). Further, US-PB was not performed in patients with severe coagulopathies unable to stop anticoagulant therapy or allergy to local anesthetics.

Ultrasound-guided periprosthetic biopsy (US-PB)

US-PB was done when joint fluid was absent. Patients were assigned to the “effusion” group (subjected to US-JA) rather than to the “non-effusion” group (subjected to US-PB) on the basis of pre-operative MRI and US examination performed by the attending radiologist. At MRI, effusion

was defined as joint fluid with homogeneous signal intensity of fluid on T2-weighted images and representing nonspecific synovitis [18]. We tried to perform US-JA in all patients with even a small amount of fluid around the implants. The procedure has been converted from US-JA to US-PB when the former resulted unsuccessful. On the other hand, no cases were converted from US-PB to US-JA, given that only patients without joint fluid underwent US-PB. The procedure was performed in a dedicated interventional room under strict sterile condition by two radiologists with 12 and 5 years of experience in musculoskeletal interventional procedures, respectively. The patient was in the supine position and iodine-based solution was used to sterilize the skin. The whole procedure was done under continuous US monitoring (MyLab Seven, Esaote, Genoa, Italy) with a convex probe (SC3121, 5-2 MHz) and a sterile cover for the US transducer. The most common method to obtain soft tissue specimens is to use a Tru-cut needle [19]. These needles are made by an internal stylet with a specimen notch at the end, which is manually or automatically advanced in the tissue to sample, and an external needle that slides over the stylet to cut the sample. The stylet advances in the tissue for 1 to 2 cm, according to the needle type. Of note, periprosthetic synovial tissue in patients with dry joint is very thin (4-5 mm) (Figures 1, 2 and 3), thus an anterior approach to biopsy (similar to that used for US-guided intra-articular injections [20]) is not feasible. For this reason, we used a lateral approach, with the needle inserted from the lateral side of the thigh, parallel to the bed, and with the tip tangent to the stem neck. Local anesthesia was obtained with topical injection with 10 ml of 2% lidocaine chlorhydrate into the skin/subcutaneous tissue and periprosthetic tissues, paying attention not to inject the joint. Then, a semiautomatic biopsy needle (14G x 10 cm, Bard Mission 1410MS, Bard Peripheral Vascular Inc., Tempe, AZ, USA) was inserted almost horizontally at a variable depth depending on patient build (approximate depth of 5 cm), passing above the greater trochanter and placing the cutting tip inside the periprosthetic synovial tissue, being superficial and tangent to the femoral neck (Figures 4 and 5). One sample was obtained for each patient and sent out for culture. We did not have a minimum required specimen size from the US-PB collection, as any synovial sample harvested from periprosthetic

tissue was considered adequate for culture analysis, excluding those cases in which only blood clots were obtained; in the latter cases, a resample was needed to remove a sample of periprosthetic synovial tissue. At the end of the procedure, after skin disinfection and medication, the patient was monitored for 30 minutes and was advised to take oral painkillers (1000 mg of paracetamol) and to use local ice packs as needed. Technical success of US-PB was defined as the ability of completing the biopsy as initially planned according to our protocol [21]. Immediate complications were recorded.

Ultrasound-guided joint aspiration (US-JA)

The aspirations were performed by the same radiologists with the patient in the supine position. After skin disinfection with iodine-based solution, US was used to detect joint effusion and periprosthetic fluid collections (Figure 6). Local anesthesia was not performed. Under US guidance, JA was done using an anterior approach with the neck of the prosthesis being the target for needle positioning (20 G spinal needle, 0.9mm x 90mm, BD, Franklin Lakes, NJ, USA). Confirmation of the correct position of the needle into the joint was both visual through US and a metal-on-metal sensation that was appreciated when the tip of the needle touched the prosthetic neck. Then, a 10-mL syringe attached to the spinal needle was used for aspiration of at least 1 mL of fluid.

Microbiologic analysis

Results of pre-operative (both US-JA and US-PB) and intraoperative sample cultures of periprosthetic material collected during revision surgery were sent out to our laboratory for cultures. Periprosthetic tissues and removed implants were treated with 0.1 % (w:v) dithiothreitol before plating on agar plates and inoculating into broths for aerobes and anaerobes growth, as previously described [22,23]. Agar plates and enrichment broths were incubated for 48 hours and 15 days, respectively, and daily checked for microbial growth. In case of broth turbidity, an aliquot was plated onto blood agar (for anaerobe and aerobes) and onto Schaedler blood agar (only anaerobes).

Colonies grown from agar plates were identified by biochemical testing performed on a Vitek 2 analyser (BioMerieux, Marcy L'Etoile France). The culture results from US-JA, US-PB, periprosthetic tissues and removed implants were considered in order to identify the type of microorganism.

Statistical analysis

Continuous variables are reported as mean ± standard deviation. Mann–Whitney U-test and Chi-square statistics were used to compare the two groups of patients subjected to US-JA and US-PB in terms of age and gender, respectively. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of both US-JA and US-PB were calculated using the final diagnosis – based on clinical, laboratoristic, surgery, and microbiology data according to International Consensus Meeting Criteria [24] – as reference standard. Results from US-JA fluid and US-PB specimen cultures were used to reach the final diagnosis according to the above-mentioned criteria [24], along with intra-operative data. Diagnostic performances of US-JA and US-PB were compared using the Chi-square test. Agreement of both US-JA and US-PB with the final diagnosis were calculated using Cohen's Kappa coefficient. The K coefficient was interpreted as poor (0), slight (0.01–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61–0.80), and almost perfect (0.81–1.00). Statistical significance was set at $P < 0.05$. SPSS software (v. 26, IBM, Armonk, NY) was used for statistical analysis.

Results

In the index period, 172 patients underwent the US-guided procedure (US-JA or US-PB) and were screened for inclusion. Fifty patients had their preoperative MRI not available for review, seven patients were excluded due to low-quality MRI, five patients were subjected to US-PB of the knee, and one patient with dry tap could not perform US-PB due to severe coagulopathy unable to stop anticoagulant therapy. After applying inclusion and exclusion criteria, 109 patients (55 males, 54 females; mean age: 68±13 years, range 23-95) were included in our analysis, of which 69 (63.3%, 36 males and 33 females; mean age: 68±14 years, range 23-95) had abundant joint effusion and underwent US-JA, while the remaining 40 with dry joint (36.7%, 19 males and 21 females; mean age: 66±12 years, range 45-91) required US-PB. Thirty-five out of 109 patients (32.1%) had PJI, while 74/109 (67.9%) had aseptic THA failure. The reasons for aseptic failures were the following: 16 aseptic loosening of the stem, 15 aseptic loosening of the cup, 6 aseptic loosening of both components, 9 adverse reaction to metal debris, 8 instability, 8 pain and osteolysis after periprosthetic fracture, 7 wear and osteolysis, 5 painful prosthesis.

No age ($P = 0.953$) or gender ($P = 0.694$) differences were found between US-JA and US-PB groups. No immediate complications were observed in both groups. Technical success of US-PB was 100%, as the procedure was carried on as planned in all cases, allowing to retrieve one sample of periprosthetic tissue for each procedure. Culture yielded bacterial growth in 13/69 fluid retrieved by US-JA (18.8%), and in 5/40 of patients (12.5%) subjected to US-PB. Cultures obtained US-JA and US-PB failed to grow any microorganism in 13 patients, who were classified as infected as confirmed by intraoperative samples. Microorganisms isolated from positive cultures with fluids retrieved by US-JA and US-PB, along with the discrepancies observed with intra-operative results, are reported in Table 1.

Sensitivity, specificity, PPV, NPV, and accuracy of US-JA were 52.2%, 97.8%, 92.3%, 80.3%, and 82.6%, while for US-PB they were 41.7%, 100%, 100%, 80%, and 82.5%, respectively.

Diagnostic performances of US-PB and US-JA were not significantly different (P = 0.779). Using the final diagnosis of infection as reference standard, we observed a moderate agreement with both US-JA (k=0.56) and US-PB (k=0.50).

Discussion

Our main finding was that US-PB was 100% feasible in patients with dry THA, with similar diagnostic performance of US-JA.

Absence of effusion can be observed both in septic and aseptic failed painful THA [9]. In a recent MRI study, effusion was seen in 76% of infected THA and 42% of non-infected THA, and it has been associated with septic THA failure [9]. Our results are in agreement, as 36.7% of our patients had dry joint and required pre-operative US-PB. Similarly, Li et al have reported 41.8% of cases with dry hip (61/146), with much lower frequencies in the knee (15%, 21/140) [13]. Thus, a non-negligible number of patients might present with dry joint, particularly in the hip. In this scenario, this novel approach might be an adjunctive tool to identify PJI in painful THA. This procedure is feasible and safe and can be performed in an outpatient setting. Notably, US-PB was feasible regardless from the patient habitus, although it might be harder to obtain periprosthetic samples in obese patients due to both thicker subcutaneous tissue with longer needle tracking and fat muscle infiltration with poorer US image quality. As a matter of fact, US guidance allows to perform US-PB safely, ensuring in real time the correct position of the tip of the needle within the targeted joint space [25–29]. Further, the lateral approach that we have tested avoids the risk of injury of neurovascular bundles, which are located in the antero-medial aspect of the thigh. No other complications such as lateral femoral cutaneous nerve injury was observed. Indeed, based on our approach, the needle is inserted laterally passing through the gluteus muscles above the greater trochanter, whereas the lateral femoral cutaneous nerve is located much more anteriorly [30].

Concerning pre-operative US-JA, our results are not much different from those reported in a meta-analysis by Qu et al, in which this procedure showed 70% sensitivity and 94% specificity in patients with failed THA, which can be considered acceptable for clinical practice [31]. The American Academy of Orthopaedic Surgeons (AAOS) and Infectious Diseases Society of America (IDSA) recommend pre-operative US-JA culture for evaluation of PJI [32,33]. Currently, US-JA is essential to determine the causative microorganisms of PJI before surgery. Further, this procedure

enables to evaluate their sensitivity to antimicrobials, giving the possibility to set up a specific and tailored therapy. US-PB has shown a diagnostic performance not significantly different to US-JA, presenting even higher specificity. Thus, even if the sensitivity of US-PB was slightly lower, this procedure could be considered as a valid alternative option in patients with dry hip.

We offer some considerations on our procedure. We performed only one biopsy sample that could have contributed to the low sensitivity in our series. Indeed, we suggest retrieving at least two biopsy samples from periprosthetic synovial tissue, which is what we already started doing in our daily clinical practice. On the other hand, we must underline that with US-JA, leukocyte esterase, white blood cell count and percentages of neutrophils can be assessed in addition to cultures and this is not possible with a biopsy sample. Previous studies have reported sensitivity and specificity of aspiration leukocyte count ranging from 36% to 100% and from 60% to 99%, and those of aspiration percentages of neutrophils ranging from 71% to 98% and from 62% to 98% [34–36]. Nevertheless, in patients with dry joint, US-JA is not feasible, thus these tests are not an option. To overcome the limitation of dry joints, some Authors have proposed the intra-articular injection and re-aspiration of saline solution on which perform culture analysis [13,15]. Heckmann et al, after a preliminary intraoperative aspiration of joint fluid, injected and re-aspirated 20 ml of normal saline into the knee and hip joints of 78 patients before arthrotomy [15]. Authors found interesting results concerning the post-lavage polymorphonuclear cells and white blood cells counts, but reported that, among patients with positive culture on pre-lavage aspiration, 40% had a negative post-lavage culture. In case less than 1 mL of synovial fluid could be aspirated, Li et al. injected and re-aspirated 10 mL of saline solution, that was divided into two equal samples for culture analysis [13]. The traditional US-JA performed in the non-lavage group showed 76.8% sensitivity, 99.1% specificity, 98.7% PPV, and 81.9% NPV, while the saline solution lavage done in patients with dry joint presented 85.1% sensitivity, 85.7% specificity, 88.9% PPV, and 81.1% NPV [13]. According to their data, saline solution lavage seems to have higher sensitivity but lower specificity than JA. In this setting, an option might be to perform a combined procedure involving saline solution lavage

first and double-specimen biopsy in patients with dry joint, with the latter procedure that could balance the lower specificity of the former. We plan to address this point in future studies.

Some limitations of our study should be considered. First, the relatively small sample size, particularly concerning the biopsy group of patients. Further larger studies might confirm our preliminary promising results. Second, as above-mentioned, more than one biopsy sample might have increased the sensitivity of periprosthetic biopsy. Third, although this work is retrospective, this is a consecutive series of patients that underwent US guided preoperative investigation for PJI as in our Research Hospital all patients' data are routinely collected. Last, the growth of any microorganism, whether or not it was concordant with intra-operative cultures, has been used for the specificity calculations. While this is not entirely unreasonable as either (or both) organisms may be truly causative, this should be considered as a limitation of this study, given its implications for antibiotic treatment due potential issues with contaminants.

In conclusion, we present a novel US-guided technique to biopsy periprosthetic synovial tissue of failed THA to rule in PJI and to identify the causative microorganism preoperatively. We found similar diagnostic performance if compared to traditional US-JA, which lead us to support future larger studies on this procedure that might be applied in patients with dry joints.

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Table 1. Microorganisms isolated from 13/69 and 5/40 positive cultures with fluids retrieved by US-JA and US-PB, respectively, along with the discrepancies observed with intra-operative results.

	ISOLATED MICROORGANISMS	DISCREPANCIES
US-JA (n=13/69)	6 *Staphylococcus epidermidis* 4 *Staphylococcus aureus* *1 Streptococcus sanguis* 1 *Cutibacterium acnes* *1 Corynebacterium pseudodyphtericum*	1. *Corynebacterium pseudodyphtericum* isolated with US-JA in a patient classified as non-infected 2. *Cutibacterium acnes* isolated with US-JA while a *Streptococcus mitis* was isolated intraoperatively
US-PB (n=5/40)	3 *Cutibacterium acnes* 1 *Staphylococcus lugdunensis* 1 *Proteus mirabilis/Enterococcus faecalis*	1. *Cutibacterium acnes* isolated with US-PB, while *Staphylococcus epidermidis* and *Staphylococcus hominis* were isolated intraoperatively

Figure captions

Figure 1. Schematic sagittal oblique anatomy. A=acetabulum; H=femoral head, with arrowhead indicating the ultrasound interface; N=neck of the prosthesis; F=femoral bone; dashed and dotted line=section where the axial scan is obtained; *=synovial tissue.

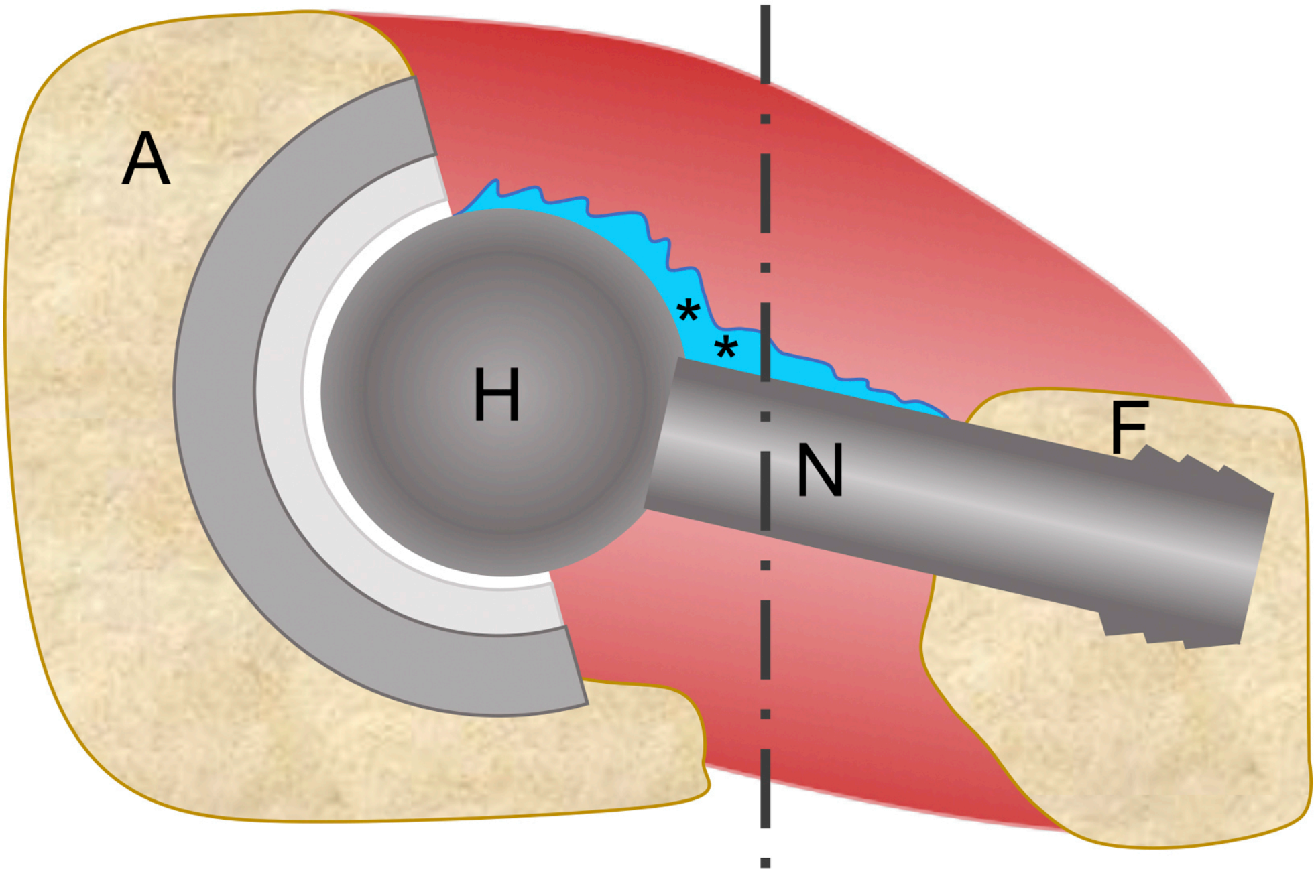
Figure 2. Sagittal oblique ultrasound image of a hip arthroplasty biopsy in a 71-year-old patient being studied for potential infection. The hip of this patient was completely dry as evaluated on pre-procedure MRI (not shown). The anatomy of the replaced hip can be seen. A=acetabulum; H=femoral head; N=neck of the prosthesis, with arrow indicating the ultrasound interface; F=femoral bone, with thick arrow indicating the ultrasound interface; dashed and dotted line=section where the axial scan is obtained; *=synovial tissue.

Figure 3. Axial ultrasound image of the same patient of figure 2. N=neck of the prosthesis; *=synovial tissue.

Figure 4. Schematic axial anatomy and procedure. N=neck of the prosthesis; *=synovial tissue.

Figure 5. Ultrasound procedure image of the same patient of figure 1. N=neck of the prosthesis; *=synovial tissue. The needle (curved arrows) is inserted almost horizontally at an approximate depth of 5 cm (shown by the centimeter scale on the right side of ultrasound images), with the cutting tip placed inside the synovial tissue, being also tangent to the femoral neck.

Figure 6. A 41-year-old female patient with infected right THA. Pelvis MRI with coronal short tau inversion recovery (A), and axial T2-weighted (B) images show effusion (*) around the implant. US-JA images (C,D) show the needle (arrows) inserted in-plane using the anterior approach with the neck of the prosthesis (void arrows) and joint effusion (*) being the target for needle positioning.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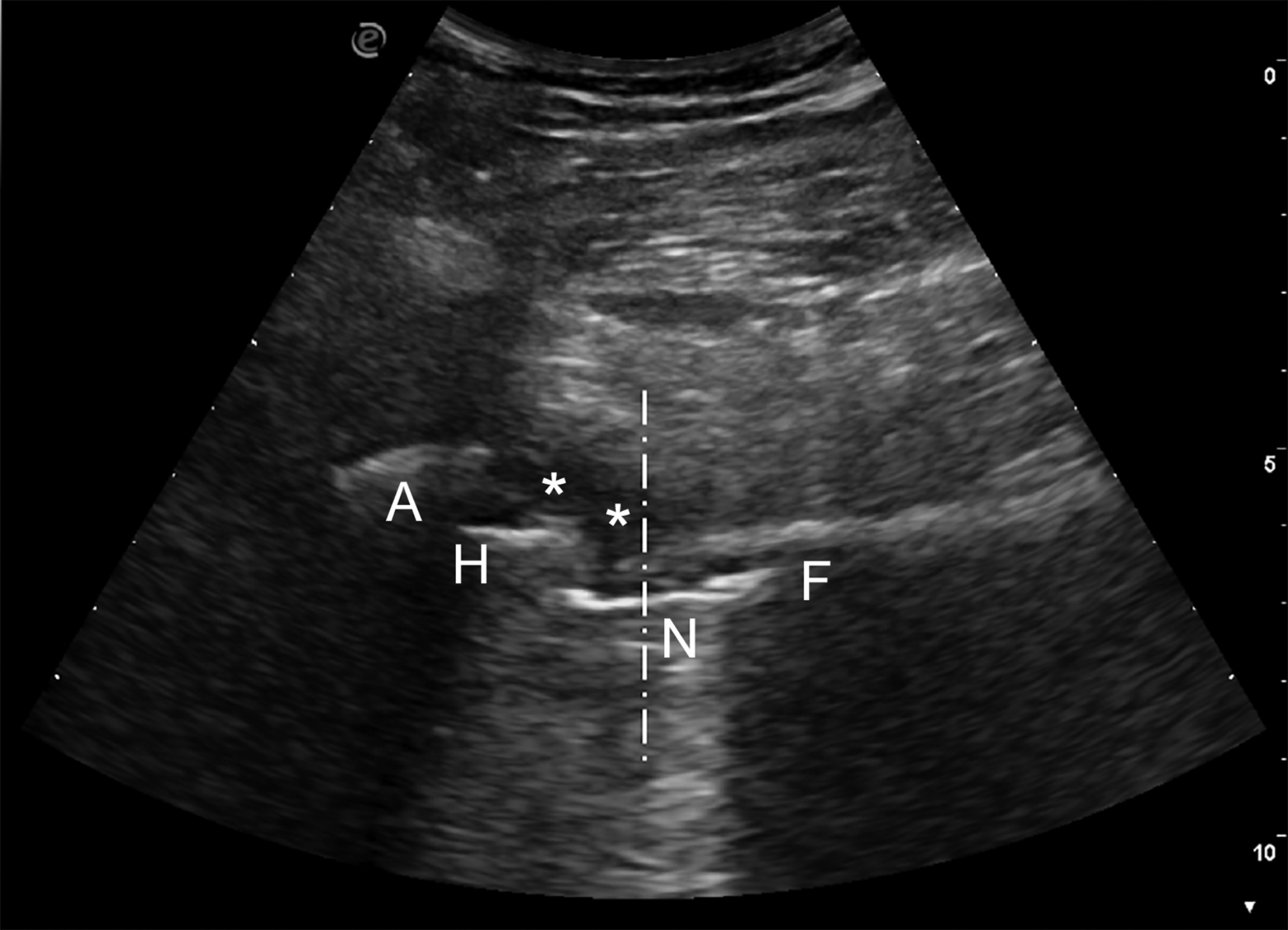
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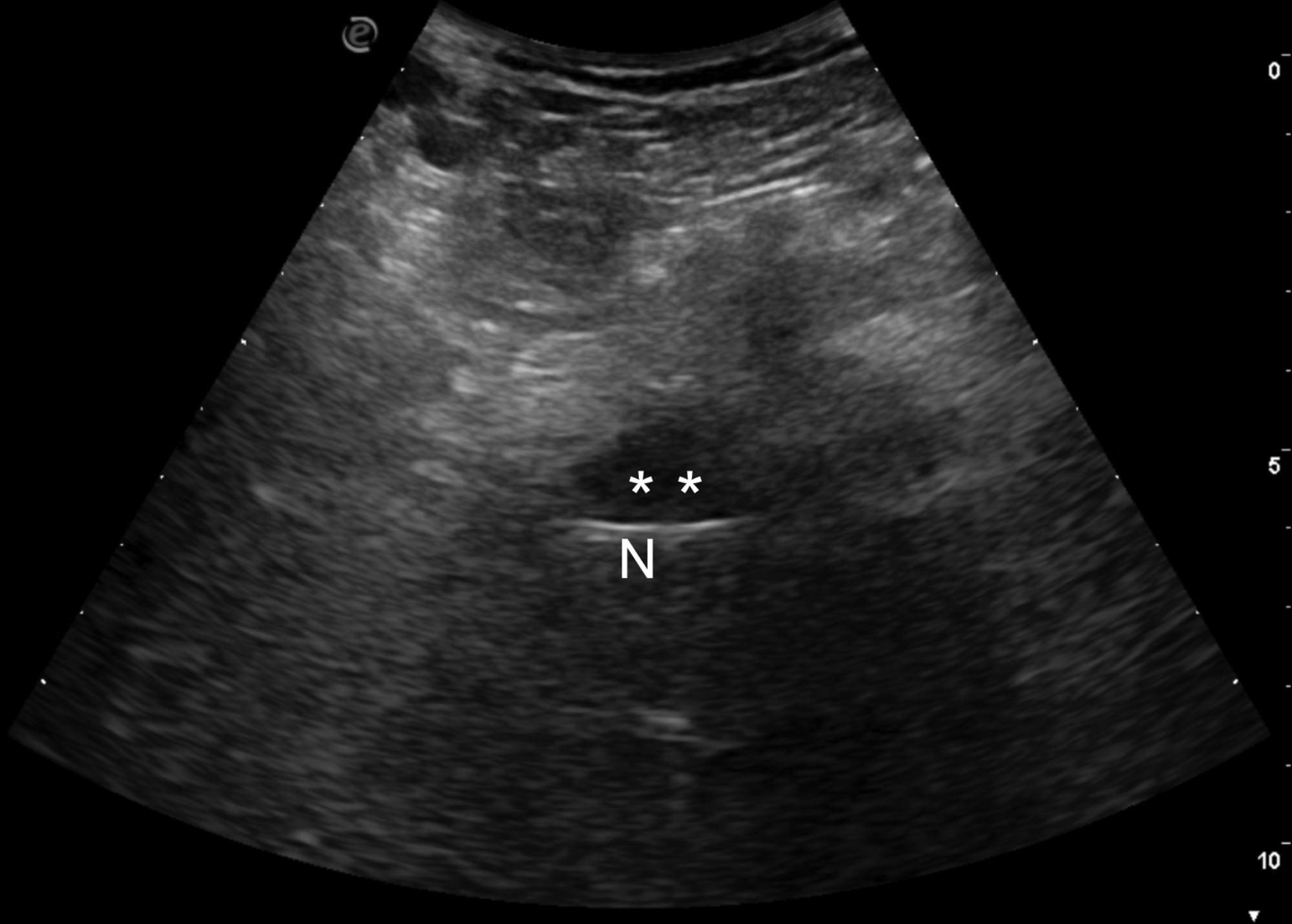
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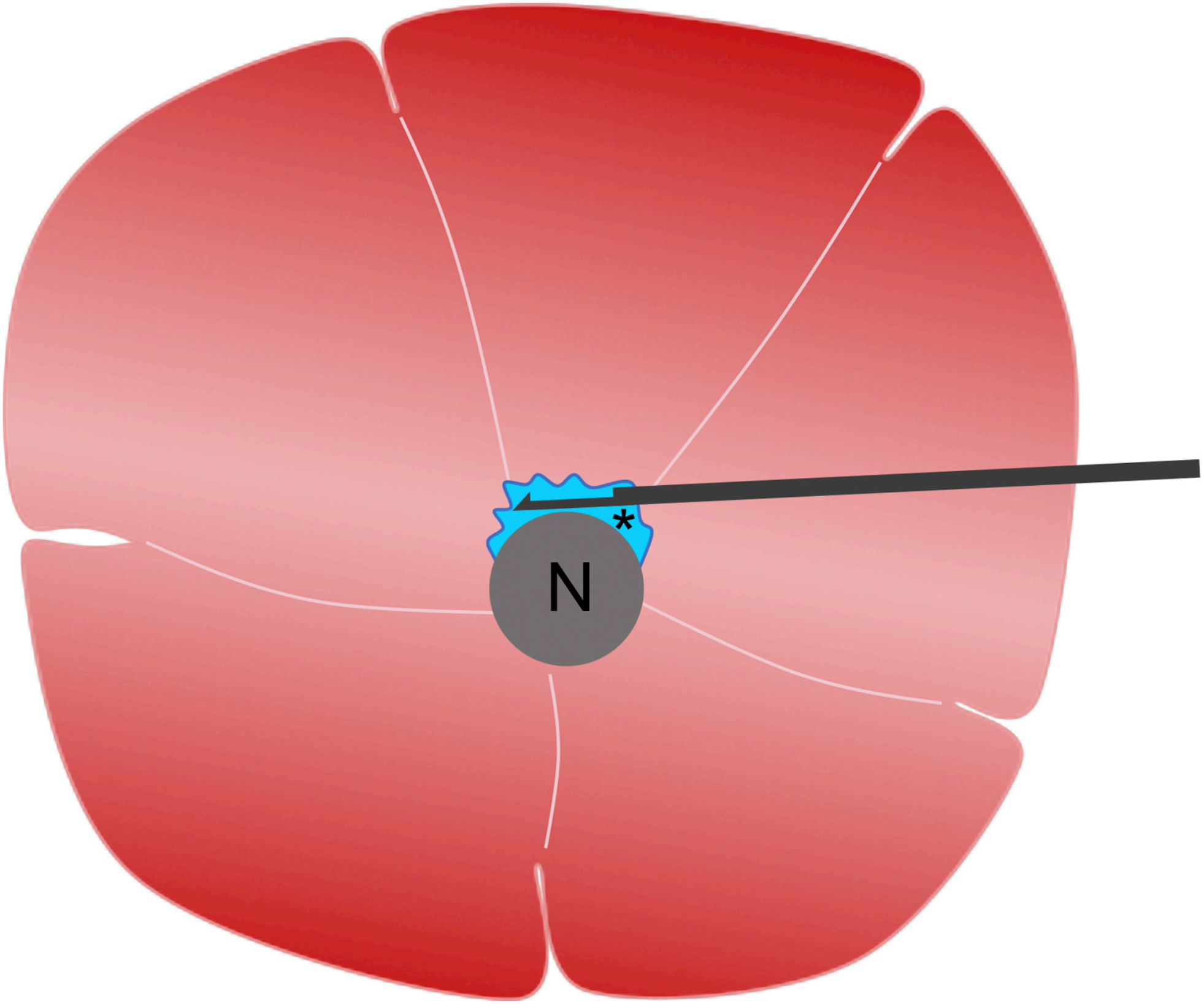
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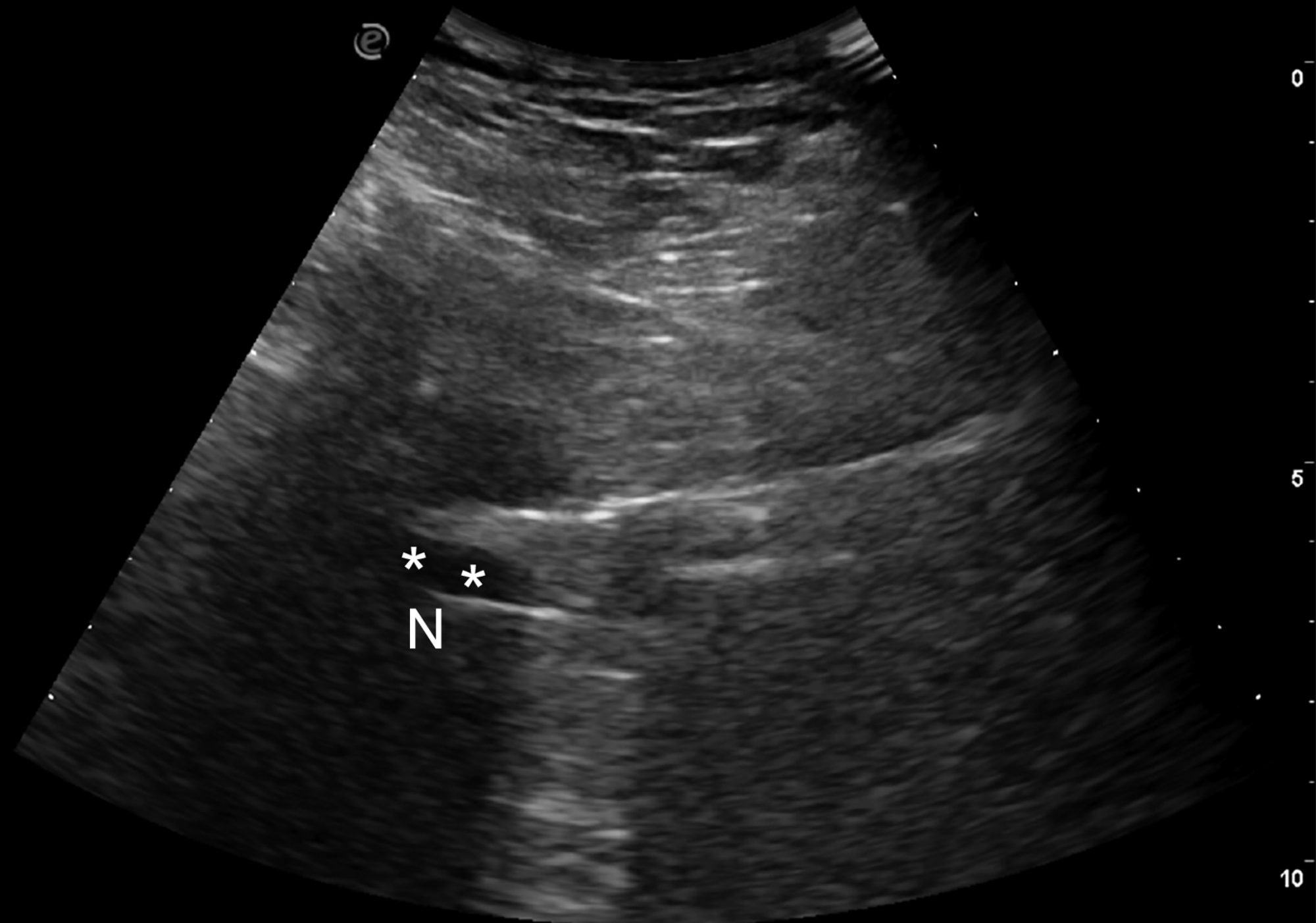
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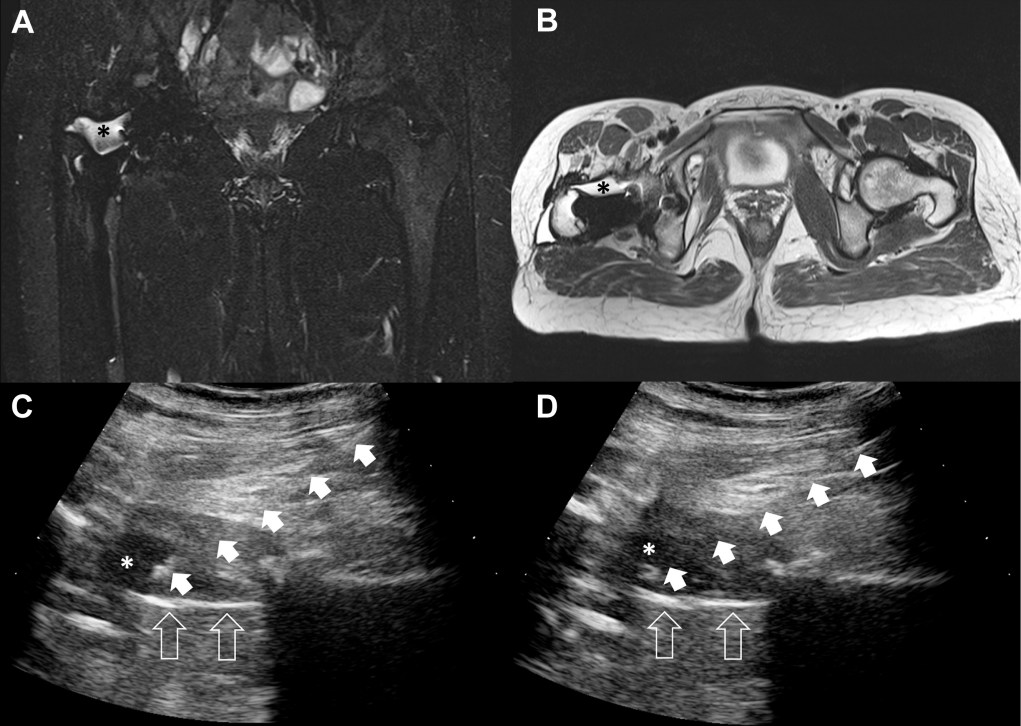
A
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C
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