The Minimally Invasive Approach to the Diagnosis of an Undifferentiated Atrial Mass: A Case Series and Review of the Literature

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INTRODUCTION

The management of a newly identified cardiac mass requires prompt evaluation and diagnosis. Although cardiac masses are typically metastases of noncardiac primary tumors, up to 25% of primary cardiac tumors are malignant and require expedited diagnosis to develop a treatment plan.[1] Improvements in noninvasive imaging techniques, particularly contrast-enhanced cardiovascular magnetic resonance imaging (CMR), cardiac computed tomography (CCT), and three-dimensional echocardiography, have allowed the noninvasive characterization and localization of cardiac masses. However, endomyocardial biopsy (EMBx) or open surgical biopsy remains the gold standard for diagnosis and at times is the only option for pathologic characterization of an undifferentiated cardiac mass. For this reason, EMBx for the diagnosis of cardiac tumors is supported by current guidelines despite the associated morbidity.[2]

Isolated atrial masses present a diagnostic dilemma. The presence of right-sided intracardiac devices such as implantable cardiac defibrillators, permanent pacemakers, and indwelling central catheters, which are prone to thrombus formation, make it difficult to differentiate between benign and malignant etiologies of a newly identified cardiac mass. These devices also obscure visualization by noninvasive imaging modalities because of artifacts induced by metallic devices and the limits of spatial resolution. Finally, the thin atrial wall portends an increased risk for cardiac perforation during EMB. Herein, through the description of three cases, we describe our institution's multidisciplinary approach to the undifferentiated atrial mass.

CASE PRESENTATION 1

A 37-year-old man with recently diagnosed stage IIIA testicular seminoma on chemotherapy presented with shortness of breath and light-headedness. Initial transthoracic echocardiography (TTE)

demonstrated a 2.0 × 2.6 cm sessile, ovoid echodensity in the right atrium adjacent to a previously placed permanent central venous catheter (Figure 1A, Video 1). Transesophageal echocardiography (TEE) confirmed the findings on TTE and demonstrated that the mass was independent of the tricuspid valve (TV) apparatus and the catheter (Figure 1B). CMR demonstrated a heterogenous, T1-hypointense mass without clear evidence of perfusion on first-pass imaging and no obvious uptake on late gadolinium enhancement imaging. Taken together, this favored a diagnosis of thrombus, especially in the presence of a central venous catheter (Figures 1C and 1D). Accordingly, the patient was started on empiric anticoagulation. However, because of persistence of the mass after several months of anticoagulation, EMBx was performed.

Under conscious sedation, venous access was established though the right femoral and right internal jugular veins. An intracardiac echocardiographic catheter was advanced to the right atrium. Intracardiac echocardiography (ICE) confirmed the location of the mass, the relationship of the mass to the TV apparatus, and the absence of a pericardial effusion. A precurved bioptome was advanced to the mass under intracardiac echocardiographic and fluoroscopic guidance (Figure 2, Video 2). Four samples were sent for frozen sections and immediate pathologic review. ICE was used to verify the absence of a pericardial effusion and damage to the TV apparatus at the end of the case. Final pathologic diagnosis revealed thrombosed cellular debris of the patient's known germ cell tumor without viable tumor. The patient underwent additional chemotherapy and autologous stem cell transplantation. After completion of treatment, follow-up TTE showed complete resolution of the right atrial mass.

CASE PRESENTATION 2

A 31-year-old man with a history of recurrent culture-negative TV endocarditis presented with recurrent fevers and rigors. The patient had undergone three prior sternotomies for culture-negative endocarditis. Two years prior, debridement of the TV apparatus with TV replacement was performed. After recurrent prosthetic valve vegetations, despite negative microbiologic evaluation, the patient underwent a tricuspid valvectomy with the plan to allow suppressive antibiotics to clear a presumed culture-negative infection. Because of progressive right-sided heart failure, the patient underwent repeat TV replacement 6 months before his current presentation.

TTE showed mild tricuspid regurgitation without evidence of endocarditis; however, the prosthetic valve leaflets were not well visualized. TEE demonstrated multiple, large, pedunculated, mobile vegetations attached to the anterior and posterior leaflets of the prosthetic valve with associated leaflet thickening and severe tricuspid regurgitation (Figure 3A, Video 3). After multidisciplinary evaluation with infectious disease, cardiac surgery, and cardiology, the patient was started on empiric antifungal and antibacterial coverage. The patient also underwent a positron emission tomography (PET)/computed

tomography (CT) to evaluate for both a nidus of infection and inflammation around the TV apparatus. PET/CT showed no evidence of fluorodeoxyglucose uptake at the TV or a focus of infection. After 2 weeks of empiric antibiotic and antifungal therapy, repeat TEE showed persistence of the unchanged TV vegetation. After a patient-centered, multidisciplinary heart team discussion, the decision was made to proceed with transcatheter aspiration and debulking of the TV apparatus and combined pathologic and microbiologic evaluation of the mass.

Under general anesthesia, a transesophageal probe was placed for procedural guidance. Right internal jugular vein access was established to advance a large-bore manual aspiration catheter into the right atrium. Multiple aspirations were performed at the level of the TV and annulus (Figure 4). TEE confirmed debulking of the vegetation. The vegetation was sent for pathologic diagnosis, which revealed loose fibrin thrombus without inflammation or microorganisms. After a prolonged antibiotic course, and subsequent development of clinical features of recurrent oral ulcerations, erythema nodosum,
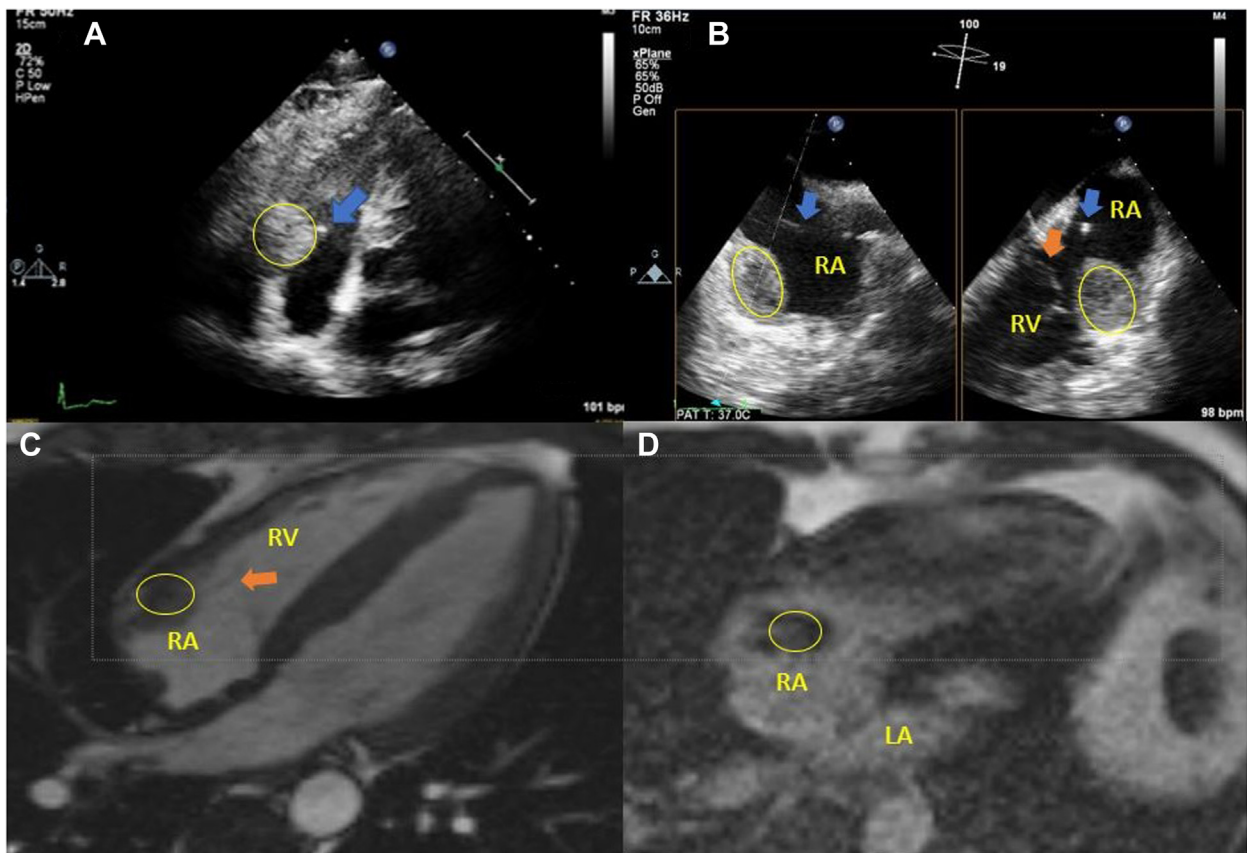
Figure 1 (A) Two-dimensional TTE, right ventricle (RV)–focused apical view, demonstrating a sessile, ovoid mass *(yellow circle)* adherent to the lateral wall of the right atrium (RA), with possible involvement of the central venous catheter *(blue arrow)*. **(B)** Two-dimensional TEE, midesophageal bicaval view, biplane evaluation of the RA demonstrating a sessile mass *(yellow circle)* fixed to the lateral wall, without involvement of the TV apparatus *(orange arrow)* or the central venous catheter *(blue arrow)*. **(C)** CMR steady-state free precession sequence, diastolic display, apical four-chamber view, demonstrating the right atrial mass *(yellow circle)* affixed to the lateral wall in close proximity to the TV *(orange arrow)*. **(D)** CMR late gadolinium enhancement sequence (phase-sensitive inversion recovery) demonstrating that the mass appears largely nonenhanced *(yellow circle)* and is suspicious for thrombus. *LA,* Left atrium.

Figure 2 (A) X-ray fluoroscopic anteroposterior projection demonstrating an intracardiac echocardiographic catheter *(blue arrow)* in the right atrium and the bioptome *(orange arrow)*. **(B)** Two-dimensional ICE, dedicated right atrial view, demonstrating the bioptome *(orange arrow)* positioned into the densest portion of the mass along the lateral wall of the right atrium *(yellow circle)*.
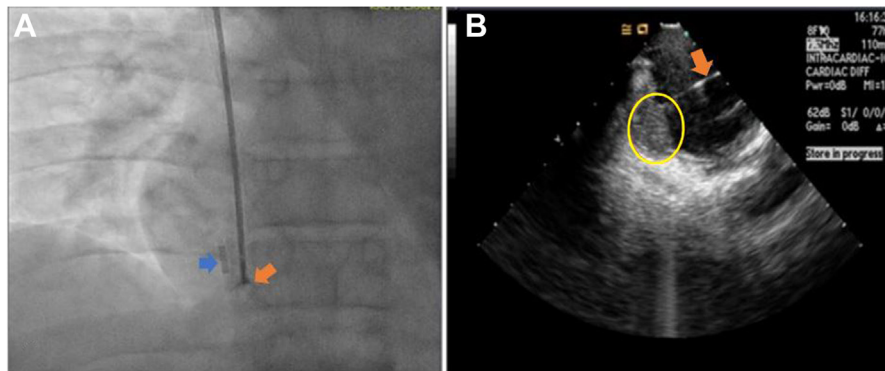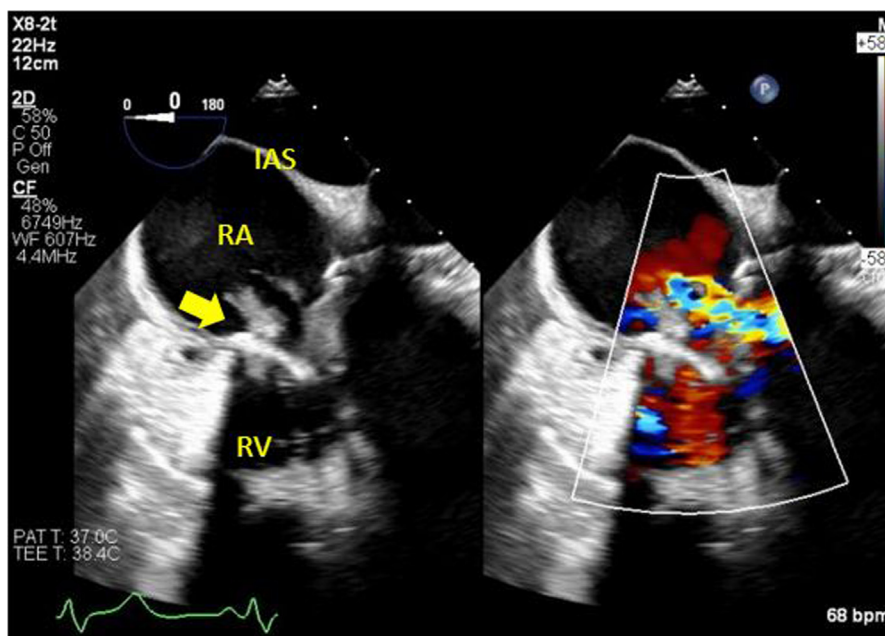

Figure 3 Two-dimensional TEE, modified apical four-chamber (0°) view without *(left)* and with *(right)* color flow Doppler, demonstrating thickening of the bioprosthetic TV leaflets with evidence of mobile vegetations *(yellow arrow)* and TR. *IAS*, Interatrial septum; *RA*, right atrium; *RV*, right ventricle.

positive pathergy on examination, and HLA-B51 positivity, the consensus diagnosis was nonbacterial, thrombotic endocarditis secondary to Behçet's disease.

CASE PRESENTATION 3

A 71-year-old woman with a history of systemic lupus erythematosus, newly diagnosed atrial fibrillation, and remote provoked deep vein thromboses presented with progressive chest pain and acute dyspnea. Computed tomographic pulmonary angiography revealed a large, circumferential, infiltrative mass involving the lateral wall of the left atrium. The mass was compressing the left pulmonary veins, encasing the left circumflex coronary artery, and narrowing the ostium of the atrial appendage (Figure 5A). CMR demonstrated a T1- and T2-isointense mass that did not suppress with fat suppression imaging.

Myocardial tagging suggested the mass was adherent to the left atrial wall and pericardium. Late gadolinium enhancement imaging showed patchy uptake within the mass. Taken together, the findings were suspicious for malignancy (Figure 5B–C). PET/CT identified a large, hypermetabolic mass involving the left atrium as well as multiple hypermetabolic lymph nodes present in the mediastinum and axilla (Figure 5D). After multiple attempts to obtain pathologic diagnosis by endoscopic fine-needle aspiration of a paraoesophageal lymph node and a percutaneous left axillary lymph node biopsy, the collaborative, patient-centered decision was made to perform EMBx.

Under general anesthesia, TEE was used for procedural guidance. A cerebral embolic protection device was placed in the innominate and left common carotid artery via the right radial artery. Under transesophageal echocardiographic guidance, a transseptal puncture was performed, allowing the placement of a steerable sheath into the left
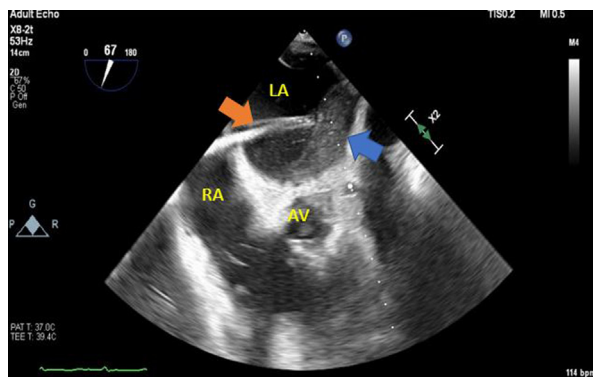
Figure 4 (A) X-ray fluoroscopic anteroposterior projection image demonstrating a 24-Fr sheath *(yellow arrow)* via the right internal jugular vein with a 24-Fr aspiration catheter *(orange arrow)* positioned at the bioprosthetic TV. **(B)** Two-dimensional TEE, midesophageal biplane systolic display of the TV, demonstrating the aspiration thrombectomy catheter *(yellow arrow)* positioned at the bioprosthetic TV vegetation *(orange arrow)*. *IAS,* Interatrial septum; *RA,* right atrium.

Figure 5 (A) Computed tomographic pulmonary angiographic protocol, coronal display, demonstrating a large mass *(blue arrow)* invading the left atrial wall and encasing the circumflex *(yellow circle)* and left pulmonary veins *(orange arrow)*. **(B)** CMR steady-state free precession sequence, axial display at the level of the left atrial mass *(yellow circle)*, demonstrating invasion of the left lower pulmonary vein *(blue arrow)*. **(C)** CMR, late gadolinium enhancement sequence (phase-sensitive inversion recovery), axial display, demonstrating patchy enhancement of the left atrial mass *(yellow circle)*. **(D)** PET/CT, axial image, demonstrating a posterior atrial mass with significant hypermetabolic activity *(yellow circle)*. *AV,* Aortic valve; *LA,* left atrium; *PA,* pulmonary artery; *RA,* right atrium.

atrium. A bioptome was directed toward the mass and samples were sent for frozen section, to ensure an adequate sample (Figure 6). Final pathologic diagnosis was consistent with diffuse large B-cell lymphoma, for which the patient was started on immediate chemotherapy.

DISCUSSION

The foregoing cases highlight several important points: (1) the use of multimodality, noninvasive, imaging including CCT, magnetic resonance imaging, three-dimensional echocardiography and PET/CT

Figure 6 Two-dimensional TEE, modified basal short-axis view, demonstrating a steerable guide *(orange arrow)* directed toward the mass *(blue arrow)* to guide bioptome sampling. *AV*, Aortic valve.
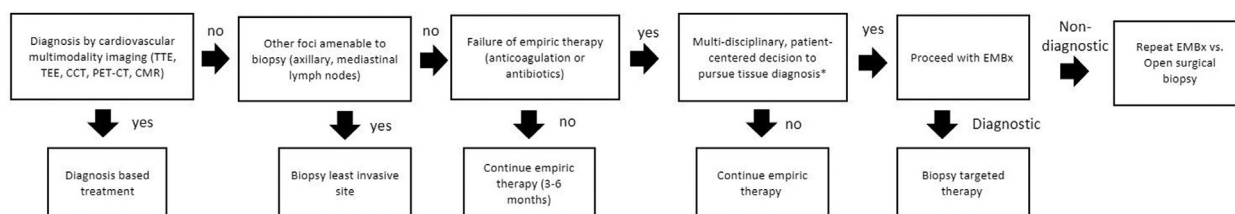

Figure 7 Algorithm for the multidisciplinary evaluation and treatment of an undifferentiated atrial mass. The figure highlights our institution's algorithm for the evaluation of an atrial mass. *Includes a cardio-oncologist, an imaging specialist, an oncologist, an interventional cardiologist, a cardiothoracic surgeon, and an interventional radiologist.

for the evaluation of a newly diagnosed cardiac mass; (2) the multidisciplinary evaluation of a newly diagnosed atrial mass, including a cardiovascular imaging specialist, a proceduralist, and an oncology specialist; and (3) an algorithmic approach to the percutaneous EMBx of a newly diagnosed atrial mass.

Figure 7 highlights our institution's algorithmic approach to a newly diagnosed right atrial mass. As highlighted in the present cases, it is critical to engage cardiovascular imaging specialists to define both the imaging characteristics of the mass itself but also to delineate the location and proximity to the atrioventricular valve apparatus and conduction system in preparation for potential EMBx. Predominantly epicardial masses are typically inaccessible by percutaneous means and may require another imaging-guided biopsy, including CCT or endoscopic biopsy.[3,4] The presence of axillary, mediastinal or other foci of biopsy associated with less morbidity should also be identified before undertaking EMBx. Additionally, in the appropriate clinical circumstance, such as persistent bacteremia or suspected device associated thrombus, empiric treatment and interval imaging should be performed to assess for resolution of the mass before proceeding with EMBx. Although the time between conservative therapy and interval imaging has not been defined, our institution typically waits 3 months. After 3 months of conservative therapy, if the diagnosis is still in question, tissue diagnosis is pursued by EMBx. If EMBx is nondiagnostic, open biopsy can be considered.

The noninvasive characterization of atrial masses is critical to define the relationship to surrounding structures and potentially reveal the etiology of the mass. When evaluating an atrial mass, TTE, TEE, ICE, CCT, and magnetic resonance imaging are often used in parallel to come to a preliminary diagnosis. PET/CT may be appropriate in select cases to define potential malignant and infectious etiologies. Table 1 highlights the advantages and disadvantages of each imaging modality. All imaging techniques are susceptible to artifacts from intracardiac devices, but through the use of multiple imaging modalities, and optimization of imaging with the assistance of a cardiology imaging specialist, these artifacts are typically overcome, allowing diagnostic-quality images. Typically, atrial masses are diagnosed using TTE. Because of the anterior location of the right atrium, TTE is often sufficient to define the location and extent of right atrial masses. However, in the case of the posteriorly located left atrial masses, TEE is typically needed to further define the mass. The use of ultrasound enhancing agents can also indicate vascularity.[5] Although typically not used as a primary diagnostic tool, ICE, particularly with novel four-dimensional ICE, can be used for intraprocedural mass characterization and procedural guidance and negate the need for transesophageal echocardiographic guidance and the need for general anesthesia.[6]

Tomographic imaging modalities in conjunction with intravascular contrast not only provide a larger field of view, thus identifying other areas of potential biopsy, but, most important, provide superior myocardial tissue definition. Given CMR's superior tissue characterization, it is typically used in conjunction with echocardiography for the evaluation of cardiac masses. In patients unable to undergo CMR, CCT can provide additional tissue characterization. CCT is most useful in localization of masses, evaluation of the mass's interaction with the coronary arteries, and demonstration of vascularity with the use of iodinated contrast dye. CCT can also be used in conjunction with fluorodeoxyglucose-enhanced PET (PET/CT), which can define the metabolic characteristics of the mass. Because of this,

Table 1 Comparison of multimodality imaging techniques for the evaluation of atrial masses

	TTE/TEE	ICE	CCT	CMR	PET/CT
Advantages	• Localization of mass, particularly with 3D echocardiography • Superior temporal resolution allows visualization of mobile masses • Hemodynamic assessment (valvular stenosis or regurgitation) • Ultrasound enhancing agent can improve delineation of mass and determine vascularity • No radiation exposure • Used in procedural guidance	• Higher spatial resolution • Enhanced visualization of right-sided structures • Venous access negates need for moderate sedation • No risk for GI trauma • Reduced ionizing radiation exposure to patient and provider	• Higher spatial resolution • Only imaging modality that allows a comprehensive evaluation of coronary arteries • Iodinated contrast to evaluate for vascularity • Large field of view to allow identification of alternative biopsy sites (lymphadenopathy, noncardiac masses)	• Higher spatial resolution (morphology, dimensions, extension, infiltration in surrounding tissue) • Superior tissue differentiation (homogeneity, infiltration into surrounding tissue) • Signal characteristics to identify histopathology (vascularity, fat, calcification) • Large field of view • Hemodynamic assessment (LV function, valvular abnormalities)	• Fluorodeoxyglucose uptake demarcates metabolic activity in infection and malignancy • Allows assessment of infiltration and metastatic spread (i.e., malignancy staging) • Assessment of response to therapy • Identification and optimization of targets for biopsy
Disadvantages	• Need for moderate sedation or monitored anesthesia care • Relatively invasive (TEE) • Limited tissue characterization • Small field of view • Shadowing artifact from metallic objects	• Cost consideration for single-use catheters • Limited temporal resolution • Smaller field of view compared with TEE • Interferes with RA devices (bioptomes, temporary pacer wires) • Risk for vascular access complications	• Radiation exposure • Modest tissue characterization • Limited in irregular rhythms because of ECG gating • Beam hardening artifact in presence of implantable cardiac devices • Risk for contrast-induced nephropathy	• Limited availability • Limited in irregular rhythms because of ECG gating • Low temporal resolution • Image degradation in presence of implantable cardiac devices • Patient claustrophobia • Rare risk for nephrogenic systemic fibrosis in patients with kidney dysfunction	• Limited availability • Dietary preparation • Limited differentiation of inflammation vs malignancy

3D, Three-dimensional; *ECG*, electrocardiographic; *GI*, gastrointestinal; *LV*, left ventricular; *RA*, right atrial.
The table highlights the advantages and disadvantages of the multimodality imaging techniques available to evaluate atrial masses.

PET/CT is particularly useful in differentiating benign from malignant tumors. A 2020 study of the diagnostic accuracy of CCT alone compared with CCT with fluorodeoxyglucose PET demonstrated the superiority of CCT with PET to differentiate benign from malignant cardiac masses. The presence of five or more of the following characteristics demonstrated 100% positive predictive value for malignancy: irregular margins, pericardial effusion, calcification, tissue invasion, solid nature, mass diameter (>30 mm), and contrast uptake.[7] However, recent studies have shown that malignant masses are still misclassified as benign on CMR alone, emphasizing the need for tissue diagnosis.[8]

Cardiac masses are well suited for characterization with CMR. CMR allows direct visualization of morphology, dimension, location, and involvement of adjacent structures. In addition, CMR can assess for tissue characterization of cardiac masses, including the presence of vascularity, fat, edema, inflammation, and scar through a variety of pulse sequences. This in turn can help narrow the differential diagnosis of cardiac masses into broad categories such as thrombus, tumor (both benign and malignant), and cysts. Acute and chronic thrombi appear isointense and hypointense, respectively, on T1- and T2-weighted images, without early or late gadolinium enhancement. Tumors can be differentiated from thrombi on the basis of strong signal enhancement in the presence of contrast on first-pass perfusion due to vascularity and occasionally show central hyperintensity on T2 sequences in the presence of central hemorrhage and necrosis.[9,10] In tumors, late gadolinium enhancement can be present if areas of necrosis have occurred; otherwise they may have heterogenous signal uptake. On the basis of CMR data, decisions to pursue treatment and thus forgo the need for tissue sampling via invasive biopsy may occasionally be appropriate. However, despite high accuracy in identifying the etiology of cardiac masses, noninvasive CMR diagnosis is not yet perfect, maintaining the advantage of histopathologic tissue sampling as the gold standard.

If the atrial mass cannot be further defined on noninvasive imaging, conservative management fails, and the diagnosis of the mass will alter the treatment, a multidisciplinary, patient-centered discussion is critical to determine the appropriate next step, which may be the need for an EMBx. A key aspect of this discussion includes the risks of percutaneous EMBx. EMBx poses the risk for perforation and resultant tamponade, procedure-induced arrhythmias, valvular damage, vascular injury, and embolization. Table 2 highlights the procedural considerations for atrial biopsy. It is our practice to use TEE for guidance of left-sided biopsy and ICE with or without TEE for right-sided biopsy. The spatial resolution of ICE is diminished in far-field left-sided structures and enhanced for near-field right-sided structures because of the placement of the transducer in the right atrium or right ventricle. Finally, ICE can be performed without the need for moderate sedation or monitored anesthesia care. In a comprehensive review of atrial biopsy, Chang et al.[11] defined the current use of multimodality imaging during atrial biopsy, finding that 49% of biopsies were performed with the use of transesophageal echocardiography guidance, 35% with intracardiac echocardiography guidance, and 12% with transthoracic echocardiographic guidance. With the use of TEE, anesthesia support for either general anesthesia or monitored anesthesia care is necessary to ensure patient comfort and immobility during biopsy.[12] Before beginning the biopsy, it is important to define the relationship of the mass to the TV or mitral valve apparatus, the free wall of the atrium, and the conduction system, as well as evaluate for baseline pericardial effusion. The appearance of the atrial mass defines the approach to biopsy. For large, pedunculated masses, it is our approach to

Table 2 Procedural considerations for atrial biopsy

Procedural aspect	Considerations
Monitoring	• ECG: evidence of conduction abnormality during biopsy • Blood pressure: hypotension for cardiac tamponade • RV pressure – evidence of diastolic equalization
Anesthesia	• General anesthesia: for TEE or as needed for patient comfort and/or cooperation • Moderate sedation: for ICE
Access	• Femoral: transseptal puncture and ICE • Internal jugular: for favorable approach to mass from SVC
Sheath	• Aspiration thrombectomy: 24-Fr introducer sheath • Transseptal puncture: 8.5- or 12-Fr directional sheath • Bioptome: 7-Fr directional sheath or 7-Fr 23-cm sheath
Biopsy method	• Sessile mass: bioptome • Pedunculated mass: aspiration or mechanical thrombectomy
Image guidance	• ICE, TEE plus fluoroscopy
Embolic protection	• Consideration of cerebral embolic protection device • Heparinization to goal ACT of 250 sec for transseptal access
Emergency contingency	• Pericardiocentesis setup available for perforation and tamponade • Temporary venous pacemaker available for high-grade AV block
Pathologic evaluation	• Intraprocedural frozen section to ensure adequate tissue sampling

ACT, Activated clotting time; *AV*, atrioventricular; *ECG*, electrocardiography; *RV*, right ventricular; *SVC*, superior vena cava.
The table lists the procedural considerations for atrial mass biopsy.

perform thrombectomy, as there is a mobile component able to be aspirated. Several systems are commercially available, including aspiration thrombectomy (FlowTriever 24- or 20-Fr aspiration catheter [Inari Medical] and AlphaVac [AngioDynamics]) or mechanical thrombectomy (Penumbra Lightning 7 or 12 [Penumbra] and AngioVac [AngioDynamics]). However, in the cases of left-sided pedunculated lesions, with an associated risk for embolization, an alternative method of biopsy is strongly recommended. For sessile or adherent masses, which may be suggestive of an organized or infiltrative process, bioptome-facilitated biopsy using a femoral venous steerable sheath (Agilis [Abbott Vascular] or Destino [Oscor]) is preferred. It is not our practice to use a side-cutting biopsy needle.[13] The optimal trajectory between the mass and the trajectory of the sheath through the inferior vena cava or the superior vena cava determines femoral or internal jugular access, respectively. Also, although commercially available preshaped bioptomes are available, the operator can also customize the shape. In the case of left-sided biopsy, heparinization and cerebral embolic protection, should be

considered because of the risk for systemic embolism. After obtaining samples, frozen sections are sent to pathology to ensure adequate sampling. Finally, it is necessary to ensure that a pericardiocentesis setup and temporary pacemaker are readily available, in the case of perforation or conduction system disturbance induced by biopsy or aspiration.

CONCLUSION

Through our institution's comprehensive, multidisciplinary, and patient-centered approach, we have developed a framework to assess atrial masses by leveraging advances in cardiovascular imaging to mitigate the morbidity associated with EMBx.

ETHICS STATEMENT

The authors declare that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

CONSENT STATEMENT

The authors declare that since this was a non-interventional, retrospective, observational study utilizing de-identified data, informed consent was not required from the patient under an IRB exemption status.

FUNDING STATEMENT

DISCLOSURE STATEMENT

Dr. Karmali is an advisory board member for Celgene, Gilead Sciences, Juno Therapeutics, Kite Pharma, Janssen, Karyopharm, Pharmacyclics, Morphosys, Epizyme, Genentech/Roche, EUSA, and Calithera; has received grants and research support from Celgene/Juno Therapeutics/Bristol Myers Squibb, Tagskeda, BeiGene, and Gilead Sciences/Kite; and is a speakers' bureau member for AstraZeneca, BeiGene, and Morphosys. Dr. Schimmel has received fellowship educational grant support from Medtronic, Boston Scientific, and Abbott Laboratories; has received research grant support from Boston Scientific, Inari Medical, and Daiichi Sankyo; is a consultant for Inari Medical and Change Healthcare; and is a speaker for Inari Medical.

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.case.2022.12.011.

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