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Primary Cardiac Angiosarcoma Diagnosed by 3D Transesophageal Echocardiography Guided Endomyocardial Biopsy – Case Report

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1. Abstract

Cardiac angiosarcomas are uncommon, primary malignant cardiac tumors, characterized by an aggressive local growth within the myocardial structures. The majority occur in the right atrium, and at the moment of diagnosis usually infiltrate into neighboring structures. Due to the lack of typical features in clinical presentation, the diagnosis of cardiac angiosarcoma is challenging. Initial clinical workup includes different imaging modalities [transthoracic (TTE) and transesophageal echocardiography (TEE), computed tomography (CT), cardiac magnetic resonance and/or positron emission tomography], but definite diagnosis can be made only with an endomyocardial biopsy (EMB), which is performed infrequently. Broad histological and immunohistochemical stainings of obtained tissue samples allow for precise tumor identification resulting in better risk stratification and targeted treatment options. However, there is still little experience with invasive in-vivo diagnosis of intracardiac masses.

We report a case of a 73-year-old female patient with symptomatic heart failure de novo and no relevant past medical history. Non-invasive imaging (TTE, TEE and contrast-enhanced CT) showed a large intracardiac mass infiltrating the right atrium wall and adjacent pericardium, and moderate pericardial effusion. Examination of tissue samples obtained during EMB and guided by 3D-TEE revealed a primary cardiac angiosarcoma. This case study highlights that EMB with the use of broad pathological analyses (immunohistochemical stainings, electron microscopy) allows for quick, safe and definite diagnosis of patients with cardiac tumors of unknown origin facilitating further management. EMB with 3D-TEE guidance is technically feasible and increases the accuracy and safety of the diagnosis of intracardiac tumors.

2. Introduction

Primary malignant cardiac tumors are extremely uncommon (<0.3% of cardiac tumors in postmortem studies) and are associated with poor prognosis [1, 2]. To increase the survival rate, an early and effective diagnostic process is necessary. Although non-invasive imaging modalities are useful, a definite diagnosis in the majority of cases requires histologic examination, which remains a gold standard.

We report a patient with new-onset heart failure (HF), in which a 3D transesophageal echocardiography (TEE) - guided endomyocardial biopsy (EMB) confirmed the diagnosis of cardiac angiosarcoma within a few days. We present the following case in accordance with the CARE reporting checklist.

3. Case Presentation

A 73-year-old female with arterial hypertension and no other relevant past medical history was admitted to hospital due to signs of HF de novo. On admission she presented shortness of breath upon exertion [New York Heart Association Class (NYHA) II]. The patient reported a 10 kg body weight loss within the previous month.

She denied chest pain, palpitations or other relevant symptoms.

On physical examination, her vital signs were as follows: hemoglobin saturation, 94% (Fraction of Inspired Oxygen (FiO2) 0.21); heart rate, 90 beats/min; blood pressure, 95/78 mmHg; and no fever. Systolic-diastolic murmur on cardiac auscultation; general peripheral oedema; signs of bilateral pleural effusion and liver enlargement were present. Laboratory studies showed the following abnormalities suggesting acute kidney injury and decompensation of HF: serum creatinine, 1.94 mg/dl; estimated glomerular filtration rate (eGFR), 25 ml/min/1,73 m2; urea, 110 mg/dl; N-terminal pro-brain natriuretic peptide, 2392 pg/ml (N: <125 pg/ml); D-dimer, 7973 ng/ml (N <500 ng/ml). The cancer biomarker was elevated: Ca 125, 290 U/ml (N: <35 U/ml). A chest X-Ray showed fluid in both pleural cavities without signs of congestions. A standard 12-lead electrocardiogram showed a normal sinus rhythm and inverted T waves in leads I, II, aVL.

A transthoracic echocardiography (TTE) revealed a large mass (90 x 73 mm) with heterogeneous echogenicity almost completely filling the cavity of the right atrium, infiltrating its wall and the visceral pericardium of the right ventricle and the apex of the heart (Figure 1 and 2). The presence of this large mass in the right atrium resulted in severe obstruction of the inflow from both venae cavae with a mean gradient difference of 7 mmHg (Figure 3). Additionally, a moderate amount of fluid around the heart with no compression upon cardiac walls (Figure 1) and fluid in the pleural cavities were observed.

A TEE confirmed a large polycyclic tumor (80 x 66 mm) with heterogeneous echogenicity, attached to the wall of the right atrium and infiltrating the right atrium wall, superior vena cava and visceral pericardium. The tumor occupied the entire right atrium causing functional tricuspid stenosis, but without invading the tricuspid valve and inferior vena cava (Figure 4).

Chest, abdomen, and pelvis contrast-enhanced computed tomography revealed a large polycyclic tumor (88 x 67 x 74 mm) with heterogeneous densities (moderately enhanced by contrast, most likely containing necrotic areas) covering most of the right atrium, the adjacent part of the pericardium and extending into the orifice of the superior vena cava; pericardial effusion; bilateral pleural effusions and osteolytic metastatic changes in the vertebral bodies of the spine without other primary tumors.

As the primary differential diagnosis suggested a primary or secondary malignant cardiac tumor, a TEE–guided EMB from the access point of the right internal jugular vein (Figure 5 and 6) was performed. Biopsy forceps (Cordis Corp) were inserted into a 7F (Cordis Corp) long sheath and advanced into the right atrium. The TEE allowed detailed visualization of the tumor, bioptome position on the tumor surface and exact selection of the sample site. Periprocedural imaging was further enhanced with the use of a 3D probe. Ten tissue samples were gathered from the tumor surface without periprocedural complications. Histochemistry, immunohistochemistry and electron microscopy study of the EMB specimens allowed visualization of a malignant vascular tumor features (Figure 7).

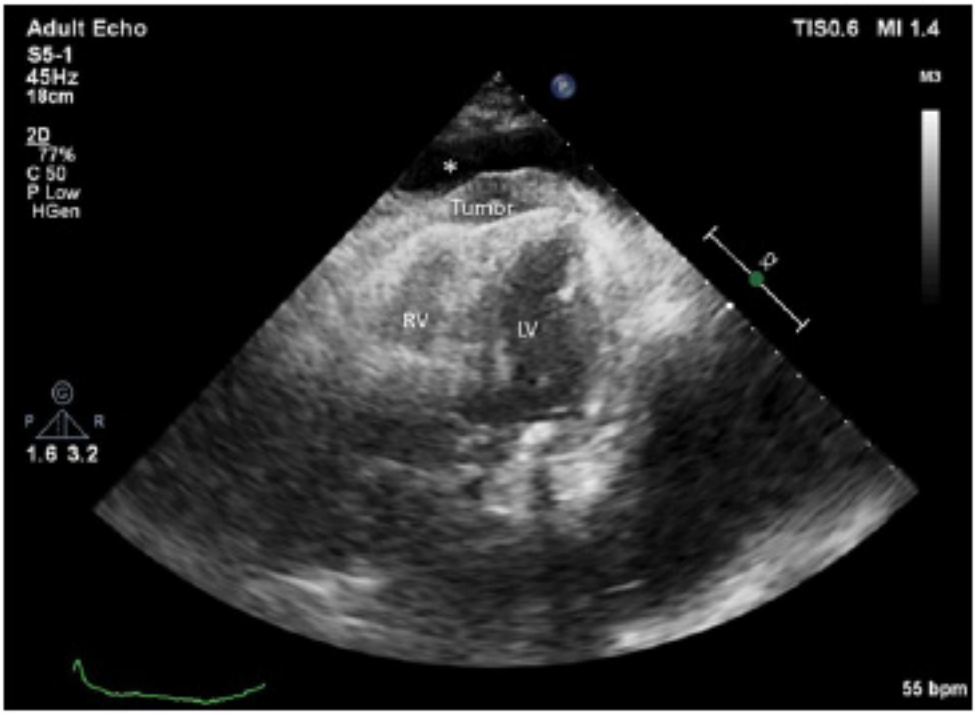

Figure 1: A four-chamber view showing the mass of the tumor surrounding the free wall of the right ventricle and the apex of the heart. Around the heart a moderate amount of fluid is visible. LV-left ventricle, RV-right ventricle, *-fluid in the pericardial sack

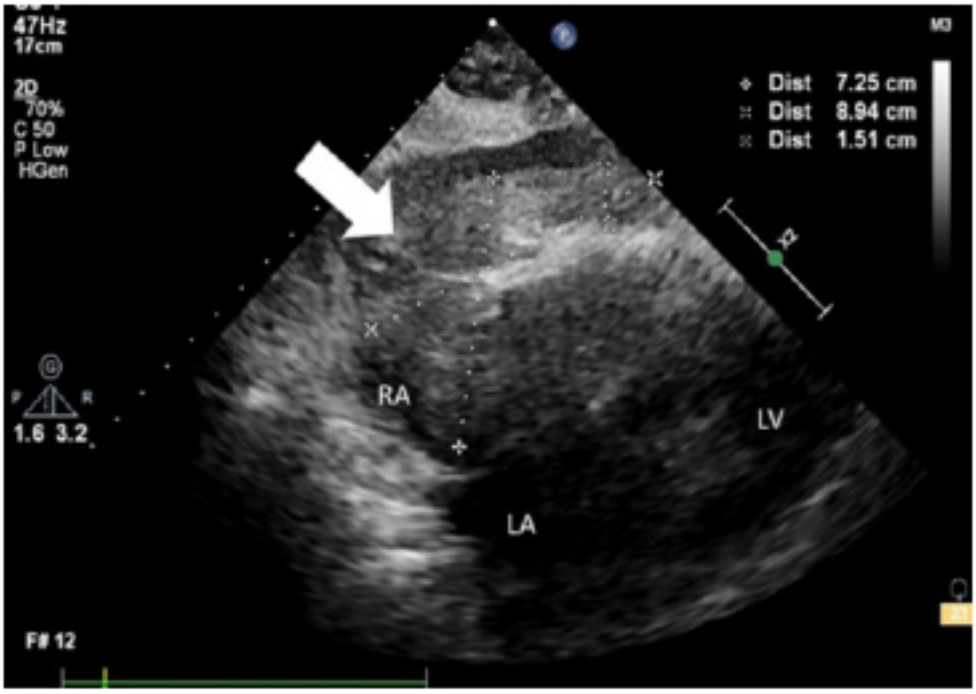

Figure 2: A large tumor with heterogeneous echogenicity (shown with a white arrow) infiltrating the wall of the right atrium and filling its cavity almost completely, visible from the substernal view. LA-left atrium, LV-left ventricle, RA-right ventricle.

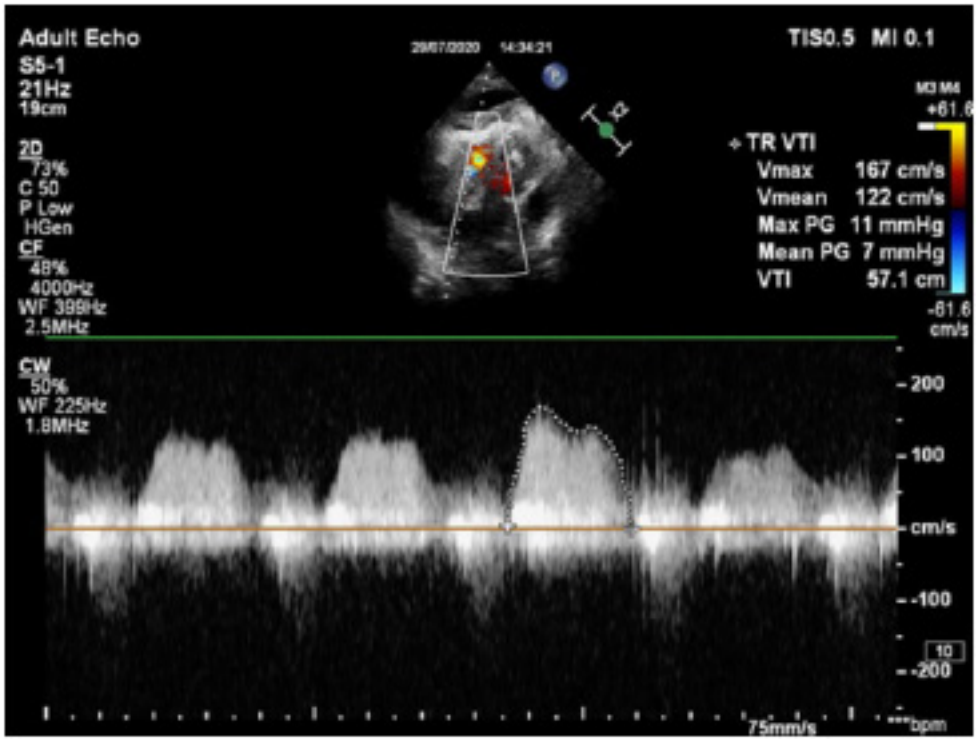

Figure 3: Maximal and mean gradient through the right atrium and the tricuspid valve assessed by continuous Doppler ultrasound measurements indicating severe obstruction of blood flow into the right ventricle.

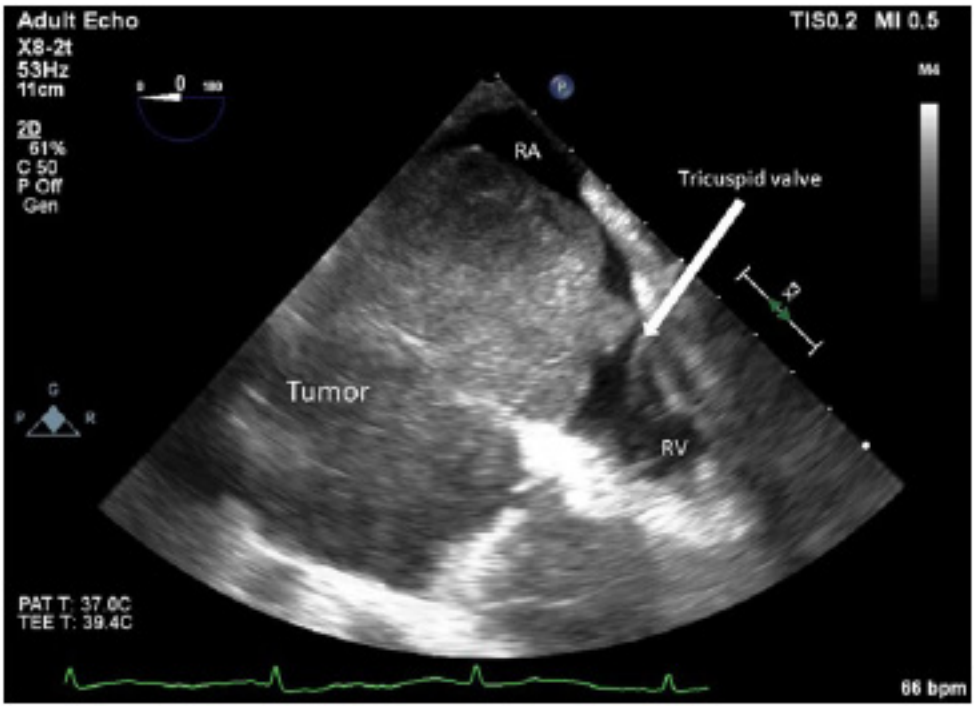

Figure 4: A modified mid-esophageal four-chamber view demonstrating a large hypoechogenic tumor infiltrating the wall of the right atrium and filling its cavity almost completely. RA-right atrium, RV-right ventricle.

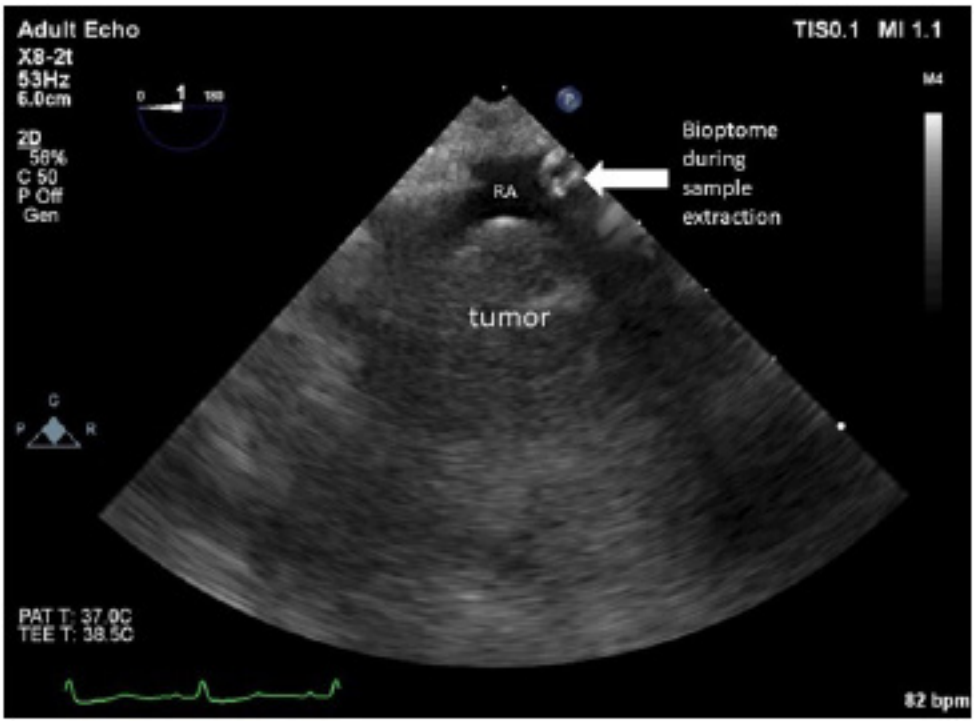

Figure 5: Tumor biopsy controlled by transesophageal echocardiography. RA-right atrium.

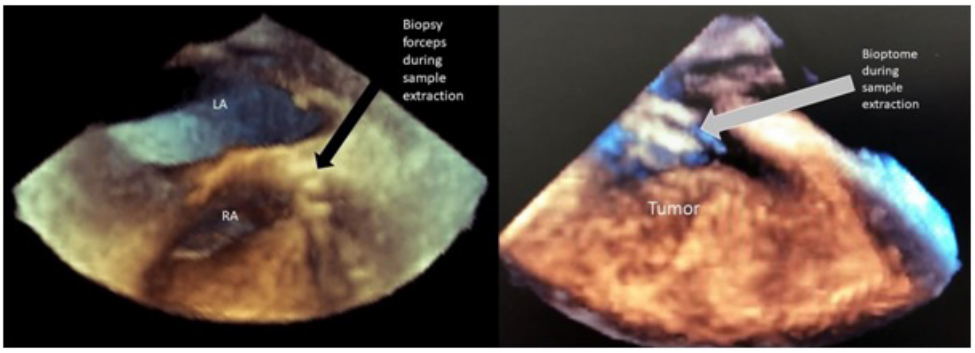

Figure 6: Tumor biopsy controlled by transesophageal echocardiography – a 3D view. LA-left atrium, RA-right atrium.

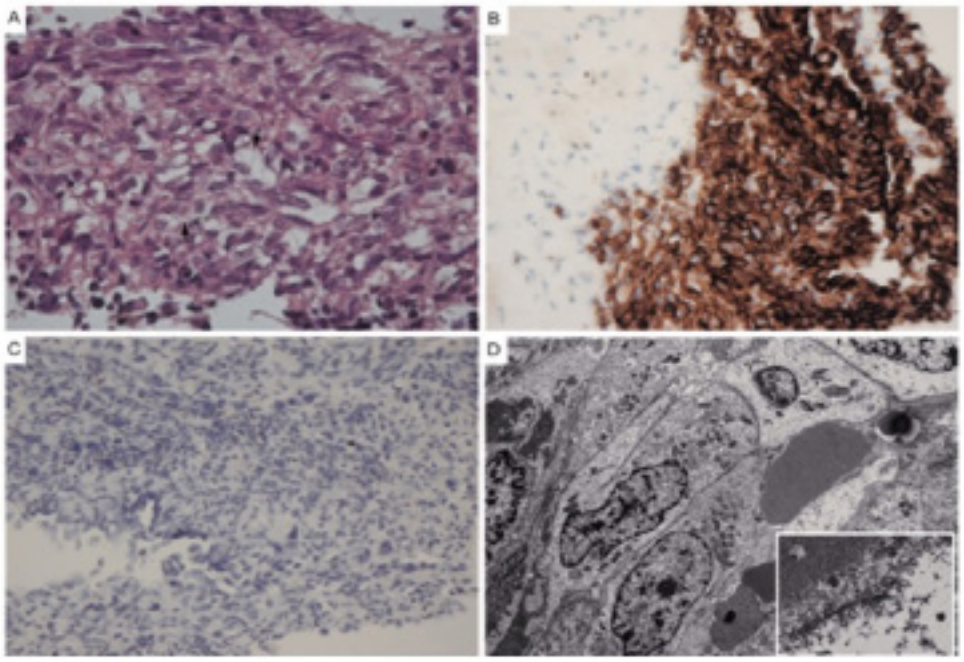

Figure 7: Primary cardiac angiosarcoma. A: Anaplastic cells with poorly formed vascular channels (arrows) (H&E); B: Strong immunohistochemical staining for CD31 marker (brown color); C: Negative immunohistochemical staining for cytokeratin filaments AE1/AE3 (brown color); D: Electron micrographs showing immature endothelial cells.

During hospitalization, she was initially treated with furosemide and i.v. fluids (under blood pressure and diuresis monitoring) presenting slight clinical improvement. However, three days after the EMB, she developed cardiogenic shock and subsequent sudden cardiac arrest. The patient died despite cardiopulmonary resuscitation.

4. Discussion

Cardiac angiosarcomas are characterized by aggressive growth and early metastases. The diagnostic and therapeutic approach is very demanding because of the intracardiac localization of the tumor. Clinical presentation of cardiac angiosarcomas depends on their size, location, status of local infiltration and/or distant metastases, relation with other cardiac structures and potential signs of hemodynamic compromise. In the majority of cases, angiosarcomas are diagnosed when the disease is already advanced with evidence of metastases, and often with atypical signs of HF [3].

Therefore, an early diagnosis of angiosarcoma is crucial for therapeutic options and the patient's prognosis. Comprehensive clinical and multimodality imaging (TTE and TEE, including 3D, contrast or intracardiac echocardiographic imaging; cardiac magnetic resonance (CMR); positron emission tomography (PET)) evaluation of cardiac tumors is fundamental to obtain a proper initial differential diagnosis [4,5,6,7]. In our case, an initial diagnosis of a malignant cardiac tumor was made by use of echocardiography, both TTE and TEE, followed by contrast-enhanced computed tomography, which revealed a huge, dense mass with areas of necrosis in the right atrium. Angiosarcomas are mostly immobile and broad-based with endocardial to myocardial growth [1]. CMR could be useful but in our patient a CMR was not performed because of kidney insufficiency. CMR findings in angiosarcomas include heterogeneous T1 and T2-weighted signal intensity and a heterogeneous contrast enhancement pattern [1]. A PET scan with the use of 18F-2-fluoro-2-deoxy-D-glucose (FDG) can reveal areas

of high FDG uptake within the mass and evidence of metastatic disease [8,9].

Histopathology is necessary to reach the final diagnosis and plan subsequent clinical management in some types of cardiac masses [10]. The histopathological features of angiosarcomas are: a highly vascularized mass with myocardial infiltration and signs of pleomorphism, necrosis and mitosis, clearly indicating diagnosis [1]. EMB is still the only method allowing for a definite diagnosis, but it is not commonly performed, despite a very low complication rate (<1%) [11,12,13]. EMB using broad histologic and immunohistochemical methods allows for the definition of the type of tumor, management of the treatment methods and better risk stratification. Echocardiography-, electroanatomic mapping- or in the future CMR-guided EMB, increases the accuracy and safety of the procedure [14]. Many echocardiographic modalities can be helpful during EBM, including intracardiac visualization [15,16]. In our case, TEE guidance allowed direct visualization of the tumor and bioptome position on its surface. We proved that biopsy forceps, when guided by TEE, are feasible for diagnosis of intracardiac tumors. The use of 3D TEE clearly indicated the place of sample collection and minimized the risk of complications. This was crucial since the right atrium cavity was to a great extent occupied with the tumor and the targeted mass was in close proximity to the atrial septum and tricuspid valve leaflets. To increase the diagnostic accuracy and sampling error, it is necessary to gather at least 5 tissue samples (recommended 5-10), each 1-2 mm in size. The main limitation of EMB is a need for experienced physicians and histopathologists, thus patients should be referred to tertiary medical centers.

In terms of treatment, angiosarcomas, when localized without infiltration of adjacent structures, may undergo surgery. However, surgery may be technically challenging and not always feasible. On the other hand, upfront chemoradiotherapy may enable definitive surgical resection. In our patient, based on the EMB results, it was possible for a consensus decision to be taken to initiate upfront chemotherapy and afterwards perform the resection of the tumor. At the moment of diagnosis, the tumor was large in size (approx. 9 x 7.5 cm) causing significant haemodynamic disturbances and infiltrating the pericardium, hence probably preventing a complete resection of the tumor. The majority of angiosarcomas have poor overall prognosis related to EMB-targeted therapeutic management and complete surgical resection of the tumor. In our patient, at the moment of diagnosis, the angiosarcoma was in an advanced stage with local infiltration and evidence of metastases in the spine.

To conclude, this case report showed that EMB guided by TEE may increase the accuracy and safety of the procedure and enable a definite diagnosis of the type of intracardiac tumor, facilitating further management.

5. Ethical Statement

The authors are accountable for all aspects of the work and ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was not obtained from the patient. Presented data do not allow for the subject to be identified.

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