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CARDIO-ONCOLOGY

CASE REPORT: MULTIDISCIPLINARY TEAM DISCUSSION

Primary Cardiac Aggressive B-Cell Lymphoma Affecting Right Ventricle and Acute Cardiovascular Events

Multidisciplinary Approach

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ABSTRACT

Primary cardiac lymphoma (PCL) is extremely rare. A few reviews comprise the available evidence. We present the case of a 70-year-old man who was immunosuppressed as a result of a previous liver transplant and who presented with PCL. This case highlights the cardiovascular issues that clinicians may face in PCL management and the importance of a multidisciplinary team approach. (JACC Case Rep. 2024;29:102562) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

CASE PRESENTATION

A 70-year-old Caucasian man with dyslipidemia and chronic liver disease caused by hepatitis C virus who had received a liver transplant 10 years earlier and who currently had a sustained viral response under immunosuppression with tacrolimus began a cardiologic study at the request of his primary care physician because of progressive exertional dyspnea. Initial test results and the physical examination were unremarkable. Therefore, an exercise echocardiogram was performed and found a heterogeneous mass infiltrating the anterolateral wall of the right ventricle. The patient was admitted for further studies.

TAKE-HOME MESSAGES

- This case highlights the complexity that clinicians may face when managing cardiovascular complications in patients with cancer.
- An MDT approach and the need for expertise in permissive cardiotoxicity are key to rapidly diagnose and make patient-oriented decisions that allow treatment of coexisting cancer and heart disease with the least detriment to both.

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

CCU = coronary care unit

CMR = cardiac magnetic resonance

CT = computed tomography

DES = drug-eluting stent

DLBCL = diffuse large B-cell lymphoma

EBV = Epstein-Barr virus

MDT = multidisciplinary team

PCI = percutaneous coronary intervention

PCL = primary cardiac lymphoma

PET-CT = positron emission tomography-computed tomography

R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone

RV = right ventricular

VTE = venous thromboembolism

QUESTION 1: WHAT IS THE INITIAL DIAGNOSTIC WORK-UP FOR CARDIAC MASSES?

Cardiac masses are often first detected by echocardiography. The differential diagnosis includes most commonly thrombi and vegetations, as well as other rare entities such as primary or secondary cardiac tumors.[1] Correlations between location and mass subtype have been reported; however, many cardiac tumors can occur in any chamber. The differential diagnosis should include a multimodal imaging approach, including echocardiography, cardiac magnetic resonance (CMR), and computed tomography (CT). CMR can assess for morphology, dimensions, location, extension, homogeneity, presence of infiltration, and tissue characterization.[2,3]

The CMR study demonstrated a solid mass of probable tumor origin located intramyocardially in the anterolateral right ventricular (RV) wall (**Figures 1A to 1D**). RV function and volumes were not evaluated in this initial CMR study because the right ventricle was occupied by the solid mass. However, initial echocardiography described no segmental contractility alterations and preserved RV function with no indirect data on pulmonary hypertension. An endomyocardial biopsy showed diffuse infiltration by a lymphoid neoplasm consisting of large cells, with positivity for CD45, CD20, CD79a, Bcl6, MUM1, Bcl2, and c-Myc but CD10 negative (**Figures 2A to 2C**). The Ki67 result was 80%, and the Epstein-Barr virus (EBV) encoding region in situ hybridization result was negative. *MYC* and *BCL6* rearrangements were found, whereas *BCL2* rearrangement was not detected. The diagnosis was post-transplant EBV-negative diffuse large B-cell lymphoma (DLBCL) not otherwise specified (World Health Organization classification) and high-grade B-cell lymphoma with *MYC* and *BCL6* rearrangements (International Consensus Classification). Positron emission tomography-CT (PET-CT) showed RV involvement with increased metabolism and no spread to other locations (**Figures 3A and 3B**). A direct bone marrow assessment excluded concordant infiltration, and the cerebrospinal fluid was free of lymphoma after cytology and flow cytometry analysis. Thus, the lymphoma was localized in the heart.

QUESTION 2: WHAT IS THE INCIDENCE OF PRIMARY CARDIAC LYMPHOMAS, AND WHAT ARE THE TREATMENT OPTIONS?

Primary cardiac lymphomas are rare, with a higher incidence in immunocompromised patients after the fifth decade of life. Clinical presentation may vary according to the heart site involved.[4] PCLs are aggressive tumors if left untreated.

The therapeutic approach of this case was challenging. Although patients with nonbulky localized DLBCLs may receive a reduced number of chemoimmunotherapy cycles as frontline treatment,[5] higher relapse rates have been reported in patients with heart involvement. Furthermore, immunosuppressive therapy could not be reduced in this case, as recommended for immunodeficiency-associated lymphoproliferative disorders. Finally, both Bcl2 and c-Myc double-expressor DLBCLs and cases with *MYC* and *BCL6* rearrangements[6] are associated with worse outcomes, thereby suggesting that more aggressive approaches may be suitable.

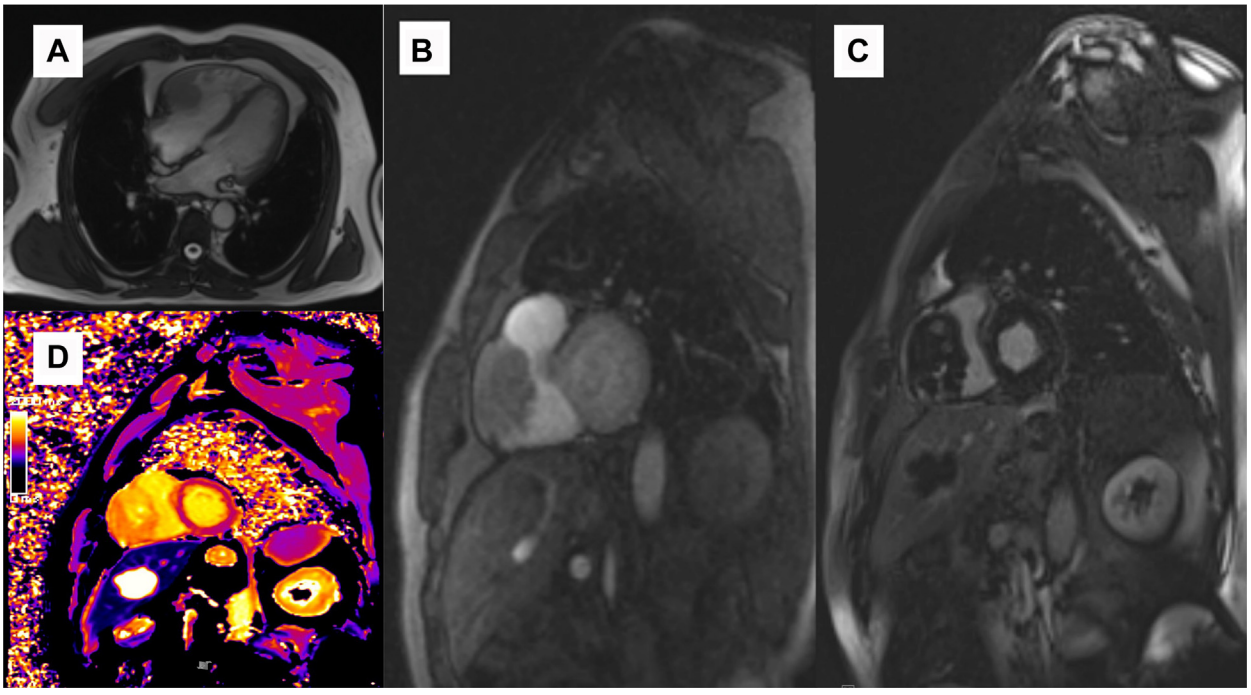
After a hematology team discussion, 6 cycles of chemoimmunotherapy, including rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP), were planned.

Antineoplastic treatment for PCL carries the risk of rapid tumor destruction, which causes cardiovascular complications, including life-threatening arrhythmias, pericardial effusion, or ventricular septal rupture.[7] The patient received cyclophosphamide-prednisone prephase treatment, then 1 first cycle of attenuated therapy (R-miniCHOP), and finally 5 R-CHOP cycles. After a multidisciplinary team (MDT) meeting, including hematology, cardio-oncology, and cardiology imaging, the first treatment steps were administered while the patient underwent cardiac monitoring in the cardiology clinic without incidents. Two months after treatment initiation and after 4 cycles, the patient was admitted to the coronary care unit (CCU) for an acute coronary syndrome (ACS).

QUESTION 3: ACS IN PATIENTS WITH ACTIVE CANCER, WHAT IS THE APPROPRIATE APPROACH?

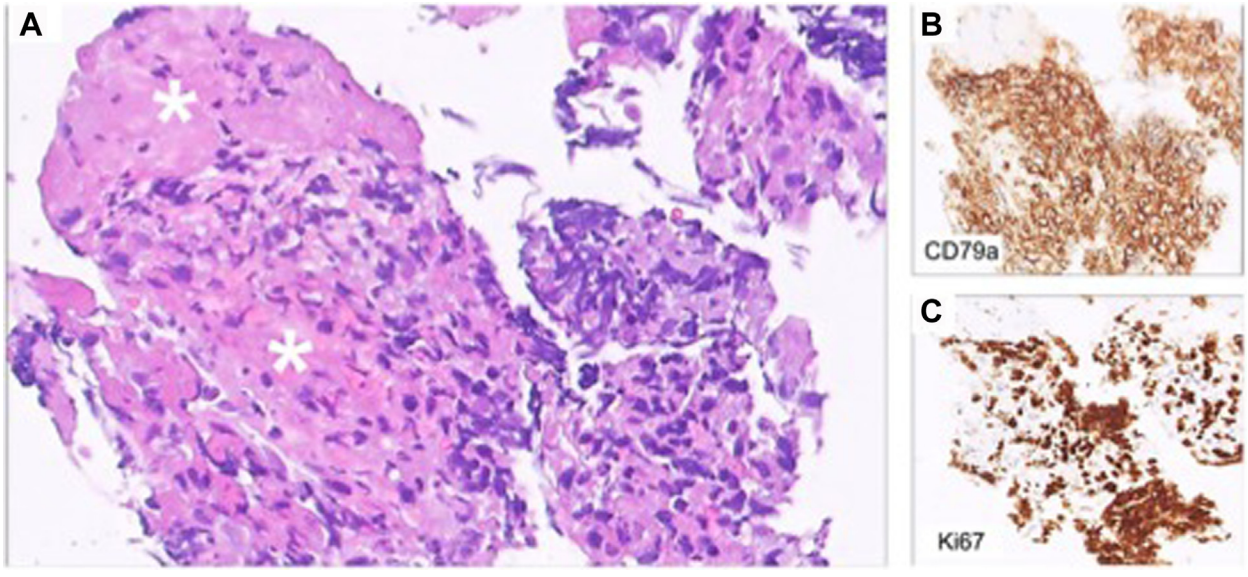
Current European Society of Cardiology guidelines[8] recommend percutaneous coronary intervention (PCI) with a drug-eluting stent (DES) in patients with cancer and type 1 ACS, with a life expectancy ≥6 months. If the patient is unstable and irrespective of life expectancy, it is also

FIGURE 1 **Cardiac Magnetic Resonance Images With Tissue Characterization Sequences**



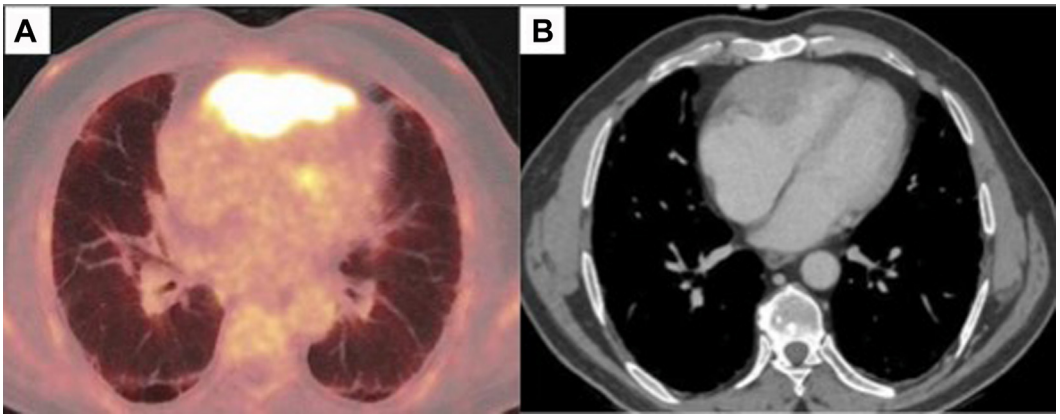
(A) A 4-chamber cine SSFP sequence showing a 6.3 cm × 4.3 cm × 7.1 cm (cephalocaudal × anteroposterior × transversal) tumoral mass in the anterolateral wall of the right ventricle and partially occupying the lumen without affecting the atrioventricular sulcus, the right coronary artery ostium, or pericardial fat. (B) Short-axis early perfusion sequence showing homogeneous vascularization. (C) Short-axis late gadolinium enhancement sequence showing heterogeneous enhancement. (D) Short-axis T1 native mapping slightly elevated values compared with myocardium (1,405 ms vs 1,194 ms).

FIGURE 2 **Histologic and Immunohistochemical Assessment of the Endomyocardial Biopsy**



Diffuse monomorphic lymphoid infiltration by large cells among the cardiac tissue (original magnification 40 ×). (A) Hematoxylin and eosin stain. Cardiac muscle is marked with white asterisks. (B) High CD79a expression. (C) High Ki67 expression (80%).

FIGURE 3 Positron Emission Tomography-Computed Tomography and Contrast Computed Tomography at Diagnosis



(A) A 4-chamber view positron emission tomography–computed tomography image showing ventricular involvement with an increase in metabolism (SUVmax 18) suggestive of viable tumor tissue. (B) A 4-chamber view contrast computed tomography image showing a homogeneous hypoattenuating mass involving the anterolateral right ventricular wall.

recommended to perform PCI given the benefits of coronary revascularization that prevail in this setting.

The patient presented with an acute inferior myocardial infarction but was hemodynamically stable, without signs of heart failure. Emergency coronary angiography was performed and detected an occluded right coronary artery with thrombotic content. PCI with a DES was performed (Figures 4A to 4C). In the CCU, the patient experienced asymptomatic atrial fibrillation, which required pharmacologic cardioversion with intravenous amiodarone. Echocardiographic control before discharge showed a lower-limit (55%) preserved left ventricular ejection fraction with mild inferolateral hypokinesia and a slightly dilated right ventricle with a preserved ejection fraction.

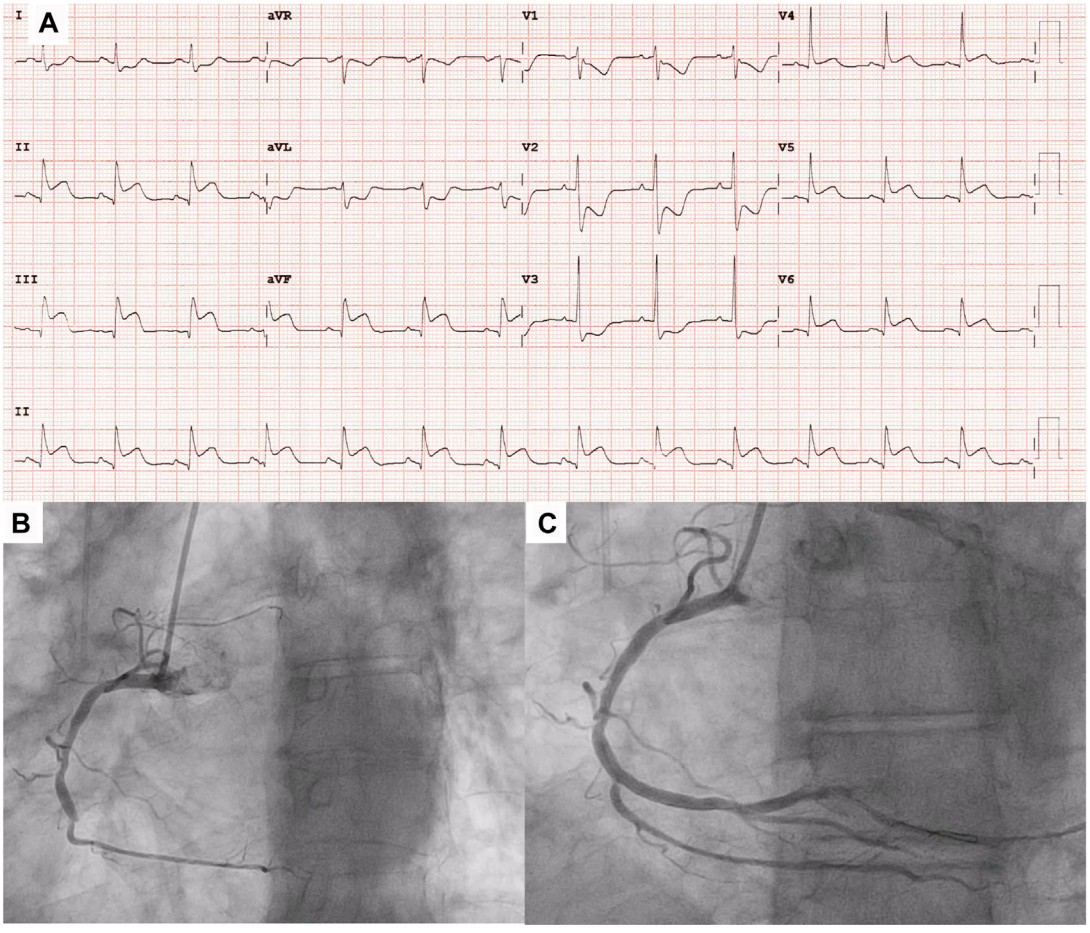
QUESTION 4: HOW DO WE DELIVER ANTITHROMBOTIC THERAPY IN PATIENTS WITH ACTIVE CANCER AND ACS?

Randomized controlled trial evidence supporting clinical decisions for antithrombotic therapy in patients with ischemic heart disease and concomitant cancer is limited. In particular, management of patients with an indication for permanent oral anticoagulation is challenging because of the increased risk of bleeding. After stenting, single antiplatelet therapy with clopidogrel for as short time as possible is suggested in addition to oral anticoagulation in patients with stable cancer.[8,9] Direct oral anticoagulants are increasingly used in cancer patients undergoing active treatment, in the setting of venous thromboembolism (VTE) and atrial fibrillation. There may be concern about drug-drug interactions in patients in active cancer treatment. Recent evidence has found that apixaban was at least neutrally safe compared with low-molecular-weight heparin for both prevention and treatment of thrombosis in cancer patients with VTE, without an effect on the risk of major bleeding.[10] This finding suggests that the combination may be safe when taken with caution. Therefore, treatment decisions should be tailored to each patient's condition. Our patient's thrombotic risk exceeded the bleeding risks, and his platelet count was over 140.0 $10^3/\mu L$. After a discussion of antithrombotic options, the patient was discharged with oral anticoagulation with apixaban and clopidogrel for no longer than 6 months, added to bisoprolol at 1.25 mg/day, enalapril at 5 mg/day, and rosuvastatin/ezetimibe at 20/10 mg/day.

QUESTION 5: ANTINEOPLASTIC TREATMENT AFTER AN ACS, IS IT SAFE?

Some drugs used to treat this patient are associated with a higher risk of ACS, such as alkylating agents (cyclophosphamide) and anti-CD20 monoclonal antibodies (rituximab).[8] Nonetheless, a permissive cardiotoxicity[11] approach was decided by the MDT. This

FIGURE 4 Electrocardiogram and Coronary Angiography

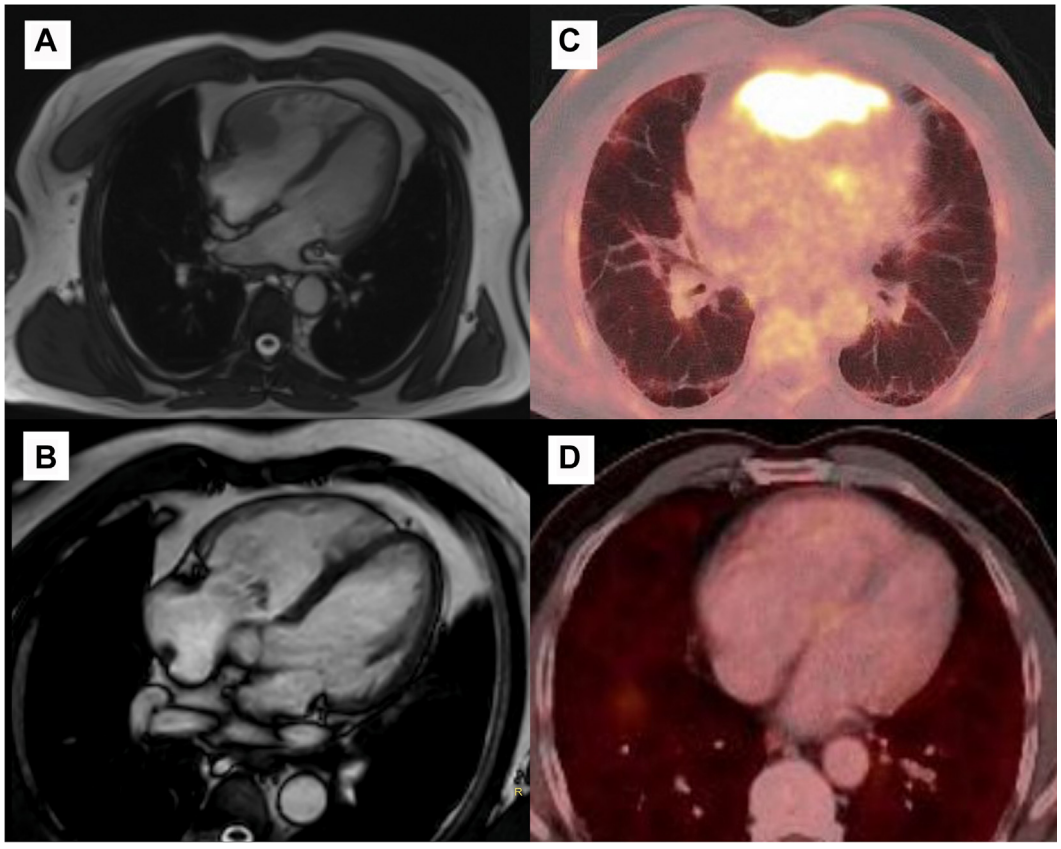


(A) A 12-lead electrocardiogram showing inferior-lateral ST-segment elevation with anterior mirror ST-segment depression. (B) Right coronary artery angiography with moderate midsegment plaque and mid-distal acute thrombotic occlusion. (C) Final angiography after revascularization with a 3 mm × 18 mm drug-eluting stent.

means to continue cancer therapy if appropriate, by understanding the cancer treatment, its alternatives, and the patient's prognosis while mitigating cardiotoxicities. In this case, considering the lymphoma characteristics and the partial metabolic response achieved after 2 cycles, the decision was to optimize the anti-ischemic treatment and to continue the initially planned therapeutic approach, with close follow-up in the cardio-oncology and hematology clinic. The patient visited the cardio-oncology clinic 1 month after discharge, and follow-up was planned according to cardio-oncology guideline recommendations for patients at very high risk of anthracycline cardiotoxicity.[8] Telephonic checkups were also performed to titrate the cardiovascular medication prescribed at discharge.

The patient completed the treatment as initially planned without further relevant incidents. End-of-treatment PET-CT revealed complete a metabolic response, confirming the morphologic remission by CMR (**Figures 5A to 5D**). The patient started a cardiac rehabilitation program with slightly depressed functional capacity and favorable prognostic indices in basal ergospirometry. One year after the ischemic event and 10 months after finishing chemotherapy, the patient is asymptomatic,

FIGURE 5 Cardiac Magnetic Resonance and Positron Emission Tomography–Computed Tomography Comparison After Treatment



(A and B) Four-chamber cardiac magnetic resonance 4 and (C and D) positron emission tomography–computed tomography (A and C, at diagnosis; B and D, after treatment) showing complete response to treatment and disappearance of the right ventricular mass.

walking >5 km daily, and has well-controlled cardiovascular risk factors.

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REFERENCES

1. Aggeli C, Dimitroglou Y, Raftopoulos L, et al. Cardiac masses: the role of cardiovascular imaging in the differential diagnosis. *Diagnostics*. 2020;10(12):1088. https://doi.org/10.3390/diagnostics10121088

2. Beroukhim RS, Prakash A, Valsangiacomo Buechel ER, et al. Characterization of cardiac tumors in children by cardiovascular magnetic resonance imaging: a multicenter experience. *J Am Coll Cardiol*. 2011;58(10):1044-1054. https://doi.org/10.1016/j.jacc.2011.05.027

3. Fernández MJ, Martín Descalzo -Buey, Menduiña GI, et al. Regression of cardiac lymphoma with chemotherapy. *JACC Case Rep*. 2024;29(2):102166. https://doi.org/10.1016/j.jacc.2023.102166

4. Petrich A, Cho SI, Billett H. Primary cardiac lymphoma. *Cancer*. 2011;117(3):581-589. https://doi.org/10.1002/cncr.25444

5. Lamy T, Damaj G, Soubeyran P, et al. R-CHOP 14 with or without radiotherapy in nonbulky limited-stage diffuse large B-cell lymphoma. *Blood*. 2018;131(2):174-181. https://doi.org/10.1182/blood-2017-07-793984

6. Li S, Young KH, Medeiros LJ. Diffuse large B-cell lymphoma. *Pathology*. 2018;50(1):74-87. https://doi.org/10.1016/j.pathol.2017.09.006

7. Shah K, Shemisa K. A "low and slow" approach to successful medical treatment of primary cardiac lymphoma. *Cardiovasc Diagn Ther*. 2014;4(3):270-273. https://doi.org/10.3978/j.issn.2223-3652.2014.04.01

8. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43(41):4229-4361. https://doi.org/10.1093/eurheartj/ehac244

9. Gevaert SA, Halvorsen S, Sinnaeve PR, et al. Evaluation and management of cancer patients presenting with acute cardiovascular disease: a consensus document of the Acute CardioVascular Care (ACVC) association and the ESC council of Cardio-Oncology—part 1: acute coronary syndromes and acute pericardial diseases. *Eur Heart J Acute Cardiovasc Care*. 2021;10(8):947-959. https://doi.org/10.1093/ehjacc/zuab056

10. Verso M, Munoz A, Bauersachs R, et al. Effects of concomitant administration of anticancer agents and apixaban or dalteparin on recurrence and bleeding in patients with cancer-associated venous thromboembolism. *Eur J Cancer*. 2021;148:371-381. https://doi.org/10.1016/j.ejca.2021.02.026

11. Porter C, Azam TU, Mohananey D, et al. Permissive cardiotoxicity: the clinical crucible of cardio-oncology. *JACC CardioOncol*. 2022;4(3):302-312. https://doi.org/10.1016/j.jaccao.2022.07.005

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