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Heart transplantation in patients with anthracycline-induced cardiomyopathy

Trasplante cardiaco en pacientes con cardiotoxicidad inducida por antraciclinas

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Abstract

Objective: *The objective of this study was to describe the clinical and imaging characteristics and the evolution of heart transplantation patients due to anthracycline-induced cardiomyopathy* **Methods:** *Patients with a diagnosis of ACM who received a heart transplantation in our institution in the period of November 2009-April 2021 were included. Clinical characteristics, pre-transplant studies, and clinical outcomes after transplantation were collected retrospectively from the electronic medical record.* **Results:** *A total of 11 patients were included in the study. The median age at the time of cancer diagnosis was 15 years (IQR 10-37 years), while the median age at the time of heart transplant was 56 years (IQR 39-62 years). Regarding post-transplant outcomes, three patients died in the post-operative period. One died 4 years after the intervention due to chronic rejection, while the other seven had a favorable evolution. No oncological relapse was observed with a median follow-up of 2.5 years (IQR 1.86-3.85 years).* **Conclusion:** *End-stage anthracycline-induced cardiomyopathy can occur many years after chemotherapy treatment, so close cardiovascular follow-up is extremely important. Heart transplantation is a treatment option after an exhaustive multidisciplinary evaluation, to minimize the risk of oncological relapse.*

Keywords: *Heart transplantation. Cardiotoxicity. Anthracycline-induced cardiomyopathy. Advanced heart failure.*

Resumen

Objetivo: *Describir las características clínicas, imagenológicas y la evolución de los pacientes trasplantados cardiacos por cardiotoxicidad inducida por antraciclinas.* **Métodos:** *Serie de casos descriptiva de pacientes consecutivos trasplantados cardiacos debido a cardiotoxicidad mediada por antraciclinas en el periodo de Noviembre de 2009 a Abril de 2021.Las características clínicas, los estudios complementarios pretrasplante y la información sobre la evolución posterior al trasplante fue recolectada de la historia clínica electrónica de forma retrospectiva.* **Resultados:** *Se incluyeron un total de 11 pacientes. La mediana de edad al diagnóstico de la patología oncológica fue de 15 años (RIC 10-37 años), mientras que la mediana de edad en la que recibieron el trasplante cardiaco fue de 56 años (RIC 39-62 años). Con respecto a la evolución posterior al trasplante, 3 pacientes murieron en el periodo del post operatorio inmediato. 1 paciente falleció a los 4 años del trasplante y los otros 7 pacientes tuvieron una evolución favorable. No se observó recaída oncológica en ningún paciente durante una mediana de seguimiento o de 2,5 años (RIC 1.86-3.85 años).* **Conclusión:** *La etapa final de la miocardiopatía inducida por antraciclinas puede ocurrir muchos años después del tratamiento con quimioterapia, por lo que es extremadamente importante*

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un seguimiento cardiológico estricto. El trasplante cardiaco es una opción en este grupo de pacientes luego de una exhaustiva evaluación multidisciplinaria, con el fin de minimizar el riesgo de recaída oncológica.

Palabras claves: *Trasplante cardiaco. Cardiotoxicidad. Miocardiopatía inducida por antraciclinas. Insuficiencia cardiaca avanzada.*

Background

Anthracyclines are chemotherapeutic agents widely used in the treatment of cancer such as sarcomas, breast cancer, and lymphomas. Their clinical effectiveness is contrasted with myocardial injury which is the main adverse effect of these drugs[1]. Anthracycline-associated cardiomyopathy (ACM) can be presented as a very mild and asymptomatic form to advanced heart failure requiring heart transplantation as definitive therapy[2]. Incidence of cardiotoxicity varies from 5 to 48% depending on the accumulated dose[3].

In a large prospective study (incidence of cardiotoxicity 9%), it was observed that 98% of these patients did not present symptoms of heart failure in the 1st year, highlighting the importance of close surveillance of the left ventricular ejection fraction (LVEF)[4].

The correct selection of candidates for heart transplantation is a particular challenge in this population. An exhaustive pre-transplant evaluation is essential to ensure a low probability of neoplastic recurrence after starting immunosuppressive treatment.

Recently, Ramu et al. have published a study where they reported the clinical characteristics as well as clinical outcomes of patients undergoing heart transplantation for ACM in the United States, but we do not have data from our local media[2].

The objective of this study was to describe the clinical characteristics and outcomes of a series of patients with diagnosis of ACM undergoing heart transplantation in a high-complexity hospital in Argentina.

Methods

We designed a series of cases of consecutive patients who received a heart transplantation with a diagnosis of ACM in our hospital. The analysis included all patients with a diagnosis of ACM and development of heart failure requiring a heart transplantation in the period November 2009-April 2021. To arrive at the diagnosis of ACM, other causes of cardiomyopathy (such as ischemic, valvular disease, and myocarditis) were ruled out by the advanced heart failure team in the pre-transplant evaluation and all were confirmed in the pathology study of the explanted hearts (Fig. 1).

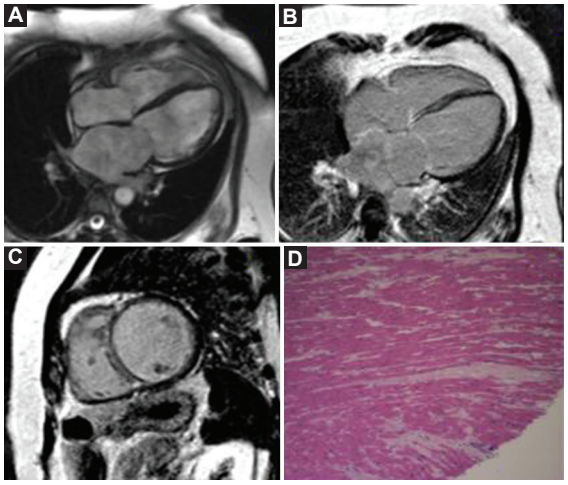

Figure 1. CMR and pathological study of the explanted heart of a patient with diagnosis of anthracycline associated cardiomyopathy. Steady state free precession (SSFP) sequences showed enlarged left and right ventricular volumes with severe biventricular dysfunction **(A).** Late gadolinium enhancement sequences of four chamber **(B)** and short axis **(C)** showed a non-specific pattern with septal midwall fibrosis. Longitudinal section showing mild-to-moderate interstitial fibrosis (Hematoxylin & Eosin, 100×, original magnification) **(D).**

The clinical characteristics, pre-transplant studies, and clinical outcomes after heart transplantation were collected retrospectively from the electronic medical record. Categorical variables were described as percentages and absolute frequency. As it is a small sample, continuous values were described as median and interquartile ranges. For the analysis, software STATA-64-version 15 was used.

Results

In the period of November 2009-April 2021, a total of 292 heart transplants were performed in our institution. A total of 11 patients (3.7%) were due to ACM and were included in this series. Eight patients were females, and three were male. The median age at the time of cancer diagnosis and chemotherapy treatment was 15 years (IQR 10-37 years), while the median age at the time of receiving a heart transplant was

56 years (IQR 39-62 years). The median time between chemotherapy and heart transplantation was 30 years (IQR 21-37 years).

Regarding the clinical presentation, six patients presented with parameters of cardiogenic shock, requiring mechanical respiratory assistance, or left ventricular assist devices, so they were included on the emergency list for heart transplantation. Table 1 shows the characteristics of the patients.

The most frequent types of primary tumors were different types of sarcoma (45.5%), followed by breast cancer (27.3%) and non-Hodgkin's lymphoma (18.2%). None of the patients presented metastasis during their oncological history and all of them had complete remission before heart transplantation. The pre-transplant studies showed that a median of LVEF by transthoracic echocardiography was 25.6% (IQR 21-28.6%) and six patients also had a decrease in the right ventricle ejection fraction. Cardiovascular magnetic resonance was performed in five patients before heart transplant. The LVEF estimated by this method was similar to that measured by echocardiography. Figure 1 shows a typical pattern of ACM with a great left ventricle volume and minimal late gadolinium enhancement.

All patients underwent right catheterization in the pre-transplant evaluation. The median cardiac index was 1.9 ml/min/m^2 (IQR 1.7-2 ml/min/m^2) and the median of pulmonary resistance was 3.6 wood units (IQR 2.5-4.8 wood units). Table 2 resumes the principal findings of pre-transplant studies.

The immunosuppression regimen consisted on: 1 g of methylprednisolone plus 1200 mg of mycophenolate mofetil and 20 mg of basiliximab before unclamping followed by tacrolimus, mycophenolate mofetil, and prednisone as maintenance. There were no differences in the regimen used between the patients in the cohort or with other transplant recipients for different cardiomyopathies.

Regarding post-transplant outcomes, three patients died in the post-operative period, two of them due to cardiogenic shock secondary to acute graft rejection and the other patient due to subarachnoid hemorrhage in the context of prolonged requirements of extracorporeal membrane oxygenation. In the long follow-up, one patient died 4 years after the intervention due to chronic rejection, while the other seven patients had a favorable evolution without readmissions for heart failure. In these patients who survived the post-operative period, no oncological relapse was observed with a median follow-up of 2.5 years (IQR 1.86-3.85 years).

Table 1. Pre-transplant clinical characteristics of patients undergoing heart transplant due to anthracycline-associated cardiomyopathy

Clinical characteristics	n = 11
Age at cancer diagnosis (years)	15 (10-37)
Age at transplant (years)	56 (39-62)
Time between chemotherapy and heart transplant (years)	30 (21-37)
Oncological disease - free time (years)	20 (5-30)
History of oncological surgery (%)	81.8 (n = 9)
History of radiation therapy (%)	81.8 (n = 9)
Prior coronary artery disease (%)	9 (n = 1)
Prior atrial fibrillation (%)	27.2 (n = 3)
Clinical presentation at the time of transplant	
Right overload (%)	27.2 (n = 3)
Left overload (%)	18.1 (n = 2)
Cardiogenic shock (%)	54.5 (n = 6)
Previous medication	
ACE inhibitors/ARA II (%)	54.5 (n = 6)
Beta-blockers (%)	90.9 (n = 10)
MRA (%)	54.5 (n = 6)
ICD/CRT (%)	27.2 (n = 3)

ACE: angiotensin converting enzyme; ARA: angiotensin receptor antagonist; MRA: mineralocorticoid receptor antagonist; ICD: implantable cardiac defibrillator; CRT: cardiac resyncronization therapy.

Discussion

In this case series, clinical characteristics and evolution of heart transplant patients due to ACM were presented.

The first interesting finding of this series is the early age of cancer diagnosis and chemotherapy treatment (15 years [IQR 10-37]), so at the time of cancer diagnosis, it is a predominantly pediatric population, which could explain why the most frequent tumors were sarcomas (45.5%, n = 5). It was also noted that the median time to require a heart transplant was 30 years (IQR 21-37). These data highlight the importance of the link between pediatric and adult cardiology to ensure the correct continuity of cardiovascular care of this population.

Another important issue is the importance of the early initiation of ventricular dysfunction treatment. In a prospective cohort by Cardinale et al., which included 2625 patients treated with anthracyclines (incidence of ACM: 9%), 98% of patients who developed toxicity did so within the 1st year after completion of treatment. All of them received treatment for ventricular dysfunction

Table 2. Characteristics of complementary pre-transplant diagnosis studies of patients undergoing heart transplant due to anthracycline associated cardiomyopathy

Analytics	n = 11
Creatinine clearance < 30 (%)	81.2 (n = 9)
Creatinine clearance 30-60 (%)	18.1 (n = 2)
NT-pro BNP (pg/ml) (IQR)	3325 (2524-8933)
US TnT (pg/ml) (n = 8) (IQR)	18.5 (15.5-36)
Pre-transplant echocardiography LVEF (%) LV end-diastolic diameter (mm)	 25.6 (21-28.6) 55 (51-56)
LV end-systolic diameter (mm)	47 (43-49)
LV end-diastolic volume (ml)	116 (91-159)
LV end-systolic volumel (ml)	78 (68-118)
Right ventricular dysfunction (%)	54.5 (n = 6)
Systolic pulmonary pressure (mmHg)	48.5 (36-54)
Pre-transplant CMR (n = 5) LVEF (%) Late gadolinium enhancement (%)	 30 (26-33) 80 (n = 4)
Right catheterization Cardiac index (l/min/m^2) Systolic pulmonary pressure (mmHg) Mean pulmonary pressure (mmHg) Pulmonary capillary pressure (mmHg) Wood units	 1.9 (1.7-2) 52 (44-56) 28 (26-30) 20 (16-22) 3.6 (2.5-4.8)

NT-Pro BNP: n-terminal pro brain natriuretic peptide; US TnT: ultrasensible T troponin; LVEF: left ventricular ejection fraction; LV: left ventricular; CMR: cardiac magnetic resonance.

and 82% showed total or partial recovery of the LVEF[4]. Previously, the same group had demonstrated the importance of the early initiation of the treatment for ACM in a 201 patients cohort. In this study, no improvement in LVEF was observed in those patients who began treatment for ventricular dysfunction 6 months after diagnosis[5]. For this reason, current clinical practice guidelines recommend exhaustive surveillance in the 1st year of chemotherapy treatment and then annual follow-up[3,6,7].

Heart transplantation in this population is a particular challenge due to the importance of the correct selection of candidates to minimize the risk of oncological relapse. The current recommendation for the inclusion of patients with a history of cancer on heart transplant list should consider a low probability of oncological recurrence. For this, joint work with oncology service is essential and it is determined by the tumor type, the therapeutic response, and the absence of metastasis, without taking into account arbitrary disease-free periods[8]. In this cohort, all patients underwent an exhaustive interdisciplinary evaluation before admission to the transplant list, with a median time free of oncological disease of 20 years [IQR 5-30]. None of the patients who survived the immediate post-operative period presented oncological relapse.

In a recently published study, Ramu et al. described the clinical course of patients undergoing heart transplantation due to ACM. This study included 18,270 patients undergoing heart transplantation. Three hundred and fifty-seven had a diagnosis of ACM, 10,662 of dilated cardiomyopathy, and 7651 of ischemic cardiomyopathy. Post-transplant mortality was similar in the three groups[2]. In our series, immediate post-transplant mortality was 27 % (n = 3). This high mortality could be explained by the fact that more than half of the patients were transplanted at an advanced stage (INTERMACS 1). Therefore, we think that it is crucial to highlight the importance of properly selecting patients for heart transplantation. Of the eight patients who survived the acute post-transplant phase, only one patient died during the 3-year follow-up.

There are some limitations of our series. First, the low number of patients included in the study. Second, due to the long time elapsed since cancer treatment, we do not know the accumulated dose of anthracyclines received, which is crucial to estimate the potential cardiotoxic damage of these chemotherapy agents. Finally, it is noteworthy that we do not have a sufficient follow-up time to assess long-term outcomes.

Conclusion

The terminal phase of anthracycline-induced cardiomyopathy can occur many years after chemotherapy treatment, so close cardiovascular follow-up is extremely important. In those eligible cases, heart transplantation is a treatment option after an exhaustive multidisciplinary evaluation to minimize the risks of oncological relapse.

Funding

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Conflicts of interest

None.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

References

1. Yang F, Teves SS, Kemp CJ, Henikoff S. Doxorubicin, DNA torsion, and chromatin dynamics. Biochim Biophys Acta. 2014;1845:84-9.
2. Ramu B, Masotti M, Tedford RJ, Cogswell RJ. Heart transplantation in adriamycin-associated cardiomyopathy in the contemporary era of advanced heart failure therapies. JACC CardioOncol. 2021;3:294-301.
3. Zamorano JL, Lancellotti P, Muñoz DR, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC position paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC committee for practice guidelines: the task force for cancer treatments and cardiovascular toxicity of the European society of cardiology (ESC). Eur J Heart Fail. 2017;19:9-42.
4. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, et al. Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 2015;131:1981-8.
5. Cardinale D, Colombo A, Lamantia G, Colombo N, Civelli M, De Giacomi G, et al. Anthracycline-induced cardiomyopathy: clinical relevance and response to pharmacologic therapy. J Am Coll Cardiol. 2010;55:213-20.
6. Dobson R, Ghosh AK, Ky B, Marwick T, Stout M, Harkness A, et al. BSE and BCOS guideline for transthoracic echocardiographic assessment of adult cancer patients receiving anthracyclines and/or trastuzumab. JACC CardioOncol. 2021;3:1-16.
7. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American society of echocardiography and the European association of cardiovascular imaging. J Am Soc Echocardiogr. 2014;27:911-39.
8. Mehra MR, Canter CE, Hannan MM, Semigran MJ, Uber PA, Baran DA, et al. The 2016 international society for heart lung transplantation listing criteria for heart transplantation: a 10-year update. J Heart Lung Transplant. 2016;35:1-23.