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How to cite this article:

Luciano LSC, Mariani Júnior J, Arrieta SR, Kajita LJ, Azeka E, Silva EER. Intimal thickening in cardiac allograft vasculopathy and intravascular ultrasound guided angioplasty of left main coronary artery and left anterior descending artery. Case report and literature review. J Transcat Interv. 2020;28:eA20190031. <https://doi.org/10.31160/JOTCI202028A20190031>

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Submitted on:

Dec 8, 2019

Accepted on:

Apr 20, 2020

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Intimal thickening in cardiac allograft vasculopathy and intravascular ultrasound guided angioplasty of left main coronary artery and left anterior descending artery. Case report and literature review

Espessamento intimal na doença vascular do enxerto e angioplastia de tronco de coronária esquerda e artéria descendente anterior guiada por ultrassom intravascular. Relato de caso e revisão da literatura

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DOI: 10.31160/JOTCI202028A20190031

ABSTRACT – Cardiac transplantation is the common final route of severe heart disease in eligible patients. Among the challenges of this treatment is cardiac allograft vasculopathy, the main cause of morbidity and late mortality after heart transplantation, accounting for 12.5% of deaths after the first year. In the last two decades, numerous studies have been published validating the measurement of maximum intimal thickening observed in intracoronary ultrasound as a predictor of poor prognosis when greater than 0.5mm. We report a case of cardiac allograft vasculopathy undergoing intravascular coronary ultrasound-guided percutaneous treatment and discuss the main characteristics of the intravascular images.

Keywords: Angioplasty; Vascular diseases; Heart transplantation; Ultrasonography, interventional

RESUMO – O transplante cardíaco é a via final comum das cardiopatias graves em pacientes elegíveis. Dentre os desafios desse tratamento está a doença vascular do enxerto, principal causa de morbidade e mortalidade tardia após o transplante cardíaco, sendo responsável por 12,5% das mortes após o primeiro ano. Nas últimas duas décadas, têm sido publicados inúmeros trabalhos validando a medida do espessamento intimal máximo observado no ultrassom intracoronário como preditor de mau prognóstico quando maior que 0,5mm. Relatamos um caso de doença vascular do enxerto submetido a tratamento percutâneo guiado por ultrassom intracoronário e discutimos as principais características da imagem intravascular.

Descritores: Angioplastia; Doenças vasculares; Transplante cardíaco; Ultrassonografia intervencional

BACKGROUND

In 2018, a total of 357 heart transplants (HTx) were performed in Brazil, almost a third of them (110 procedures) in the state of São Paulo.¹

Chronic humoral rejection, manifested as cardiac allograft vasculopathy (CAV), is the main cause of late morbidity and mortality after HTx, accounting for up to 12.5% of deaths after the first year. Its incidence has remained high over the past two decades, and a better prognosis can be expected when diagnosis and treatment are made early.²

We describe a case of CAV undergoing percutaneous coronary intervention (PCI) guided by intravascular coronary ultrasound (IVUS) and discuss the main characteristics of the intravascular imaging findings in this scenario.

This study was approved by the Ethics Committee of the *Instituto de Cardiologia de Santa Catarina*, protocol 3,980,853, CAAE: 30566820.4.0000.0113.

CASE REPORT

A 13-year-old female patient who underwent orthotopic heart transplant with bicaval technique at 7 years of age, due to dilated cardiomyopathy of unclear etiology. Diagnosis of depression, under psychiatric treatment.

Admitted to the Emergency Room of the *Instituto do Coração* of the *Hospital das Clínicas*, Medical School, University of São Paulo, in August 2019, with complaints of chest tightness, dizziness, nausea, lip cyanosis, asthenia and headache. The admission laboratory tests showed an increase in B-type natriuretic peptide (BNP) levels as compared to previous test results (39 to 103pg/mL). Normal transthoracic echocardiogram, with preserved left ventricular systolic and diastolic functions at rest. An endomyocardial biopsy was performed, which showed no signs of acute cellular (grade OR) or humoral rejection. Coronary angiography showed a 90% focal stenosis of the ostium and an 80% stenosis in the mid-segment of the left anterior descending artery (LAD) (Figure 1).

Figure 1. Initial angiographic aspect.

After HeartTeam discussion, we opted for PCI of coronary lesions during the same hospital stay, as a bridge to heart retransplantation.

Under general anesthesia and via right femoral access, after selective catheterization of the left coronary artery and intravenous infusion of unfractionated heparin, monitored by activated clotting time, the LAD was predilated with a 2.0×20mm semi-compliant balloon for the insertion of an IVUS catheter, which showed a thin LAD in its middle third, with a maximal intimal thickening (MIT) of 0.25mm, a minimal luminal area (MLA) of 4.1mm², and a minimal

luminal diameter of 2.21mm (reference segment in the middle third of LAD). The identified lesion was predominantly fibrotic, according to the gray scale IVUS evaluation, affecting the ostium and the entire proximal and middle third segments, and was concentric with the vessel lumen (eccentricity index of 0.40), resulting in an MLA of 2.17mm² in the ostium, and a plaque burden of 77%. No calcification of any type was identified, whether superficial or deep, at any point of the lesion (Figure 2). All IVUS runs were performed with automatic pullback at 0.5mm/sec and also, manually, whenever necessary.

Figure 2. Ostium and middle third of the left anterior descending artery.

Then, a 2.0×23 mm everolimus-eluting stent (EES) was implanted in the middle third of the LAD and a 3.0×32mm stent was implanted in the left main coronary artery (LMCA)-LAD, with minimal overlapping, post-dilated with 2.5×15mm, 3.0×15mm, and 3.5×15mm non-compliant (NC) balloons, with a final dilation between LMCA-LAD and between LMCA-left circumflex artery (LCx) using the kissing-balloon technique with a 3.5×15mm NC balloon and a 3.0×15mm NC balloon, respectively.

The LMCA-LAD control IVUS showed the stents were well apposed, symmetrical (symmetry index=0.90), without dissections at their edges, with no axial or longitudinal geographic miss, with no plaque prolapse from them and expanded, with a 4.26mm² intrastent MLA in the middle third of the LAD, 6.40mm² in the proximal third, and 11.04mm² in the LMCA.

The LCx control IVUS after post-dilation with the kissing-balloon technique showed absence of lesions or dissections in its ostium/proximal third, and a 0.65mm MIT was identified in its proximal third (Figure 3).

The final coronary angiography revealed an excellent angiographic aspect, absence of residual stenoses, and a Thrombolysis in Myocardial Infarction (TIMI) grade 3 flow, and this result was maintained after 3-month follow-up (Figure 4).

Figure 3. Proximal third of the left circumflex artery.

Figure 4. Final coronary angiography and 3-month follow-up coronary angiography.

The heart transplant team opted for relisting the patient for transplant, considering the unfavorable prognosis of cardiac allograft vasculopathy with the characteristics seen on angiography and intravascular images (MIT >0.5mm).

DISCUSSION

Observational studies have shown that the angiographic severity of transplant coronary heart disease is directly proportional to the risk of graft dysfunction/failure and major adverse cardiovascular events (MACE).³⁻⁵

Since the early 1990's and especially in the last decade, numerous studies have been published describing, improving and validating the IVUS measurements of maximal intimal thickness as a predictor of poor prognosis when greater than 0.5mm.⁶⁻¹¹

In 2010, the International Society for Heart and Lung Transplantation (ISHLT) standardized a nomenclature for CAV based on its angiographic severity. This classification, ranging from CAV0 to CAV3, according to severity and importance, takes into account graft dysfunction, which can reclassify CAV from CAV1 or CAV2 to CAV3.

The identification of an angiographic lesion producing more than 70% stenosis in a single primary vessel is classified as CAV2, and characterized as of moderate importance by ISHLT. Although coronary angiography remains the gold standard for the diagnosis of CAV,² this classification does not take into account the prognostic importance of the IVUS findings, which has been validated in the last three decades. The coronary intimal thickening (IT) is measured by intravascular imaging and may change the clinical perspective in the short- and medium-run.

The diagnosis of abnormal concentric intimal thickening is the most sensitive tool for diagnosing CAV.¹² This process occurs more quickly in the first year after transplantation.¹³ An MIT ≥ 0.5 mm in this period indicates rapidly progressive CAV.¹⁴ Due to its high positive predictive value, the information provided by IVUS has been used as secondary outcomes in large clinical trials on drugs for the prevention and treatment of CAV.¹²

In 2015, Potena et al. observed that an increase in MIT ≥ 0.35 mm between the first and the fifth years after transplantation is consistently related to a higher rate of MACE, even among patients with normal or stable coronary angiography.¹⁰

The disadvantages of IVUS are increased time and risk of the procedure, limited availability and increased costs. However, this procedure is of vital importance in patients with unexplained graft failure, *i.e.*, those with normal coronary angiography and absence of detectable signs of rejection.¹² This imaging method was used not only to optimize the results of this complex intervention, but also as a tool for prognostic stratification of this scenario.

Coronary angioplasty with stenting in CAV is widely used as a palliative treatment only, and it serves as a bridge to

cardiac retransplantation, despite the lower rates of restenosis with the use of drug-eluting stents (DES), when compared to the use of bare metal stents (BMS).

Cheng et al. conducted the largest study evaluating long-term clinical and angiographic outcomes after treatment of CAV using EES.¹⁵ Their findings show that, although the use of DES does not prevent the progression of CAV in non-revascularized territories, there was a high stent patency rate, comparable to that observed after treatment of disease in the native coronary artery. Previous studies with first-generation DES showed 12.5% to 22.6% binary restenosis rates (angiographic stenosis $\geq 50\%$) in 12 months, whereas EES produced a 3% rate in that same period. The survival rate observed at 3 years after PCI with EES for treatment of CAV was 83.8%, similar to the expected survival for the graft without CAV, suggesting percutaneous treatment of CAV with EES, associated with early and frequent angiographic monitoring, can normalize survival. In addition, the MACE-free 3-year survival rate was 75.8%, suggesting that CAV patients with strict clinical-angiographic follow-up may survive without infarction and no retransplantation required. The mean time to perform the control angiography was 23.2 ± 15.9 months. There are no reports in the literature on long-term follow-up (greater than 5 years) of patients undergoing coronary intervention due to the poor prognosis in this context.

High rates of revascularization of new lesions and rapidly progressive CAV in untreated territories justify the role of intensive angiographic monitoring after the first PCI in heart transplant recipients.¹⁵ In this complex clinical and angiographic context, individualized clinical and intervention strategies should always go hand-in-hand with common sense, in an attempt to offer these patients the longest possible survival with the best quality of life in this period.

FINANCING SOURCE

None.

DECLARATION OF CONFLICTS OF INTEREST

The authors declare there are no conflicts of interest.

CONTRIBUTION OF AUTHORS

Conception and design of the study: LSCL and JMJ; data collection: LSCL, JMJ, SRA, LJK, EA and EERS; data interpretation: LSCL, JMJ, SRA, LJK, EA and EERS; writing of the text: LSCL and JMJ; approval of the final version to be published: LSCL, JMJ, SRA, LJK, EA and EERS.

REFERENCES

1. Associação Brasileira de Transplante de Órgãos (ABTO). Registro Brasileiro de Transplantes 2018. Dimensionamento dos

- Transplantes no Brasil e em cada estado (2011-2018) [Internet]. RBT. 2018 [citado 2020 Fev 4];14(4):1-97. Disponível em: http://www.abto.org.br/abtov03/Upload/file/RBT/2018/Lv_RBT-2018.pdf
2. Bacal F, Marcondes-Braga FG, Rohde LE, Xavier Júnior JL, Brito FS, Moura LA, et al. 3ª Diretriz Brasileira de Transplante Cardíaco. Arq Bras Cardiol. 2018;111(2):230-89.
3. Costanzo MR, Naftel DC, Pritzker MR, Heilman JK 3rd, Boehmer JP, Brozena SC, et al. Heart transplant coronary artery disease detected by coronary angiography: a multiinstitutional study of preoperative donor and recipient risk factors. Cardiac Transplant Research Database. J Heart Lung Transplant. 1998;17(8):744-53.
4. Keogh AM, Valentine HA, Hunt SA, Schroeder JS, McIntosh N, Oyer PE, et al. Impact of proximal or midvessel discrete coronary artery stenoses on survival after heart transplantation. J Heart Lung Transplant. 1992;11(5):892-901.
5. Prada-Delgado O, Estévez-Loureiro R, Paniagua-Martín MJ, López-Sainz A, Crespo-Leiro MG. Prevalence and prognostic value of cardiac allograft vasculopathy 1 year after heart transplantation according to the ISHLT recommended nomenclature. J Heart Lung Transplant. 2012;31:332-3. <https://doi.org/10.1016/j.healun.2011.12.006>
6. Rickenbacher PR, Pinto FJ, Lewis NP, Hunt SA, Alderman EL, Schroeder JS, et al. Prognostic importance of intimal thickness as measured by intracoronary ultrasound after cardiac transplantation. Circulation. 1995;92:3445-52. <https://doi.org/10.1161/01.cir.92.12.3445>
7. Ramasubbu K, Schoenhagen P, Balgith MA, Brechtken J, Ziada KM, Kapadia SR, et al. Repeated intravascular ultrasound imaging in cardiac transplant recipients does not accelerate transplant coronary artery disease. J Am Coll Cardiol. 2003;41:1739-43. [https://doi.org/10.1016/S0735-1097\(03\)00339-5](https://doi.org/10.1016/S0735-1097(03)00339-5)
8. Costa ES, Wang R, Susin MF, Veiga SL, Diniz FC, Brofman PR, et al. Assessment of cardiac allograft vasculopathy in cardiac transplantation: experience of a Brazilian center. Arq Bras Cardiol. 2012;99(4):886-91. <https://doi.org/10.1590/S0066-782X2012005000084>
9. Kobashigawa JA, Pauly DF, Starling RC, Eisen H, Ross H, Wang SS, et al. Cardiac allograft vasculopathy by intravascular ultrasound in heart transplant patients. Substudy from the everolimus versus mycophenolate mofetil randomized, multicenter trial. JACC Heart Fail. 2013;1(5):389-99. <https://doi.org/10.1016/j.jchf.2013.07.002>
10. Potena L, Masetti M, Sabatino M, Bacchi-Reggiani ML, Pece V, Prestinenzi P, et al. Interplay of coronary angiography and intravascular ultrasound in predicting long-term outcomes after heart transplantation. J Heart Lung Transplant. 2015;34(9):1146-53. <https://doi.org/10.1016/j.healun.2015.01.990>
11. Watanabe T, Seguchi O, Yanase M, Fujita T, Murata Y, Sato T, et al. Donor-transmitted atherosclerosis associated with worsening cardiac allograft vasculopathy after heart transplantation: serial volumetric intravascular ultrasound analysis. Transplantation. 2017;101(6):1310-9. <https://doi.org/10.1097/TP.0000000000001322>
12. Skorić B, Čikeš M, Ljubas-Maček J, Baričević Ž, Škorak I, Gašparović H, et al. Cardiac allograft vasculopathy: diagnosis, therapy, and prognosis. Croat Med J. 2014;55(6):562-76. <https://doi.org/10.3325/cmj.2014.55.562>
13. Yeung AC, Davis SF, Hauptman PJ, Kobashigawa JA, Miller LW, Valentine HA, et al. Incidence and progression of transplant coronary artery disease over 1 year: results of a multicenter trial with use of intravascular ultrasound. Multicenter Intravascular Ultrasound Transplant Study Group. J Heart Lung Transplant. 1995;14(6 Pt 2):S215-20.

14. Kobashigawa JA, Tobis JM, Starling RC, Tuzcu EM, Smith AL, Valentine HA, et al. Multicenter intravascular ultrasound validation study among heart transplant recipients: outcomes after five years. *J Am Coll Cardiol.* 2005;45(9):1532-7. <https://doi.org/10.1016/j.jacc.2005.02.035>
15. Cheng R, Vanichsarn C, Patel JK, Currier J, Chang DH, Kittleson MM, et al. Long-term clinical and angiographic outcomes of percutaneous coronary intervention with everolimus-eluting stents for the treatment of cardiac allograft vasculopathy. *Catheter Cardiovasc Interv.* 2017;90(1):48-55. <https://doi.org/10.1002/ccd.26830>