

CASE REPORT

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A medical epopee: recurrent fungal endocarditis, heart transplantation and chylopericardium

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Abstract

Background: *Candida* prosthetic endocarditis is associated with high mortality rates and valve replacement surgery, together with antifungal treatment, play a major role in eradicating the fungal infection. Valve reoperations in these scenarios may be relatively common due to the high infection relapse rates and, in some cases, heart transplantation may be an imposing therapy for infection resolution and for the heart failure related to the myocardial reoperation injury. Among the many postoperative complications related to heart transplantation, chylopericardium is a rare but challenging example.

Case presentation: We report the case of a 55-year-old man who was admitted to our hospital with a 1-month history of progressive dyspnea and fatigue. His past medical history included four open-heart surgeries for aortic and mitral valve replacement due to recurrent *Candida parapsilosis* infective endocarditis. Transthoracic echocardiogram showed a markedly reduced left ventricular systolic function and normofunctioning bioprosthetic valves. An inotropic dependency condition led to heart transplantation surgery. In the early postoperative period, a persistent chylous fluid started to drain from the pericardial tube, compatible with the diagnosis of chylopericardium. The lack of clinical response to total parenteral nutrition and intravenous infusion of octreotide imposed the need of interventional radiology with diagnostic lymphography through cisterna chyli puncture and thoracic duct catheterization, confirming the presence of a lymphatic fistula. A successful treatment outcome was achieved with percutaneous thoracic duct embolization using coils and n-butyl-cyanoacrylate glue, possibiliting hospital discharge.

Conclusions: Fungal endocarditis requires combined treatment (surgical and antimicrobial) for eradication. Valve replacement, while necessary, may lead to severe ventricular deterioration and heart transplantation may be the only viable therapeutic solution. Among the several postoperative complications of heart transplantation, chylopericardium is an uncommon and defiant example. Advances in interventional radiology like the percutaneous embolization allow a less invasive and highly efficient approach for this complication.

Keywords: Infective endocarditis, Heart transplantation, Pericardium

Background

Some patients, like a Greek epic legend, face true medical challenges in real life. *Candida* prosthetic endocarditis represents a major defiance in clinical practice due to its devastating potential, requiring surgical intervention and prolonged antimicrobial therapy. Although rare, corresponding to less than 1% of all infective endocarditis, this

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condition determines high mortality and relapse rates [1]. In this scenario, the necessary cardiac reoperations could be associated with left ventricular function impairment and severe systolic heart failure, sometimes imposing the need of a more definitive therapeutic approach like heart transplantation [2]. Among the many complications related to cardiac transplantation, chylopericardium represents a rare but challenging example, adding another contest in the postoperative period. We present a unique case report that brought together this entire sequence of events.

Case presentation

We present a clinical report of a 55-year-old male patient with a past medical history of four open-heart surgeries for aortic and mitral valve replacement. His first cardiac surgery was performed in 2009 and consisted in mitral valve replacement using a bioprosthesis due to symptomatic severe mitral regurgitation related to an anterior leaflet prolapse [3]. Due to regular sports practice and fearing major bleedings related to anticoagulant therapy the patient refused to receive a mechanical prosthesis at this point.

A year later, he received biological mitral prosthesis replacement for symptomatic severe paraprosthetic leak, with a good postoperative outcome [3]. In March 2013, he presented to the emergency department with a 2-week history of daily fever. Serial blood cultures were positive for *Candida parapsilosis* and transesophageal echocardiography showed multiple vegetations attached to the mitral prosthesis and native aortic valve. Given the diagnosis of fungal infective endocarditis, another cardiac surgical approach was necessary, consisting of combined mitral and aortic valve replacement using biological prostheses [4]. After a 6-week antifungal treatment with liposomal amphotericin-B, the patient was discharged

from hospital on suppressive antifungal therapy with oral fluconazole for a year. After 3 years, the patient searched for emergency medical care with a 1-week history of high fever (39 °C). Once again, *Candida parapsilosis* was isolated from blood cultures and intravenous antifungal treatment with liposomal amphotericin-B was started. *Candida* endocarditis relapse was confirmed by transesophageal echocardiography, revealing mitral and aortic prosthesis with leaflet thickening and large vegetations with extension into the left atrium (Fig. 1, panels a, b). Then, the patient underwent his fourth operation: mitral and aortic prosthesis replacement (Fig. 2) [4]. Transient inotrope dependence resulted in a prolonged postoperative intensive care unit period, related to left ventricular dysfunction (ejection fraction of 40%). Once again, a new 6-week liposomal amphotericin-B cycle was performed. This time, the patient definitely remained on suppressive antifungal therapy with oral fluconazole.

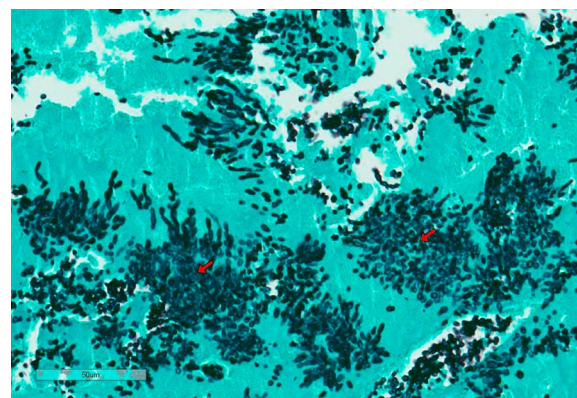


Fig. 2 Histopathology of excised mitral bioprosthesis. Grocott's methenamine silver stain showing fungal hyphae and yeasts (red arrows)

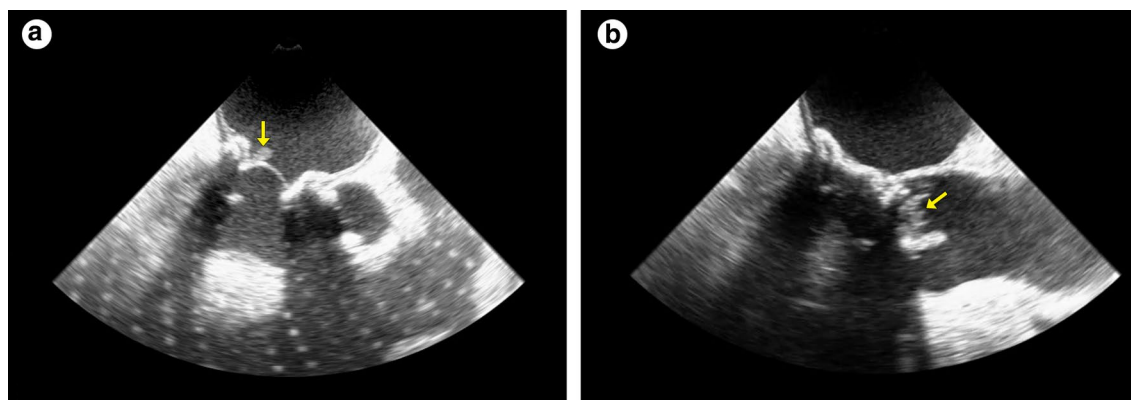


Fig. 1 **a** A large fungal vegetation on mitral prosthesis (yellow arrow). **b** Aortic prosthesis vegetations (yellow arrow)

During the follow-up period, there was a worsening of the left ventricular ejection fraction up to 25%. Hospitalizations for acute decompensated heart failure became recurrent despite optimized pharmacological treatment and cardiac resynchronization therapy.

Due to clinical deterioration he was admitted to the cardiology unit of our institution with acute decompensated heart failure, requiring inotropic support with dobutamine in addition to intravenous diuretic therapy. After multidisciplinary evaluation, he was included in the national heart transplantation waiting list with priority criteria (inotrope dependence) [5]. After 3 months of waiting, he finally underwent orthotopic heart transplantation. The initial postoperative period was marked by acute kidney injury, requiring continuous venovenous hemofiltration and hemodialysis. Fortunately, there was a favorable outcome, with effective weaning of vasoactive drugs and recovery of kidney function. Between the 10th and 12th postoperative days, a persistent massive chylous fluid, with a typical “milky” appearance, started to drain from the pericardial tube. The high triglyceride level in the aspirated pericardium fluid (800 mg/dl) was compatible with chylopericardium diagnosis. Initially, clinical treatment with total parenteral nutrition and intravenous infusion of octreotide was attempted. However, after 1 week of treatment, the maintenance of high chylous pericardial drainage configured a clinical therapeutic failure. After a multidisciplinary discussion, invasive lymphangiography was proposed.

Lymphangiography and thoracic duct embolization were performed in a dedicated interventional radiology suit, according to the following steps: (1) inguinal

lymph nodes guided puncture followed by microbubble contrast infusion for regional lymphatic ducts anatomic evaluation; (2) lymphangiography with lipiodol infusion (Guerbet, Villepint, France); (3) the lack of contrast impregnation into the upper abdomen and cisterna chyli led to a retrograde access approach; (4) left upper limb phlebography allowed the thoracic duct ostium identification and its retrograde catheterization; (5) thoracic duct lymphangiography showed a lymphopericardial fistula with lipiodol leakage into the pericardial sac; (6) thoracic duct embolization using micro coils and n-butyl-cyanoacrylate glue was performed (Fig. 3, panel a). The amount of contrast (lipiodol) used was 50 ml and the duration of the procedure was 3 h.

In the first postoperative day, there was a significant reduction in the drainage flow (160 ml). However, in the subsequent days, there was a progressive increase in the daily drainage volume. A new approach was then performed by transhepatic percutaneous direct puncture of the cisterna chyli, using 50 ml of lipiodol contrast. Another thoracic duct embolization with liquid agent n-butyl-2-cyanoacrylate was achieved, taking 3 h of procedure (see Additional file 1 to watch the thoracic duct lymphangiography video confirming the lymphopericardial fistula). In the immediate postoperative period, there was a marked reduction in drainage flow, sustained in the subsequent days. (Fig. 3, panels b, c). Finally, after a prolonged period of hospitalization, the patient was discharged in excellent clinical conditions. Table 1 presents a timeline with the main reported events in this case (see Additional file 2 to access a slide set containing details of the case presentation). At the 6-months follow-up,

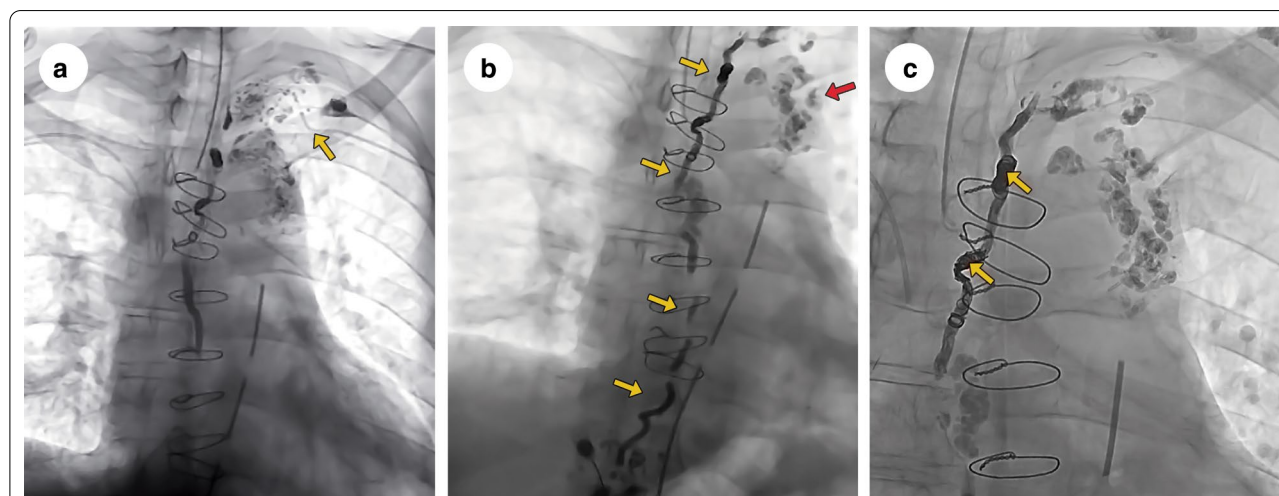


Fig. 3 **a** Retrograde thoracic duct catheterization (yellow arrow) with lipiodol leakage into the pericardial sac. **b** Transhepatic cisterna chyli puncture. Note the lipiodol into the thoracic duct (yellow arrows) and the lymphopericardial fistula (red arrow). **c** Embolized thoracic duct with micro coils (yellow arrows)

Table 1 Timeline of the main reported events

| 2009 | 2010 | 2013 | 2016 | 2019 | 2019 At the 10th to 12th postoperative day | 2019 At the 20th and 24th postoperative day | 2019 At the 30th postoperative day |
|---|--|--|---|--|--|---|---|
| Mitral valve replacement (bioprosthesis) | Mitral bioprosthesis replacement | Mitral and aortic valve replacement | Mitral and aortic bioprosthesis replacement | Heart transplantation | Chylopericardium | Thoracic duct percutaneous embolization | Hospital discharge |
| Indication: symptomatic anterior leaflet prolapse | Indication: Severe paraprosthetic leak | Indication: <i>Candida parapsilosis</i> endocarditis | Indication: <i>Candida parapsilosis</i> endocarditis recurrence | Indication: Severe systolic heart failure with inotrope dependence | | | |

the patient was in good clinical condition and pleased to have recovered his quality of life, without cardiovascular symptoms.

Discussion and conclusions

Recurrent fungal endocarditis and valve replacement procedures

Our patient experienced the dramatic natural history of candida prosthetic endocarditis, characterized by high morbidity mainly related to elevated recurrence rate (around 36%) despite combined treatment (valve replacement and long-term antifungal therapy) [1]. Candida prosthetic endocarditis is a rare entity, corresponding up to 3.4% of valvar prosthetic endocarditis, with a high mortality rate (up to 50% in a 5-year period) [3]. Interestingly, the patient did not have any risk factors related to fungal endocarditis such as immunosuppression, parenteral nutrition and intravenous drug use. In fact, the source of the fungal infection has not been identified in this case. From an etiological perspective, *Candida albicans* is the most frequently involved agent [4]. Despite valve replacement surgery, a 6-week in-hospital antifungal treatment with intravenous liposomal amphotericin-B and a year of continuous suppressive antifungal therapy with oral fluconazole the patient had prosthetic endocarditis recurrence 3-years later by the same agent: *Candida parapsilosis*. Concerning the factors related to this therapeutic failure and recurrence of the infection, it is possible that a longer period of postoperative suppressive antifungal therapy (>1 year), as described in some case series, could prevent this relapse [3, 4].

After 4 open-heart cardiac surgeries, an inexorable complication arose for our patient: severe systolic left ventricular dysfunction. In a retrospective study, Ataka et al. found that up to 2/3 of patients with second/third valvar reoperation had a significant loss of ventricular function (around 25%), possibly related to ischemic/reperfusion injury in the previous operations

[2]. Regarding this case, serial echocardiographic evaluation documented a progressive worsening of left ventricular function (up to 25%) associated with secondary pulmonary artery hypertension, without concomitant prosthetic valve dysfunction. Recurrent hospital admissions for decompensating heart failure requiring inotropic support have become frequent, despite pharmacological treatment optimization. Even the implementation of cardiac resynchronization therapy has not been able to mitigate symptoms and hospitalizations. In view of this poor evolution, the patient was referred for heart transplantation evaluation.

Heart transplantation complicated by chylopericardium

Taylor et al. found that about 4% of patients undergoing heart transplantation had their cardiomyopathy related to a valvular pathology, representing a small proportion when compared to other etiologies such as ischemic or dilated cardiomyopathy [6]. The reasons for this low prevalence can be justified by the possibility of surgical correction (repair or valve replacement) in most of the valve diseases, with heart transplantation restricted to those subgroups considered inoperable or at high surgical risk. One of the major concerns related to heart transplantation for patients with valvular cardiomyopathy is the association with increased pulmonary vascular resistance, especially in mitral valve disease. This finding may impair the immediate postoperative period with right ventricular failure and hemodynamic deterioration.

After successful orthotopic heart transplantation, our patient was diagnosed with chylopericardium in the early postoperative period. Chylopericardium is a rare condition with variable clinical presentation, involving the development of a lymphatic fistula to the pericardium [7]. The most common etiologies are idiopathic (56%), after valve replacement surgery (9%), coronary artery bypass grafting (6%) and heart transplantation (3%) [7]. It is very likely that during the heart transplantation, the

dissection of multiple adhesions related to previous redo operations has caused an accidental injury to the thoracic duct, culminating in the installation of the chylopericardium. Confirmatory testing requires a total triglycerides concentration at the pericardium effusion > 500 mg/dL, cholesterol/triglyceride ratio < 1.0, predominance of lymphocytic cells and negative cultures [7]. Conservative treatment may be successful in up to 50% of patients and recommended for patients with daily pericardium drainage less than 1000 mL. Low-fat adapted diets, rich in medium chain triglycerides, or even total parenteral nutrition are the main therapeutic strategies [7]. Surgical treatment usually consists of thoracic duct ligation [8]. However, the anatomical identification of the thoracic duct represents a major difficulty issue during surgery, leading to the development of less invasive therapies as percutaneous embolization [9]. The approach to the thoracic duct can be performed by anterograde access (via cisterna chyli puncture or direct thoracic duct catheterization) or by retrograde route through direct thoracic duct ostium catheterization into the subclavian vein [10, 11]. Embolization is usually performed by using liquid agents and/or micro coils with technical and clinical success rates up to 79% and 72%, respectively [12, 13]. In this case, our interventional radiology team selected the retrograde access for embolization. A second complementary embolization was performed three days later, via cisterna chyli direct puncture, with a successful fistula repair. A literature review identified four reported cases of chylopericardium after heart transplantation: in two cases, conservative treatment warranted clinical success; in the other cases, after an initial conservative treatment, surgical intervention was required for definitive resolution [12–15]. This is the first case report of thoracic duct embolization for chylopericardium treatment after heart transplantation. This technique can be effective and a less morbid alternative to open heart surgery.

Regarding the patient's perspective, it is worth highlighting the strength that has always motivated him during the many interurrences experienced. Despite some disappointments and moments of uncertainty, he has never lost confidence in the medical team. His willingness and cooperation were crucial for the positive outcomes achieved.

From an educational point of view, this case report brings some relevant conclusions: (1) fungal endocarditis requires a strict clinical follow-up after hospital discharge with special care in implementing and maintaining antifungal suppression therapy to avoid recurrence; (2) cardiac reoperations, even when necessary, can lead to permanent ventricular dysfunction; (3) heart transplantation remains a method for definitive clinical recovery in refractory heart failure; (4) integrated multidisciplinary

work in the form of heart team is essential to ensure favorable clinical outcomes in such challenging scenarios.

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s12872-020-01755-z>.

Additional file 1. Thoracic duct lymphangiography video confirming the lymphopericardial fistula after infusion of the lipiodol contrast.

Additional file 2. Slide set containing details of the case presentation.

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None.

Authors' contributions

AS drafted the manuscript. GMG, SM, ABM and RGG interpreted and revised the manuscript. RGG was the interventional radiologist responsible for the procedure. RMT and FAG were the surgeons of the case. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used in the case are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

This study was approved by the Research Ethics Committee of the Hospital Israelita Albert Einstein (committee's reference number: 4.287.317). A written informed consent was obtained from the patient.

Consent for publication

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Competing interests

The authors declare that they have no competing interests.

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