Official journal of the Spanish Society of Chemotherapy

Clinical-Pathologic Conference

A young patient with fever after heart transplantation

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Article history
Received: 10 July 2018; Revision Requested: 20 July 2018; Revision Received: 29 July 2018; Accepted: 31 July 2018

PRESENTATION OF CASE (DR. ANTONIO RAMOS)

A 31-year-old male, suffering from obstructive hypertrophic cardiomyopathy (K847 mutation of MYH7 gene), referred a long history of heart problems. At the age of 15, a pacemaker was implanted that had to be removed after 4 months due to infection, whose etiologic agent we ignore. At the age of 20 years, he received an implantable cardioverter defibrillator (ICD) that had to be replaced 8 years later, after an episode of heart failure, by a cardiac resynchronization therapy device (CRTD).

The patient's chest x-rays can be seen in figures 1 and 2.

At age 31, the patient's ventricular function situation required the implantation of an artificial ventricular assist heart of the Berlin Heart Excor type (figures 3 and 4). During the postoperative period (48 hours) the patient received prophylactic treatment with broad-spectrum antimicrobials consisting of vancomycin (1g/12 hours), rifampicin (600 mg/24 hours) and fluconazole (400 mg/24 hours) during 2 days.

The patient was discharged 18 days after implantation, showing redness and slight maceration at the entrance of the cannulas (figure 5). Six weeks after, the presence of purulent exudate was evident at the entrance of the return cannula on the right side

The patient had no fever or general manifestations and a swab culture taken of the peri-cannular exudate grew *Pseu-*

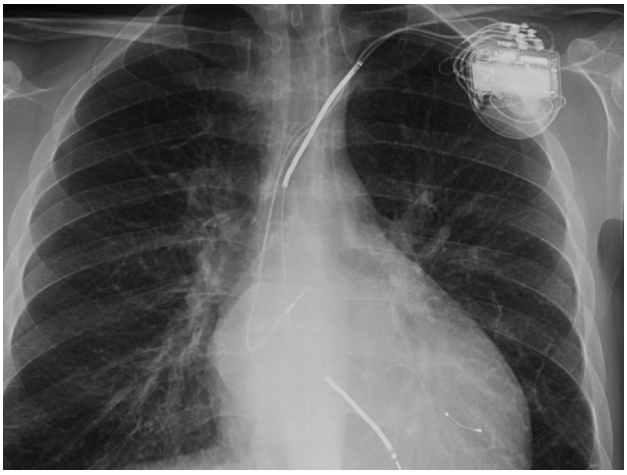

Figure 1 PA. Chest X ray. November 2011

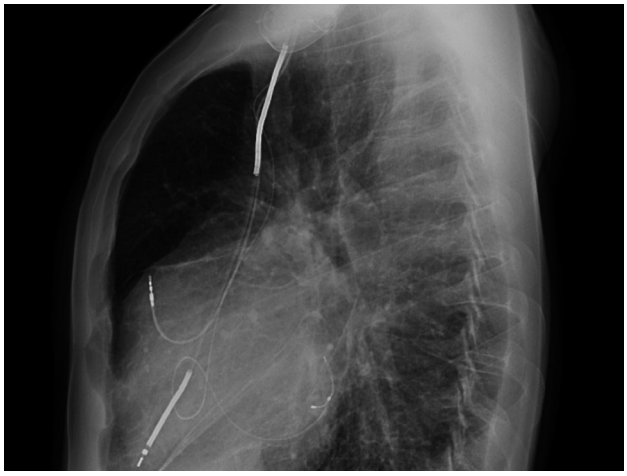

Figure 2 Lateral Chest X ray. November 2011

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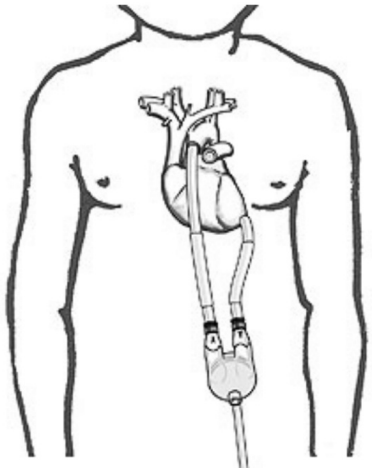

Figure 3 Berlin Heart Excor device

Figure 4 Berlin Heart Excor implanted in the patient

domonas aeruginosa, susceptible, among other drugs, to ciprofloxacin. It was treated with oral ciprofloxacin, 500 mg/12 h for 21 days, with improvement of the referred lesion.

Orthotopic heart transplantation. One month after completing this treatment, the patient received an orthotopic cardiac transplant, with no particular technical complications, with an extracorporeal circulation time of 192 minutes and an ischemic time of 175 minutes. The recipient was PPD positive, had IgG antibodies for Cytomegalovirus (CMV), Varicella-Zoster virus (VZV), Herpes simplex virus (HSV), and *Toxoplasma*. The donor was a 26-year-old male who died of cerebral hemorrhage, with no relevant serological discordance with the recipient.

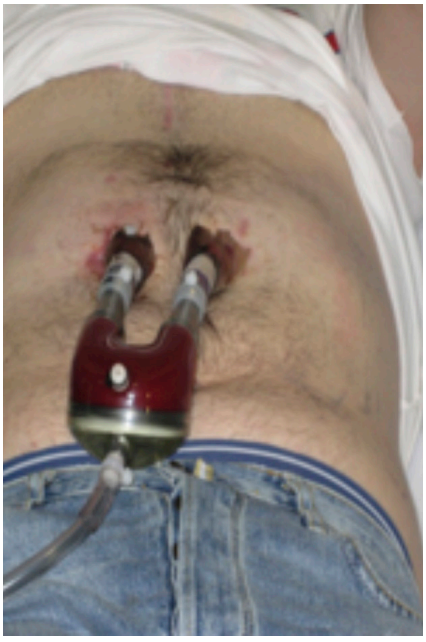

Figure 5 Redness at the entrance of the return cannula inlet

A fragment of the previously implanted CRTD electrode had to be left in place in the innominate vein trunk after several unsuccessful attempts for its removal.

Postoperative complications. The patient suffered several post-transplant complications. First, a primary graft failure with severe right ventricular failure and moderate left ventricle failure with cardiogenic shock. It required implantation of extracorporeal membrane oxygenation (ECMO), with left femoral cannulations (artery and vein), intra-aortic balloon counter-pulsation, vasoactive drugs at high doses and administration of nitric oxide. The ECMO was removed on the 9th postoperative day after clinical and graft function improvement.

In the postoperative period, *C. parapsilosis* fungemia was associated with infection of a vascular catheter, which was treated with fluconazole (400 mg/day) for 17 days along with catheter removal. The patient also suffered a severe polyneuropathy of the critically ill and an important left inguinal hematoma as a complication of the former cannulation of the femoral artery.

In the sixth postoperative week, fever (38.1 ºC) appeared with no apparent focus nor significant changes in physical examination. The patient did not have bladder or vascular catheters at the time. A chest x-ray, urinary sediment and tran-

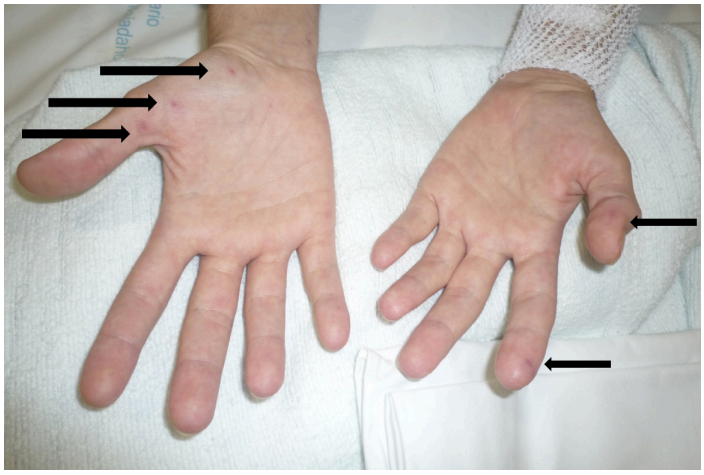

Figure 6 | **Hand lesions**

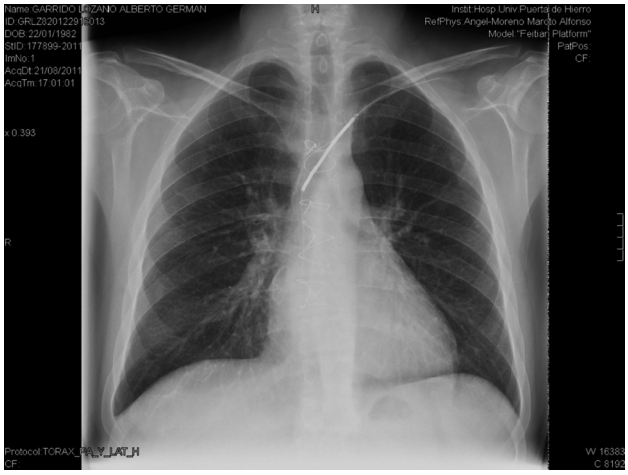

Figure 7 | **Chest X-ray (PA) at the time of admission**

sthoracic-echocardiography (TTE) were normal. At 24 hours, *P. aeruginosa* (susceptible to usual drugs, including ciprofloxacin) was isolated in 2 out of 4 vials of blood cultures. The patient received treatment with imipenem (500 mg/6 hours, IV) for one week and ciprofloxacin (500 mg/12 hours orally) for another week.

The patient was finally discharged, on the day + 62 after his transplant, in good general condition on the following medication: cyclosporine (250 mg bid), mycophenolate (500 mg, bid), orednisone (15 mg qd), acyclovir (200mg tid), cotrimoxazol (800/160 mg every 48h), nystatin (1 rinse / tid), isoniazid (300 mg/qd) and weekly CMV PCR determinations requested.

At 9 weeks after the intervention, the patient was able to do an active life, walking 2-3 km. per day, including aerobic exercise. He experienced progressive weight and muscle mass gain and was essentially asymptomatic from the cardiac point of view.

Readmission. In the 15th week after transplantation, the patient began with fever, chills, occipital headache and asthenia. He had a single episode of diarrhea, without pathological products and there was no clear infectious focus. The patient referred not have travelled to the countryside or any changes in his medication. All CMV PCR viral load determinations up to that moment were negative.

On physical examination the patient was eupneic and well perfused. Blood pressure was 110/70 mmHg, heart rate 70 bpm and his basal oxygen saturation was 96%. A minimal pan-focal systolic murmur I/VI was heard, pulmonary auscultation was normal and the abdomen was not painful to palpation, showing a possible spleen enlargement at 2 cm from the costal rim.

On the palms of the hands and feet, maculopapular erythematous lesions were noticeable (figure 6).

Additional tests taken at admission included: Urea 81 mg/dl, creatinine 1.4 mg/dl, C-reactive protein 161 mg/l, LDH 332 UI/l, ALT (GPT) 30 UI/l, GGT 124 UI/l, Bilirubin 0.9 mg/dl., Leukocytes 3,580/mm^3, Neutrophils 2,870/m^3, Lymphocytes 430/mm^3, Hemoglobin 8.2 g/dl, Platelets 100,000/ml, Procalcitonin 0.1 ng/ml.

Urine sediment examination showed bacteriuria without hematuria nor cylinders. INR 1.26, APTT 30.

Posterior anterior and lateral chest X rays are shown in figures 7 and 8. The ECG was unremarkable.

C-Reactive protein was normal. A TTE performed on admission was reported as follows: No signs of endocarditis. Mitral, aortic, tricuspid and pulmonary valves of normal morphology and flow. It is difficult to visualize the end of the electrode in the innominate trunk, but no vegetations are visible. Ventricular function is normal. No evidence of pericardial effusion.

Several diagnostic procedures were performed.

DIFFERENTIAL DIAGNOSIS (DR. MARINO BLANES)

Thank you very much for inviting me to discuss this clinical case. I am totally unaware of the final diagnosis of this patient.

To begin, and as a tribute to Prof. Bouza, I have rescued this work published by him in the Treaty of Internal Medicine, Medicine, in 1987, which outlined a way to approach the differential diagnosis of patients with suspected infection [1]. The acronym PASEO is derived from the initials Patient, (Antecedents) Background, Syndrome, Etiology and Organization. I will follow that acronym order.

We have here a 31 year-old patient, who underwent a cardiac transplant four months ago, with a history of hypertrophic obstructive cardiomyopathy of rapid progression that

has had to be treated, very early in his life, and before accessing to cardiac transplantation, with ICD, a CRTD and, finally, with a ventricular assistance of the Berlin Heart Excor type. He suffered an infection at the point of entry of the cannulas by *P. aeruginosa* which was treated with oral ciprofloxacin for 3 weeks. After cardiac transplantation, an electrode of the original ICD remained inside the innominate veins. In the postoperative period of the cardiac transplant, there were several complications, mainly an initial graft failure requiring ECMO for 9 days, a *C. parapsilosis* fungemia related to a catheter, that was treated with fluconazole (400 mg/day) and removal of the catheter. He also had a bacteremia due to *P. aeruginosa* in the sixth week post-transplantation, without an obvious source of origin, which was treated with Imipenem, followed by ciprofloxacin in a total cycle of 14 days. A TTE at the time was negative. After these complications, the patient could be discharged and quickly recovered an active life, that seemed to suggest the beginning of the end of the problem.

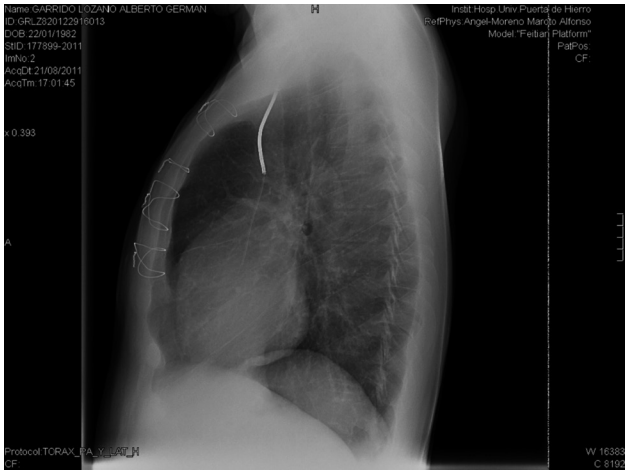

Figure 8 | **Chest X-Ray (lateral) at the time of admission**

In this context, fever reappeared and, in my opinion, two very important facts emerged: splenomegaly and lesions on palms and plants reminiscent of Janeway spots. There were no signs of infectious endocarditis (IE) in the TTE but the conjunction of fever, splenomegaly and Janeway spots suggests this diagnosis.

Several topics permit to assess the situation of this patient that include: Ventricular-Assist Device Infections, IE in heart transplant patients, infections related to pacemaker electrodes or infected aneurisms or pseudoaneurysms.

Left Ventricular-Assist Devices (LVADs) have revolutionized the treatment of advanced heart failure, but infections remain very significant and prevalent as a cause of complication. Infections can be classified as driveline related (superficial or deep), metastatic and bacteremic. Overall from 13 to 80% of LVDAs implanted suffer one or more infectious complications [2-4], particularly nowadays, in which LVDAs remain implanted much longer when they are used as a bridge to heart transplantation. Infections can be superficial, at the portal of entrance of vascular lines, but echography can help to show deeper collections around the tubes. PET-CT may help to pinpoint to distal metastatic infections such as bone infections or endocarditis. The pathogens are generally skin saprophytes but *S. aureus*, *P. aeruginosa* and Enterobacteriaceae are also common [4-7]. Polymicrobial infections have also been reported and the implantation of a second pathogen in an initially monomicrobial infection is also known. This is frequently the case *of P. aeruginosa*.

Another potential approach to this case may be based on the unquestionable existence of recurrent *P. aeruginosa* infection. Although we are not told whether the *P. aeruginosa* of

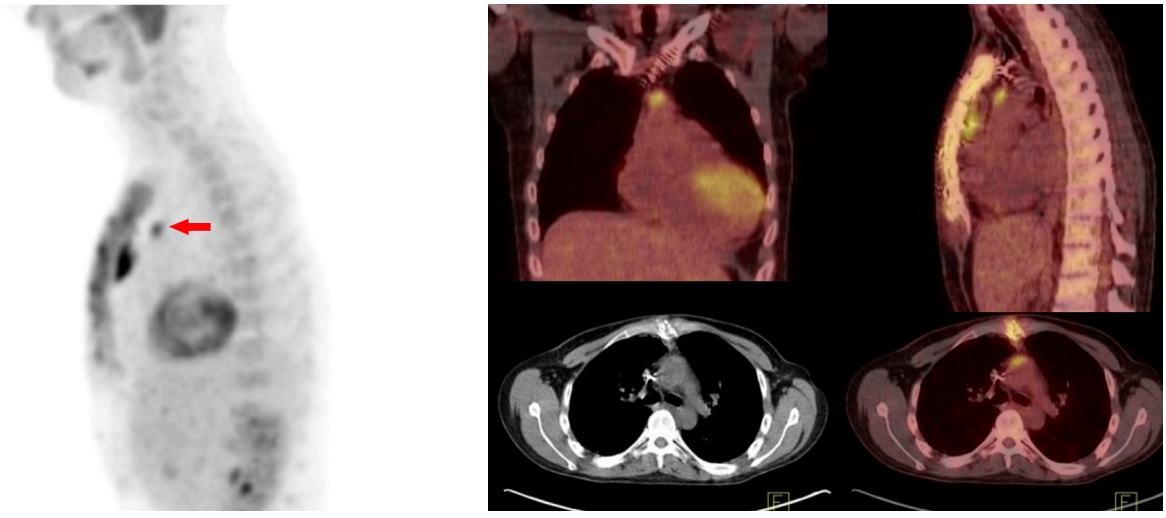

Figure 9 | **PET-TC performed at the last admission**

Table 1 **Etiology of 1,804 episodes of Infective Endocarditis collected in Spain (GAMES research group). Modified from Muñoz P, et al. [24].**

	Total n=1,804	Native non-IVDU n=1,079
Definite IE	1,498 (83.0)	919 (85.6)
Possible IE	300 (16.6)	155 (14.4)
Etiology		
Staphylococcus spp.	728 (40.3)	382 (35.3)
S. aureus	426 (23.6)	278 (25.8)
MSSA	360 (84.5)	235 (84.5)
MRSA	66 (15.5)	43 (15.5)
CoNS	302 (16.7)	104 (9.7)
Streptococcus spp.	440 (24.4)	329 (30.5)
S. bovis	117 (6.4)	80 (7.4)
S. viridans group	223 (12.3)	171 (16.0)
Others	100 (5.5)	79 (7.3)
Enterococcus spp.	230 (12.7)	142 (13.2)
Other Gram-positives	26 (1.4)	14 (1.3)
Gram-negative	93 (5.2)	53 (4.9)
Fungi	44 (2.4)	21 (1.9)
Negative blood cultures	264 (14.7)	152 (14.0)

IE: infective endocarditis. CoNS: coagulase-negative staphylococci, IVDU= intravenous drug users, MRSA: methicillin-resistant *S. aureus*, MSSA: methicillin-susceptible *S. aureus*. Other Gram-positives: *Abiotrophia* 9, *Corynebacterium* 6, *Gemella* 8, *Listeria* 3. Gram-negatives: *Acinetobacter* 2, *Actinobacillus* 4, *Alcaligenes* 1, *Bartonella* 4, *Brucella* 1, *Campylobacter* 3, *Cardiobacterium* 2, *Coxiella* 15, *Enterobacter* 3, *Escherichia* 13, *Haemophilus* 7, *Klebsiella* 3, *Moraxella* 1, *Neisseria* 2, *Pseudomonas* 11, *Salmonella* 3, *Serratia* 2, *Stenotrophomonas* 1, *Tropheryma* 5, *Yersinia* 1. Fungi: *Aspergillus* 5, *Scedosporium* 1, *Candida* 37, *Rhodotorula* 1.

the different episodes were the same, recent studies show that a high proportion of the *P. aeruginosa* recurrent episodes are generally identical to those of the original episode and that most recurrent episodes are, therefore, relapses of infections not fully eradicated with previous treatments [9-12]. Recurrent *P. aeruginosa* bacteremia may be a manifestation of IE of the aortic root [13] and also an expression of infection on intra-cardiac foreign bodies [14]. In a review of *P. aeruginosa* endocarditis, published by Lin et al. in 2016, in non-drug-addict patients, recurrence occurred in 33% of the episodes [15].

Infective endocarditis in a transplanted heart. The peripheral stigmata of IE have been recognized for many years, and Osler's nodes and Janeway lesions are among the diagnostic criteria for infective endocarditis [8, 16-18]. Janeway lesions are strongly associated with endovascular infection and occur as a result of micro-emboli that can often lead to the formation of micro-abscesses with microorganisms isolated in culture. They have prognostic value since patients who suffer from them have a higher incidence of complications [19]. However, they have been described not only in IE but also after arterial cannulations, ECMO, ... [20-23]. Therefore, in the case of this patient, we can assume that there is a left endovascular infection that could be IE, residual electro-catheter related infection or a mycotic aneurysm.

In the case of IE, its etiological spectrum is well known, with a predominance of bacterial Gram-positive microorganisms. Table 1 shows the most frequent etiologies in the Spanish series of GAMES [24]. Paterson et al. showed in 1998 a high incidence of fungal etiologies and uncommon bacterial microorganisms in IE occurring in heart transplant recipients [25]. Sherman-Weber et al. corroborated this situation showing in a series of 10 patients with posttransplant IE, that 3 episodes were caused by *Aspergillus spp.* and a case by *P. aeruginosa* [26].

We must not forget that the febrile episode that occurred in the 15th week after transplant, happened at the time of maximum depression of cellular immunity due to immunosuppressive medication. However, given the well-defined endovascular infection syndrome suggested by the clinical manifestations of this case, I believe that such immunosuppression can only serve to modulate alternative possible etiologic agents in the sense of introducing, at least as a possibility, microorganisms that prevail in patients with impaired cellular immunity and are not common in immunocompetent patients [27].

In the case of microorganisms causing infection in pacemakers, conventional Gram-positive cocci predominate, but about 9% of the cases in a series collecting 816 patients found Gram-negative bacilli as causal agents [28,29]. Same proportions are reflected in the GAMES Spanish series on 169 devices [24].

It should be noted that in this case, since the residual electrode is located in the unnamed venous trunk, the microembolization would be directed to the right side and pulmonary territory. A right-left shunt (permeable oval foramen, pulmonary arterio-venous shunt, etc.) would be necessary to explain for the appearance of embolisms in left territory.

Moving to the possibility of aortitis or pseudoaneurysms, the incidence of cases caused by Gram-negative bacilli reaches 20-40% in some series [30-35], being *Salmonella* spp. a particularly prone microorganism.

Mycotic aneurysms are a rare (<1%) but well-known complication after heart transplantation [36-45]. Possible sites of the pseudoaneurysm formation include suture lines, cannulation sites, and needle holes of the aorta. In a compilation of cases reported up to 2011, out of 19 total cases, 4 were caused by *Pseudomonas* spp. (3, *P. aeruginosa* and 1 *Pseudomonas* spp. [43] .

Despite the frequency of the most probable etiologies in the different scenarios, it is necessary to highlight the history of repeated infection by *P. aeruginosa*, which undoubtedly has a relevant weight when it comes to establishing the possible aetiology of the process. As a Gram-negative microorganism

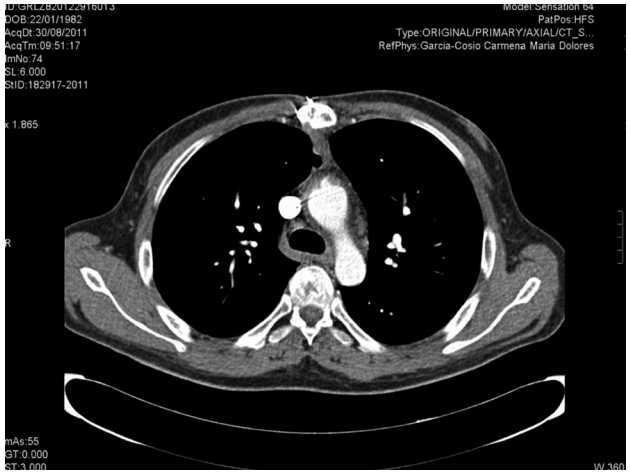

Figure 10 CT angiography of the aortic root

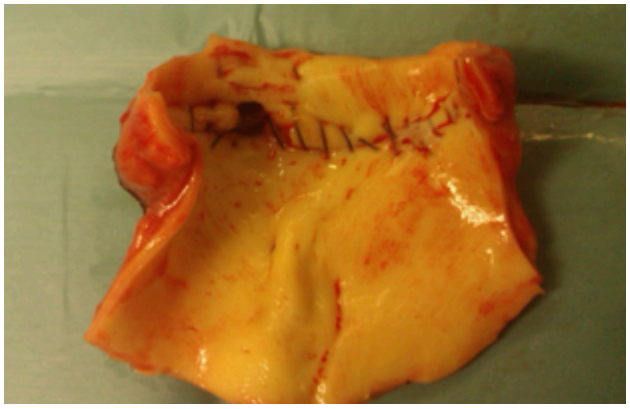

Figure 11 Resected aortic root fragment including the aortic suture that showed the presence of a pseudoaneurysm.

it is a less common aetiology of EI or endovascular infection. In spite of this, we have just reviewed that on device and/or electrode or in the case of mycotic aneurysms their frequency is higher and should be considered as a first etiological possibility. The possibility that *C. parapsilosis* candidemia was the cause cannot be ruled out either.

Moving already towards the O of the PASEO (Organization), this patient was probably admitted with the idea of performing some of the following complementary tests: transesophageal-echocardiography (TEE), an angio-TAC or a PET-TAC, repeat blood cultures, and make studies of the fundus of the eye and search in for other possible embolisms (MRI brain). If the new blood cultures are negative, biopsies of the skin lesions may help confirm an etiologic diagnosis (more in the case of bacteria). The ultimate intention of the admission, in my opinion, is also the possibility of considering a surgical review to eliminate and infectious focus.

DIAGNOSIS (DR. MARINO BLANES)

P. aeruginosa or alternatively *C. parapsilosis* as a cause of infective endocarditis or endarteritis.

EVOLUTION OF THE PATIENT (DR. ANTONIO RAMOS)

Indeed, as indicated by Dr. Blanes, the patient had a TEE, that showed a suggestive image of vegetation (6 mm in size) on the pacemaker lead. Transplant sutures appeared prominent but without signs of infection. Repeated blood cultures demonstrated persistence of the growth of *P. aeruginosa* in 4 out of 4 blood samples and the isolates, on this occasion, were resistant to ciprofloxacin. The patient was treated with meropenem (2 g IV tid) and tobramycin (300 mg qd), initially scheduled for 6 weeks. This left him afebrile but one week after starting treatment, control blood cultures remained positive for the same microorganism. The possible existence of an intravascular pseudoaneurysm in the recipient aorta was also considered. At that time, the PET-TAC result (figure 9) showed pathological uptake at the level of aortic suture. The sternal retro-sternal uptake was considered an effect of the post-surgical changes and no uptake was seen in the remains of the CRTD electrode.

The aortic TC angiography (figure 10) showed the presence of a clear pseudoaneurysm at the level of the aortic suture.

Surgical intervention. For all of the above, surgery was scheduled to review the aortic root lesion and remove the residual pacemaker lead. As well as revision of the mediastinum.

During surgery, the aortic pseudoaneurysm was confirmed and resected, and the aortic arch was replaced by a vascular prosthesis. The rest of the electrode were removed through percutaneous route. *P. aeruginosa* was isolated both from the aortic pseudoaneurysm and from the removed electrode.

After surgery, the postoperative evolution was uneventful, the patient's control blood cultures were negative and a 6-week course of antibiotic treatment with ceftazidime (2 g IV tid) and tobramycin (5 mg/kg IV qd) was administered.

Pathology findings of the surgical specimen showed a pseudoaneurysm penetrating the line of the aortic suture (figure 11). The histology report showed infiltrates with polymorphonuclear leukocytes.

The situation of the patient at the present time is very good and he is carrying out normally his daily life duties.

FINAL DISCUSSION

In a large series reviewing 247 patients who underwent LVAD implantation at Mayo Clinic in the USA, 215 (87%) had simultaneously CIED at the time of LVAD implantation and six (3%) subsequently developed CIED infections. Half developed

lead-related endocarditis and the other three had pocket infection [46]. The pathogens most frequently causing endocarditis were *P. aeruginosa* (especially, after chronic infection of the cutaneous entrance of the cannulas), *S. aureus* and coagulase-negative staphylococci. The most effective treatment in cases of infections of both devices is their joint withdrawal, which was not always possible.

A multicentric study about LVAD infections showed a high incidence (23%), at a median time of 2.9 months from LVAD implantation. LVAD-related infections were restricted to the driveline 36 exit site (n=17), had loco-regional extension (n=13), or reached the internal pump (n=3). *P. aeruginosa* was isolated in 27 % of cases. Twenty-two underwent heart transplantation with no cases of posttransplant infection. The use of continuous or iterative course of antibiotics until transplantation, or recovery, is the rule for most centers [47]. Other experiences with permanent LVAD noted less risk of infection [48].

The cumulative incidence of endocarditis in patients undergoing heart transplantation is around 1.5%, much higher than in the general population [26]. This complication has been related to the use of left ventricular assist devices (LVAD) before transplantation, infections transmitted by the graft, nosocomial infections such as surgical or catheter-associated infections, endomyocardial biopsies and immunosuppressive treatment. The most frequent locations are the mitral valve and the tricuspid valve. Cannulation of the aorta in patients with LVAD and vascular anastomoses can also favor intravascular infection through the production of endothelial damage. The most frequent pathogens are *S. aureus* and *A. fumigatus*. However, cases have been described by *P. aeruginosa* with involvement of the aortic suture and in patients undergoing pretransplant LVAD [19.46.49].

Finally it should be noted that an infected aneurysm of the thoracic aorta is a very rare condition characterized by a high mortality. Most cases are caused by *Salmonella* spp or *S. aureus*. Due to the risk of aorta rupture surgical treatment is mandatory [4].

FINAL DIAGNOSIS

Relapsing infection due to *P. aeruginosa* in a patient undergoing cardiac transplantation.

Sequential infection of a Left Ventricular-Assist Device, a residual electrode of a cardiac resynchronization therapy and the aortic suture.

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