Mitral valve pseudoaneurysm secondary to infective endocarditis due to Escherichia Coli ESBL

Endocarditis due to Gram-negative bacteria not belonging to to the HACEK group is rare. Escherichia Coli (E. coli) has been the etiological agent reported in less than 50 cases (1) and even less frequent are the species of E. Coli that produce extended spectrum beta-lactamase (ESBL) (1). The urinary tract is the main source of infective involvement, favored by risk factors such as diabetes mellitus, structural heart disease, prosthetic material, immunosuppression, use of intravenous drugs and advanced age. In the case of native valves, E. coli has affinity for those in the left side of the heart, especially the mitral valve. (2,3) Pseudoaneurysm is a complication of infective endocarditis (IE), more common in the aortic valve, particularly in prosthetic valves. (4) The microorganisms that cause endocarditis are usually streptococci, enterococci, and staphylococci, the latter being easily identifiable in blood cultures and the most common causative agents in both native and prosthetic valves. (5,6)

We present the case of a female patient with mitral valve IE due to E. coli ESBL complicated with pseudoaneurysm of the posterior mitral leaflet and multiple septic emboli. This 64-year-old patient, smoker, hypertensive, diabetic, with a history of peripheral artery disease, consulted a health center due to persistent fever lasting for 15 days associated with an episode of postural instability at home. Blood cultures were performed; resulting positive for E. Coli ESBL, and antibiotic treatment with meropenem was initiated.

Her evolution was unfavorable, presenting progressive dyspnea and acute pulmonary edema. A color Doppler transthoracic echocardiogram (TTE) showed a mobile image in the anterior mitral leaflet, so the condition was interpreted as IE. The antibiotic scheme was rotated to imipenem and gentamicin and in the evolution, she presented a right facio-brachio-crural neurological focus. Brain magnetic resonance imaging showed multiple focal images in the right cerebellar hemisphere and in the subcortical white matter of both hemispheres, consistent with embolic foci (Figure 1A). She progressed with daily febrile episodes without new bacteriological rescue and non-oliguric acute renal failure, without dialysis requirement. She was referred to our center for surgical resolution of her complicated IE resistant to medical treatment. She was admitted afebrile, without signs of heart failure, alert and oriented in person and space, but disoriented in time.

In the TTE, mobile images were observed in both mitral valve leaflets, approximately 20 mm in length. The transesophageal echocardiography showed a cavitated image in the posterior mitral leaflet measuring 2.53 cm × 1.92 cm diameter, with internal flow compatible with valvular pseudoaneurysm, and moderate mitral regurgitation, interpreted as secondary to altered valve structure (Figure 2).

In the abdominal ultrasound, millimetric echogenic images compatible with embolisms were observed in the spleen and both kidneys. Ocular fundus revealed uveitis with extensive bilateral vitreous involvement of systemic origin.

A new brain magnetic resonance imaging was performed, where hyperintense T1-weighted images were observed in the right putamen and globus pallidus, and in the bilateral temporal lobe compatible with subacute bleeding (Figure 1B).

Given the condition of native mitral valve IE with E. coli rescue, complicated with pseudoaneurysm of the posterior leaflet, moderate mitral regurgitation and septic impacts on the central nervous system (CNS), spleen, kidney and eyes, surgical treatment was decided.

Surgery confirmed the echocardiographic findings,

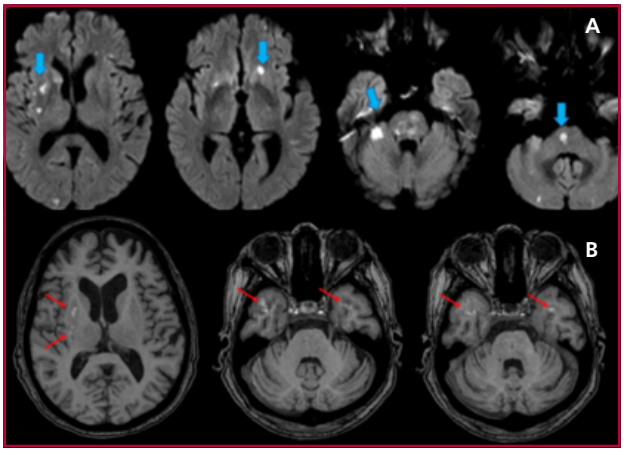

Fig. 1. Brain Magnetic resonance imaging. **A.** Multiple signal changes in the pons, right cerebellar hemisphere, and subcortical white matter of both hemispheres; **B.** Hyperintense T1-weighted images in the putamen, right globus pallidus, and bilateral temporal lobe compatible with subacute bleeding

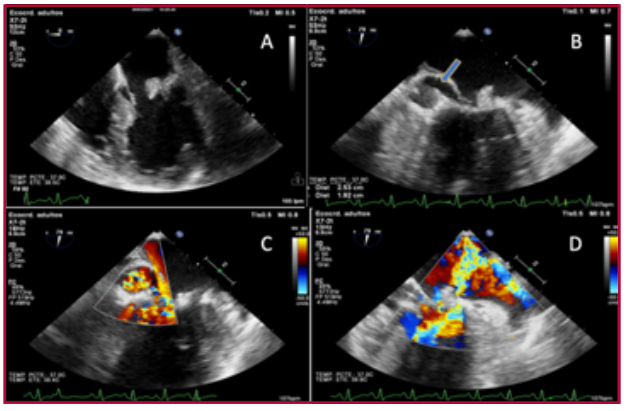

Fig. 2. Transthoracic echocardiography. **A.** Valve thickening and mobile images in both leaflets; **B.** Pseudoaneurysm of the posterior mitral leaflet, with 2.53 cm × 1.92 cm diameter (blue arrow); **C.** Abnormal turbulent flow inside the pseudoaneurysm; **D.** Moderate mitral regurgitation.

with visualization of 3 cm long vegetations in the anterior and posterior mitral leaflets, an infected cavity of 3 cm diameter in the P2 segment with fibropurulent content, and extension to the ventricular wall.

The cavity was filled with autologous pericardium and mitral valve replacement was performed.

The patient evolved in a torpid manner with shock refractory to high doses of vasopressors and kidney failure requiring dialysis, and died on the fifth postoperative day.

Pathological anatomy showed a thickened valve, with friable areas, valve tissue with the presence of vegetations formed by fibrohistiocytic inflammatory elements, granulation tissue, calcium deposits, and fibrinpioleukocyte material.

Infective endocarditis continues to be a serious disease with high morbidity and mortality, especially when complicated with pseudoaneurysms, abscesses, or septic embolisms; so it is necessary to make an early diagnosis using echocardiography, clinical and microbiological criteria to adopt medical-surgical decisions to prevent its spread.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material).

Ethical considerations

Not applicable.

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Therapeutic challenges of long-term paced congenital AV block

Patients with congenital atrio-ventricular (AV) block dependent on permanent pacemaker stimulation of right-heart chambers may develop ventricular dyssynchrony and eventual heart failure. These patients constitute a complex therapeutic challenge at the time of decision-making, either for system inherent complications as for a variety of external circumstances.

We present the case of a 44-year-old female patient with congenital complete AV block diagnosis, who presented a syncope at the age of 18 years, and received dual-chamber pacemaker implantation with stimulation in the right atrium (RA) and right ventricular (RV) apex. The generator was replaced on four occasions. During follow-up, an echocardiogram initially showed mild left ventricular systolic function (LVSF) impairment, that progressed in 2012 to moderate impairment. Treatment with bisoprolol and ramipril was started, with typical blood pressure (BP) values between 80/50 and 90/60 mmHg. The ECGs showed pacemaker activity with atrial and ventricular unipolar stimulation and QRS width 180 msec., and capture with left bundle branch block image. A cardiac computerized axial tomography (CAT) performed on February 11, 2017 evidenced left ventricular ejection fraction (LVEF) of 57%, and absence of significant coronary lesions. On March 9, 2018 she presented an isolated episode of dyspnea and a new CAT revealed severe LVSF impairment, LVEF of 29% and medial and apical segment hypokinesia. In addition, dual-atrial dilation was reported with preserved ventricular diameters. Right coronary and circumflex arteries presented non-significant fibrolipid plaques in the proximal third. During the next months, the patient was asymptomatic. The ECGs and Holter monitoring did not show evidence of pacemaker dysfunction or ventricular ectopy, bur exhibited very frequent isolated

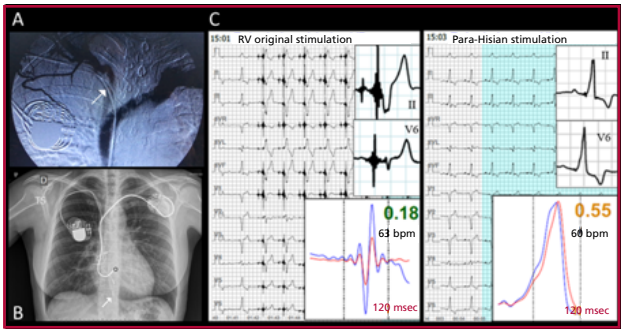

Fig. 1. A. Right subclavian venography. Contrast persistence is observed in the contralateral subclavian vein due to its previous injection and collateral circulation. The arrow indicates the occlusion. B. Anteroposterior chest X-ray showing the two pacemaker systems. The catheter trajectory to the para-Hisian region was highlighted and the arrow shows the original stimulation site in the right ventricle. C. The left panel shows the tracing resulting from stimulation with the original catheters together with the Synchromax record curves. The right panel illustrates the response to para-Hisian stimulation

supraventricular extrasystoles (5.42%). The patient was considered to be in stage B heart failure (structural heart disease in the absence of symptoms) and functional class I (NYHA). Treatment with atorvastatin was started, and due to the low BP values sacubitril/valsartan was avoided and treatment was continued with ramipril and bisoprolol. Considering that her condition was due to dyssynchrony secondary to prolonged RV apical stimulation, cardiac resynchronization therapy (CRT) was postulated. (1) Before defining the resynchronization strategy and because during the previous generator change there were difficulties to replace the atrial catheter, a bilateral subclavian venography was performed on July 2, 2019, showing right subclavian vein occlusion with signs of fibrosis and abundant collateral circulation, and patent contralateral subclavian vein. (Figure 1 A). With this finding, right subclavian venoplasty was considered to have low probability of success. After evaluating different possibilities, implantation of a dual-chamber DDDR pacemaker was chosen, conditional for nuclear magnetic resonance (NMR) imaging, to stimulate the RA and His bundle. (2,3) This strategy allows decreasing the number of endocavitary catheters compared with traditional CRT and thus, the risk of face and upper extremity edema. As the patient depended on pacemaker, with ventricular catheter implanted 26 years ago, the old system could be used as transient support and then proceed with its removal.

There is growing evidence that His bundle stimulation is equivalent to traditional resynchronization stimulating the coronary sinus. (2,3) The implant was guided by radioscopy, and His bundle was located with deflectable quadripolar catheter by right femoral puncture. The electrogram of the catheter electrode to be implanted on the His bundle and a signal-averaged ECG (SA-ECG) (Synchromax) were recorded to establish the degree of electric synchrony modification. The latter is a device whose software acquires, processes and averages cardiac electrical signals, allowing real-time estimation of the degree of intraventricular synchrony, mainly comparing leads II and V6, which are the ones that best correlate with intraventricular septum and left ventricular lateral wall activation, when the stimulation is generated in different heart areas (4-6) Very high thresholds were measured at the His bundle, so the catheter was relocated in a slightly anterior and inferior position (Figure 1B), resulting in acceptable thresholds [2.0V (0.5 ms)] with a reduction of 23 msec. in QRS duration. The ECG (SA-ECG) (Synchromax) evidenced a positive correlation with only a minimum degree of dyssynchrony (Figure 1C). The removal procedure of the old catheters was postponed until achieving LVSF improvement. Six months later, a new Doppler echocardiogram showed atrial volume reduction and a significant improvement of LVSF with LVEF of 51%, normal left ventricular mitral filling flow, and dyssynchrony indices compatible with mild dyssynchrony. Shortly after, the patient presented palpitations and brief episodes of dyspnea. Lack of capture of the new atrial catheter was confirmed, with preserved detection and no evidence of displacement. Surgery was decided to remove the previous pacemaker system and reimplantation of the new atrial catheter. Transiently, the new pacemaker was programmed in VDD mode with partial improvement. Palpitations at night persisted and a new Holter evidenced nocturnal AV dyssynchrony due to low atrial frequency and frequent atrial extrasystoles (5.46%). At that moment, due to the sanitary emergency and the measures adopted for the COVID-19 pandemic, both the patient and the treating physician requested postponing the intervention. Since the battery of the old pacemaker system had a useful life of two years, it was decided to temporarily profit from this advantage to maintain heart rate and simultaneously AV synchrony. Therefore, the pacemaker was programmed in DDD mode at 55 bpm, with an AV interval of 300 msec., while the new system was reprogrammed in VDD mode at 50 bpm to sense both spontaneous atrial activity as the one generated by the previous system, with an AV interval of 150 msec. to preserve para-Hisian stimulation (Figure 2). The patient presented immediate clinical improvement and a new Holter monitoring showed adequate AV synchrony and absence of ectopic atrial activity. Currently, the patient is followed-up by telemedicine and awaits resolution of the postponed surgery.

The decision to implant a dual chamber DDDR pacemaker to stimulate the atrium and para-Hisian region through the left subclavian vein was taken as alternative

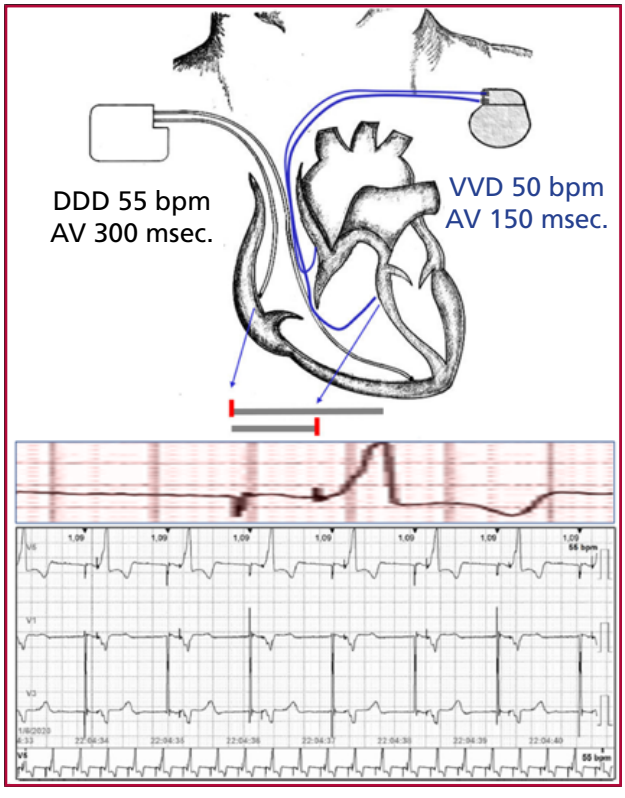

Fig. 2. Schematic representation of both system programming and the resulting Holter tracing

to traditional resynchronization with a three-chamber stimulation device. During implantation, use of SA-ECG software (Synchromax) was a rapid and useful tool to discriminate the slightest dyssynchrony and choose the best site to implant the catheter. In extreme sanitary emergencies we cannot always strictly apply therapeutic guidelines and are faced with the need of finding practical solutions that solve problems, if only temporarily. The previous system acted as support, and when a late and symptomatic failure of the new atrial catheter occurred during follow-up, telemetric reprogramming of the systems allowed maintaining dual-chamber stimulation.

Conflicts of interest

EXO (www.exo.com.ar/exo@exo.com.ar) provided on loan a Synchromax device to the Electrophysiology Unit of the Cardiology Service of Hospital Británico to investigate its clinical applications without any financial incentive or other obligation.

Ethical considerations

The patient granted informed consent to communicate her case.

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Femoral Mycotic Pseudoaneurysm Rupture by Salmonella

Mycotic pseudoaneurysms are a rare but severe disease due to their association with early rupture and high morbidity and mortality depending on the location. Salmonella is a frequent cause of this vascular pathology in patients with predisposing factors.

We present the case of a 72-year-old male patient with history of smoking, hypertension, dyslipidemia, coronary angioplasty with stent, and angioplasty with wallstent placement in the left common femoral artery more than 10 years ago, due to chronic obstructive artery disease with intermittent claudication. He consulted the medical emergency room for confusional syndrome, with fever (38°3 C). Laboratory tests revealed leukocytosis, 19.700 white blood cells/mm^3, and CRP 229 mg/L. He had negative serology for HIV and negative urine culture, and blood culture with 2/2 development of *Salmonella spp and S. paratyphi A.* typification. Brain computed axial tomography presented no pathological findings and CT angiography of the abdomen and pelvis evidenced a small 32 mm dilation in the infrarenal aorta. The echocardiogram showed LVEF 40%, without intracardiac vegetations. He started empiric antibiotic treatment with ceftriaxone and evolved afebrile, with a decrease in white blood cells, and negative blood cultures on the first and fifth day of antibiotic treatment.

On the ninth day, the patient suddenly presented arterial hypotension and pain in the left iliac fossa, associated with an 8-point hematocrit drop. Computed tomography angiography showed contained left common femoral artery pseudoaneurysm rupture, at the level of the wallstent implantation site, with a 15 x 7.5 cm retroperitoneal hematoma (Figure 1). Urgent 7 x 50 mm self-expanding stent graft (Viabahn®) implant was performed via contralateral femoral percutaneous access inside the walltent, which was permeable and undamaged, with evidence of contrast extravasation due to rupture of the arterial wall (Figure 2). The patient evolved afebrile, with negative blood cultures and cardiac Doppler echocardiography without vegetations; he completed 15 days of intravenous antibiotic treatment and then received ciprofloxacin 750 mg every 12 hours orally until completing 6 months. He is asymptomatic at 2-year follow-up.

The term "mycotic aneurysm or pseudoaneurysm" corresponds to an infective vascular disease, regardless of the type of germ and its pathophysiology.

The bacteriology of mycotic aneurysms has undergone constant change. In the pre-antibiotic era, the most common causes were syphilis and tuberculosis, while enterococci, streptococci, and pneumococci were responsible for the majority of mycotic aneurysms secondary to infective endocarditis. Currently, the most common germs in mycotic aneurysms are Staphylococcus aureus, followed by *Salmonella spp*. (1,2)

Salmonella spp are gram-negative bacteria that have a propensity to adhere to previously injured endothelial

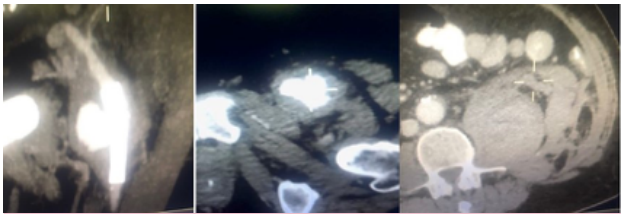

Fig. 1. Computed tomography angiography: contained rupture of a common femoral artery pseudoaneurysm at the level of the previous stent implantation site with ipsilateral retroperitoneal hematoma

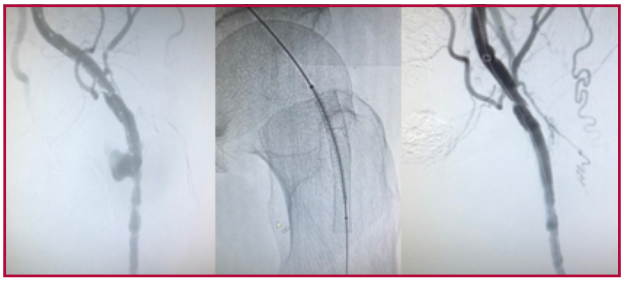

Fig. 2. Endovascular exclusion of the arterial rupture with a Viabahn covered stent, inside the previous intact and patent wallstent.

tissue. Sower and Whelan in 1962 found that *Salmonella* was the cause of mycotic aneurysm in a patient with preexisting atherosclerosis, and described the first successful treatment. Wang et al. in their series, also suggested that atherosclerotic plaques could predispose to *Salmonella* vascular infection and to subsequent pathogenesis of mycotic pseudoaneurysms. (3) In addition, these bacteria can colonize and cause infection of preexisting true aneurysms.

According to the literature up to 25% of adults over 50 years of age with Salmonella bacteremia develop a vascular infection. (3) Cases of aneurysms due to *Salmonella* in the literature were generally reported in men over 60 years, suffering from hypertension, diabetes mellitus, and atherosclerosis. (4) *Salmonella* pseudoaneurysm has also been reported in immunocompromised patients treated with corticosteroids. (5)

Traumatic or iatrogenic factors could cause endothelial damage, facilitating the possibility that bacteria from blood circulation invade the arterial wall developing a mycotic pseudoaneurysm.

In a recent series of *Salmonella* aneurysm, most patients presented, as the most frequent manifestations, recurrent fever associated with chills and pain at the aneurysm site. (4)

The diagnosis of mycotic pseudoaneurysm is confirmed by imaging studies, added in most cases to the isolation of the causative germ in blood culture and/or the aneurysm wall. However, the diagnosis should not be excluded in patients with negative cultures, since they could have received empirical broad-spectrum antibiotic therapy. (1,2)

Multislice computed tomography angiography is the imaging method of choice because it allows locating and characterizing vascular lesions, detecting complications, and surgical or endovascular treatment planning.

The anatomical location of mycotic *Salmonella* aneurysms was described, in order of frequency, in the infrarenal aorta, thoracic aorta, and iliac or distal vessels.

The complications of mycotic aneurysm caused by this germ are severe, including early rupture, which is the most frequent, septic embolism, and infected hematoma of the psoas in those located in the infrarenal aorta or iliac artery. (1,4,6)

In a recent review, Guo et al. found that the incidence of aneurysm rupture was 17.5%, lower than the previous 53% reported by Kam et al., which is attributed to an improvement in therapeutic procedures and an increase in diagnostic suspicion. (4,5)

The management of a mycotic pseudoaneurysm must be individualized, considering characteristics such as location, vascular anatomy, and patient's surgical risk.

Surgical therapeutic options include conventional surgery (local debridement and in situ or extra-anatomical revascularization), and endovascular treatments (covered stent implantation). Whatever therapy is chosen, it must always be associated with adequate antibiotic treatment (dose and duration) to reduce recurrence and improve survival. Untreated mycotic aneurysms or that receive antibiotic therapy as the only treatment have a fatal prognosis in most cases. (1,4)

Endovascular treatment offers faster recovery with less morbidity and mortality than conventional surgery, and is the first option in patients at high surgical risk.

However, open surgery was superior to endovascular treatment in the removal of infected foci and the reduction of recurrent infection in the late postoperative period.

The mortality rates, without discriminating the location, of mycotic aneurysms due to *Salmonella*, reported by Guo et al. were 21.4% and 7.1% for open surgery and endovascular intervention, with recurrent infection of 0% and 17.8%, respectively. (4)

It is known that mortality from mycotic aneurysms or pseudoaneurysms varies significantly according to their location. Karl Sörelius et al. reported a 5-year mortality rate of 40% in *Salmonella* mycotic aortic aneurysms undergoing endovascular treatment, with most events occurring within the first 90 days. However, they described a lower rate of infection recurrence, compared to mycotic aneurysms caused by other germs. (1)

In *Salmonella* mycotic aneurysms, intravenous or oral antibiotic treatment is recommended for 6 weeks, and it can be prolonged if positive blood cultures or elevated acute phase reactants persist. Long-term suppressive antibiotic therapy should also be considered in some cases, as for example in the endoprosthetic treatment of mycotic aortic aneurysm. (1.4)

Finally, strict follow-up of patients treated for a mycotic aneurysm or pseudoaneurysm is suggested, due to the risk of potentially fatal recurrent infections.

In conclusion, *Salmonella* is a frequent cause of mycotic aneurysm in any location, which should be suspected in men over 60 years of age with predisposing factors

such as hypertension, diabetes or atherosclerosis, who present with fever and/or pain associated with positive blood cultures. Due to its high morbidity and mortality, early surgical treatment (conventional or endovascular) is indicated, always accompanied by prolonged antibiotic therapy to prevent recurrence.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/ Supplementary material).

Ethical considerations

Not applicable

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Cardiac arrest due to electromechanical dissociation in patients treated with bortezomib. Two recent clinical cases at Basurto University Hospital

We present two recent cases of cardiac arrest at our center in patients with cardiac amyloidosis under treatment with bortezomib. The first case was a 40-year-old woman, smoker, with no relevant personal history. She was admitted to our center for a first episode of congestive heart failure. Among the complementary tests performed on admission, ECG showed low-voltage and pseudo-infarct pattern (Figure 1), NT-proBNP level of 2954 pg./mL and proteinogram with monoclonal kappa light chain peak together with a kappa/lambda light chain ratio of 25.8, suggestive of underlying hematological disease. The study was completed with an echocardiogram, which revealed preserved left ventricular systolic function, moderate concentric left ventricular hypertrophy and a "cherry on top" strain pattern (Figure 2) suggestive of light chain cardiac amyloidosis (AL), a diagnosis confirmed by endomyocardial biopsy. After hematological assessment, daratumumab + cyclophosphamide + bortezomib + dexamethasone in-hospital treatment was decided to evaluate its tolerance. On the next day following treatment administration the patient presented two syncopal episodes, practically one after the other, and she was transferred to the coronary care unit for close monitoring. An hour later, she had an initially hypotensive episode after a vagal stimulus (vomiting), followed by severe bradycardia and asystole. Advanced cardiopulmonary resuscitation (CPR) was performed, but without achieving spontaneous circulatory recovery, the patient finally died.

The second case corresponds to a 55-year-old male patient, smoker, hyperlipidemic, diagnosed 2 months ago with AL cardiac amyloidosis. The last echocardiogram had revealed moderate-severe left ventricular hypertrophy with preserved systolic function. Chemotherapy was initiated with cyclophosphamide and bortezomib. On the day of admission, he presented out-of-hospital cardiac arrest, with pulseless electrical activity. He was treated by an emergency service, and after 2 advanced CPR cycles, he recovered pulse, was sedated, intubated and transferred to our hospital. He stayed in the cardiac intensive care unit for 13 days, where therapeutic hypothermia was performed with favorable outcome, allowing extubation with no neurological sequelae. It was interpreted that the condition could have been triggered in part by bortezomib.

Cardiac amyloidosis is caused by amyloid deposits in the cardiac tissue. (1) Light chain cardiac amyloidosis develops due to the production of abnormally folded immunoglobulin light chains by B plasma cell clones associated with different lymphoproliferative disorders. (1) Practically any dyscrasia affecting B lymphocytes (myeloma, lymphoma, macroglobulinemia, etc.) can produce this monoclonal protein and elicit amyloidosis. (1) Sudden death, that is usually due more to electromechanical dissociation than to ventricular arrhythmias, is one of the clinical presentations in patients affected by this disease. (1) Bortezomib, a drug included in the group of protea-

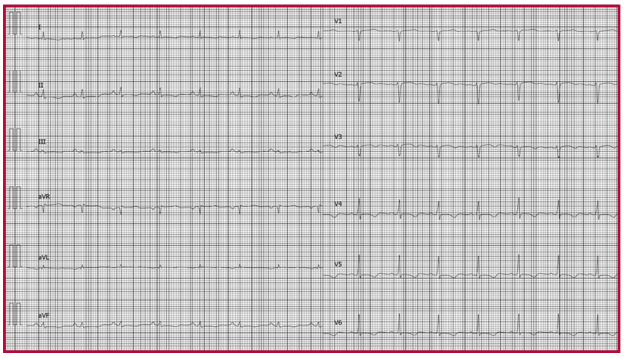

Fig. 1. Electrocardiogram showing sinus rhythm with relevant low voltage and pseudo-infarct pattern

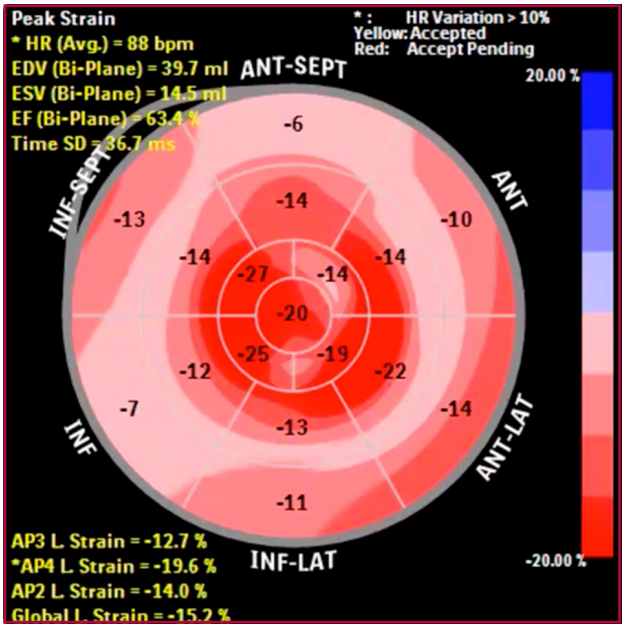

Fig. 2. Echocardiogram. Strain pattern with characteristic "cherry on top" image, suggestive of cardiac amyloidosis.

some inhibitors, has become, in combination with other agents, the treatment basis for patients with de novo multiple myeloma, as well as for maintenance or relapse/refractoriness phase therapy. (2) Despite being a widely used and effective agent, it may cause relevant adverse events: peripheral neuropathy, myelosuppression or cardiac/skeletal adverse events. (2) There are imprecise data on the potential cardiotoxicity of bortezomib, as this drug is occasionally used with other cardiotoxic agents, or in patients with cardiovascular disease risk factors, making it difficult to establish if the cardiovascular event is due solely to its use. (2) Nonetheless, several articles associating it with adverse cardiovascular events such as heart failure, conduction abnormalities as complete atrioventricular block, atrial fibrillation, ischemic heart disease, pericardial effusion, orthostatic hypotension, and even cardiac arrest in some case reports, have been published since its approval,. (2,3) In a 2014 meta-analysis including 5718 patients with a variety of neoplasms, bortezomib was not shown to increase the risk of cardiotoxicity compared with control, although in the subgroup analysis of patients with multiple myeloma, bortezomib was associated with greater cardiotoxicity with respect to patients without multiple myeloma treated with this drug. (4) It is difficult to demonstrate in a disease such as cardiac amyloidosis, which can elicit sudden death per se due to electromechanical dissociation, that death is secondary to a cardiotoxic effect of bortezomib. There are cases published in the literature in which death or syncopal events have been preceded by the administration of this drug. In our hospital we have seen several cardiac arrest episodes with fatal outcome after initiation of bortezomib treatment; in fact, in patients receiving this drug, the first cycles are administered under hospitalization and electrocardiographic monitoring. We should point out that in the first case the cardiac arrest occurred after a vagal stimulus, with initial hypotension and subsequent progressive bradycardia and asystole, similar to a cardioinhibitory syncope pattern, though in this case with ensuing death. There are isolated case reports in which intense vagal stimulation with underlying heart disease have resulted in death. (5,6) We consider this as a possible pathophysiological mechanism that could have triggered this event. In conclusion, we believe that the information should be expanded in this respect with future studies with an adequate sample size to clarify whether bortezomib can predispose to cardiac arrest, and also to understand the pathophysiological mechanisms of death in these cases. Until then, we will continue controlling our patients with close monitoring during the administration of these cycles to intervene in case adverse events appear.

Conflicts of interest

None declared.

(See authors' conflicts of interest forms on the website/Supplementary material).

Ethical considerations

Not applicable.

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