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BEGINNER

CASE REPORT: CLINICAL CASE

Late-Onset Infection in a Leadless Pacemaker

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ABSTRACT

Infection of leadless pacemakers (LPM) is rare, even in patients at high risk for infections. Only 3 cases of LPM infection have been documented in the literature, all occurring within 1 month of device implantation. We report the first case, to our knowledge, of late-onset LPM infection, developing almost 2 years after implantation. (**Level of Difficulty: Beginner.**) (J Am Coll Cardiol Case Rep 2022;4:101645) © 2022 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

An 89-year-old woman presented to the emergency department with generalized weakness, chest pain, and shortness of breath for 6 hours. Two days prior, she had been diagnosed with cellulitis of her right forearm and treated with oral cephalexin. Physical examination findings were unremarkable except for the presence of an arteriovenous graft on her right forearm, with faint erythema not involving the graft.

PAST MEDICAL HISTORY

The patient had a history of type 2 diabetes mellitus; heart failure with preserved ejection fraction; coronary artery disease; moderate aortic stenosis; end-stage renal disease, for which she was on hemodialysis via arteriovenous graft access; and seronegative rheumatoid arthritis, for which she was on daily prednisone and leflunomide. Approximately 1.5 years prior (558 days), the patient underwent atrioventricular node ablation and concomitant implantation of a leadless pacemaker (LPM) (Micra, Medtronic) because of episodes of junctional bradycardia and paroxysmal atrial fibrillation with rapid ventricular response refractory to maximally tolerated drug therapy. Despite a high risk of stroke (CHA_2DS_2-VASc score: 9), the patient was not anticoagulated because of a history of severe gastrointestinal bleeding.

LEARNING OBJECTIVES

- To demonstrate that LPM infection can occur late after device implantation.
- To show that agents that inhibit endothelialization, such as leflunomide, may predispose LPM to late infections.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis included acute coronary syndrome, decompensated heart failure, pulmonary embolism, worsening aortic stenosis, pacemaker malfunction, and sepsis.

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ABBREVIATIONS AND ACRONYMS

ECG = electrocardiogram

LPM = leadless pacemaker

RBB = right bundle branch

INVESTIGATIONS

The patient was normotensive (125/57 mm Hg) and afebrile (36.7 °C). Electrocardiogram (ECG) showed a ventricular paced rhythm at 60 beats/min. Troponin was mildly elevated (0.36 ng/mL), similar to prior values. Chest radiography findings were negative for pulmonary edema or infiltrates. Blood count revealed leukocytosis (23,380 leukocytes/μL). Empiric antibiotic therapy was initiated. Blood cultures grew methicillin-sensitive *Staphylococcus aureus*. Transthoracic echocardiogram showed no changes compared to a study done 1 year prior (left ventricular ejection fraction: 70%; aortic valve area: 1.28 cm^2). The LPM was not well visualized on transthoracic echocardiogram because of poor acoustic windows in its region (Video 1). A transesophageal echocardiogram was requested because of the presence of a pacemaker and revealed a vegetation on the mid to distal part of the LPM (**Figure 1,** Video 2), a vegetation vs Lambl's excrescence (fibrous strands at valvular coaptation sites) on the aortic valve, and a large thrombus within the left atrial appendage. During her inpatient course, the patient quickly deteriorated with lethargy and neurologic deficits. Brain computed tomography showed acute left cerebral infarcts and cerebritis, concerning for septic emboli.

MANAGEMENT

It was discussed with the patient's family that the infection would not resolve unless the LPM was extracted. However, given the patient's advanced age, comorbidities, cerebral infarcts, and extremely frail status, the family declined invasive procedures, so the device was not extracted, and the patient was transitioned to comfort care.

DISCUSSION

We report a case of infection of an LPM 1.5 years after its implantation in an immunocompromised (on prednisone/leflunomide) patient on dialysis. The infection was likely caused by hematogenous bacterial seeding of the device in the setting of bacteremia following a forearm skin infection. To our knowledge, this is the first reported case of late-onset infection in an LPM.

LPMs are known for their resistance to infection. Although transvenous pacemakers have an infection rate ranging from 0.7% to 2.1%, no cases of LPM infection were reported in clinical trials enrolling more than 3,000 patients.[1] Studies including patients with high risk for cardiac device infection (eg, diabetes, cancer, end-stage renal disease, bacteremia, endocarditis) also did not report LPM infections.[1,2]

There are only 3 cases of documented LPM infection reported in the literature, all occurring within 30 days of device implantation. In 2 of these cases, the LPM had been implanted immediately following explantation of an infected transvenous device. In all 3 cases, the LPM was extracted, and infection was then successfully cleared.[3-5]

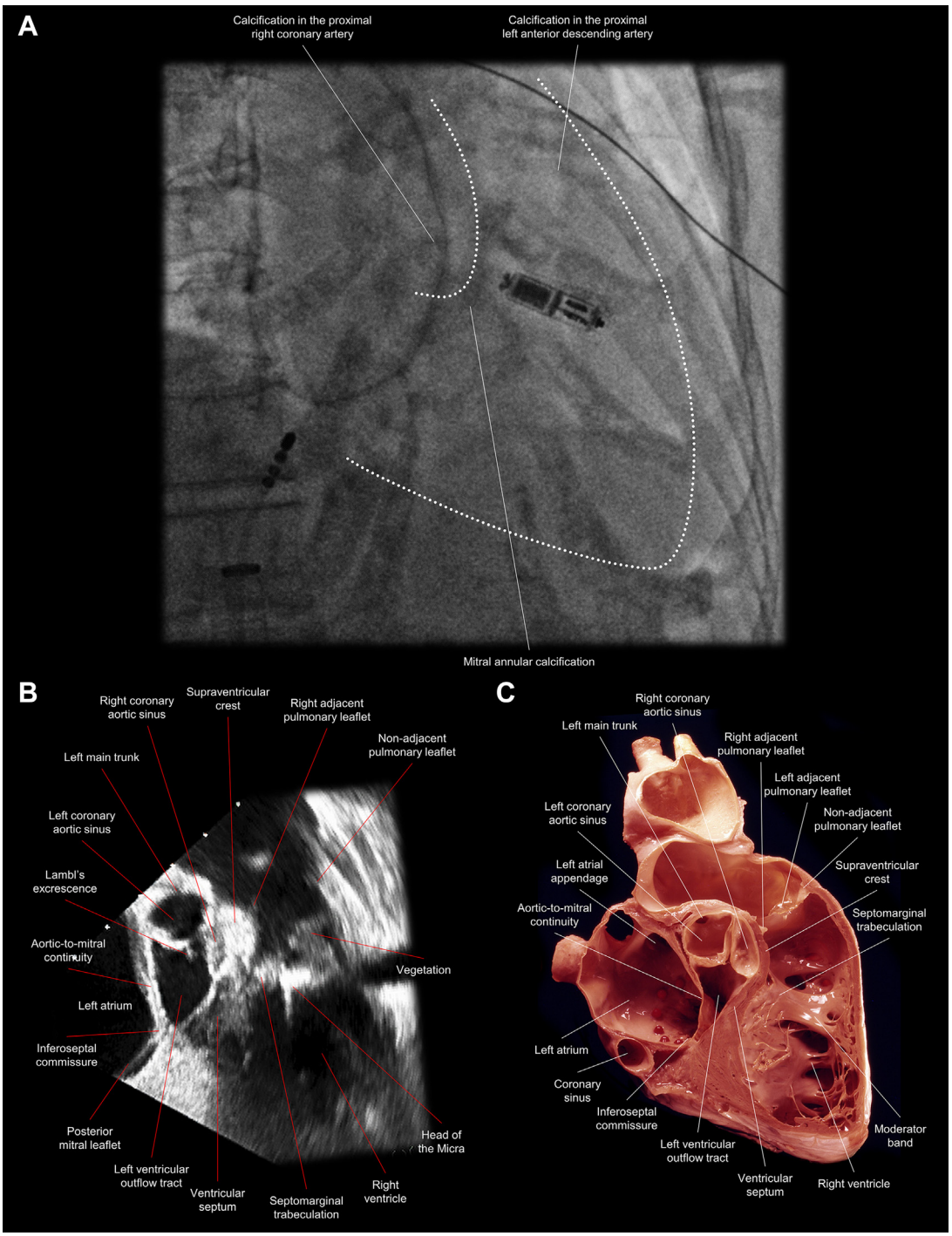
The mechanisms that explain the apparent resistance of LPMs to infection are still not fully understood, but encapsulation (endothelialization) of the LPM probably plays a pivotal role by reducing or eliminating the surface area of the device exposed to the bloodstream, thus preventing pathogens from accessing the device to seed infection.[1] Presumably, LPMs are completely endothelialized around 4 months after implantation.[6] All 3 previously documented cases of LPM infection occurred early, within 1 month of device implantation, at a time when full endothelialization of the device is not expected.

The infection in our case occurred 558 days after device implantation; therefore, our case is the first reported case of an LPM late infection ("late" defined here as infection more than 1 month after implantation). Our patient did not undergo autopsy, so we cannot confirm whether the device was fully endothelialized, but failure to endothelialize remains the most likely explanation in this case. A primary contributing factor was likely leflunomide use, a pyrimidine synthesis inhibitor agent, which has been shown to disrupt normal endothelial cell proliferation and migration.[7]

The lack of histologic diagnosis may raise the possibility that the mobile echodensity attached to the LPM was a thrombus (or a secondarily infected thrombus) rather than a vegetation. The ability of echocardiography to distinguish between vegetation and thrombi is limited; however, prior reports of LPM-attached thrombi were thin adherent structures representing various stages of fibrotic encapsulation and endothelization.[8] A mass-like echodensity, as was seen in our patient, in the setting of *Staphylococcus aureus* bacteremia made a vegetation much more likely, also similar to descriptions of the previously reported LPM infections.[3,4]

An interesting observation in our case is that, compared with previous ECGs, the patient's ECG following device infection showed possible right bundle branch (RBB) injury (**Figure 2**). Considering that the LPM had been implanted adjacent to the moderator band (**Figure 1,** Videos 2 and 3),

FIGURE 1 **Comparative Images Showing the Anatomic Location of the Leadless Pacemaker and a Large Vegetation Attached to It**



(A) A right anterior oblique fluoroscopic view shows that the leadless pacemaker was implanted along the septomarginal trabeculation, at the base of the moderator band; white dots delineate the right ventricle and pulmonary root. **(B)** A transesophageal echocardiographic view of the corresponding sectional plane shows a large vegetation (1.4 × 0.8 cm) attached to the mid to distal part of the leadless pacemaker and extending toward the pulmonary valve. **(C)** An anatomic image shows the corresponding sagittal plane of the right ventricular outflow tract. (Illustration courtesy of UCLA Cardiac Arrhythmia Center, Wallace A. McAlpine MD Collection.)

FIGURE 2 The 12-Lead Electrocardiogram Before and After Leadless Pacemaker Infection, Suggesting Right Bundle Branch Injury

Although the change is minor, the appearance of a positive notch within the QRS complex of V_1, indicative of a delay in right ventricular depolarization, may be caused by an infectious involvement of the right bundle branch in the setting of right ventricular septal pacing near the base of the moderator band. An alternative explanation for the notch would be that it represents a myocardial scar or anisotropic conduction in the setting of chronic or acute hemodynamic shifts, given that the V_1 voltage dropped from 14 mV to 10 mV and the P-wave developed a deeper negative deflection suggestive of a P-mitrale pattern. The electrocardiograms were recorded 9 months apart and, for the low- and high-pass filters, were set at 150 Hz and 0.05 Hz, respectively. Of note, the shift in precordial transition (V_5 preinfection vs V_4 during infection) seems to reflect only changes in the position of the leads, as this shift was not consistent across serial electrocardiograms.

which contains the RBB, it is possible that the RBB was damaged because of contiguous infection of the ventricular tissue in contact with the device.

FOLLOW-UP

The patient died 3 days after the transition to palliative care.

CONCLUSIONS

Infection of LPMs is rare, and the only 3 documented cases occurred within 1 month of device implantation. We reported the first case of late-onset infection in an LPM, 1.5 years after its implantation.

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KEY WORDS **cardiac implantable electronic device, infection, leadless pacemaker**

APPENDIX **For supplemental videos, please see the online version of this paper.**