First-in-man implantation of a gold-coated biventricular defibrillator: Difficult differential diagnosis of metal hypersensitivity reaction vs chronic device infection

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Introduction
Regardless of the success story of cardiac pacing, the majority of the delayed complications of cardiac device implantations are systemic infections. The incidence of pacemaker infections is described with wide ranges between 0.13% and 19.9% of implants.1 In almost all cases, device infection leads to timely removal of the device, including the electrodes. Furthermore, the infectious process can be complicated by generalization (sepsis) and colonization of the heart valves.2 Unfortunately, owing to biofilm formation on foreign body surfaces, detection of probable pathogens can be difficult, resulting in a high rate of microbiologically false-negative samples. Clinically, a device infection usually presents as dermatitis with skin reddening, itching, local pain, and swelling.1

Besides bacterial infection, a rare differential diagnosis of metal allergy to components of the device, including electrodes, has to be taken into account. An allergic dermatitis can be hard to differentiate from local appearances of infection, but it is not associated with fever or leukocytosis and goes along with negative blood cultures and inconspicuous intraoperative swabs. The prevalence of delayed-type hypersensitivity has been estimated at approximately 1.5% to 2.5% of chronic implantable electronic devices (CIED).1,3

Pacemaker housings are predominantly made of an alloy usually consisting of over 99% titanium with trace levels of other metals. Although contact hypersensitivity reaction to metals is common in Europe, affecting 27% of the general population, isolated titanium allergy is rare in the field of type IV allergic reactions. Nevertheless, in a recent cohort study 11 of 24 patients (46%) developed a hypersensitivity to titanium when examined by lymphocyte transformation test.1 The scheme of Gell and Coombs3 for hypersensitivity reactions (1963) classifies type IV to be a cell-mediated immunity with delayed response. This process is mediated by T-cell lymphocytes and is most probably responsible for contact dermatitis to metals.4

Avoiding titanium exposure to the body tissue can only be achieved by sheathing of the device surface. Besides using biocompatible polymers, there are individual reports of gold coating. Gold plays a significant role in medical implants, especially in patients with allergic reactions to implant material as well as patients at risk of infection, owing to its excellent biocompatibility, anti-inflammatory properties, and high resistance to bacterial colonization.

Case report
We report implantable cardioverter defibrillator (ICD) implantation using a gold-coated device following evidence of titanium hypersensitivity, thereby illustrating the difficult differential diagnosis of metal allergy vs chronic device infection.

The patient is a 64-year-old man who underwent cardiac resynchronization therapy defibrillator explantation twice owing to suspected local pocket infection. In a third attempt, a gold-coated device was implanted.

He suffered from an ischemic cardiomyopathy with significant reduction of the left ventricular ejection function (echocardiographic <25%) and heart failure in clinical-stage New York Heart Association (NYHA) class III–IV.

Electrocardiographically, he presented with first- to second-degree atioventricular block, broad left bundle branch block (QRS width 168 ms), and echocardiographic signs of desynchronization.

Therefore, we implanted a biventricular ICD (Amplia; Medtronic, Minneapolis, MN) in a left pectoral submuscular pocket in January 2018. Within a short time period, the patient reported a pronounced clinical benefit in response to
biventricular pacing, leading to an improvement of heart failure class from NYHA stage III to I. Four weeks later, minimal redness at the implantation site developed without any signs of systemic infection. Owing to aggravation of the local signs, the system was explanted 8 weeks after implantation, combined with an appropriate antimicrobial therapy of systemic infection. Owing to aggravation of the local redness at the implantation site developed without any signs of inflammation parameters were unchanged with mildly increased C-reactive protein and normal procalcitonin levels and leukocyte count, but a mild hypereosinophilia.

To exclude maintenance of subclinical infection deriving from the left-sided knee endoprosthesis, open synovial biopsy was performed by arthroscopy. The microbiological culture of the specimen remained sterile. The dental focus of periodontitis was extracted. The loss of biventricular pacing led to a significant clinical deterioration, twice with hospitalization for heart failure decompensation, illustrating the clinical benefit of cardiac resynchronization. Therefore, not implanting a new endovascular system seemed to be inappropriate, in concordance with the patient’s preference. We discussed the clinical problem in the members’ forum of the Heart Rhythm Society. An independent skin disease (pyoderma gangrenosa) could not be confirmed. The dermatologic skin patch testing failed to demonstrate the expected typical dermatitis due to titanium allergy in a short exposure period. Prolonging the exposition beyond 72 hours has the downside of promoting unspecific reactions, as well as mechanical alterations in response to metal chips scratched into the skin, and was therefore refused by the consulting allergologist. Although infection with coagulase-negative staphylococci (CoNS) could not be fully excluded, in the absence of any systemic inflammatory reaction a rare but plausible differential diagnosis was found in a metal contact allergy to titanium. After extensive discussion and consultations with the manufacturer, we decided to order a gold coating of the device for the third procedure.

In contrast to pacemaker devices, the ICD has a greater surface. The coating gold layer is applied through an argon-assisted vapor deposition process. The thickness of the layer, including the initial adhesion layer, does not exceed 8.000 angstrom (= 0.8 μm), thereby not impacting defibrillation function. Of clinical relevance is that the consistency of the gold layer cannot be guaranteed by the manufacturer following an ICD shock (manufacturer’s communication).

The implantation of the gold-coated Viva XT (Medtronic, Minneapolis, MN) defibrillator in a left pectoral submuscular pocket and polyurethane-sheathed electrodes was performed in September 2019 (Figure 2). Repeated positron emission tomography / computed tomography scan did not show any
infectious focus. Antibiotic prophylaxis consisted of cefazolin. The generator was placed in a submuscular pocket, wrapped in a commercial antimicrobially coated envelope (Tryx). Our patient was discharged from the hospital with inconspicuous local appearance without hematoma.

On follow-up in January 2020, the pocket and the scar showed no irritation; resumption of resynchronization was accompanied by a complete recovery of his exertion capacity.

Discussion

The allergic reaction to components of an ICD is a rare differential diagnosis to a systemic infection. In our case 2 operative revisions were driven by the suspicion of infection. Early inflammation of a generator pocket infection is hard to differentiate from noninfectious skin reaction. However, early explantation of a colonized CIED prevents life-threatening infectious generalization with a mortality rising to 6%–15% with systemic inflammation. The differentiation of the underlying cause is even more complicated because foreign bodies are mainly colonized by commensals of the physiological skin flora, mainly CoNS.6 Colonization of a CIED can occur via hands of anyone handling the device or airborne from the operation room.2,7 Contamination of the microbiological culture can take place during sampling, transport, or culture processing. To solve this problem extensive microbiological culturing has to be implemented to any discharging wound by obtaining bedside blood cultures, intraoperative swabs and performing microbiological culture of the explanted material. Recently it has been shown that consistent species detection from at least 2 different sites is indicative for causative infectious organisms. For CoNS (n = 64) concordance of each culture to causative organism was demonstrated for blood, lead, and pocket swabs as 87%, 78%, and 67%. An exclusive positive pocket swab was considered as not consistently reliable.8 In any case, the clinical situation, guideline-conforming handling, and the necessity to avoid generalization by early device and electrode extraction do not allow to wait for the spontaneous course to achieve an etiological differentiation.

An allergic mechanism was suggested by the laboratory finding of mild hypereosinophilia without general leukocytosis in November 2018 before the second explantation procedure, and the fluorodeoxyglucose uptake surrounding the knee prosthesis in addition to the device region.

Although a pacemaker metal allergy was reported as early as 1970,9 it is a rare event. Only extensive diagnostic investigations can substantiate the suspicion of metal allergy.10 Besides its mechanical qualities, titanium is largely regarded as a weak sensitizer for body tissue and is therefore used for numerous implants. A negative allergy test does not exclude hypersensitivity to titanium.11,12 Patch testing with titanium is the gold standard in diagnostics, but is not yet well standardized. Thus, after exclusion of a local infection as far as possible, the suspicion of a titanium allergy remains a possible differential diagnosis. Nevertheless, a local infection cannot be completely excluded at any time.

To our best knowledge, this is the first case of implantation of a gold-coated biventricular defibrillator.13 Owing to the sparse literature, we discussed the problem in the membership forum of the Heart Rhythm Society and got valuable contributions from the participants. Proposed solutions included not performing a new implantation, which seemed to be not suitable with regard to the clinical effect. Repeatedly, the existence of an independent dermatological disease and a subclinical infection eluding microbiological examinations were included in the considerations. Finally, there was the recommendation for plastic or gold coating of the system.

Obviously, only the very long-term clinical course will provide the answer to the question whether avoiding contact with the titanium surface will solve the problem. Our case report exemplifies the long-lasting ordeal of patients with a rare differential diagnosis, leading to extensive interventions (eg, repeated cardiac device procedures and surgical interventions elsewhere) to exclude an infectious focus. Owing to the rarity of a clinically relevant hypersensitivity, the high frequency of competing infection, and the exclusive way of diagnosing an allergic reaction, these courses are often tedious and complicated. Clinical suspicion is the most important step in differential diagnosis.11

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