B-Cell lymphoma at the site of pacemaker generator

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Introduction

The total number of cardiovascular implantable electric devices (CIEDs) has reached more than 1 million implants per year.[1,2] Comparatively, cases citing the development of non-Hodgkin lymphoma (NHL) in pacemaker and implantable cardioverter-defibrillator pockets are extremely rare. The following is a discussion of the pathomechanism of this rare infection.

Case report

An 81-year-old man with a history of hypertension and sick sinus syndrome had a dual-chamber pacemaker (VDD, active fixation Guidant 4457 lead) implanted on the right side following syncope 14 years previously. Apart from a history of hypertension and surgical treatment of an intervertebral disk, the patient's medical records were unremarkable. Ten years after pacemaker implantation, a superficially spreading malignant melanoma localized paravertebrally was excised. Owing to battery depletion, a generator exchange was performed 12 years later with downgrade to a single-chamber pacemaker (VVI), as the patient had developed permanent atrial fibrillation and bradyarrhythmia. Two years later, the patient noticed a swelling in the pacemaker-lodging pocket that had developed over a 3-week period. He denied fever, and blood cultures were negative. The local clinical examination was atypical for infection. The skin in direct proximity to the scar was slightly reddened, but no differences in skin temperature could be assessed. The swelling was located caudally and somewhat distant to the generator and appeared to be elastic without fluctuation, 4 cm × 3 cm in diameter (Figure 1).

The patient's laboratory findings showed unsuspicious C-reactive protein (4.4 mg/L), leukocyte count (6.99/nL), and lactate dehydrogenase (268 U/L). No vegetations were detected by transthoracic or transesophageal echocardiography. Although we could not confirm the presence of infection, the patient was scheduled for removal of the device. No antibiotic medication was given prior to surgery.

The generator was surgically removed and the lead extracted using a locking stylet and a 14 French laser sheath (Spectranetics, Colorado Springs, CO). There were no signs of infection and no purulent fluid was found. Peculiar friable, lipomatous beige-brown tissue surrounding the generator pocket was excised. The microbiological workup was negative for smears taken at the pocket site and the suture sleeve, but *Staphylococcus epidermidis* was cultured from the tip of the lead after prolonged incubation. Histological workup revealed a diffuse large-cell B-cell lymphoma. Immunohistochemical studies confirmed these cells to be B cells expressing CD20, CD3, BCL6, BCL2, and MUM1, with proliferation index KI67 97% (Figure 2). Staging revealed no further locations of the lymphoma. The patient received R-CHOP chemotherapy (rituximab, cyclophosphamide, hydroxydaunomycin, vincristine, prednisone) and radiation therapy. We implanted a Micra transcatheter pacing system (Medtronic Inc, Minneapolis, MN) prior to the patient's hospital discharge. He is doing well, with no signs of recurrence after follow-up for more than 1 year.

Discussion

Even though very uncommon, NHL has been known to develop near CIEDs. The question arises whether this condition may be related to a specific pathomechanism.

Ten patients with NHL following pacemaker and CIED implantation (including our study patient) were identified through literature research (Table 1).

The patients that were documented as having developed NHL were all male. The average age of the patients was 71.5 (mean 74) years. Pacemakers were involved in 5 cases (1 single-chamber, 4 dual-chamber) and implantable cardioverter-defibrillators in 5 cases (3 single-chamber, 2 dual-chamber). Device dwelling time was 94 months (range, 7–240 weeks). Repeat CIED surgery occurred for 6 patients, and the time elapsed from the most recent repeat CIED surgery was 58.5 months (range, 2–216 months). Five patients received implantations on the left side, 2 patients received right-sided implantation, and the implantation side was unidentified for 3 patients.

KEYWORDS Cardiovascular implantable electronic device; Implantable cardioverter-defibrillator; Infection; Lead extraction; Non-Hodgkin lymphoma; Pacemaker
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KEY TEACHING POINTS

- Pocket infections of cardiovascular implantable electric devices (CIED), even years after implantation, are increasing. Explantation of the devices is commonly accepted, even without confirmation of an infection.
- The presentation of non-Hodgkin lymphoma presenting 2 years after generator exchange broadens the differential in circumstances where chronic, smoldering infection is considered.
- Histological analysis of tissue specimens from the pocket wound should be considered, as well as the collection of wound and lead smears at the time of CIED procedures.

A history of CIED infection was observed in only 1 patient. Swelling at the pocket site seemed to be the most common clinical sign. The proximal end of abandoned leads eroding through the tumor was reported for 1 patient. Most patients claimed no systemic clinical signs. Fever was observed in 2 patients. A history of a malignant disease prior to the current lymphoma at the pocket site was observed in 2 patients. One patient had a history of bilateral lung transplantation.

The number of pacemakers and implantable cardioverter-defibrillators implanted annually worldwide is difficult to determine, even more so when considering the number of patients treated in the past. NHL has a wide range of histological appearances and heterogenous clinical features.[3]

Hojo and colleagues[4] suggested chronic inflammatory stimulation as an agent for NHL at the site of a CIED. However, the author did not mention a history of infection at the site of CIED implant. The authors also failed to state any signs of infection, either as positive blood culture or as a positive microbiological smear of the pacemaker pocket. The same can be said for the case reported by Moruzzo and colleagues,[5] who described an NHL following chronic inflammation of a pacemaker pocket. They also failed to mention any microbiological proof of infection. *Staphylococcus epidermidis* was faintly grown from the tip of the lead extracted from our patient after prolonged incubation. We considered the microbiological finding most likely to be a contaminant from the extraction process.

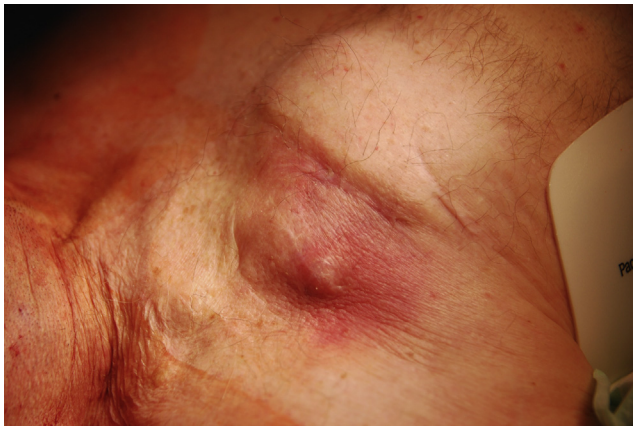

Figure 1 Local image of pacemaker pocket. Note the slightly reddened skin surrounding the scar and the swelling of the generator pocket caudally.

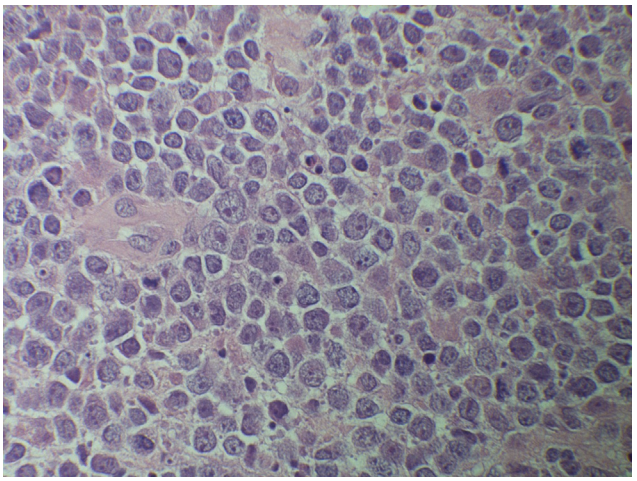

Figure 2 Lymphoma cells, hematoxylin–eosin, magnification ×200.

The incidence of NHL is estimated to be approximately 5.5 per 100,000 men and women per year.[6] Primary cardiac lymphomas represent about 1% to 5.6% of all primary cardiac tumors, whereas cardiac localizations of systemic NHL are much more frequent, representing 20% to 28% of secondary cardiac neoplasms.[7] Overall, these are rare events. Lymphomas at the site of previous cardiac surgery have been described in only a few cases.[8–10]

Smoldering infection is occasionally found in repeat CIED surgery and lead extraction. In addition to the generator pocket itself, suture sleeves or lead tips located away from the generator pocket are often involved. However, clinical signs of malignancy were scarcely found. The authors admit that samples for histological workup are rarely retrieved.

Table 1 Citations of non-Hodgkin lymphoma in cardiovascular implantable electric device pockets

Author	Year	Journal	Country
Hojo N	2003	Int J Hematol	Japan
Nemec J	2008	Pace	USA
Moruzzo D	2009	Leuk Lymphoma	Europe Italy
Nayar V	2010	Europace	Europe Great Britain
Kojodjojo P	2011	Europace	USA
Patris V	2014	J Card Surg	Europe Greece
Snorek M	2017	BMC Cardiovasc Disord	Europe Czech Republic
Zarifi C	2018	J Cardiol Cases	USA
Fleißner F	2018	J Thorac Cardiovasc Surg Rep	Europe Germany
Keyser A	2020	HeartRhythm Case Rep	Europe Germany

Infection has an influence on the development of some lymphomas, either by inhibition of immune function or by induction of chronic inflammatory response. Namely, Epstein-Barr virus, *Helicobacter pylori*, hepatitis C virus, *Borrelia burgdorferi*, and *Chlamydia psittaci* have been associated with the development of lymphomas.[11] Considering that only 10 patients have been described as developing an NHL at the generator site, with 1 of these patients having a history of infection and 1 having a history of NHL, and considering the number of patients overall treated with CIEDs, a causal relationship between CIED and the development of NHL remains rather unlikely.

The authors address several limitations. The systemic literature research of patients with NHL at the site of their CIED might not be exhaustive. Not all suspicious tissues in patients with repeat CIED procedures may have been analyzed by institutions dealing with CIED procedures, nor can we assume that all findings of NHL found in the setting of CIEDs have been published.

Conclusion

The number of patients developing NHL at the site of CIED is minuscule. The cause of development of NHL related to CIEDs remains uncertain. Thus, further insights considering the pathomechanism of the development of NHL at the site of CIED pockets should be obtained. In patients with an unusual appearance of the pocket tissue, histological analysis of tissue specimens removed from the pocket should be considered, as well as taking smears of the wound and leads at the time of the CIED procedure.

Acknowledgments

The authors certify that they have obtained the appropriate patient consent form in which the patient has given his consent for use of his images and other clinical information to be reported in the journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

The Ethics Committee of the University of Regensburg approved the retrospective analysis (reference number 19-1485-104). This institutional review board waived the need for informed consent.

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

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