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CASE REPORT

[^{99m}Tc]Tc-HMPAO-WBC detection of cardiac implantable electronic device infection mimicking nST acute myocardial infarction

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ABSTRACT

Cardiac implantable electronic device infection (CIED) is a rare complication, ranging from 0.5-1% in the first 6-12 months after device implantation. In the absence of a standardized protocol, the diagnosis of CIED infection is difficult due to a nonspecific clinical presentation. In some cases, the inflammatory process can mimicking as another cardiovascular disorder, including acute myocardial infarction. Today, the diagnosis of infection is based on the Duke criteria, including clinical, microbiological and echocardiographic data. However, the diagnostic accuracy of the criteria for device-related infective endocarditis is significantly reduced. Presented clinical case highlights the importance of increased vigilance in patients who have undergone device implantation and, in particular device replacement, and the usefulness of nuclear imaging techniques in asymptomatic patients or patients with an atypical clinical picture.

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INTRODUCTION

Early and effective diagnosis of infectious complications after pacemaker implantation is a difficult and important problem for modern medicine. The prognosis of cardiac implantable electronic device (CIED) infection largely depends on the timeliness of diagnosis, which is based on the modified Duke criteria, including clinical, microbiological, and echocardiographic features [1]. The sensitivity of the criteria is no more than 80% or lower. In recent years, the quality of diagnosis of IE has improved significantly due to a widening of the spectrum of imaging modalities. The use of high-resolution imaging equipment allows early detection of endocardial lesions and embolic complications. In 2015, the diagnostic algorithm for CIED infection positron emission computed tomography/CT with ^{18}F-fluorodeoxyglucose (2-[^{18}F]FDG PET/CT) and single-photon emission computed tomography (SPECT/CT) with ^{99m}Tc or ^{111}In labelled leucocytes was introduced [1]. However, these imaging methods are still limited in use in asymptomatic patients or patients with an unclear clinical picture.

CASE REPORT

A 78-year-old man was admitted to the hospital by the ambulance with complaints on chest pain, breathlessness and increased blood pressure up to 160/100 mmHg.

He had a history of Grade I hypertension (about 20 years), persistent atrial fibrillation and three ineffective MAZE procedures (at 2011, 2014 and 2015 year). An Evia DR-T (BIOTRONIK, UK) pacemaker providing permanent dual-chamber stimulation was implanted in 2015. In 2016, the atrial electrode has been reimplanted to a new Selox SR53 because of its dislocation. Since 2017, the patient has noted inspiratory dyspnea and a decreasing of exercise tolerance.

Interpretation of the ECG performed in the emergency department was impossible, as the heart rhythm was controlled by cardiac implantable electronic device (CIED). However, the presence of extrasystoles indicated the CIED malfunction (Figure 1A). The dynamic of biochemical blood markers is shown in Table 1, which demonstrates that there was an increase of high-sensitivity Troponin-I (hsTn-I) level with normal values of other markers of myocardial damage. Within one hour of admission the patient underwent selective diagnostic coronary angiography, which identified 50% stenosis of the 1st obtuse marginal brunch (OMB1), 40% stenosis of the 2nd obtuse marginal brunch (OMB2), 40% stenosis of proximal segment of right coronary artery (RCA) and 30% stenosis of proximal segment of left anterior descending artery (LAD). According to the Thrombolysis in Myocardial Infarction (TIMI) Risk Score, blood flow was 3 in all arteries. Transthoracic echocardiography (TTE) showed atrial dilatation, akinesis of the anterioseptal wall of left ventricle (LV), hypokinesis of the anterior left ventricle (LV) wall and decreasing of left ventricle ejection fraction (LV EF) up to 55%. The end-diastolic volume (EDV) and end-systolic volume (ESV) were 129 ml and 64 ml, respectively. Based on the history, complaints and the results of laboratory and instrumental examination tests, the patient was diagnosed with acute anterior non-Q myocardial infarction without ST-segment elevation. The patient was treated with antiplatelet and anticoagulant therapy, nitrates and beta-blockers [2]. On the 7th day, the patient was discharged from the clinic in a satisfactory condition.

Three weeks later, the patient was again admitted to the emergency unit with moderate chest pain and was hospitalized with a suspected recurrent myocardial infarction. Upon entry to the clinic, hsTn-I was elevated to 0.480 ng/ml with normal creatine kinase (CK) and creatine kinase myocardial band isoenzyme (CK-MB) levels (78 units/l and 11.7 units/l, respectively) and no specific ECG changes (Figure 1B). In the blood, analysis showed an increase of the erythrocyte sedimentation rate up to 25 mm/hour. TTE showed retention of akinesis of the anterioseptal wall of left ventricle and hypokinesis of the anterior left ventricle (LV) wall. LV EF was 55%, EDV 129 ml, ESV 64 ml. No vegetations on the valve, leads or electrodes were visualized. The patient was observed in the hospital for one week. The laboratory findings during the second hospitalization are shown in Table 2.

Based on the patient's complaints, history and laboratory findings, the diagnosis of recurrent acute myocardial infarction was unlikely. At the same time, persistent elevation of hsTn-I with normal values of other cardiac-specific enzymes indicated the presence of myocardial damage. Moreover, the presence of zones of local LV contractility abnormalities and decreased LV EF required the exclusion cardiac inflammation. Transesophageal echocardiography (TEE) could not be performed due to a severe gag reflex. Cardiac magnetic resonance imaging (CMR) was contraindicated to the patient because of the

implanted cardiac device. On this reason, a scintigraphy with [^{99m}Tc]Tc-HMPAO labelled leukocytes was performed on the seventh day of hospitalization.

Preparation and quality control of white blood cells (WBC) labelled with [^{99m}Tc]Tc-HMPAO was performed in accordance with EANM Guidelines [3]. The first whole body scan was acquired at 30 minutes after an intravenous infusion of 300MBq of [^{99m}Tc]Tc-HMPAO -WBC using a dual-detector Philips Forte SPECT scanner (Philips Medical Systems, The Netherlands).

Further SPECT/CT images were obtained using SPECT/CT scanner GE Discovery NM/CT 570c (GE Healthcare, Milwaukee, WI, USA) equipped CZT detectors at 4 (early images) and 24 hours (delayed images) after injection of labelled WBC [4]. After reconstruction of the early scintigraphic images and overlap with CT images a low intensity uptake of labelled WBC in the right atrium, in the area of the CIED electrode placement was found (Figure 2). After 24 hours, an intense focal uptake of the labelled leukocytes collocated with the previously defined area was found. Moreover, along the atrial-ventricular lead and in the ventricular electrode position, additional foci of labelled WBC uptake were registered (Figure 3).

Repeated TEE (with Midazolam medication, 0.025 mg/kg intramuscular, 30 minutes before the examination) was successful and showed an atrial electrode vegetations up to 6-7 mm. However, multiple microbiological blood tests were performed five times, but no bacterial growth was found.

Based on the results of the TEE and SPECT/CT as well as on clinical and laboratory findings, the patient was diagnosed with cardiac device-related infective endocarditis (CDRIE). Therefore, serum presepsin levels were additionally estimated which exceeded the upper reference limit by three times (544 pg/ml) and procalcitonin test indicated a systemic infection.

According to 2015 ESC Guidelines for the management of infective endocarditis [1] two large Duke criteria confirm a final diagnosis of the disease. In this case, these were abnormal [^{99m}Tc]Tc-HMPAO-autoleukocyte uptake and the atrial electrode vegetation, which allowed to start an antibiotic therapy. The patient was treated with Vancomycin 500 mg intravenous drip twice daily (9 days).

The patient was consulted by endovascular surgeon and an arrhythmologist. According to their consensus extraction of electrodes following by their reimplantation was recommended to the patient after the end of the antibiotic therapy. However, the patient refused the intervention, because he noted an improvement in health, particularly reduction in dyspnea and chest pain. Also, hsTn-I and CRP levels decreased, that's why the patient was discharged with the recommendation to continue antibiotic therapy with Linezolid.

Table 1. Dynamics of blood enzymes during the first hospital admission

Values	Checkpoints				
	At admission	2nd day	4th day	6th day	Reference
White blood cells (×109/l)	4.2		3.45	3.77	4.00-9.00
Neutrophils, %	64.7		53.9	58.6	47-72
Lymphocytes, %	32.8		32.8	27.6	49-40
Monocytes, %	10.4		10.4	9.8	3-11
ESR, mm/h	6		6	7	2-12
CK, U/L	102	87	96	101	24-145
CK-MB, U/L	17	13	13.7	13.6	0-25
CRP, mg/l		13		10	<5
hsTn-I, ng/ml	0.39	0.34	0.93	1.1	0-0.04
Glucose, mmol/l	6.9		4.49	5.21	3.8-6.10
HDL, mmol/l	1.3				>1
LDL, mmol/l	2.10				<3
Cholesterol, mmol/l	3.6				3.5-5.20
Triglycerides, mmol/l	0.43				0.15-1.7

Table 2. Dynamics of biochemical blood values during the second hospitalization

Values	Checkpoints				
	At admission	7th day	[^{99m}Tc]Tc - HMPAO leukocytes SPECT/CT (7th day) Start of antibiotic therapy (8th day)	10th day	12th day	16th day
White blood cells (×109/l)	4.58	5.64		5.13	5.25	4.77
ESR, mm/h	25	26		24	19	15
CRP, mg/l	13.1	23.3		43.5		25
CK, U/L	78	78		83	63	59
CK-MB, U/L	10.8	11.7		10.9	10.7	10.5
hsTn-I, ng/ml	0.48	0.54		0.44	0.36	0.31
Presepsin, pg/ml (reference 0-209 pg/ml)				544		426
Procalcitonin test, ng/ml				>0.5		
D-dimer, ng/ml		<250				
Nitriuretic peptide, pg/ml	2830					

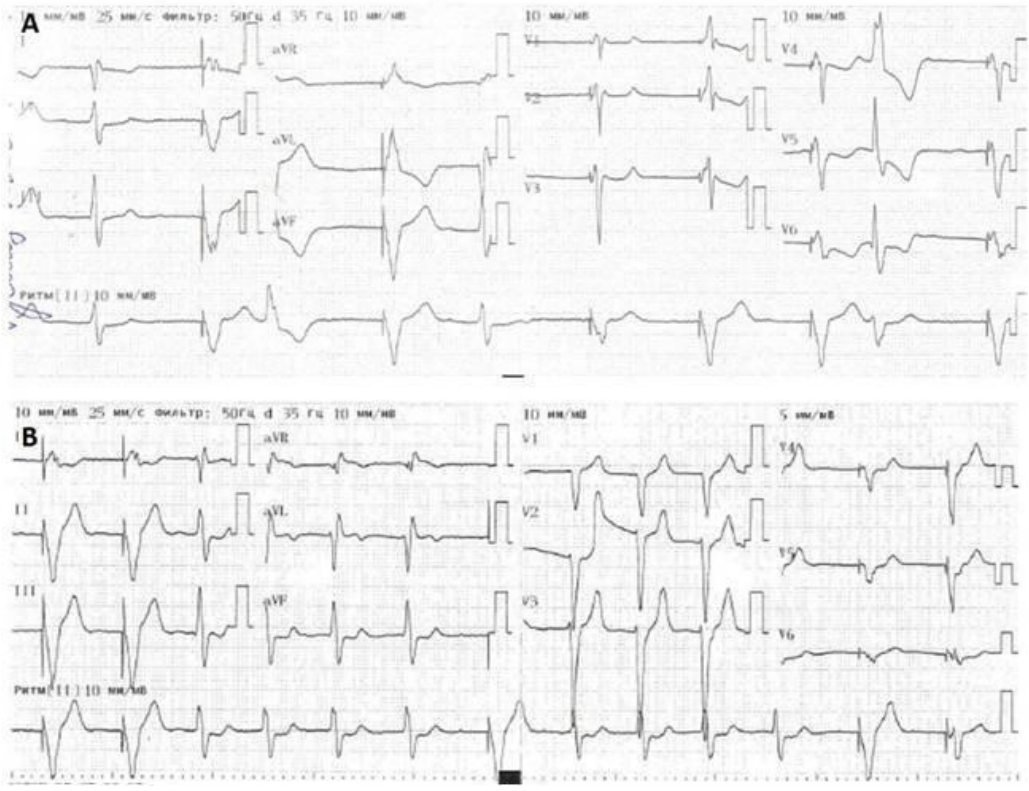

Fig 1. Electrocardiogram of a patient performed on admission to hospital. Speed rate 25mm/s, recording amplitude 10mm/mV, filter 35 Hz. (A) First admission: The heart rhythm is controlled by cardiac implantable electronic device. Heart rate - 60 beats/min, QRS complex 196 ms, QT interval 542 ms, myocardial ischemia or myocardial damage cannot be excluded. (B) Second admission: The heart rhythm is controlled by cardiac implantable electronic device. Heart rate - 82 beats/min, QRS complex 166 ms, QT interval 420 ms. Atrial fibrillation rhythm. Electrical axis of the heart isdeviation to the right Intraventricular conduction abnormality. Insufficient R-wave growth in V1-V3

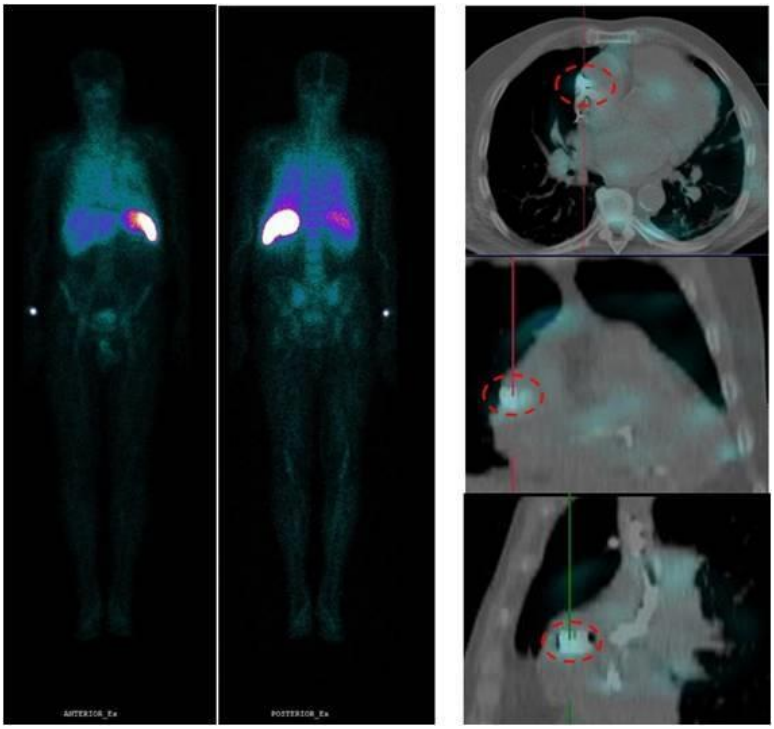

Fig 2. Labelled WBC scintigraphy. Whole Body images taken 30 minutes after labeled [^{99m}Tc]Tc-HMPAO WBC administration, anterior and posterior projections. The spleen, liver, and red bone marrow are visualized on the images, in accordance with the physiological distribution of the labelled WBC (left). SPECT/CT images in axial, frontal and sagittal views (up down), taken 4 hours after labelled [^{99m}Tc]Tc-HMPAO WBC administration. Low-intensity focal hyperfixation of the labelled WBC in the right atrial electrode site (highlighted in red) is visualized in the images (right)

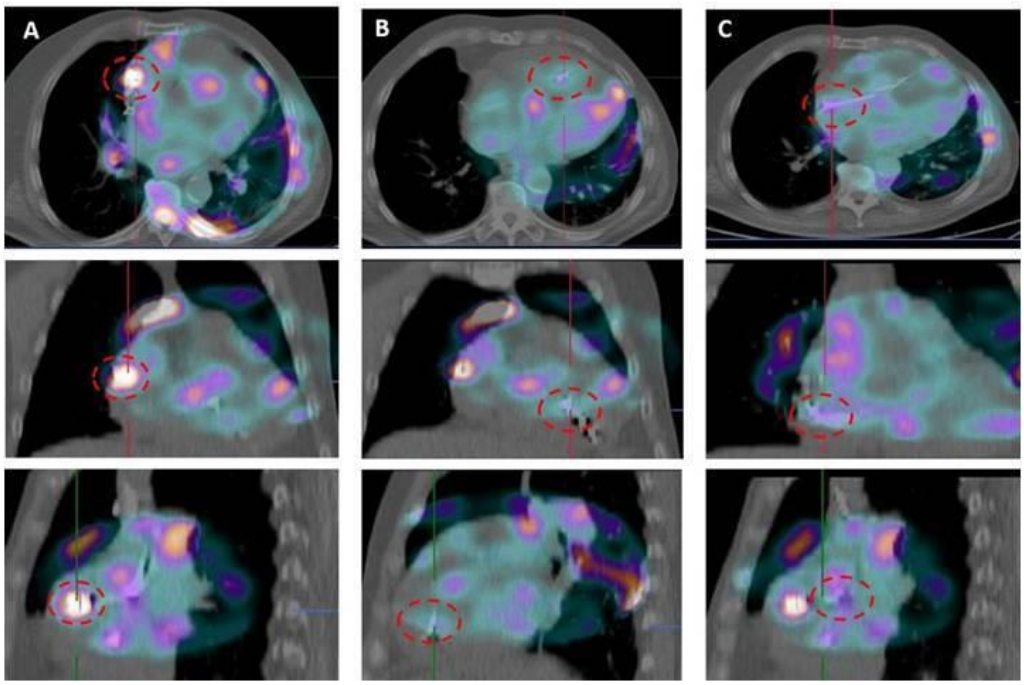

Fig 3. SPECT/CT images in axial, frontal and sagittal views (up down) 24 hours after labelled [^{99m}Tc]Tc-HMPAO WBC administration. High-intensity focal accumulation of labelled [^{99m}Tc]Tc-HMPAO WBC in the right atrial electrode site (A), medium-intensity foci of hyperfixation along the lead in the right ventricle (B) and in the ventricular electrode fixation site (C) (highlighted in red) are visualized in the images

DISCUSSION

Characteristics of the clinical manifestation of both early and late local and systemic inflammation after CIED implantation are described in detail previously [5]. CIED infection is a rare complication, ranging from 0.5 - 1% in the first 6-12 months after device implantation. However, the more complex the implanted system the higher is risk of complications [1, 6]. In addition, there is a two-four times higher risk of infection complications after device replacement compared to primary implantation [7].

In clinical practice, CIED infection is usually classified as pocket infection and device-related infective endocarditis. Diagnosing of pocket infection cause difficulties only at an initial stage of the disease. However, the diagnosis of CDRIE is difficult due to a nonspecific clinical presentation and often-long period between device implantation and onset of infection symptoms. Differentiating between pocket infection and CDRIE is also frequently difficult [4, 8]. Distinguishing if the infection is limited to the generator or extending to the leads and the endocardial surface is problematic. In addition, for patients with any CIED infections a transvenous lead extraction or complete device removal is recommended. [9]. This requires the use of reliable diagnostic criteria of CIED infection.

To date, there is no standardized protocol for a robust diagnosis of CDRIE. For this reason, the only available tool is the modified Duke criteria based on clinical, microbiological, and echocardiographic data [1, 8]. Several studies have found that 20–50% of CDRIE patients are asymptomatic for various reasons for a long time [10, 11]. In particular blood cultures are positive only in 20% to 67% of patients with systemic infection [12, 13] and TTE does not allow differentiating between vegetations and thrombotic masses on the electrodes. Also, a normal echocardiographic examination does not rule out CDRIE. [1, 4, 14]. Hence, the diagnostic accuracy of the Duke criteria for CDRIE diagnosis is significantly reduced [1].

For this reason, nuclear imaging techniques such as radiolabelled leucocyte scintigraphy and 2-[^{18}F]FDG PET/CT scanning, which have high sensitivity and specificity, have been proposed for use as additive tools in the diagnosis of CDRIE [1, 8].

Erba et al. reported that SPECT/CT with [^{99m}Tc]Tc-HMPAO leukocytes has a 94% sensitivity in the diagnosis of infectious and infective complications associated with CIED infection, and a 95% negative predictive value for excluding CIED infection in patients with febrile fever or sepsis [4]. In contrast to 2-[^{18}F]FDG PET/CT, labelled leukocyte scintigraphy is the preferred method of imaging septic inflammation because the mechanism of accumulation is based on the natural migration of labelled WBCs into the inflammatory lesion. Therefore, it can be used earlier than 8 weeks after surgery [1]. This method is also able to identify extracardiac septic emboli by whole-body scanning. The problem of low resolution of SPECT/CT may be resolved by using CZT gamma cameras [15].

In the study of Małecka A. et al, the significance of SPECT/CT with [^{99m}Tc]Tc-HMPAO leukocytes in the diagnosis of CDRIE was assessed [16]. Radionuclide examination was performed in 40 patients with intracardiac masses detected by echocardiography. Verification of the diagnosis was based on the modified Duke criteria. The results showed a sensitivity of 73.7%, a specificity of 81% and an accuracy of 77.5%. The agreement between scintigraphy and the modified Duke criteria by Landis and Koch was moderate but statistically significant ($\kappa = 0.548$, $p < 0.001$). In a randomised analysis of the results among patients who did not receive antibiotic therapy, the agreement between these tests was the best. The authors concluded that SPECT/CT with [^{99m}Tc]Tc-HMPAO labelled leukocytes is highly effective in the diagnosis of CDRIE [16].

Despite the high efficacy of SPECT/CT with [^{99m}Tc]Tc-HMPAO labelled leukocytes, this imaging technique, is still only an additional tool for the diagnosis of CIED infection in patients with suspected IE. Positive imaging of cardiac uptake of [^{99m}Tc]Tc-HMPAO labelled leukocytes is one of the major diagnostic criterion of modified Duke criteria. However, in the absence of a second major diagnostic criterion, e.g. negative TTE/TOE or negative blood cultures, as well as minor criteria, the diagnosis of CDRIE will be rejected. Thus, the current clinical guidelines [1] do not clearly recommend the use of nuclear imaging modalities, leaving the decision making to physicians.

CONCLUSION

This clinical case highlights the importance of increased vigilance in patients who have undergone device implantation and, in particular, device replacement. It should be noted that current diagnostic criteria for CIED

infection are not applicable in asymptomatic or uncertain patients. For an early and effective diagnosis of endocarditis, physicians should also consider the presence of symptoms of heart failure and/or circulatory disorders in patients with implanted cardiac devices.

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