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CASE REPORT

Very delayed sinus arrest during complete remission of diffuse large B-cell lymphoma invading right atrium

Sağ atriyum tutulumu yapan diffüz büyük B-hücreli lenfomanın tam remisyonu sırasında çok gecikmiş sinüs arresti

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Summary– Diffuse large B-cell lymphoma (DLBCL)-associated arrhythmias may be due to cardiac involvement or may be chemotherapy-induced. There have been no reports of significant arrhythmias with normal cardiac function occurring during the complete remission of DLBCL. A 57-year-old female, who had had no history of abnormal electrocardiograms (ECGs) in annual medical checkups, was admitted to our hospital because of low-grade fever, night sweats, and weight loss. On admission, ECG revealed a variable rhythm consisting of sinus beats and occasional escape beats. Computed tomography and ^{18}F-fluorodeoxyglucose positron emission tomography and computed tomography (FDG-PET/CT) revealed two masses in the right atrium (RA) and the uterus. Total hysterectomy was performed, and pathological findings were consistent with diffuse large B-cell lymphoma (DLBCL). Chemotherapy (R-CHOP) was initiated. After two chemotherapy cycles, RA tumors disappeared, and bradyarrhythmia simultaneously converted to sinus rhythm without antiarrhythmic drug therapy. Six months after completion of chemotherapy, FDG-PET/CT revealed negative uptake in the RA and the uterus. The patient attained complete remission of DLBCL, but ECG showed bradycardia because of sinus arrest. Our case suggests that DLBCL-induced arrhythmia can occur even after its remission and should be monitored.

Özet– Diffüz büyük B hücreli lenfoma (DLBCL) ile ilişkili aritmiler, kardiyak tutuluma veya kemoterapiye bağlı olabilir. DLBCL'nin tam remisyonu sırasında normal kardiyak fonksiyona sahip hastalarda meydana gelen önemli aritmiler bildirilmemiştir. Yıllık sağlık kontrollerinde anormal elektrokardiyogram (EKG) öyküsü olmayan 57 yaşında kadın hasta düşük nabız, ateş, gece terlemeleri ve kilo kaybı nedeniyle hastanemize başvurdu. Başvuru sırasında EKG, sinüs atımları ve ara sıra kaçış atımlarından oluşan değişken bir ritim gösterdi. Bilgisayarlı tomografi ve ^{18}F-florodeoksiglukoz pozitron emisyon tomografisi (FDG-PET/BT) sağ atriyum (RA) ve uterusta iki kitle ortaya çıkardı. Total histerektomi yapıldı ve patolojik bulgular diffüz büyük B hücreli lenfoma (DLBCL) ile uyumluydu. Kemoterapi (R-CHOP) başlandı. İki kemoterapi küründen sonra, RA tümörleri kayboldu ve bradiaritmi, antiaritmik ilaç tedavisi olmaksızın aynı anda sinüs ritmine dönüştü. Kemoterapinin tamamlanmasından altı ay sonra, FDG-PET/CT RA ve uterusta tutulum saptanmadığını ortaya koydu. DLBCL'de tam remisyon sağlandı, ancak EKG'de sinüs arresti nedeniyle bradikardi görüldü. Olgumuz, DLBCL'ye bağlı aritminin remisyondan sonra bile ortaya çıkabileceğini ve izlenmesi gerektiğini düşündürmektedir.

Diffuse large B-cell lymphoma (DLBCL)-associated arrhythmia may be due to its cardiac involvement or chemotherapy. Tumor-related electrocardiographic (ECG) changes are closely related to coexisting cardiac involvement, and there have been no reports of significant arrhythmia in normal LV function during complete remission of DLBCL. Chemotherapy-induced ECG changes and/or arrhythmias occur either in an early or late phase during chemotherapy. In the early phase, ECG changes (ST-segment elevation or depression, T-wave inversion, decreased QRS voltage, and prolonged QTc interval) are transient and nonspecific. In the late phase, arrhythmia can occur in parallel with the cardiac dysfunction induced by chemotherapy. Herein, we present a case of late-onset si-

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nus arrest during complete remission after chemotherapy in patients with DLBCL.

CASE REPORT

A 57-year-old female without a history of abnormal ECG in annual medical checkups was admitted to our hospital because of low-grade fever, night sweats persisting for 2-month, and body weight loss of 5 kg in 4 months. Because anemia was pointed out by her general practitioner, she was referred to our hospital for further evaluation. Laboratory data showed hemoglobin 8.7 g/dL, potassium 4.4 mEq/L, lactate dehydrogenase (LDH) 482 IU/L, C-reactive protein 4.8 mg/dL, soluble interleukin-2 receptor (sIL-2R) 22,500 U/mL, and brain natriuretic peptide 259 pg/mL. The ECG was recorded using an ECG-2550 (Nihon Kohden, Tokyo, Japan) with a calibration of 10 mm/mV and a speed of 25 mm/sec.

ECG revealed a variable rhythm consisting of sinus beats (Figure 1A) and occasional escape beats (Figure 1A; arrow) with a ventricular rate of 90 beats per minute. There was no ST deviation indicative of myocardial ischemia. Computed tomography (CT) revealed two masses in the right atrium (RA) (27×20 mm and 20×12 mm) and the uterus (100 mm with central necrosis), the lymph node swelling of mediastinum and para-aorta, and hepatosplenomegaly. There was no evidence of pulmonary embolism. ^{18}F-fluorodeoxyglucose positron emission tomography and computed tomography (FDG-PET/CT) showed uptake in the RA (Figure 2A; arrow) (maximum standardized uptake value of 22) and the uterus (maximum standardized uptake value of 16) (Figure 2A; arrowhead). Transthoracic echocardiograms (TTEs) demonstrated low-echoic nonmobile masses (25×18 mm and 18×10 mm) attached on the atrial septal side of RA (Figure 2C; arrow), with no evidence of wall thickness or pericardial effusion, and left ventricular ejection fraction (LVEF) was 71%. Four days after admission, malignant lymphoma was suspected towing to the atypical lymphocyte in the peripheral blood smear, but there were no superficial lymph nodes or tumors subject to biopsy to confirm the diagnosis. In this context, total hysterectomy was performed for pathological diagnosis. Histological and immunohistochemical studies revealed that the uterus tumor cells showed dense proliferation of large centroblastic cells with abundant pale cytoplasm by hematoxylin and eosin staining and positive for CD20 and multiple myeloma oncogene 1 but negative for CD5, CD10, and B-cell lymphoma. These findings were consistent with DLBCL. Consequently, the first cycle of chemotherapy (R-CHOP: rituximab 500 mg, cyclophosphamide 1000 mg, doxorubicin 67 mg, vincristine 1.7 mg, prednisolone 100 mg) was administered. Three weeks after initial chemotherapy (after completion of 1 cycle), the RA tumors were retracted to 17×7 mm (Figure 2D: arrow). Six weeks after initial chemotherapy (after completion of 2 cycles), the RA tumors almost disappeared (Figure 2E: arrow). When the tumor disappeared, bradyarrhythmia was converted to sinus rhythm without antiarrhythmic medical therapy (Figure 1B). Six months after initial chemotherapy (after completion of 8 cycles), cumulative doxorubicin dosage was 360 mg/m^2, and the patient maintained sinus rhythm without

Abbreviations:

CT	*Computed tomography*
DLBCL	*Diffuse large B-cell lymphoma*
ECG	*Electrocardiogram/ Electrocardiographic*
FDG-PET	*^{18}F-fluorodeoxyglucose positron emission tomography*
LDH	*Lactate dehydrogenase*
LVEF	*Left ventricular ejection fraction*
RA	*Right atrium*
sIL-2R	*Soluble interleukin-2 receptor*
TTE	*Transthoracic echocardiogram*

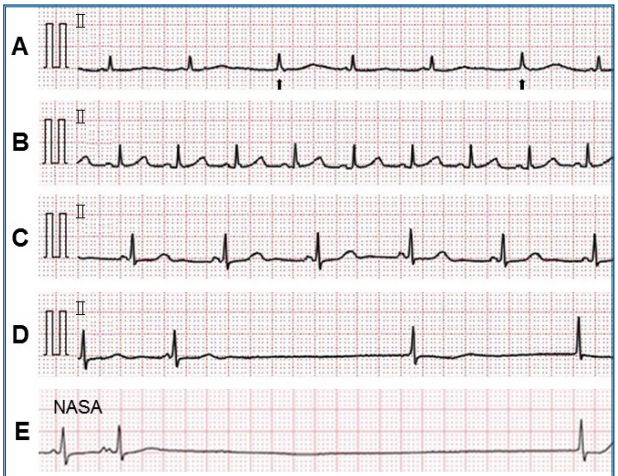

Figure 1. Electrocardiography of the presented case **(A)** on admission, **(B)** 6 weeks after initial chemotherapy, **(C)** 6 months after initial chemotherapy, and (**D** and **E**) 1 year after initial chemotherapy. **(A)** A variable rhythm consisting of sinus beats and occasional junctional escape beats (arrow) with a ventricular rate of 90 beats per minute. **(B)** Sinus rhythm with a ventricular rate of 109 beats per minute. **(C)** Sinus rhythm with a ventricular rate of 75 beats per minute. **(D)** Sinus arrest with a pause of 2.8 sec. **(E)** Sinus with a long pause of 4.3 sec with Holter monitor. Electrocardiography was recorded at a calibration of 10 mm/mV and a speed of 25 mm/sec. There is no record of the recuperation of the sinus nodes with a regular sinus P-wave.

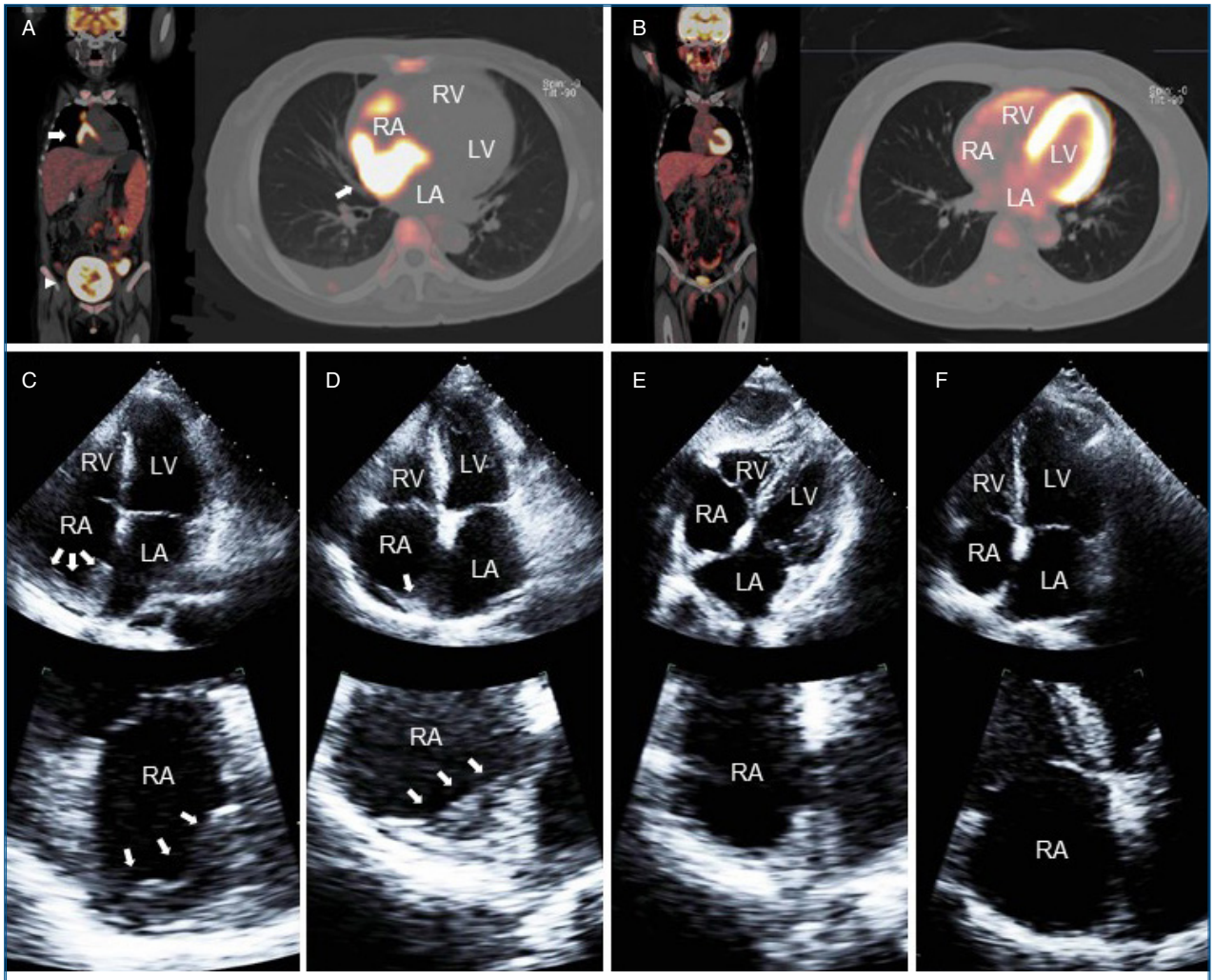

Figure 2. ^{18}F-fluorodeoxyglucose positron emission tomography and computed tomography **(A)** on admission and **(B)** 6 months after initial chemotherapy. **(A)** Uptake in the RA (arrow) (maximum standardized uptake value of 22) and uterus (maximum standardized uptake value of 16). **(B)** Negative for uptake in the RA and uterus. Transthoracic echocardiographic follow-up of apical four-chamber view at end-diastole **(C)** on admission, **(D)** 3 weeks after initial chemotherapy, **(E)** 6 weeks after initial chemotherapy, and **(F)** 1 year after initial chemotherapy. **(C)** Low-echoic non-mobile masses (25×18 mm and 18×10 mm) attached on the atrial septal side of RA. **(D)** RA tumors shrank to 17×7 mm. **(E)** RA tumor almost disappeared. **(F)** RA tumor does not relapse.
LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle.

tumor relapse (Figure 1C). One year after initial chemotherapy, FDG-PET/CT revealed negative uptake in the RA and the uterus (Figure 2B), TTE showed no RA tumor relapse, and LVEF remained normal at 78% (Figure 2F). Laboratory data showed potassium 4.3 mEq/L, LDH 225 IU/L, and sIL-2R 446 U/mL. Therefore, it was conceivable that the possibility of the late recurrence of DLBCL in the RA was extremely low, and she attained a complete metabolic remission. Annual ECG checkups revealed the sinus arrest without complaints of syncope, faintness, or dizziness at the outpatient department (Figure 1D). Holter monitor was performed for further evaluation (maximal pause 4.3 sec; no record of the recuperation of the sinus nodes with a regular sinus P-wave (Figure 1E; 2:42 PM, maximal heart rate; 96 beats per minute; sinus rhythm; 9:45 AM, minimum heart rate; 29 beats per minute; sinus bradycardia; 3:11 AM, average heart rate 64 beats per minute). There was no ST deviation indicative myocardial ischemia either of 12-lead ECG or Holter. The patient had an uneventful course except for sinus arrest and no recurrence of DLBCL until 3 years after complete remission.

Table 1. The reported arrhythmias associated with the agents included in the R-CHOP regimen*

	ST	SB	CAVB	PAC	SVT	AF	PVC	VT	QTc/TdP	SCD
Rituximab	C	C	C	-	+	++	C	C	C/C	C
Cyclophosphamide	+++	C	C	++	++	++	++	C	C/-	-
Doxorubicin	+++	++	C	+++	++	+++	+++	++	+++/C	+
Vincristine	-	-	-	-	-	C	C	-	-	-

AF: atrial fibrillation; C: case reports; CAVB: complete atrioventricular block; PAC: premature atrial complexes; PVC: premature ventricular tachycardia; SB: sinus bradycardia; SCD: sudden cardiac death; ST: sinus tachycardia; SVT: supraventricular tachycardia; TdP: torsades de pointes; VT: ventricular tachycardia.
*Adjusted from Buza et al.[6]
-: not available; +: uncommon (< 1%); ++: common (1% to 10%); +++: very common (> 10%).

DISCUSSION

The causes of DLBCL-associated arrhythmia include myocardial damage due to cardiac involvement or chemotherapy. The timing of arrhythmia onset depends on the etiology. Cardiac involvement of DLBCL have been reported to be associated with various types of ECG changes such as giant negative T waves change[1], ventricular tachycardia,[2] complete atrioventricular block,[3] atrial fibrillation,[4] and atrial flutter.[5] However, these ECG changes related to its cardiac involvement are all early-onset, and there have been no reports of late-onset ones after the complete remission of a tumor. The reported arrhythmias associated with the agents included in the R-CHOP regimen and arrhythmias are summarized in Table 1.[6] All of the agents included in the R-CHOP regimen may have the potential to cause chemotherapy-induced arrhythmia. However, vincristine-induced arrhythmia is extremely rare. Rituximab-induced arrhythmia includes atrial arrhythmias such as supraventricular tachycardia and atrial fibrillation. Various types of cyclophosphamide-induced ECG changes arrhythmias can be seen, including nonspecific ST-T changes, atrial fibrillation, and prolonged QTc interval, but lethal arrhythmia (ventricular fibrillation or bradycardia requiring pacemaker implantation) is rare.[6] Ramireddy et al.[7] reported that transient complete atrioventricular block requiring pacemaker implantation immediately after cyclophosphamide administration. Doxorubicin-induced arrhythmias can be seen both in the early phase (during or immediately after doxorubicin administration) and even in the late phase (many years after the cessation of therapy). In the early-onset one, arrhythmias are transient, and some ECG changes such as nonspecific ST-T changes were reported.[8,9] In the late phase lethal arrhythmia can occur, but it is based on impaired LV systolic function owing to doxorubicin-induced cardiomyopathy,[10] which can occur in dose-dependent manner, and its cumulative dose threshold was reported to be 450 mg/m^2.[11]

It is important to identify the time of onset or etiology of the arrhythmia. In our case, regarding the onset time, the patient had annual medical checkups including ECG, and no abnormalities had been pointed out on the ECG. Thus, we speculated that the patient was highly likely to have developed sinus disease after her admission. Regarding the etiology, it is hard to distinguish whether the etiology of the late-onset sinus arrest is cardiac involvement of DLBCL or chemotherapy-induced myocardial injury. Cyclophosphamide-induced cardiac toxicity generally occurs at doses higher than 60 mg/kg, but the patient was at a dose of 20 mg/kg. Moreover, cyclophosphamide-induced complete atrioventricular block was observed, which was reported to occur at early phase (within 24 hours) after administration. Taken together, it is thought to be unlikely as a cyclophosphamide-induced arrhythmia. It was also atypical as doxorubicin-associated arrhythmia because of well-preserved LV function, no evidence of LV dilatation, and cumulative doxorubicin dosage as low as 360 mg/m^2. The conduction pathways might be injured because of the tumor development near the sinus node. Because myocardial tissue could not be obtained, it was impossible to perform a histopathological assessment of the sinus node or conduction pathway tissue. Although either or both of them might contribute to the development of late-onset arrhythmia, it remains inconclusive. Moreover, it is also possible that those were merely a coincidence. To the best of our knowledge, this is the first report of late-onset of sinus arrest in normal LV function during complete remission of

DLBCL. Significant arrhythmias may develop many years after the cessation of chemotherapy and should be monitored closely.

We presented a case of very late-onset sinus arrest during complete remission of DLBCL after chemotherapy. Our case suggests that DLBCL-related significant arrhythmias can occur even after complete remission of tumor and should be monitored closely.

Informed Consent: Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

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Conflict-of-interest: None

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Anahtar Kelimeler: Kardiyotoksisite; kardiyak tümör; aritmi