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Case Report

CASE REPORT

A case of Takotsubo cardiomyopathy after chemotherapy

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Abstract

Here we present the case of a patient with diffuse large B-cell lymphoma who was admitted to hospital for an elective autologous peripheral blood stem cell transplant after cytotoxic treatment with lomustine, cytarabine, cyclophosphomide and etoposide (LACE). On the final day of chemotherapeutic treatment, she developed sudden onset dyspnoea. Electrocardiography confirmed acute antero-lateral T-wave inversion. She went onto have coronary angiography that demonstrated unobstructed coronary arteries. Left ventriculography demonstrated apical ballooning, consistent with Takotsubo (stress) cardiomyopathy. The link between chemotherapy and Takotsubo cardiomyopathy has become increasingly recognized in recent years, although causality remains to be established and the mechanism of action is not yet fully understood.

INTRODUCTION

Takotsubo cardiomyopathy (TC) is characterized by transient systolic dysfunction related to hypokinesis, akinesis or dyskinesis of left ventricular mid-segments with or without the apical segment involvement, in the absence of obstructive coronary artery disease [1]. It is typically accompanied by new ST-segment elevation and/or T-wave inversion on electrocardiography (ECG) or an elevated troponin [2]. The first documented case was of a patient who presented to a Japanese hospital in 1983 with an unexpected left ventricular structure [1] resembling a Japanese octopus trapping pot, known as a takotsubo, which has a round bottom and narrow neck [3]. Also known as stress-induced cardiomyopathy, TC has been linked to emotional stressors, such as grief and anger, as well as physical stressors including acute infection, major surgery and chemotherapy [4].

CASE REPORT

A 73-year-old woman with a diagnosis of tonsillar stage IV-B diffuse large B-cell lymphoma (DLBCL) came to our institution for an elective autologous peripheral blood stem cell transplant after cytotoxic treatment with lomustine, cytarabine, cyclophosphomide and etoposide (LACE). On admission, she was in clinical remission. Her past medical history included hypertension, asthma, Graves' disease (treated with radioactive iodine over 10 years ago), hiatus hernia and left total knee replacement. Her regular medications included lansoprazole 30 mg, ramipril 10 mg and ferrous fumarate 210 mg. She was a non-smoker, with minimal alcohol consumption. Physical examination and vital signs were unremarkable. Laboratory work included haemoglobin 115 g/l (reference range 114–150 g/l), platelets 408×10^9/l ($150–400 \times 10^9$/l), white blood cell count 8.6×10^9/l ($4.2–11.2 \times 10^9$/l), creatinine 60 μmol/l (95–108 μmol/l) and C-reactive protein 5.3 mg/l (0 – 5 mg/l). Electrocardiography (ECG), chest X-ray and lung function tests were all unremarkable, and left ventricular ejection fraction (LVEF) on echocardiography (ECHO) was 65%.

On the morning of the stem cell infusion date, following 7 days of chemotherapy, the patient developed sudden onset dyspnoea. She did not have chest pain, cough, palpitations, syncope or diaphoresis. In terms of vital signs, oxygen saturation

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dipped to 92% on air (improved to 98% with 2 l of oxygen supplementation), respiratory rate 20 breaths per minute, blood pressure 130/73 mmHg, heart rate 110 bpm and temperature 36.6°C. Physical examination elicited an elevated jugular venous pressure, normal heart sounds and bilateral lower zone crepitations on auscultation of the chest. ECG demonstrated new onset T-wave inversion in leads II, aVF and V3 – V6 (Fig. 1) and the high-sensitivity troponin level was 400 ng/l (reference range 0–15 ng/l). Initial bedside ECHO reported a dilated left ventricle with mildly impaired systolic function (LVEF 45%) and anteroseptal hypokinesia. Two days later, coronary angiography revealed unobstructed coronaries (Fig. 2a and b) and a left ventriculogram confirmed apical ballooning consistent with TC (Fig. 3a and b). Over the following 2 weeks, the patient was diuresed with furosemide 80 mg and commenced on carvedilol 10 mg. Despite subsequently contending with two episodes of neutropenic fevers relating to the chemotherapy regime received, her cardiac symptoms improved and T-wave inversion on ECG had improved

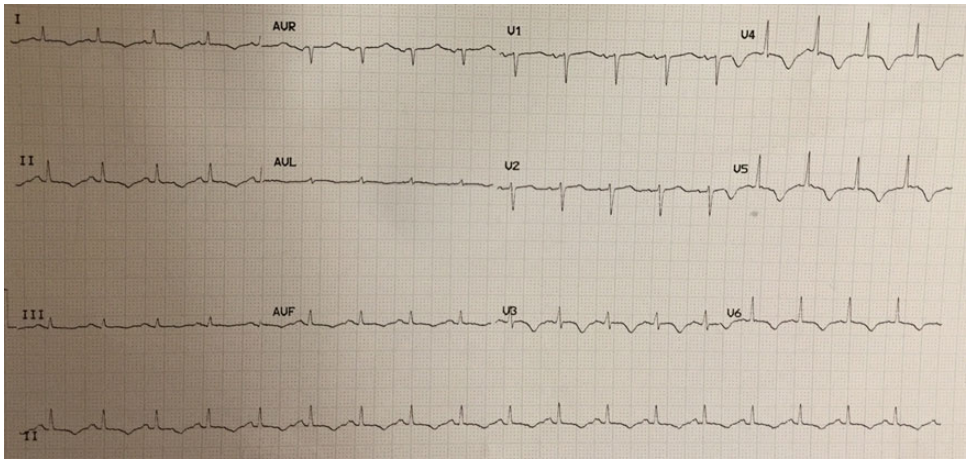

Figure 1: New onset T-wave inversion in leads II, aVF and V3–V6 following onset of dyspnoea.

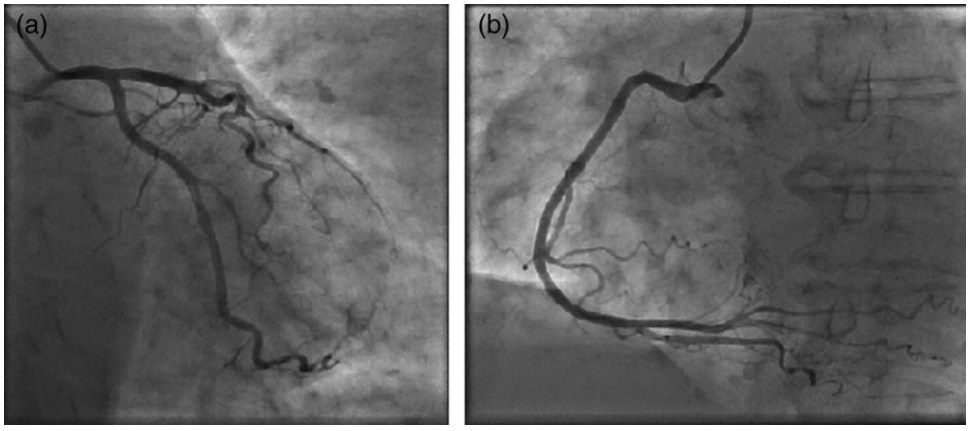

Figure 2: (**a**) Coronary angiogram showing unobstructed left main, left anterior descending and left circumflex coronary arteries. (**b**) Coronary angiogram showing an unobstructed right coronary artery.

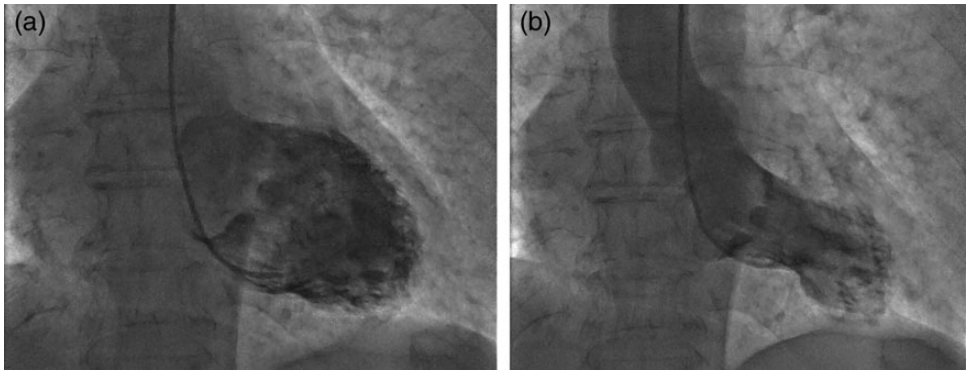

Figure 3: (**a**) Apical ballooning on left ventriculogram in diastole. (**b**) Apical ballooning on left ventriculogram in systole.

(Fig. 4). She was successfully discharged from hospital with planned outpatient clinic follow up. A repeat ECG 2 months later no longer showed T-wave inversion (Fig. 5a and b) and a repeat ECHO was performed 3 months later demonstrating good bi-ventricular function (LVEF 60%) with no evidence of regional wall motion abnormalities.

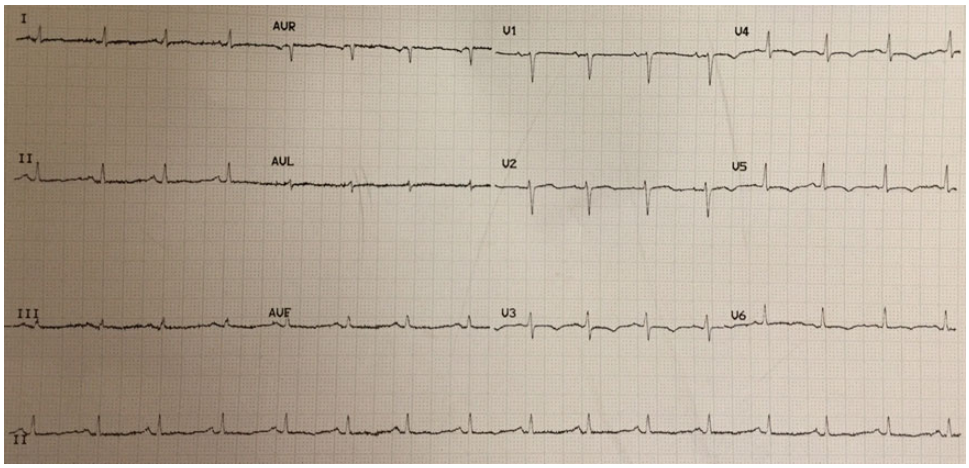

Figure 4: Improvement of T-wave inversion prior to discharge from hospital.

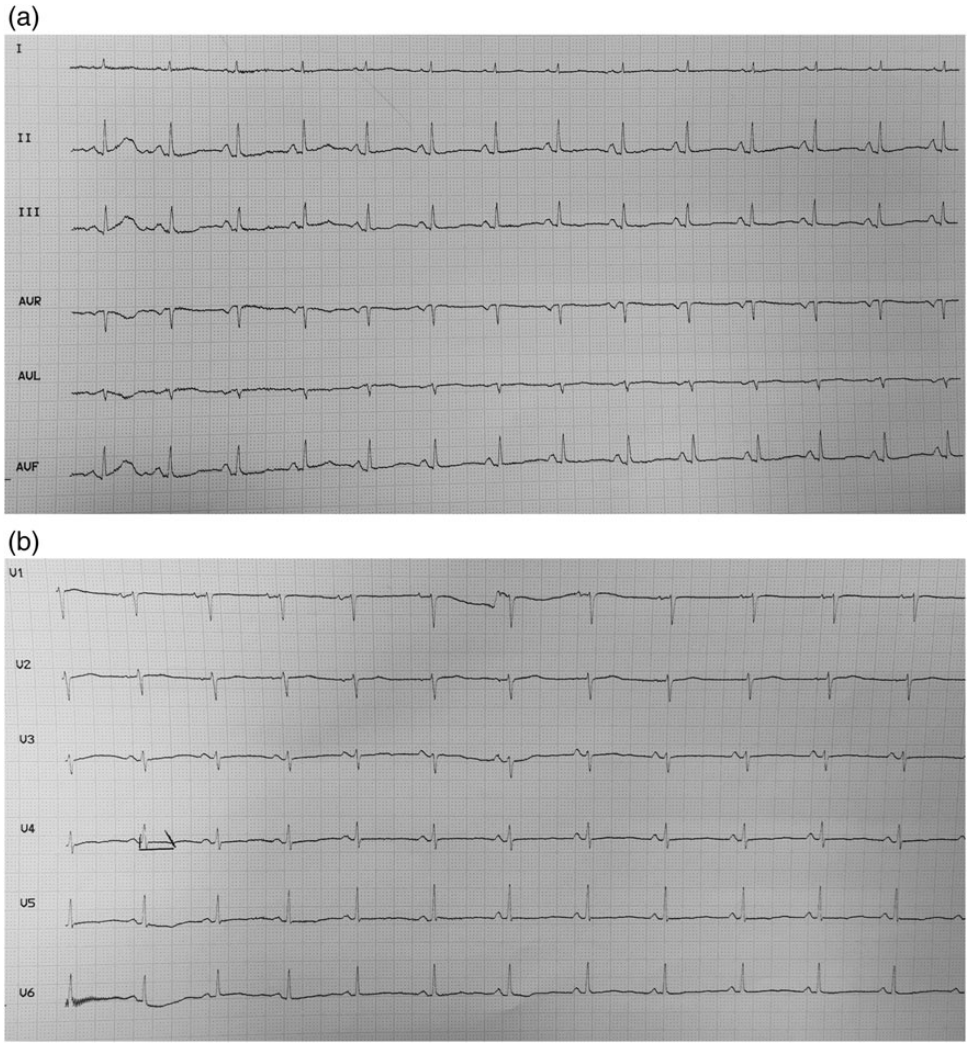

Figure 5: (**a**) ECG showing resolution of T-wave inversion in limb leads 2 months after discharge from hospital. (**b**) ECG showing resolution of T-wave inversion in chest leads 2 months after discharge from hospital.

DISCUSSION

The link between chemotherapy and TC has become increasingly recognized in recent years, particularly with the use of 5-fluorouracil (5-FU) [5]. The patient described in this case report received LACE for the treatment of DLBCL. To date, neither lomustine nor etoposide has been implicated in the development of TC. There is a paucity of evidence in the literature linking cytarabine and cyclophosphamide to TC; however, no firm causality has yet been established [6, 7].

Classically, TC has been linked to emotional stress [4]. Although the patient in this case outwardly displayed very little anxiety about her diagnosis and chemotherapeutic regime, it is possible that she felt a heightened degree of internal emotional stress that may have contributed to the development of TC. However, the role of physical stressors is likely to be more significant. The most commonly accepted explanation for the mechanism of TC centres on the excessive release of catecholamines in response to a physiological stressor [5]. Noradrenaline was found to have deleterious effects on cardiac myocytes which was mitigated by β-adrenoreceptor blockade, suggesting that β-blockers could be beneficial in TC [8]. Cancer is a pro-inflammatory state associated with excess levels of catecholamines which, in the context of this case, may have contributed to the physiological stress involved in triggering TC [9].

Chemotherapy, much like cancer, promotes increased sympathetic tone with resulting elevation of catecholamines. The anthracycline class of chemotherapeutic agents (namely doxorubicin and daunorubicin) commonly used in haematological maligancies is associated with cardiotoxicity. This occurs as a result of pro-apoptotic enzymes in the myocyte mitochondria triggering myocyte death and, in turn, a cardiomyopathy [6]. Despite the association with cardiotoxicity, there is minimal evidence that anthracyclines cause TC. Goel *et al*. [6] published the case of a 55-year-old gentleman who developed TC while being treated with dual chemotherapy with daunorubicin and cytarabine for acute myeloid leukaemia. To date, it is the only case in the literature suggesting a possible link between these agents and TC. 5-FU, another chemotherapeutic agent, causes cardiotoxicity in around 2–4% of cases [5] and has been increasingly linked with TC [6]. Of the agents used in this current case report, cardiotoxicity has been occasionally reported with cytarabine, cyclophosphamide and etoposide [10]. Of those, only cytarabine and cyclophosphamide have been possibly associated with TC [6, 7]. Currently, there are no specific guidelines to steer a decision about the choice of further chemotherapy in this case if required in future. Based on expert opinion, cardiotoxic agents should be avoided and alternative chemotherapeutic options include busulfan or melphalan.

In conclusion, this case highlights the possibility that chemotherapeutic agents could contribute to the development of TC, adding to the limited amount of current literature documenting this potential link. To our knowledge this is the first case of TC reported for a patient receiving LACE chemotherapy.

CONFLICT OF INTEREST STATEMENT

None declared.

FUNDING

None.

ETHICAL APPROVAL

Not applicable.

CONSENT

Patient signed consent was obtained.

GUARANTOR

Tamir Malley.

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