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Case Report

Alemtuzumab induced ST-segment elevation and acute myocardial dysfunction

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ABSTRACT

Cardiac toxicity as a side effect of chemotherapeutic agents has been well reported in the literature. Cardiac toxicity secondary to alemtuzumab has been reported, presenting as congestive heart failure and arrhythmias. Here we report a case of acute myocardial dysfunction after administration of a test dose of alemtuzumab. Our patient was a 66-year-old man with a history of small lymphocytic lymphoma/chronic lymphocytic lymphoma who received a test dose of alemtuzumab. Twenty minutes post administration, the patient developed nausea, vomiting, rigors, and tachycardia. Electrocardiography (ECG) showed acute ST-segment elevations in contiguous leads V2–V6, I, and AVL with no associated chest pain. Bedside echocardiogram showed akinesis of the anterior septum, apex, distal anterior wall, and decreased left ventricular ejection fraction. Cardiac catheterization showed non-critical occlusive disease and no intervention was undertaken. Post-catheterization ECG revealed resolution of ST segment elevations, TWI in V4–V6, and prolongation of corrected QT. Repeat echocardiogram 10 days after the event demonstrated no improvement in wall motion or ejection fraction. We discuss the possible mechanisms causing ST-elevations and acute myocardial dysfunction after treatment with alemtuzumab.

<Learning objective: Alemtuzumab can cause acute myocardial dysfunction after administration of a test dose. Considering that this is a serious adverse effect, detailed cardiac evaluation and a high level of caution are recommended before administration of alemtuzumab. While no clear etiology could be identified for this side effect, excessive and acute cytokine release triggered by alemtuzumab administration is a possible explanation. This could be potentially attenuated by using anti-interleukin-6 or tumor necrosis factor inhibitors.>

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Introduction

The spectrum of cardiovascular adverse effects secondary to cancer chemotherapy has expanded with the development of new chemotherapeutics, which now includes multiple biologic agents [1]. Cardiac toxicity of several chemotherapeutic agents including anthracyclines (doxorubicin, daunorubicin), alkylators (cyclophosphamide, cisplatin), antimetabolites (5-fluorouracil, capecitabine),

and targeted agents (trastuzumab, bevacizumab) has been well documented [2].

Alemtuzumab is a humanized monoclonal antibody that targets the CD52 antigen, which is a glycoprotein present on the cell membrane of most T- and B-lymphocytes. It was initially approved by the US Food and Drug Administration for the treatment of fludarabine-refractory chronic lymphocytic leukemia. Currently, it is utilized in the treatment of other diseases such as multiple sclerosis, mycosis fungoides, and Sezary syndrome, and in some conditioning regimens for bone marrow, kidney, and islet cell transplantation [3–6]. The well-defined adverse effects of alemtuzumab include headache, hypotension, rash, anemia, neutropenia, fever, chills, and autoimmune thyroid disorders [5]. Notable cardiotoxic side effects of alemtuzumab include congestive cardiac failure [4], arrhythmias, and acute myocardial infarction [7].

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Case report

We present a 66-year-old man with a five-year history of small lymphocytic lymphoma/chronic lymphocytic lymphoma, who was initially treated with rituximab and bendamustine. Treatment was complicated with severe allergic reactions, prompting continuation of treatment with the study drug CAL101 for 4 months. Subsequently, he received 2 cycles of fludarabine and cyclophosphamide before he was admitted to the hospital for progressive dyspnea and fever. Due to progression of his disease, the decision was made to switch therapy to alemtuzumab and the patient received a 3 mg test dose.

Twenty minutes after administration of the test dose, the patient developed diaphoresis, tachycardia, nausea, vomiting, rigors, and chills. Due to persistent tachycardia, an electrocardiogram (ECG) was obtained, demonstrating ST segment elevations in precordial (V3–V6) and limb leads I, and aVL (Fig. 1a). Despite these changes the patient denied any chest pain. Bedside transthoracic echocardiogram (TTE) showed akinesis of the anterior septum, apex, distal anterior wall, and a moderately decreased left ventricular ejection fraction with normal right ventricular size and function. These echocardiogram findings were new compared to the TTE that was performed 15 days prior to the event demonstrating normal left ventricular size, wall motion, and function. Troponin levels sent 1 h after drug administration were within normal limits [troponin-T = 0.01 ng/mL (normal range <0.011 ng/mL), creatine kinase (CK)-MB% = 8.29, CK-MB = 2.8 ng/mL (normal range <3 ng/mL), and creatine phosphokinase (CPK) = 34 U/L (normal range: 20–200 U/L)].

Considering the new findings on ECG and echocardiogram there was concern for acute myocardial infarction. The patient was emergently treated with aspirin, clopidogrel, and was started on a continuous heparin infusion. Immediately thereafter, the patient underwent cardiac catheterization (Fig. 2). Cardiac catheterization revealed a patent left main artery, 30% occlusion of the mid-left anterior descending, 70% occlusion of the D1, patent right coronary artery, patent ramus, an ejection fraction of 45%, left ventricular end diastolic pressure of 6 mmHg, and an akinetic apex. No therapeutic intervention was performed during the catheterization.

Post-catheterization the patient had a heart rate of 95 beats per min. On physical examination a S4 gallop was noted at the left sternal border and coarse crackles were heard bilaterally at the bases. ECG revealed stabilization of the ST segments, T wave inversion in V4–V6, a prolonged QT, and no pathologic Q waves (Fig. 1b). Repeat echocardiography approximately 16 h after initiation of alemtuzumab and post-catheterization corroborated left ventricular dysfunction (ejection fraction: 45%) and akinesis of the antero-septum, apex, and distal anterior wall. Cardiac markers 12 h after the event showed no significant changes (CPK 34 → 55 U/L, CK-MB% 8.2% → 7.4%, and troponin-T 0.01 → 0.03 ng/mL).

A repeat echocardiogram 10 days after drug administration showed no improvement in left ventricular function (Fig. 3). Unfortunately, the patient died 16 days after the administration of alemtuzumab due to progression of his disease and a follow-up echocardiogram to assess reversibility of left ventricular dysfunction was not possible. Autopsy could not be obtained.

Discussion

Cardiac toxicity in the form of congestive cardiac failure and arrhythmias has been previously documented after treatment with alemtuzumab [1,4,8]. However, some studies report no evidence of cardiac toxicity [9,10]. Therefore, a causal relationship between alemtuzumab remains a subject of debate within the literature.

The initial differential diagnosis for our case was broad, including myocardial stunning, Takotsubo syndrome [11], chemotherapy-induced cardiomyopathy, coronary vasospasm, and myocardial infarction with rapid thrombus dissolution due to heparin administration. Coronary vasospasm and acute myocardial infarction were the least likely diagnoses given the lack of significant troponin elevation. Basquiera et al. [7] reported a patient who developed non-ST segment elevation myocardial infarction (NSTEMI) after a 3 mg IV test dose of alemtuzumab followed by subcutaneous infusion of a 10 mg dose. After the second infusion, the patient developed fevers, dyspnea, typical chest pain, and hypotension. Subsequently the patient was diagnosed with non-ST elevation myocardial infarction. The same symptoms recurred after the fourth administration of 30 mg of alemtuzumab. Therefore, for

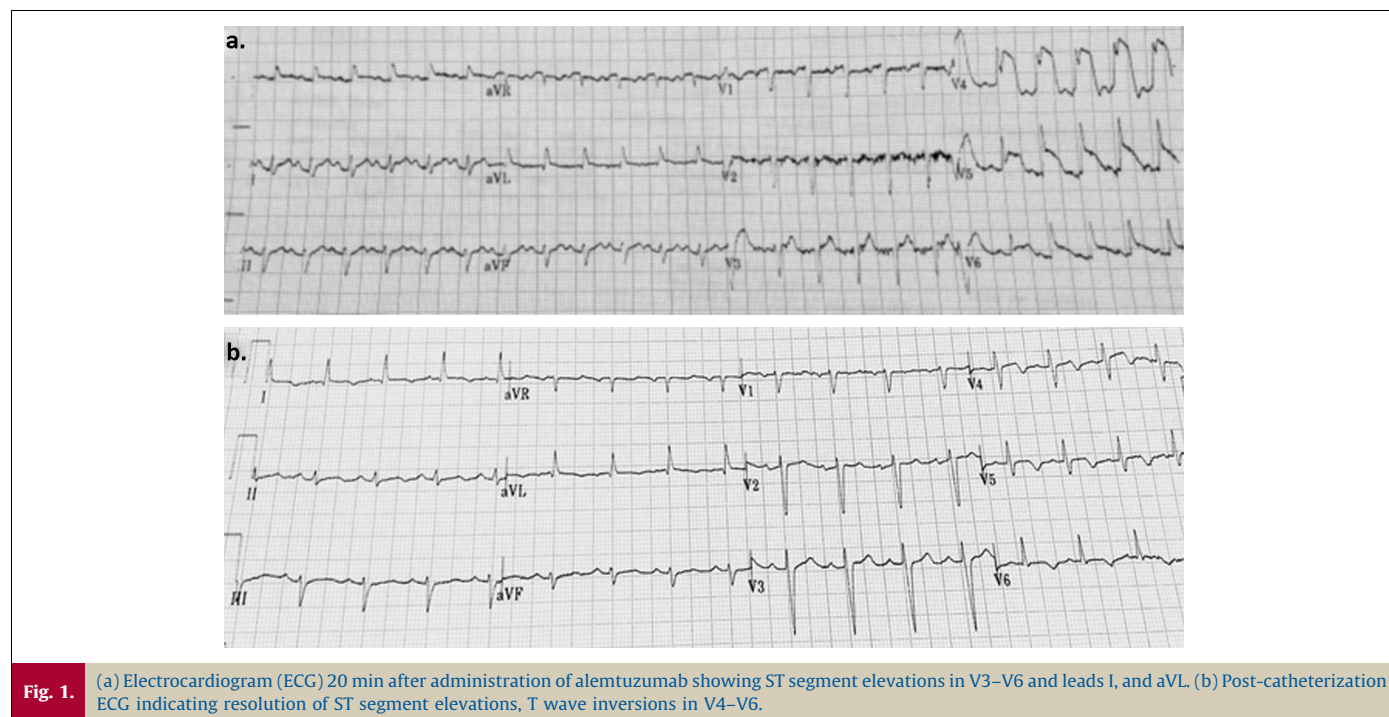
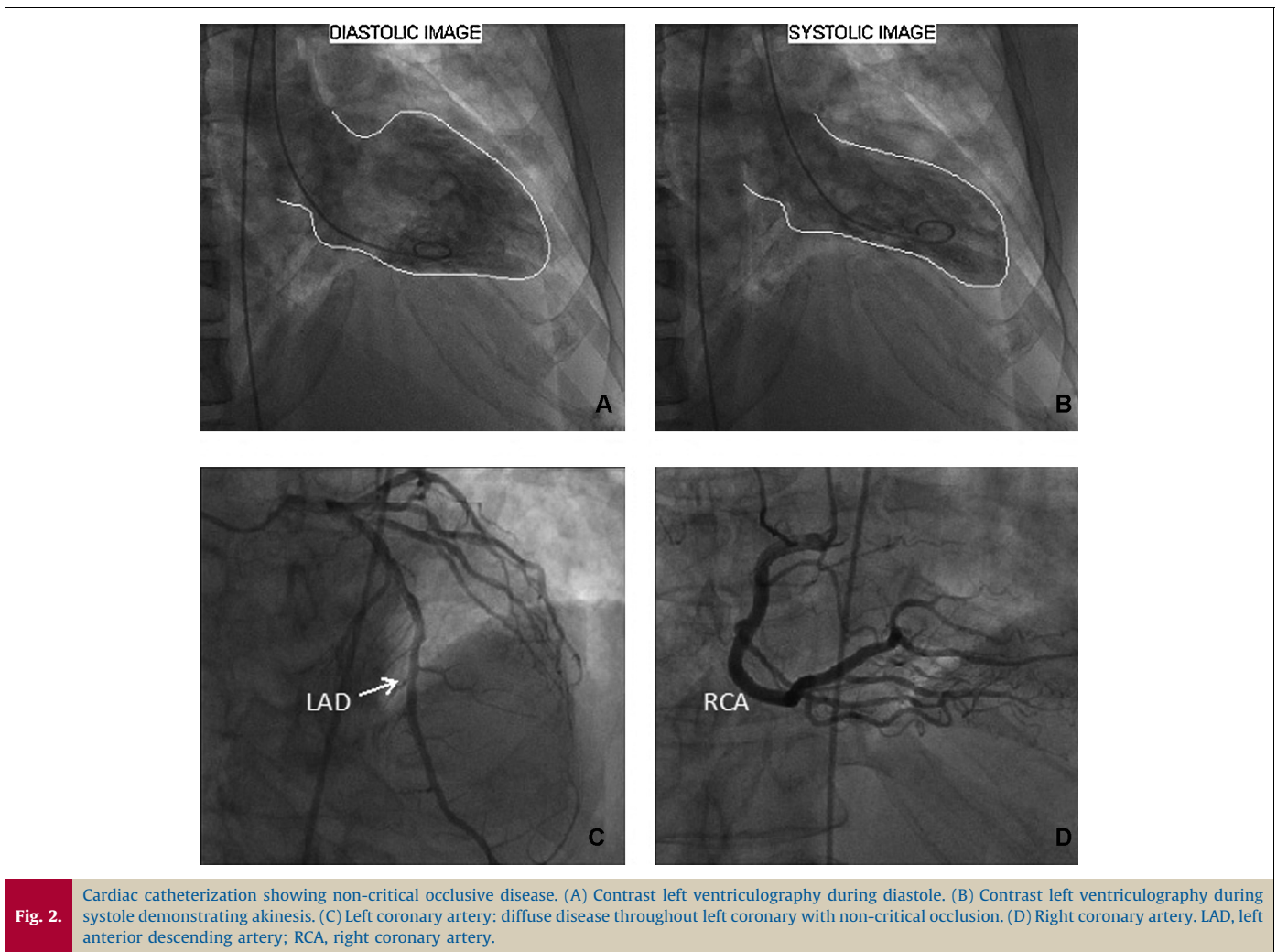
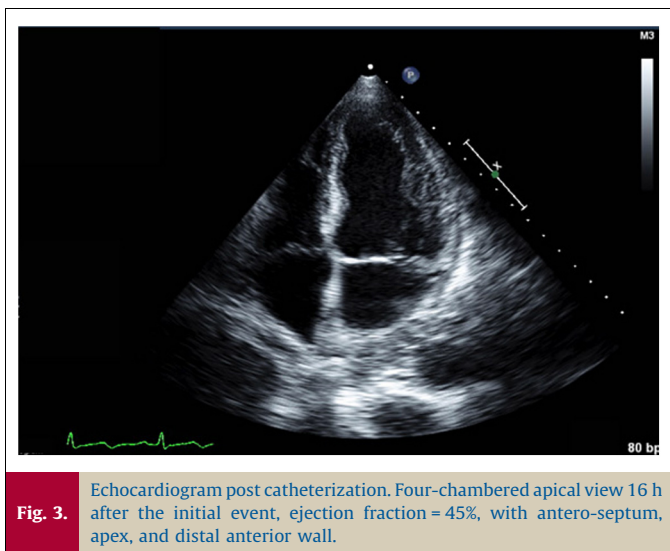


Fig. 1. (a) Electrocardiogram (ECG) 20 min after administration of alemtuzumab showing ST segment elevations in V3–V6 and leads I, and aVL. (b) Post-catheterization ECG indicating resolution of ST segment elevations, T wave inversions in V4–V6.



the last 6 doses of alemtuzumab, nitroglycerin patches were preventively placed with no further episodes of chest pain. Damaj et al. [8] reported a case of coronary vasospasm associated with fever, chills, and severe chest pain after infusion of 10 mg of alemtuzumab. As opposed to these reports, our patient experienced systemic symptoms such as nausea, vomiting, diaphoresis, rigors,



and chills, but never complained of chest pain. Furthermore, our patient showed acute ST elevations on ECG and did not show a significant increase in cardiac markers.

Our case presentation is similar to takotsubo or apical ballooning syndrome (ABS) [11], which could be induced by microvascular coronary spasm or direct catecholamine-mediated myocardial stunning [12]. ABS is defined as: (1) transient hypokinesis, akinesis, or dyskinesis in the left ventricular mid segments with or without apical involvement; regional wall motion abnormalities that extend beyond a single epicardial vascular distribution; and frequently, but not always, a stressful trigger; (2) the absence of obstructive coronary disease or angiographic evidence of acute plaque rupture; (3) new ECG abnormalities (ST-segment elevation and/or T-wave inversion) or modest elevation in cardiac troponin; and (4) the absence of pheochromocytoma and myocarditis [11]. A few cases of takotsubo cardiomyopathy developing after exposure to bevacizumab (a vascular endothelial growth factor inhibitor) have been reported [13]. In those cases, left ventricular function recovery was observed at 15 and 21 days. Although our case is similar to ABS, the patient did not fully fit the modified Mayo Clinic criteria for takotsubo as there was no increase in the level of troponin and hypokinesis of the wall was still evident one week later.

The association between cardiac adverse events, alemtuzumab, and T-cell malignancies may be explained by a cytokine-release syndrome, which is caused by increased levels of serum tumor necrosis factor (TNF), interferon, and interleukin-6 [4,7]. Alemtuzumab may trigger the T cells to secrete these cytokines,

leading to coronary vasospasm or even transient myocardial dysfunction without infarction (stunning of the myocardium) [4,8]. This cytokine release-related mechanism could explain why cardiac adverse effects of alemtuzumab have been reported mainly in patients with T-cell malignancies. An alternative mechanism for the myocardial damage caused by alemtuzumab could be a direct toxicity to the cardiac myocytes. Although there is no evidence that CD52 is expressed on cardiac myocytes, it can bind to the T cells that infiltrate the myocardium and cause myocyte dysfunction or electrical disturbances as an unwanted secondary effect [14–16]. While the pathophysiology in our case could be explained by any of the mentioned mechanisms, lack of immunohistochemistry and other pathophysiologic data limits the accurate understanding of the underlying mechanism.

In summary, we report a patient with the diagnosis of small lymphocytic lymphoma/chronic lymphocytic lymphoma, who was treated with a test dose of alemtuzumab and developed acute myocardial dysfunction. While no clear etiology could be identified, excessive and acute cytokine release triggered by alemtuzumab administration is a possible explanation, which could be potentially attenuated by using anti-IL-6 or TNF inhibitors. Further investigation is warranted to understand the mechanisms causing adverse effects of chemotherapeutic agents.

Conflict of interest

All other authors state that they have no conflicts of interest.

References

- [1] Monsuez JJ, Charniot JC, Vignat N, Artigou JY. Cardiac side-effects of cancer chemotherapy. *Int J Cardiol* 2010;144:3–15.
- [2] Khawaja MZ, Cafferkey C, Rajani R, Redwood S, Cunningham D. Cardiac complications and manifestations of chemotherapy for cancer. *Heart* 2014;100:1133–40.
- [3] Ciancio G, Burke 3rd GW. Alemtuzumab (Campath-1H) in kidney transplantation. *Am J Transplant* 2008;8:15–20.
- [4] Lenihan DJ, Alencar AJ, Yang D, Kurzrock R, Keating MJ, Duvic M. Cardiac toxicity of alemtuzumab in patients with mycosis fungoides/Sezary syndrome. *Blood* 2004;104:655–8.
- [5] Minagar A, Alexander JS, Sahraian MA, Zivadinov R. Alemtuzumab and multiple sclerosis: therapeutic application. *Expert Opin Biol Ther* 2010;10:421–9.
- [6] Skoetz N, Bauer K, Elter T, Monsef I, Roloff V, Hallek M, Engert A. Alemtuzumab for patients with chronic lymphocytic leukaemia. *Cochrane Database Syst Rev* 2012;2:CD008078.
- [7] Basquiera AL, Berretta AR, Garcia JJ, Palazzo ED. Coronary ischemia related to alemtuzumab therapy. *Ann Oncol* 2004;15:539–40.
- [8] Damaj G, Rubio MT, Audard V, Hermine O. Severe cardiac toxicity after monoclonal antibody therapy. *Eur J Haematol* 2002;68:324.
- [9] Lundin J, Kennedy B, Dearden C, Dyer MJ, Osterborg A. No cardiac toxicity associated with alemtuzumab therapy for mycosis fungoides/Sezary syndrome. *Blood* 2005;105:4148–9.
- [10] Sleigh KA, Smith ME, Rule SA. Cardiac involvement with mycosis fungoides: could this explain alemtuzumab toxicity? *Leuk Lymphoma* 2008;49:2022–4.
- [11] Prasad A, Lerman A, Rihal CS. Apical ballooning syndrome (Tako-Tsubo or stress cardiomyopathy): a mimic of acute myocardial infarction. *Am Heart J* 2008;155:408–17.
- [12] Wittstein IS. Stress cardiomyopathy: a syndrome of catecholamine-mediated myocardial stunning. *Cell Mol Neurobiol* 2012;32:847–57.
- [13] Franco TH, Khan A, Joshi V, Thomas B. Takotsubo cardiomyopathy in two men receiving bevacizumab for metastatic cancer. *Ther Clin Risk Manag* 2008;4:1367–70.
- [14] Coles AJ, Wing MG, Molyneux P, Paolillo A, Davie CM, Hale G, Miller D, Waldmann H, Compston A. Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. *Ann Neurol* 1999;46:296–304.
- [15] Moreau T, Coles A, Wing M, Isaacs J, Hale G, Waldmann H, Compston A. Transient increase in symptoms associated with cytokine release in patients with multiple sclerosis. *Brain* 1996;119(Pt 1):225–37.
- [16] Ottaviani G, Matturri L, Rossi L, Jones D. Sudden death due to lymphomatous infiltration of the cardiac conduction system. *Cardiovasc Pathol* 2003;12:77–81.