CASE PRESENTATION

Acute drops in ejection fraction in contemporary cardio-oncology: old diagnosis, new offenders

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Abstract: Acute left ventricular (LV) dysfunction is a common manifestation of cardiotoxicity related to modern cancer treatment, including novel immunotherapies. As immune checkpoint inhibitor (ICI) therapy is increasingly used, different clinical forms of LV dysfunction are observed. Suspicion for ICI-induced cardiotoxicity prompts a complete cardiovascular evaluation, including transthoracic echocardiography and global longitudinal strain. We present 3 cases of ICI-induced cardiotoxicity with a common denominator, an acute drop in LV ejection fraction, but with 3 different etiologies: Takotsubo cardiomyopathy, ischemia, and myocarditis. Clinicians must be aware of the potential risk for immune-related adverse events, including the various forms of cardiotoxicity.
Keywords: Cardio-oncology, cardiotoxicity, immunotherapy, myocarditis, Takotsubo cardiomyopathy.

Rezumat: Disfuncția ventriculară stângă acută este o manifestare frecventă a cardiotoxicității tratamentelor anti-neoplazice, inclusiv a noilor imunoterapii. Adoptarea pe scară largă a imunoterapiei cu inhibitori ai punctelor de control imune (IPCI) a dus la identificarea diferitelor forme de disfuncție ventriculară stângă ce pot apărea ca efecte adverse. Suspiciunea clinică de cardiotoxicitate indusă de IPCI impune o evaluare cardiovasculară completă, incluzând ecocardiografia transtoracică și „strain-ul" ventricular. Prezentăm 3 cazuri de cardiotoxicitate indusă de IPCI cu un numitor comun (disfuncția ventriculară stângă acută), dar cu etiologii diferite: ischemie, cardiomiopatie Takotsubo și miocardită. Clinicienii trebuie să aibă în vedere potențialul IPCI de a induce efecte adverse, inclusiv diversele forme de cardiotoxicitate.
Cuvinte cheie: Cardio-oncologie, cardiotoxicitate, imunoterapie, miocardită, cardiomiopatia Takotsubo.

INTRODUCTION

Left ventricular dysfunction is a common clinical manifestation of cardiotoxicity related to modern cancer therapy[1]. A precise definition of cardiotoxicity in oncology is still subject to debate, but experts describe it as a decrease of >10% in left ventricular ejection fraction (LVEF) to values of <53% as measured by two-dimensional echocardiography within a variable time frame following initiation of cancer treatment[2]. Guidelines recommend the use of transthoracic echocardiography (TTE) to screen for cardiotoxicity, as it is the most readily available imaging modality.[2] Since measurement of LVEF with TTE is limited by interobserver variability, global longitudinal strain might be able to provide incremental value[3].

Novel immunotherapies have led to improvements in cancer survival, even in malignancies previously associated with poor prognoses. Immune checkpoint inhibitors (ICIs) target T cell activation pathways in order to increase the host immune response against cancer cells. These agents can activate both anti-tumor and autoreactive T cells, the latter being responsible for immune-related adverse events involving especially the lungs, gastrointestinal system, liver, endocrine system, and skin[4]. Initial reports about ICI-associated cardiotoxicity described it as a rare occurrence, with the risk being higher in cases of combination immunotherapy[5]. ICIs, however, can cause severe cardiac adverse events, which are refractory to glucocorticoids. When cardiotoxicity is suspected, a complete

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cardiovascular workup is required for diagnosis and risk assessment. We present the clinical manifestations and diagnostic workup of 3 patients who suffered from acute drops in ejection fraction of different etiologies related to ICI therapy for cancer.

CASE SERIES

Patient 1. An 81-year-old woman with a history of myelodysplastic syndrome treated with nivolumab and ipilimumab, presented with dyspnea for 3 days, with onset during her third nivolumab infusion. Subconjunctival hemorrhage of the right eye and scattered ecchymoses on both arms were seen, in the context of 25.000 platelets/µl. She was admitted for possible pneumonia (Figure 1A) and nonspecific T-wave abnormalities on electrocardiogram (ECG) (Figure 1B). On TTE, an acute drop in LVEF was noticed, with new wall motion abnormalities concerning for ischemic- or stress-induced cardiomyopathy (Figure 1, C1-C2). Coronary angiography revealed normal coronary arteries, but ventriculography was suggestive of apical Takotsubo stress cardiomyopathy (Figure 1, D1-D4).

Patient 2. An 82-year-old man with acute myelogenous leukemia treated with azacitidine and nivolumab presented for worsening anxiety. His labs were notable for troponin T of 39 ng/ml with rising CK and a platelet count of 29,000/µL. Chest X-ray revealed bilateral lower lobe linear atelectasis and bibasilar pneumonia (Figure 2A). ECG showed minor ST depressions in the anterior and lateral leads (Figure 2B). Baseline TTE 2 months prior, before chemotherapy, had been normal

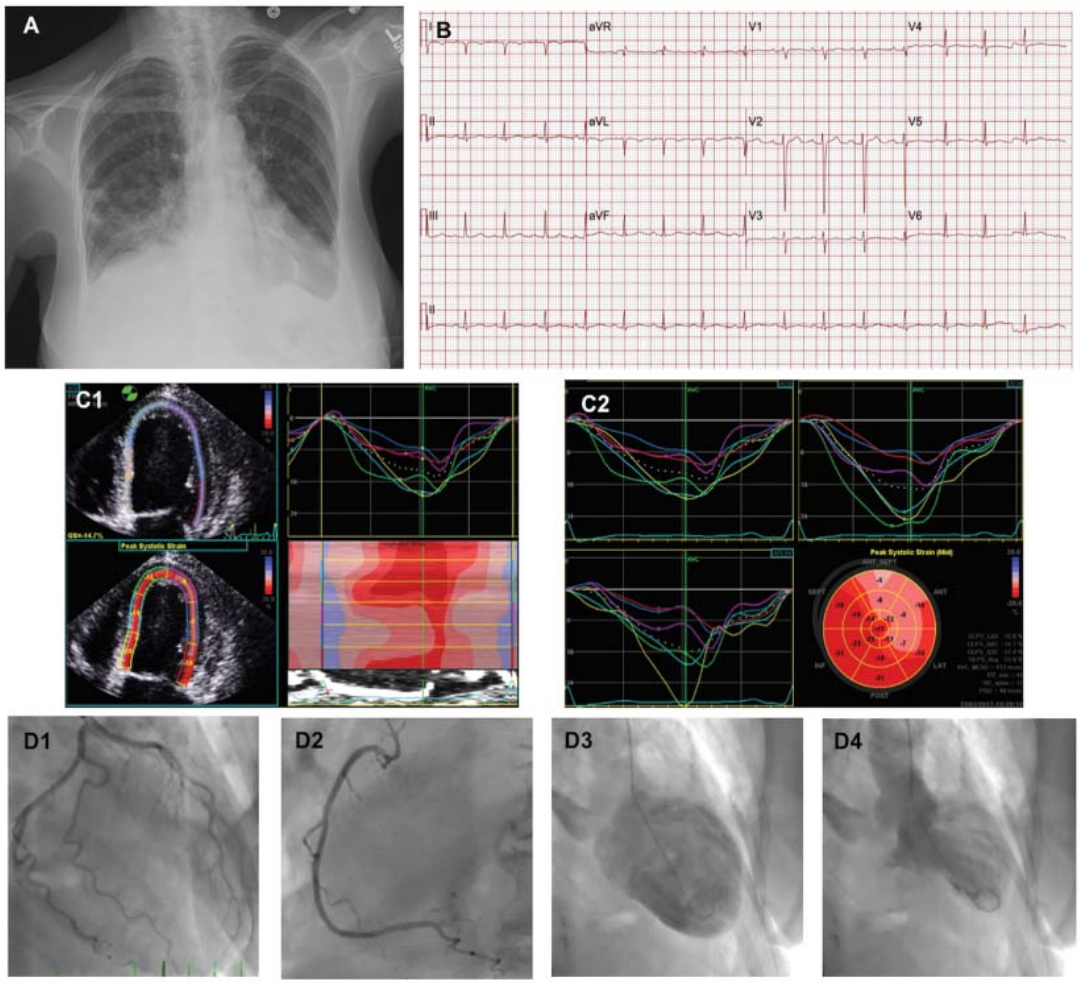

Figure 1. Takotsubo stress cardiomyopathy during treatment with nivolumab and ipilimumab. Chest X-ray showing possible pneumonia and bilateral pleural effusions (A). Electrocardiogram with nonspecific T-wave abnormalities (B). On transthoracic echocardiogram, new anteroapical and lateral wall motion abnormalities can be seen (ventricular systolic strain 4 chamber view, C1). Myocardial strain imaging revealed a global longitudinal peak strain of -15.9% (C2). Coronary angiography revealed normal coronary arteries (D1-D2) and ventriculography was suggestive of apical Takotsubo stress cardiomyopathy (D3-D4).

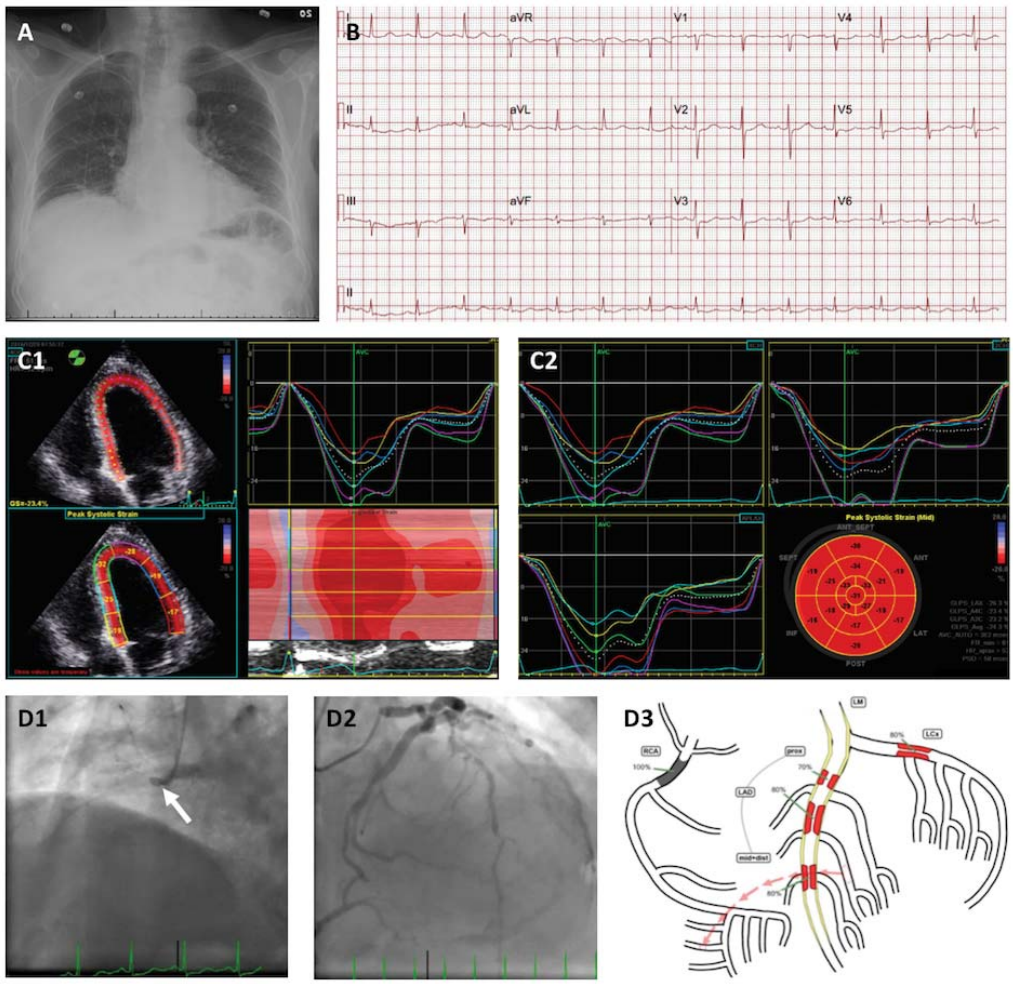

Figure 2. Acute coronary syndrome during treatment with nivolumab and azacitidine. Chest X-ray revealed bilateral lower lobe linear atelectasis and bibasilar pneumonia (A). Electrocardiogram showed minor ST depressions in the anterior and lateral leads (B). Normal transthoracic echocardiogram before chemotherapy (C1-C2). Coronary angiography showed triple vessel disease (D1-D3), with chronic total occlusion of the proximal right coronary artery (D1, arrow), and 70-80% stenoses of the left anterior descending and left circumflex arteries (D2).

(Figure 2, C1-C2). At the current presentation, new global left ventricular systolic dysfunction was found, with anteroseptal wall motion abnormalities, and a LVEF of 30-35%. Coronary angiography revealed triple vessel disease (Figure 2, D1-D3), the culprit of his systolic dysfunction.

Patient 3. A 68-year-old man on combination immunotherapy with durvalumab and tremelimumab for 1 month for metastatic pleomorphic gluteal sarcoma presented for weakness and dyspnea. Chest X-ray showed pleural metastatic disease and left lower lobe airspace disease concerning for atelectasis, aspiration, or infection (Figure 3A). ECG was concerning for ventricular tachycardia or supraventricular wide-complex tachycardia with aberrancy (Figure 3B). An acute coronary syndrome treatment protocol was initiated, but after CK increased >24.000 U/L, rhabdomyolysis and myositis were suspected. Myocardial strain measurement showed global hypokinesia and LVEF of 30-35%, suggestive of myocarditis (Figure 3, C1-C2). Coronary angiography did not reveal any hemodynamically significant coronary lesions (Figure 3, D1-D3), but the patient developed a complete heart block, which required the placement of a temporary pacemaker under fluoroscopic guidance (Figure 3, D1).

DISCUSSION

Immune-related adverse events have been described with various frequencies during treatment with ICIs, from 64-80% with ipilimumab, to 79% with pembrolizumab[4]. The highest occurrence was reported when

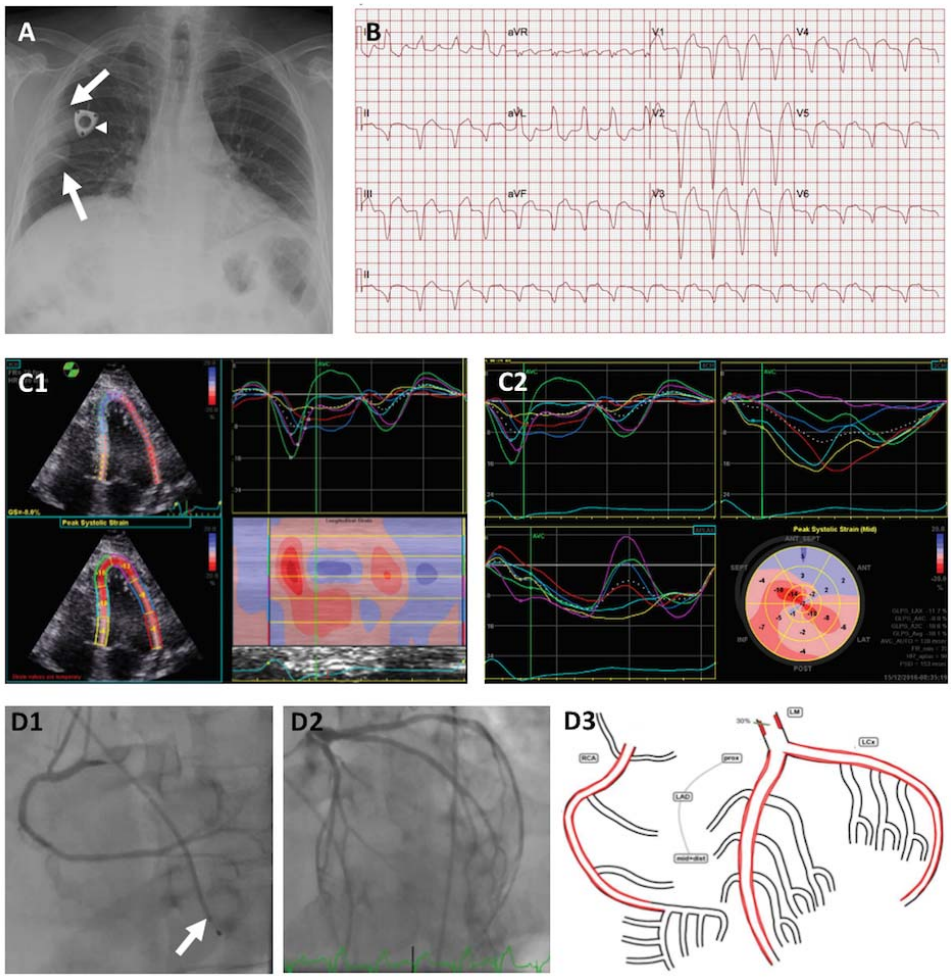

Figure 3. Myocarditis during treatment with durvalumab and tremelimumab. Chest X-ray showing right pleural metastatic disease (A, thin arrows), an appropriately placed chemotherapy port (A, arrowhead), and left lower lobe airspace disease worrisome for atelectasis, aspiration, or infection. Electrocardiogram was concerning for ventricular tachycardia or supraventricular wide-complex tachycardia with aberrancy (B). Echocardiographic strain measurement (4 chamber view, C1) showed global longitudinal peak strain of -10.1% (C2), with global hypokinesia and LVEF of 30-35%, suggestive of myocarditis. Coronary angiography did not reveal any significant coronary lesions (D1-D3; D1 arrow pointing at temporary pacemaker lead).

multiple agents were used, 96% with combination ipilimumab plus nivolumab[6]. The true incidence of cardiac toxicity with ICIs is thought to be underreported due to the lack of routine cardiac assessment in most clinical trials and variable timeframe for the appearance of cardiotoxicity[5]. Several animal models have highlighted plausible mechanisms for the cardiotoxicity of ICIs. The inhibition of CTLA-4 and PD-1 can lead to dilated cardiomyopathy and autoimmune myocarditis, induce autoantibodies against cardiac troponin and myosin, or potentiate T cells targeting antigens shared by both the heart and the tumor[7]. It is unclear whether these mechanisms can be extrapolated to humans.

Cardiotoxicity induced by ICI can present in many forms, from asymptomatic cardiac biomarker elevations to cardiogenic shock, but congestive heart failure, arrhythmias, and conduction abnormalities have been more commonly reported[5]. Myocarditis is a rare side effect of immunotherapy, but it is severe and difficult to manage[7]. In addition to myocarditis, Takotsubo stress cardiomyopathy has also, albeit rarely, been described[8]. ICIs can also trigger cardiac events in patients with pre-existing cardiac disorders[9], as was the case of our patient who was diagnosed with triple-vessel coronary artery disease after ICI administration, with prior normal baseline cardiac function. Immunotherapy could play a role in the destabilization of atherosclerotic lesions[7], as reported by Tomita et al in a case of acute coronary syndrome after nivolumab in a previously asymptomatic patient[10].

The recommendations for diagnosing ICI-induced cardiotoxicity include a complex array of tests: ECG,

cardiac biomarkers (troponin, CK, CK-MB, brain natriuretic peptide), cardiac imaging (echocardiography, cardiac magnetic resonance), coronary angiography, and endomyocardial biopsy[5]. Considering the several possible mechanisms underlying cardiotoxicity, different markers and diagnostic modalities could provide complementary information, better defining the cardiovascular status and risk for each oncology patient.

CONCLUSIONS

As novel immunotherapies are increasing in popularity, clinicians must be aware of the potential risk for immune-related adverse effects. Although rare, ICI-induced cardiotoxicity is severe and may present with a multitude of clinical manifestations. An acute drop in ejection fraction may signal cardiotoxicity, posing for a complete cardiovascular workup. A collaboration between the oncologist and the cardiologist is essential for acute and long-term management of patients with ICI-induced cardiotoxicity.

Conflicts of interest: none declared.

References

1. Kenigsberg B, Wellstein A, Barac A. Left Ventricular Dysfunction in Cancer Treatment: Is it Relevant? JACC Heart Fail 2018;6:87-95.
2. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, Ganame J, Sebag IA, Agler DA, Badano LP, Banchs J, Cardinale D, Carver J, Cerqueira M, DeCara JM, Edvardsen T, Flamm SD, Force T, Griffin BP, Jerusalem G, Liu JE, Magalhaes A, Marwick T, Sanchez LY, Sicari R, Villarraga HR, Lancellotti P. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2014;15:1063-1093.
3. Khouri MG, Ky B, Dunn G, Plappert T, Englefield V, Rabineau D, Yow E, Barnhart HX, St John Sutton M, Douglas PS. Echocardiography core laboratory reproducibility of cardiac safety assessments in cardio-oncology. J Am Soc Echocardiogr 2018;31:361-371.e363.
4. Stucci S, Palmirotta R, Passarelli A, Silvestris E, Argentiero A, Lanotte L, Acquafredda S, Todisco A, Silvestris F. Immune-related adverse events during anticancer immunotherapy: pathogenesis and management. Oncol Lett 2017;14:5671-5680.
5. Escudier M, Cautela J, Malissen N, Ancedy Y, Orabona M, Pinto J, Monestier S, Grob JJ, Scemama U, Jacquier A, Lalevee N, Barraud J, Peyrol M, Laine M, Bonello L, Paganelli F, Cohen A, Barlesi F, Ederhy S, Thuny F. Clinical features, management, and outcomes of immune checkpoint inhibitor-related cardiotoxicity. Circulation 2017;136:2085-2087.
6. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, Schadendorf D, Dummer R, Smylie M, Rutkowski P, Ferrucci PF, Hill A, Wagstaff J, Carlino MS, Haanen JB, Maio M, Marquez-Rodas I, McArthur GA, Ascierto PA, Long GV, Callahan MK, Postow MA, Grossmann K, Sznol M, Dreno B, Bastholt L, Yang A, Rollin LM, Horak C, Hodi FS, Wolchok JD. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med 2015;373:23-34.
7. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, Hicks M, Puzanov I, Alexander MR, Bloomer TL, Becker JR, Slosky DA, Phillips EJ, Pilkinton MA, Craig-Owens L, Kola N, Plautz G, Reshef DS, Deutsch JS, Deering RP, Olenchock BA, Lichtman AH, Roden DM, Seidman CE, Koralnik IJ, Seidman JG, Hoffman RD, Taube JM, Diaz LA, Jr., Anders RA, Sosman JA, Moslehi JJ. Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med 2016;375:1749-1755.
8. Anderson RD, Brooks M. Apical Takotsubo syndrome in a patient with metastatic breast carcinoma on novel immunotherapy. Int J Cardiol 2016;222:760-761.
9. Heinzerling L, Ott PA, Hodi FS, Husain AN, Tajmir-Riahi A, Tawbi H, Pauschinger M, Gajewski TF, Lipson EJ, Luke JJ. Cardiotoxicity associated with CTLA4 and PD1 blocking immunotherapy. J Immunother Cancer 2016;4:50.
10. Tomita Y, Sueta D, Kakiuchi Y, Saeki S, Saruwatari K, Sakata S, Jodai T, Migiyama Y, Akaike K, Hirosako S, Fujisue K, Yamamura S, Miyazaki S, Takashio S, Izumiya Y, Nakamura K, Tsujita K, Ichiyasu H, Fujii K. Acute coronary syndrome as a possible immune-related adverse event in a lung cancer patient achieving a complete response to anti-PD-1 immune checkpoint antibody. Ann Oncol 2017;28:2893-2895.