A case of COVID-19 masquerading as presumed Trastuzamab induced subclinical cardiotoxicity

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Abstract

A 48-year-old woman was diagnosed with right-sided Grade 2 invasive breast carcinoma. Prior to initiation of chemotherapy, transthoracic echocardiogram (TTE) demonstrated normal systolic function with left ventricular ejection fraction (LVEF) 64% and global longitudinal strain (GLS) 21%. Following adjuvant chemotherapy with four cycles of anthracycline, twelve cycles of Paclitaxel, and two cycles of Trastuzamab chemotherapies, TTE demonstrated reduction in LVEF to 56% and GLS of -18% (14% relative reduction compared to baseline). Further investigation revealed recent symptomatic COVID-19 infection coinciding with functional impairment and decision was made to continue Trastuzumab therapy without cardioprotective agents. Subsequent TTE demonstrated improved systolic function, indicating the importance of taking history of significant viral infections during chemotherapy standard of care.

Introduction:

The ongoing Coronavirus disease 2019 (COVID-19) global pandemic has resulted in over six million deaths worldwide.[1] In addition to primary acute respiratory symptoms, COVID-19 has been demonstrated to have multisystem involvement.[2]Cardiovascular system manifestations include thrombosis, acute coronary syndrome, arrhythmias, myocarditis, and evidence of subclinical myocardial dysfunction, with increased risk of mortality observed following myocardial injury.[3] Cardiac resonance imaging (CMR) provides the highest diagnostic accuracy for acute myocarditis, however speckle tracking echocardiography (STE) derived strain analysis offers a more pragmatic alternative. STE examination has demonstrated sub-clinical myocardial involvement of patients with only mild/ moderate COVID-19 symptoms.[4]

Case Report:

A 48-year-old woman was diagnosed with right sided Grade 2 invasive breast carcinoma (no special type (NST), oestrogen receptor/ progesterone receptor (ER/PR) negative and human epidermal growth factor receptor 2 (HER2) positive), in April 2021. She had received adjuvant chemotherapy with four cycles of anthracycline, twelve cycles of Paclitaxel, and two cycles of Trastuzamab chemotherapies, to be followed by bilateral mastectomy and adjuvant radiation and on-going Trastuzumab. Prior to the initiation of chemotherapy, a transthoracic echocardiogram (TTE) demonstrated normal left ventricular (LV) systolic function, with LV ejection fraction (LVEF) of 64% with a global longitudinal strain (GLS) of -21% (Figure 1, A). She had routine cardiac surveillance as is clinical practice at our centre with a repeat TTE (August 2021) after anthracycline therapy and prior to commencement of Trastuzamab (Figure 1, B). This demonstrated LVEF of 59% with GLS of -19% (9% relative reduction in GLS compared to baseline). As is standard of care, a TTE is performed at 3 monthly intervals after commencement of Trastuzumab. Her next routine 3 monthly TTE (November 2021) demonstrated a further reduction in LVEF to 56% and GLS of -18% (14% relative reduction compared to baseline (TTE measurements were repeated by an experienced and independent sonographer

and verified by the consulting cardiologist), triggering review by a cardiologist (Figure 1, C). There was no significant change in blood pressure, heart rate, LV volumes, LA volume or E/e' over this period.

At cardiologist review, the patient reported no cardiovascular symptoms, in particular no dyspnoea, fatigue, or pedal oedema. She mentioned that she had COVID-19 infection (although having been vaccinated prior (x 2 doses) in late September 2021 and had mild – moderate symptoms of dyspnoea and fatigue for approximately three weeks, though she denied any chest pain or palpitations., she did not have any blood tests (for cardiac biomarkers), require hospitalisation, and did not receive specific antiviral therapy. On examination, she had a heart rate of 60 bpm, was normotensive with a blood pressure of 124/78 mmHg, with normal heart sounds, no murmurs or rubs. Electrocardiogram showed sinus rhythm with normal axis, and non-specific T wave inversion in leads III and aVF.

The patient had an asymptomatic drop in LVEF of 9% and 14% relative reduction in LV GLS compared with her baseline study whilst on Trastuzumab, and therefore met criteria for commencement of cardioprotective therapy (angiotensin-converting enzyme inhibitor +/- Beta blocker therapy). However, given the history of COVID infection in the interim with resolution of symptoms subsequently, a decision was made to continue with Trastuzumab therapy with TTE surveillance after further two cycles of Trastuzamab, without initiation of cardioprotective therapy.

At follow up, the patient reported no further symptoms and did not have dyspnoea or fatigue. Her TTE in January 2022 demonstrated improved LVEF of 59% and GLS of -19% (Figure 1, D). She has subsequently continued Trastuzumab with standard clinical surveillance, without commencement of cardioprotective agents.

Discussion:

Myocardial dysfunction and heart failure secondary to cancer therapy (cardiotoxicity) is an important cause of patient morbidity and mortality in cancer survivors.[5] Anthracycline-induced cardiotoxicity has a cumulative, dose dependant, and non-reversible presentation with cellular apoptosis. Myocardial dysfunction and/ or heart failure can be delayed for a number of years due to compensatory mechanisms.[5] The highly effective treatment of monoclonal antibody Trastuzumab for HER2 positive breast cancer demonstrates partially reversible acute myocardial dysfunction with immediate improvements in left ventricular ejection fraction (LVEF) following Trastuzumab cessation, however with an ongoing subclinical reduction of LV GLS.[5, 6]

Prevention and management of cancer therapy induced cardiotoxicity is important for long term patient outcomes and requires screening, risk stratification, and ongoing monitoring as strategies.[7]Baseline cardiac assessment should include medical history, electrocardiography, cardiac imaging with determination of systolic, diastolic, and subclinical dysfunction with strain analysis, and/ or troponin assessment.[5] Cardiac imaging is typically performed with TTE with evaluation of LVEF and GLS, where a reduction in LVEF by >10% to below 55% or a GLS relative reduction of 11-15% from baseline are indicative of cardiotoxicity.[7] Follow-up cardiac imaging is recommended at the completion of anthracycline therapy, and then every 3 months during Trastuzumab treatment.[5] Minimising risk of cardiotoxicity includes anthracycline dose modification and sequential administration of anthracyclines and Trastuzumab.[7]

Acute myocardial dysfunction has also been described in patients following infection with COVID-19, with reduction in GLS an independent indicator of COVID-19 related death.[4, 8] Impairment has been demonstrated in both LVEF and GLS in an apical sparing pattern typical of a reverse-stress/ Takotsubo cardiomyopathy.[9] The prevalence of myocardial dysfunction following COVID-19 infection in the wider population remains unknown, however there is 20 – 30% reported myocardial involvement in hospitalised patients.[10] Conflicting reports have been presented regarding improvement of LVEF and GLS following COVID-19 recovery, which may indicate a need for ongoing monitoring and/or administration of cardioprotective agents.[8, 9]

Myocardial dysfunction is a recognised sequela of both cancer therapy related cardiac dysfunction and COVID-19 infection. In this case our patient demonstrated myocardial dysfunction during Trastuzamab therapy, albeit following a COVID-19 infection. Recovery was observed in the course of ongoing Trastuzamab treatment without administration of cardioprotective agents, indicating a probable subclinical myocarditis

following COVID-19 infection. This indicates the importance of taking a history of prior COVID-19 infection, or indeed other significant viral infections that may alter LV function, in patients undergoing chemotherapy, with ongoing TTE surveillance.

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References:

1. Center JHUoMCR. COVID-19 dashboard by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU) 2022 [June 21, 2022]. Available from: https://coronavirus.jhu.edu.

2. Shao H, Ghaly HSA, Varamini1 P. Coronavirus disease 2019: An overview of the complications and management. ITPS. 2021;4(1):1-28.

3. Giustino G, Pinney SP, Lala A, Reddy VY, Johnston-Cox HA, Mechanick JI, et al. Coronavirus and cardiovascular disease, myocardial injury, and arrhythmia: JACC focus seminar. J Am Coll Cardiol. 2020;76(17):2011-23.

4. Stöbe S, Richter S, Seige M, Stehr S, Laufs U, Hagendorff A. Echocardiographic characteristics of patients with SARS-CoV-2 infection. Clin Res Cardiol. 2020;109(12):1549-66.

5. Plana JC, Galderisi M, Barac A, Ewer MS, Ky B, Scherrer-Crosbie M, et al. 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(10):1063-93.

6. Stoodley P, Tanous D, Richards D, Meikle S, Clarke J, Hui R, et al. Trastuzumab-induced cardiotoxicity: The role of two-dimensional myocardial strain imaging in diagnosis and management. Echocardiography. 2012;29(6):E137-E40.

7. Zamorano JL, Lancellotti P, Rodriguez Muñoz D, Aboyans V, Asteggiano R, Galderisi M, et al. 2016 ESC Position Paper on cancer treatments and cardiovascular toxicity developed under the auspices of the ESC Committee for Practice Guidelines: The Task Force for cancer treatments and cardiovascular toxicity of the European Society of Cardiology (ESC). Eur J Heart Fail. 2017;19(1):9-42.

8. Lassen MCH, Skaarup KG, Lind JN, Alhakak AS, Sengeløv M, Nielsen AB, et al. Echocardiographic abnormalities and predictors of mortality in hospitalized COVID-19 patients: the ECHOVID-19 study. ESC Heart Fail. 2020;7(6):4189-97.

9. Chao CJ, DeValeria PA, Sen A, Lee H, Pedrotty DM, Patel B, et al. Reversible cardiac dysfunction in severe COVID-19 infection, mechanisms and case report. Echocardiography (Mount Kisco, NY). 2020;37(9):1465-9.

10. Haryalchi K, Olangian-Tehrani S, Asgari Galebin SM, Mansour-Ghanaie M. The importance of myocarditis in Covid-19. Health Sci Rep. 2022;5(1):e488-n/a.

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