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Should we always blame cancer treatment? – a case of large atrial septal defect in a patient with breast cancer and progressive right ventricular dilatation

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Abstract

We report a case of large atrial septal defect (ASD) in a 62-year-old female who was under regular echocardiographic follow-up on human epidermal growth factor receptor 2 (HER2) targeted treatment. She had progressive right ventricular dilatation and tricuspid regurgitation on serial echocardiograms, initially thought to represent cancer therapy related cardiotoxicity. However, further investigations revealed the presence of an ASD, which was treated with percutaneous closure.

Keywords: Atrial septal defect; Right ventricular dilatation; Breast cancer; Anti-HER2 treatment.

Introduction

Breast cancer is a significant global health concern and has recently surpassed lung cancer as the most diagnosed cancer worldwide. It is the leading cause of cancer deaths in women [1]. Approximately 15-20% of all breast cancer cases exhibit human epidermal growth factor receptor 2 (HER2) overexpression or gene amplification. This has been historically associated with more aggressive tumour behavior and poorer prognosis [2]. Anti-HER2 treatments, such as trastuzumab (Herceptin) and pertuzumab have revolutionized cancer therapy and have dramatically changed breast cancer survival and prognosis. Trastuzumab and pertuzumab are humanized monoclonal antibodies that target different regions of the HER2 tyrosine kinase receptor, effectively blocking the HER2 signalling pathway, thus, reducing tumor progression and invasion [3,4]. The HER2-signaling pathway, however, plays a crucial role in the survival and adaptive responses of myocardial cells to various stressors. As a result, anti-HER2 therapies inhibit cellular repair mechanisms and exert various cardiotoxic effects [5], from asymptomatic reduction in left ventricular systolic function to cardiomyopathy with left or right ventricular failure, hypertension, venous thromboembolism, pulmonary hypertension, and arrhythmias [6-8]. As cardiotoxicity is the most anticipated adverse effect related with anti-HER2 treatment, other cardiac diagnoses may be missed. We present a case of large atrial septal defect (ASD) in a breast cancer patient with progressive right heart dilatation and right ventricular (RV) dysfunction thought to be related to anti-HER2 therapy.

Case presentation

A previously fit and well 62-year-old female was diagnosed with left breast cancer via the national screening program. She had no significant co-morbidities, risk factors or family history of cardiac disease. The breast tumour was radiologically 40 mm,

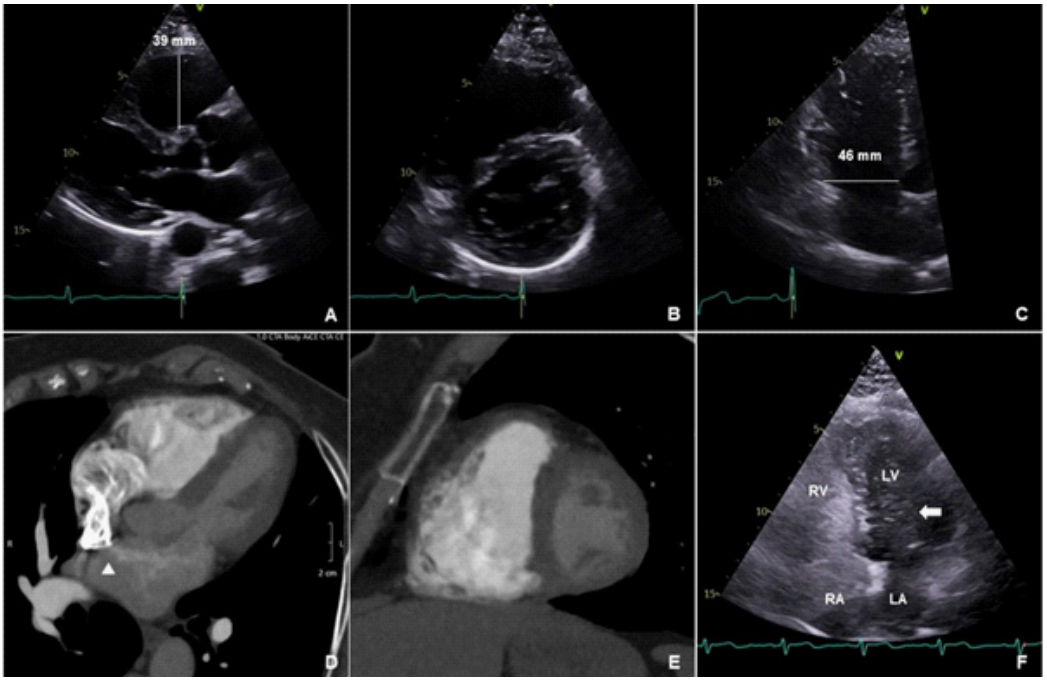

Figure 1: (A-C) Transthoracic echocardiogram images on parasternal long axis, parasternal short axis at the level of the mitral valve, and apical RV focused view showing a dilated RV. **(D,E)** Cardiac computed pulmonary angiogram showing a dilated RV and possible interatrial communication (arrowhead). **(F)** Bubble echocardiogram showing a large number of bubbles crossing through the interatrial septum into the left cardiac chambers (arrow). LA: Left Atrium; LV: Left Ventricle; RA: Right Atrium; RV: Right Ventricle.

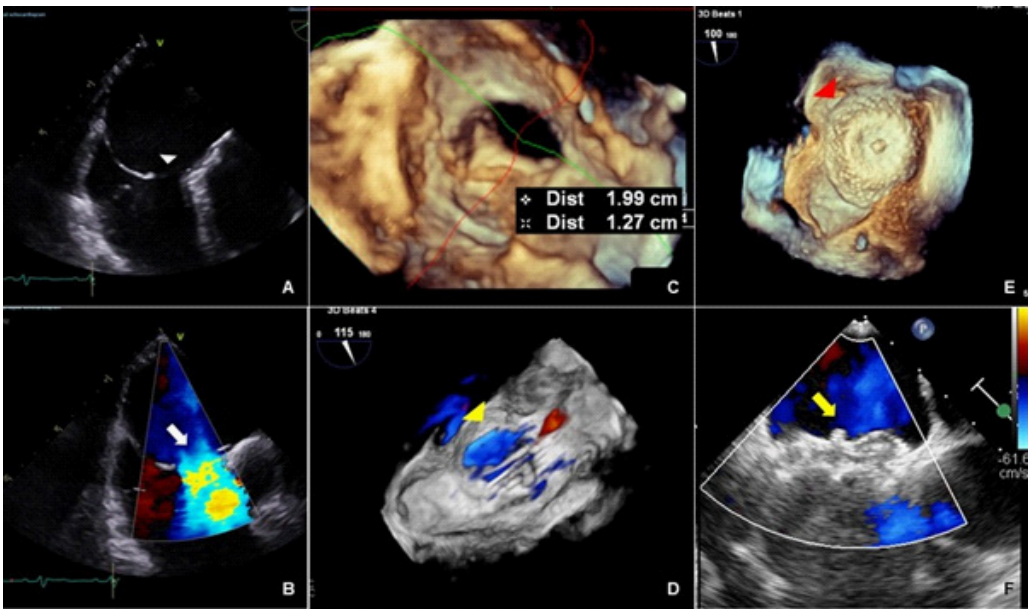

Figure 2: (A,B) Transoesophageal echocardiogram (TOE) 2D images showing the large atrial septal defect (ASD) (white arrowhead) with a large left-to-right shunt (thick white arrow). **(C,D)** 3D TOE images showing the exact dimensions of the ASD and the large shunt (yellow arrowhead). **(E,F)** TOE images post-ASD closure showing a well-seated occluder device on 3D view from the right atrial aspect (red arrowhead), with no residual flow demonstrated on color Doppler (yellow arrow).

grade 3 invasive ductal carcinoma HER2 positive, oestrogen receptor negative. She had neoadjuvant chemotherapy with pertuzumab and trasuzumab for 16 weeks and then underwent elective wide local incision with sentinel node biopsy. She had a complete pathological response with no evidence of residual invasive or in-situ carcinoma. Following surgery, she had radiotherapy, adjuvant pertuzumab and bisphosphonates therapy.

Through the course of the cancer treatment, the patient had regular transthoracic echocardiograms, as per the guidelines, which showed normal left ventricular (LV) size and systolic function, but a progressively dilating right ventricle (RV), with mild-moderate tricuspid regurgitation (Figure 1A-C). No evidence of a cardiac shunt. The patient was initially asymptomatic from a cardiac perspective and had no clinical signs of heart failure but

progressively developed exertional breathlessness. Her electrocardiogram showed normal sinus rhythm. Cardiac MRI scan was performed to accurately assess ventricular dimensions and systolic function and showed normal LV size and systolic function (ejection fraction 62%). RV volumes were within normal limits, but the RV appeared relatively dilated compared to the left. RV function was normal, with an ejection fraction of 59%. There was a small amount subepicardial enhancement in the mid-lateral LV wall, reflecting previous and now healed myocarditis or minor fibrosis from previous chemotherapy. A stroke volume difference between the two ventricles was seen, which could not be explained by the mild-to-moderate tricuspid regurgitation. Furthermore, the interatrial septum appeared aneurysmal and mobile, so an atrial shunt could not be excluded. We also referred the patient for a CT pulmonary angiogram (CTPA) to rule out pulmonary embolism in the context of malignancy as a cause for the right ventricular dilation. The CTPA was negative for pulmonary embolism or any significant lung disease but demonstrated again dilatation of the right ventricle compared to the left ventricle (Figure 1D-3); a possible shunt at the interatrial level was seen (Figure 1D, arrowhead), but not reported. A bubble echocardiogram showed a large number of bubbles crossing through the interatrial septum (Figure 1F).

The patient subsequently underwent a transoesophageal echocardiogram, which revealed a large secundum atrial septal defect (ASD) (2 x 1.3 cm) in the superior aspect of the interatrial septum (Figure 2A-D). Pulmonary venous drainage was normal. The patient was referred to the adult congenital heart disease clinic in a tertiary centre. She had successful percutaneous closure of the ASD (Figure 2E-F).

Discussion/conclusion

Chemotherapy treatments are known to have cardiotoxic effects and require regular echocardiographic surveillance. The most common cardiotoxic effect of anti-HER2 therapies is LV systolic dysfunction. While the impact on LV function has long been recognised, recent studies suggest significant decline in parameters of RV function and direct RV dysfunction or secondary to pulmonary hypertension or pulmonary embolism. Oncology doctors are aware of cardiac side effects and refer cancer patients to cardiology using the referral criteria published in the guidelines. The role of the cardiologist is to differentiate if the cardiac pathology is indeed the result of chemotherapy, or an underlying undiagnosed cardiac pathology is present. In our case, the patient exhibited RV dilatation, initially suspected to result from isolated RV failure or pulmonary hypertension, both of which are recognized chemotherapy-related complications. However, further investigation revealed an unexpected finding of a large ASD, which was unrelated to chemotherapy and was incidentally discovered, and then, successfully treated.

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