Takotsubo Syndrome and Cancer

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Abstract

Takotsubo Syndrome (TTS) is defined by transient ventricular dysfunction in the absence of culprit obstructive coronary artery disease. During acute presentation, patients present with typical ECG, echocardiographic and cardiac magnetic resonance imaging features. We present two cases of TTS in the context of cancer, with a wide range of complimentary tests, and then briefly discuss the pathophysiology and clinical presentation of TTS, highlighting the importance of appropriate management of TTS both during the acute phase and follow-up. The association between TTS and cancer is mentioned, with the possibility, in some cases, that TTS represents a paraneoplastic syndrome.

Clinical Cases

Case 1

A 75 year old lady was admitted to her oncology unit after feeling generally unwell over the previous month, with increasing generalised pain, appetite suppression and dehydration. She had background of metastatic thyroid cancer, for which she had recently been started on multiple VEGFR kinase inhibitor Lenvatinib. She also had previous history of hypertension, which was treated with Propranolol and Amlodipine. Her blood pressure had been more difficult to control since initiation of Lenvatinib. Her cardiovascular assessment prior to treatment confirmed normal left ventricular ejection fraction (LVEF) with mild left ventricular hypertrophy with no regional wall motion abnormalities.

During her admission, most of her medications were discontinued, including her Lenvatinib and Propranolol. The patient became increasingly anxious as a result of her health condition and withdrawal of her targeted molecular cancer therapy. Four days following admission she awoke in the middle of the night with central chest pain. She remained haemodynamically stable and her initial ECG showed unspecific ST changes in the precordial leads with flattening T waves. As the patient remained pain-free and there was no definite ST elevation, an urgent angiogram was withheld. The next morning blood tests confirmed her Troponin I peaked at 158 ng/L (normal range < 20) with a BNP of 2202 ng/L (normal range < 20). Evolving ECGs showed isoelectric J point with widespread T wave inversion and prolonged QTc (Fig. 5.1). She was then transferred to our cardiac unit.

Her resting transthoracic echocardiogram showed apical akinesia (Fig. 5.2). This, in conjunction with a modest Troponin

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Fig. 5.1 Successive ECG during presentation of TTS. (**a**) ST elevation in V2-V3 with minimal (<1mm) ST depression in I, aVL, V5 and V6. (**b**) Evolving changes with ST elevation in V2-3 and evolving T wave inversion. (**c**) Widespread deep T wave inversion in precordial leads with QTc 560 ms
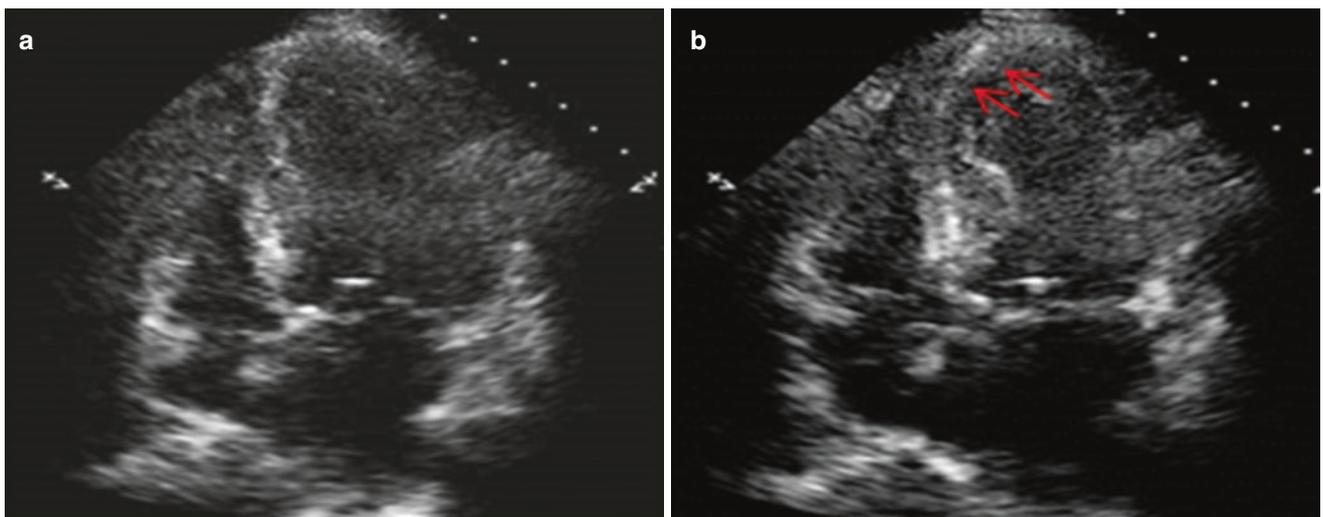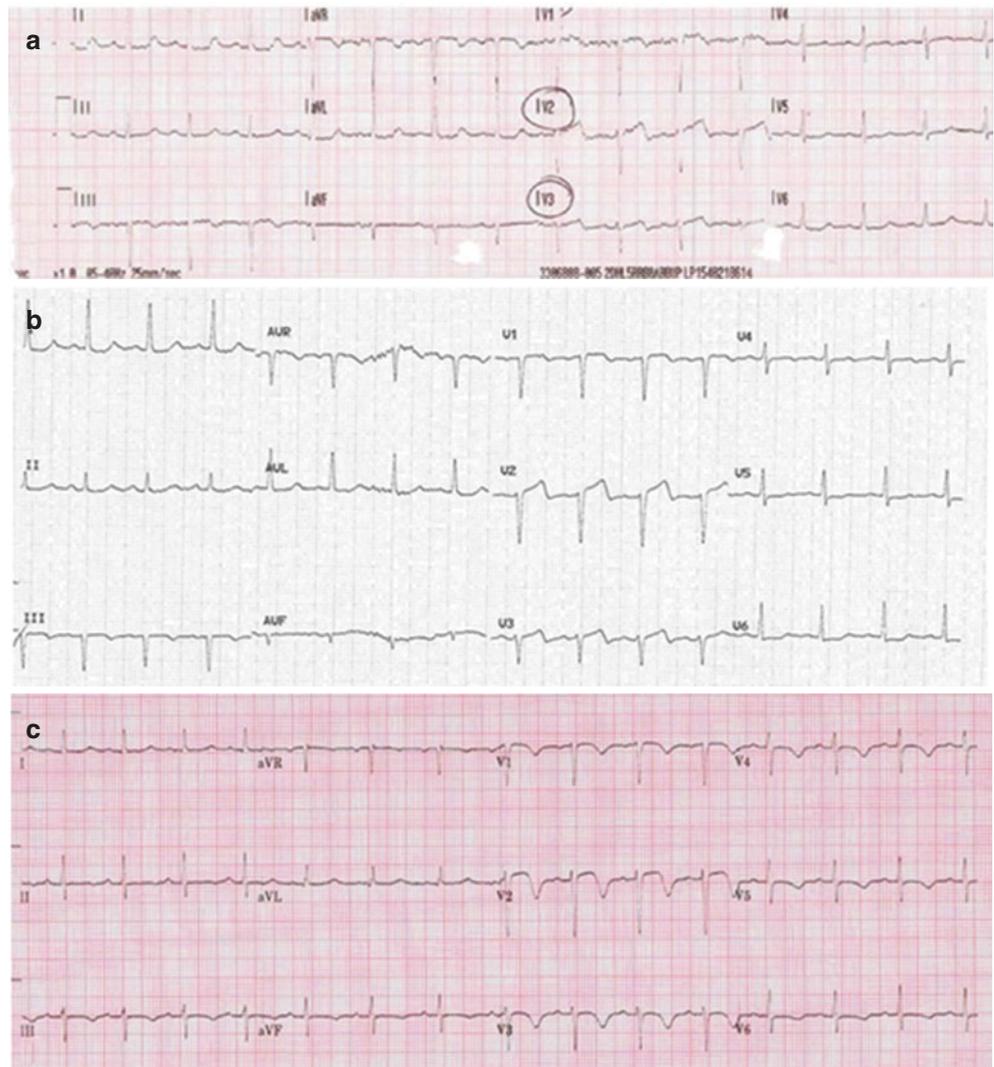

Fig. 5.2 Echocardiographic images during the acute phase of TTS. (**a**) Apical 4-chamber view at the end of diastole showing normal cavity size and myocardial thickness. (**b**) Apical 4-chamber view at the end of systole showing good contraction of basal segments with septo-apical dyskinesia (*arrows*).
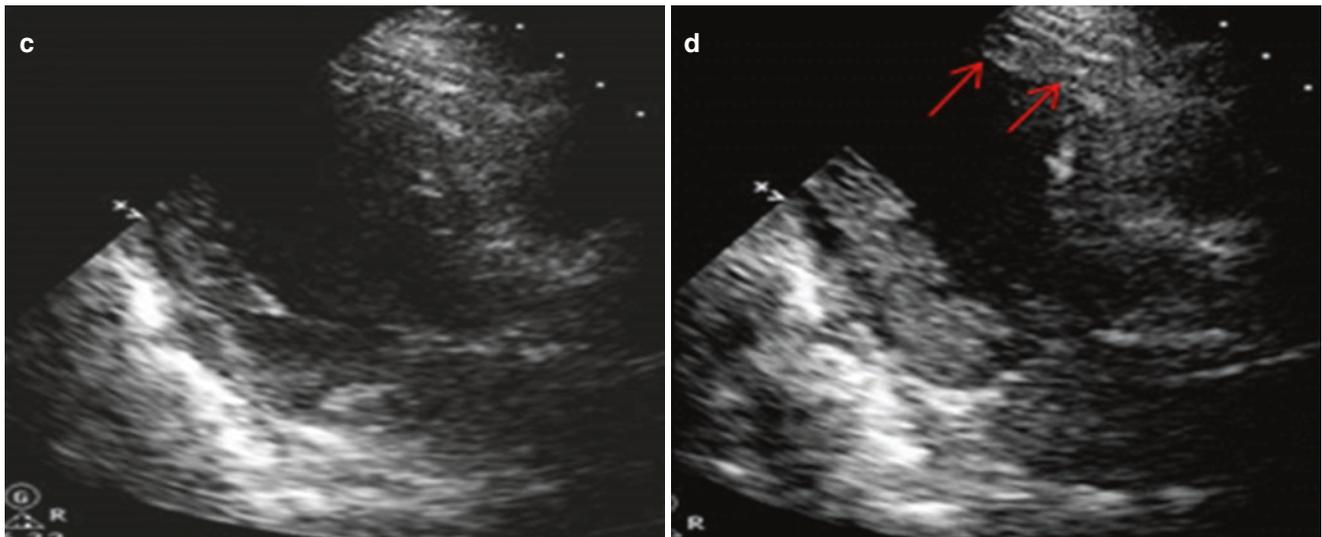
Fig. 5.2 (continued) (**c**) Modified parasternal long axis at end diastole. (**d**) Modified parasternal long axis showing dyskinetic apex (*arrows*)
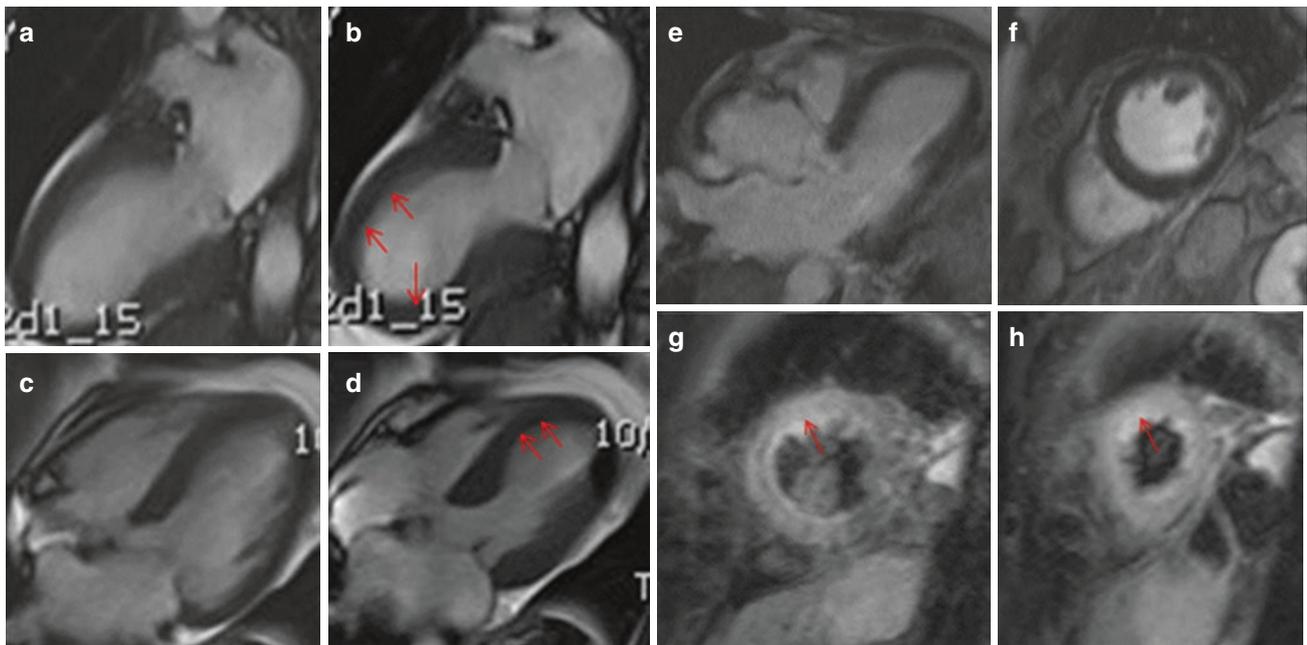

Fig. 5.3 CMR images with LGE and STIR. (**a**) Two-chamber view at end-diastole showing normal cavity size and wall thickness. (**b**) Two-chamber view at end-systole with apical dyskinesia (see *red arrows*). (**c**) Four-chamber view at end-diastole. (**d**) Four-chamber view at end-systole with septo-apical dyskinesia (see *red arrows*). (**e**) Four-chamber LGE. No evidence of uptake ruling out scarring or fibrosis. (**f**) Short axis LGE at mid-ventricular level. No evidence of LGE. (**g**) STIR image at mid-ventricular level. There is an area of oedema in the antero-septum (*red arrow*). (**h**) STIR image at the apex shows extension of oedema to the antero-apical segment (*red arrow*)

rise and substantial ECG changes and BNP elevation raised the suspicion of Takotsubo syndrome (TTS). A Cardiac Magnetic Resonance (CMR) scan was performed, which confirmed the diagnosis: apical akinesia in the absence of myocardial infarction on late gadolinium enhancement (LGE). Furthermore, the Short TI Inversion Recovery (STIR) sequences confirmed the presence of oedema/inflammation in the apical myocardium, as typically observed in TTS patients (Fig. 5.3). An invasive

angiogram was deemed unnecessary and a CT coronary angiogram (CT-A) ruled out significant coronary disease (Fig. 5.4).

The patient was monitored in a level 2 setting under ECG monitoring and treated with low dose of Carvedilol. Her QTc remained prolonged (532 ms) with partial improvement with intravenous magnesium supplementation. She recovered over the next 4 days, and was discharged back home and cancer treatment was switched to Vandetanib. Unfortunately,
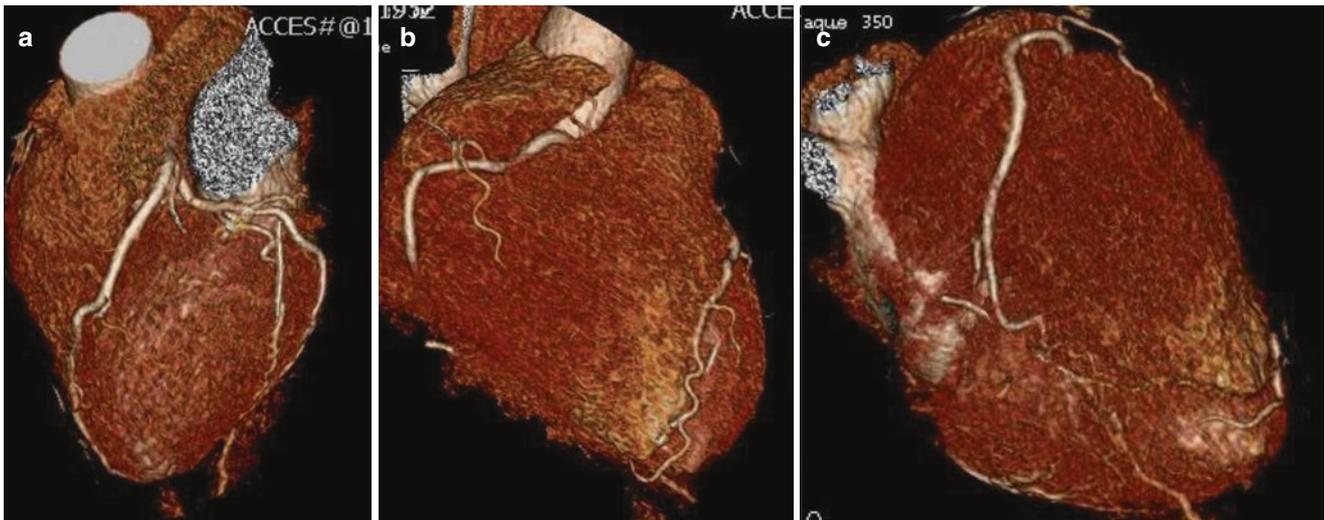
Fig. 5.4 CT-A showing absence of significant coronary disease. (**a**) Unobstructed left main (LM), Left Anterior Descending (LAD) and Circumflex coronary arteries. (**b**) Proximal Right Coronary Artery (RCA) with no evidence of atheroma. (**c**) Distal RCA and posterior descendant artery (PDA) with no significant disease

she did not tolerate chemotherapy and died 2 months later as a result of her metastatic malignancy.

Case 2

A 62 year old lady presented in the accident and emergency (A&E) Department with central chest pain. She had a background of hypertension and a previous hysterectomy with bilateral oophorectomy at the age of 45. She was on no regular medication. She had been under increasing stresses in the previous months due to personal issues including illness in a family member and death of her family dog. Her ECG showed acute ST changes (Fig. 5.5) which, in conjunction with persistent chest pain in spite of standard management, prompted an urgent coronary angiogram (Fig. 5.6). There were no flow-limiting lesions, albeit a significant lesion in the origin of the first diagonal. During the procedure, the patient ended pain free. As a consequence, she was managed medically with carvedilol, enalapril, aspirin and statins, with symptomatic relief.

An echocardiogram was performed (Fig. 5.7), showing apical and mid-ventricular circumferential hypokinesia with hyperdynamic basal segments. There was no significant left ventricular outflow tract obstruction. The CMR (Fig. 5.8) showed mid-ventricular and apical wall motion abnormalities, with no evidence of myocardial infarction or fibrosis. Active and extensive oedema of the hypokinetic segments was present on the STIR images. The patient remained monitored while her QTc remained extremely prolonged (> 500 ms), and she recovered over 6 days.

Following discharge, the patient was still reporting anginal symptoms, mainly on exertion but also in the context of anxiety. A physiological stress echocardiogram was per-
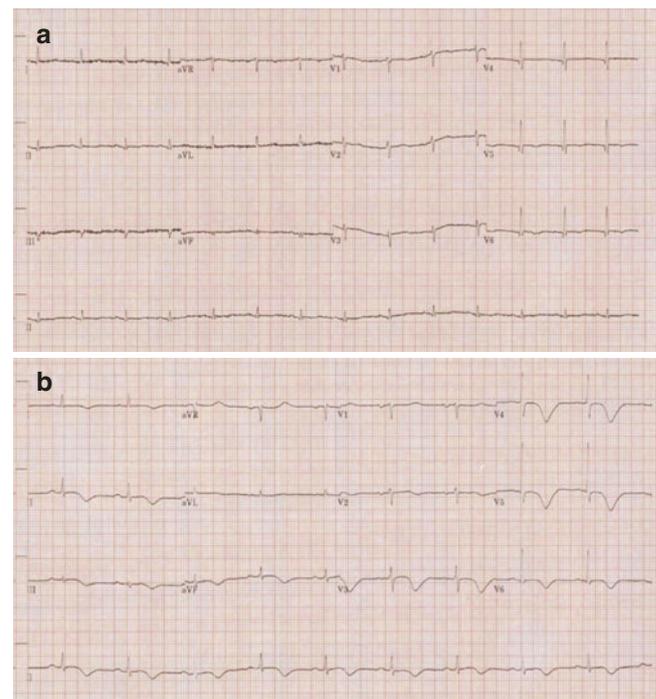

Fig. 5.5 Serial ECGs during acute phase of TTS. (**a**) Flattening T wave in the anterior leads with inversion in V4-V6. (**b**) Widespread T wave inversion with associated QTc prolongation (540 ms)

formed (Fig. 5.9), which confirmed stress-inducible apical akinesia. For completion, a cardiac Iodine-123 meta-iodo-benzyl-guanidine (mIBG) scan was requested to assess for sympathetic myocardial innervation (Fig. 5.10). It confirmed a reduction in the noradrenaline uptake and functional innervation of the apical segments, in keeping with a recent episode of TTS.
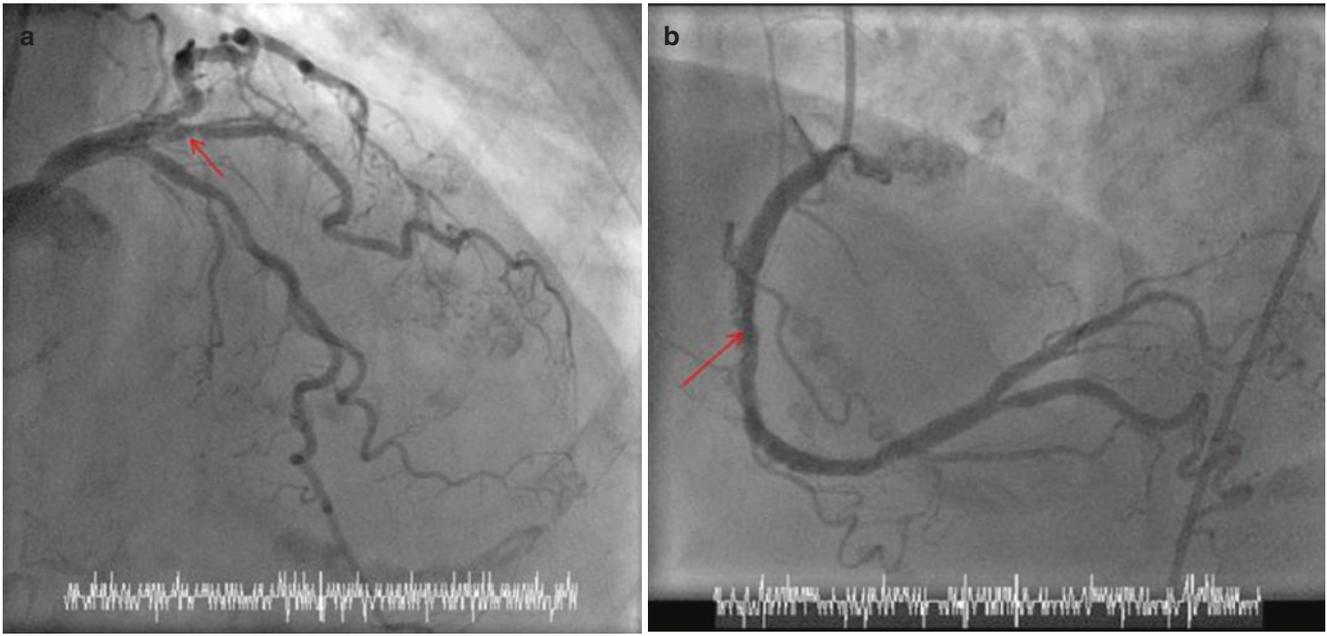
Fig. 5.6 Coronary angiography during acute presentation—significant but non-limiting flow lesions: (**a**) Unobstructed LM, LAD and Circumflex coronary arteries. There is a significant lesion in the first Diagonal branch (*red arrow*). (**b**) Moderate lesion in the mid RCA (see *red arrow*)
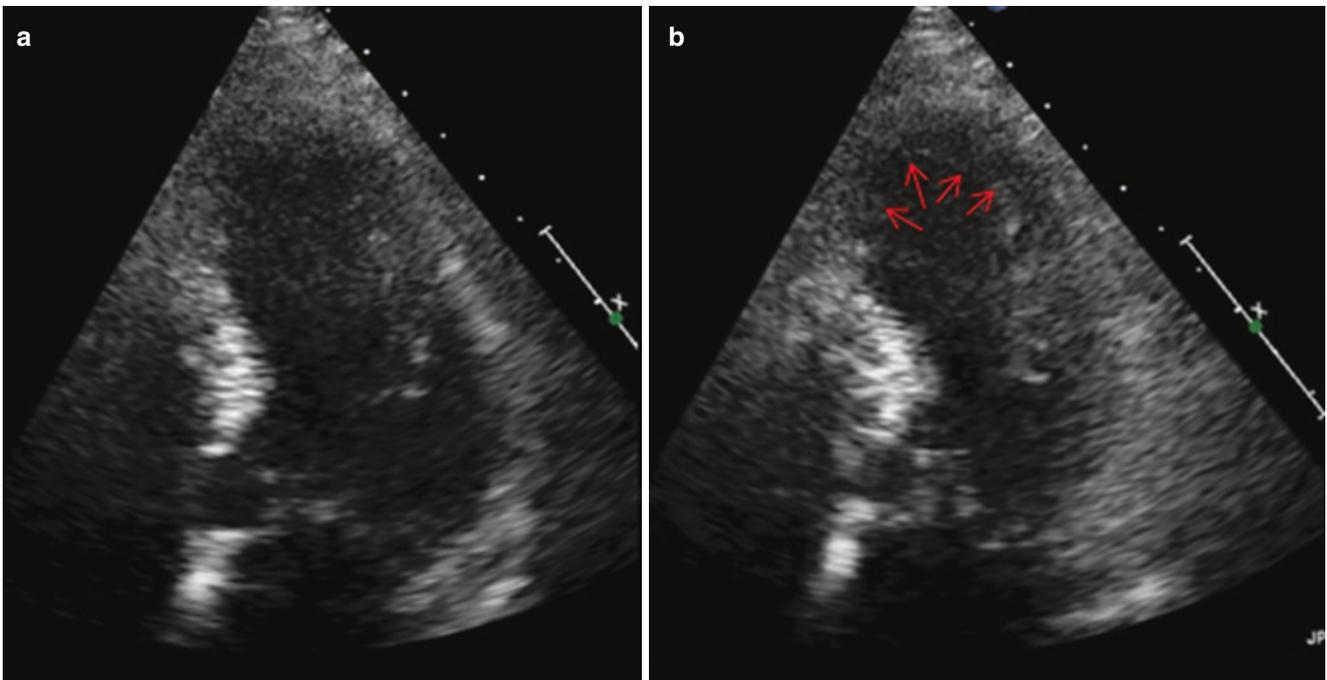

Fig. 5.7 Four-chamber apical views on transthoracic Echo. (**a**) End-diastole. (**b**) End-systole. Note hyperdynamic bases and apical *ballooning* (*red arrows*)

The patient was followed up in our heart failure service, with a program of cardiac rehabilitation and psychological input. She eventually managed to control her symptoms. Two years after the episode, she was diagnosed of a right breast cancer.

Discussion

Takotsubo syndrome (TTS) is defined by chest pain in the presence of transient regional wall motion abnormalities of left, right or both ventricles, which frequently extend beyond a single coronary distribution, in the absence of culprit coronary artery disease or other forms of cardiomyopathy [1]. The acute event is usually preceded by a stressful trigger, either emotional or physical. Contributing factors, although not diagnostic, are post-menopausal women (90% of cases), acute cerebrovascular accidents, drug abuse, mood disorders, malignancy, chronic liver disease and sepsis [2].

Electrocardiographic abnormalities comprise new and reversible ST-segment elevation or depression, acute left bundle branch block, T wave inversion (typically deep and widespread) and QTc prolongation, which is a risk factor for cardiac arrest and warrants ECG-monitoring in the acute
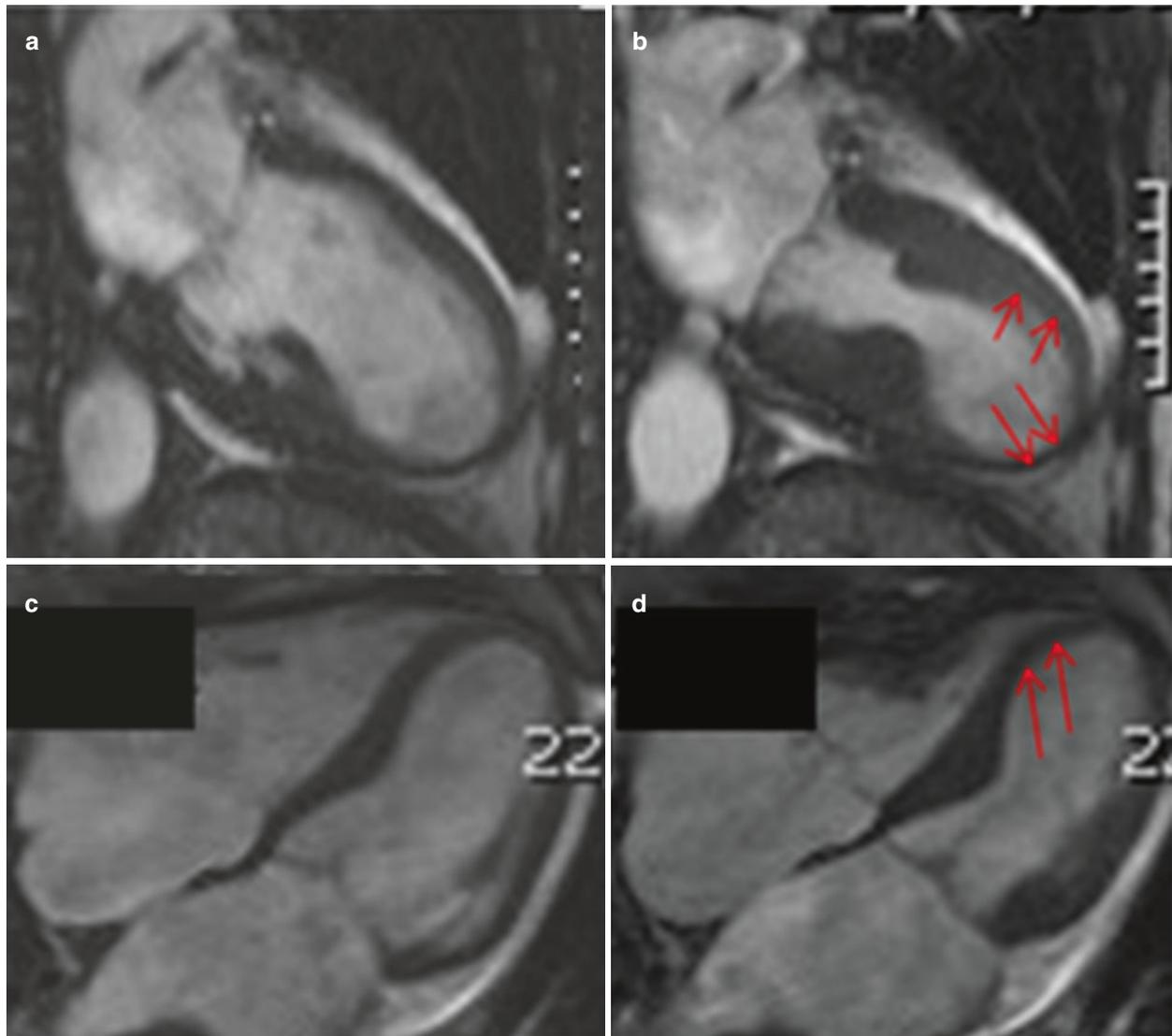
Fig. 5.8 CMR typical of Takotsubo syndrome. (**a**) Two-chamber (end-diastole). (**b**) Two-chamber (end-systole). Distinct apical dyskinesia (see *arrows*). (**c**) Four-chamber (end-diastole). (**d**) Four-chamber (end-systole). Distinct septo-apical dyskinesia (see *arrows*).
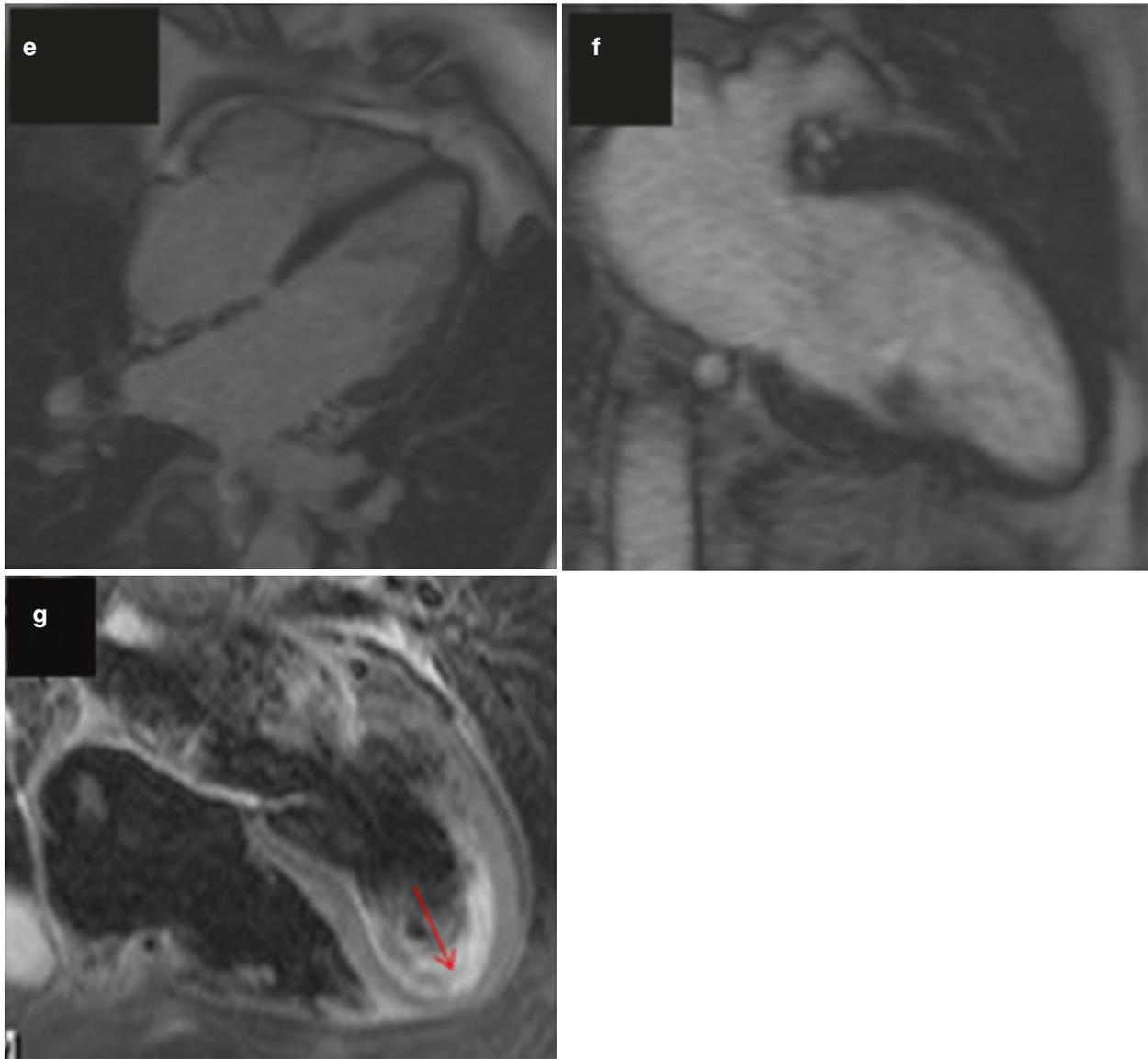
Fig. 5.8 (continued) (**e**) Absence of LGE in the 4-chamber view. (**f**) Absence of LGE in the 2-chamber view. (**g**) Extensive apical oedema in the STIR images (see *arrow*)

phase. The degree of elevation of natriuretic peptides (BNP or NT-proBNP) is disproportionately high as compared to a mild cardiac troponin rise, given the degree of myocardial dysfunction.

Based on cardiac imaging, there have been various anatomical variants of TTS, the most common being apical (80%), midventricular variant (10–15% of cases) and inverted or basal variant (5%). CMR will add information about tissue characterisation. Typically, there will be signs of acute oedema/inflammation on the STIR images in the absence of myocardial infarction on LGE.

The pathophysiology of TTS is complex and only partially understood [3, 4]. Based on animal models and secondary forms of TTS (phaeochromocytoma, subarachnoid haemorrhage), catecholamines appear to play an important role and frequently, although not always, there is a "sympathetic storm" following an acute stressor. This may lead to a form of catecholamine-induced cardiotoxicity. Hypotheses include stimulus trafficking of the β2-Adrenergic Receptor (β2-AR) in response to high levels of epinephrine, with a switch to the cardioprotective, but negatively inotropic G_i secondary messenger pathway. This pathway has cardioinhibitory and
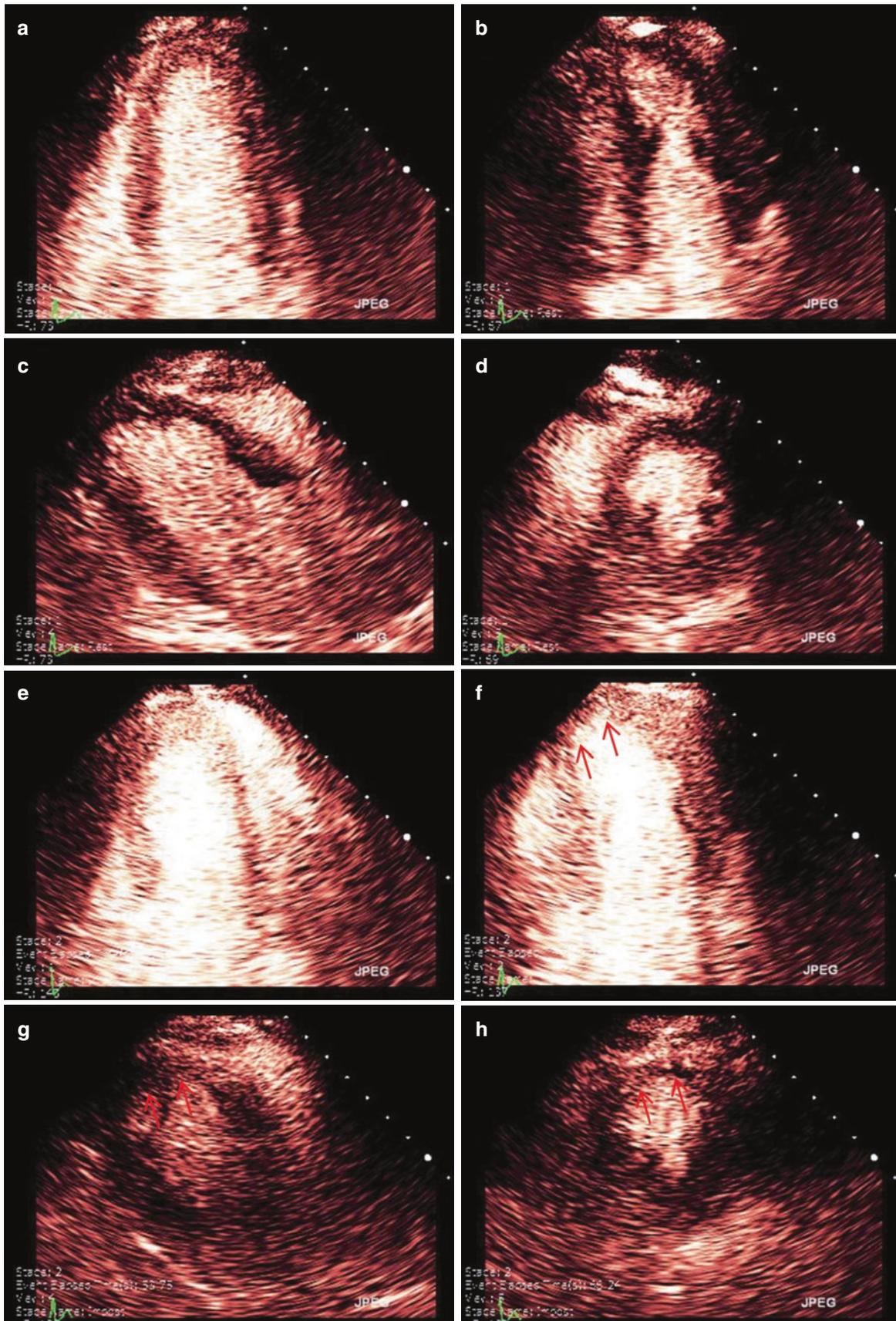
Fig. 5.9 Physiologic stress echocardiography with images at rest (**a–d**) and post-exercise (**e–h**) showing inducible septo-apical and antero-apical akinesia (*red arrows*). (**a**) Apical 4 Chamber (end-diastole). (**b**) Apical 4 Chamber (end-systole). (**c**) Parasternal long axis (end-systole). (**d**) Parasternal short axis at the level of papillary muscles (end-systole). (**e**) Stress Apical 4 Chamber (end-diastole). (**f**) Stress Apical 4 Chamber (end-systole). (**g**) Stress Parasternal long axis (end-systole). (**h**) Stress Parasternal short axis at the level of papillary muscles (end-systole)

Fig. 5.10 Bull's eye (**a**, **c**) and 3D reconstruction (**b**, **d**) of left ventricular mIBG scan showing distinct apical defect (*red arrows*)
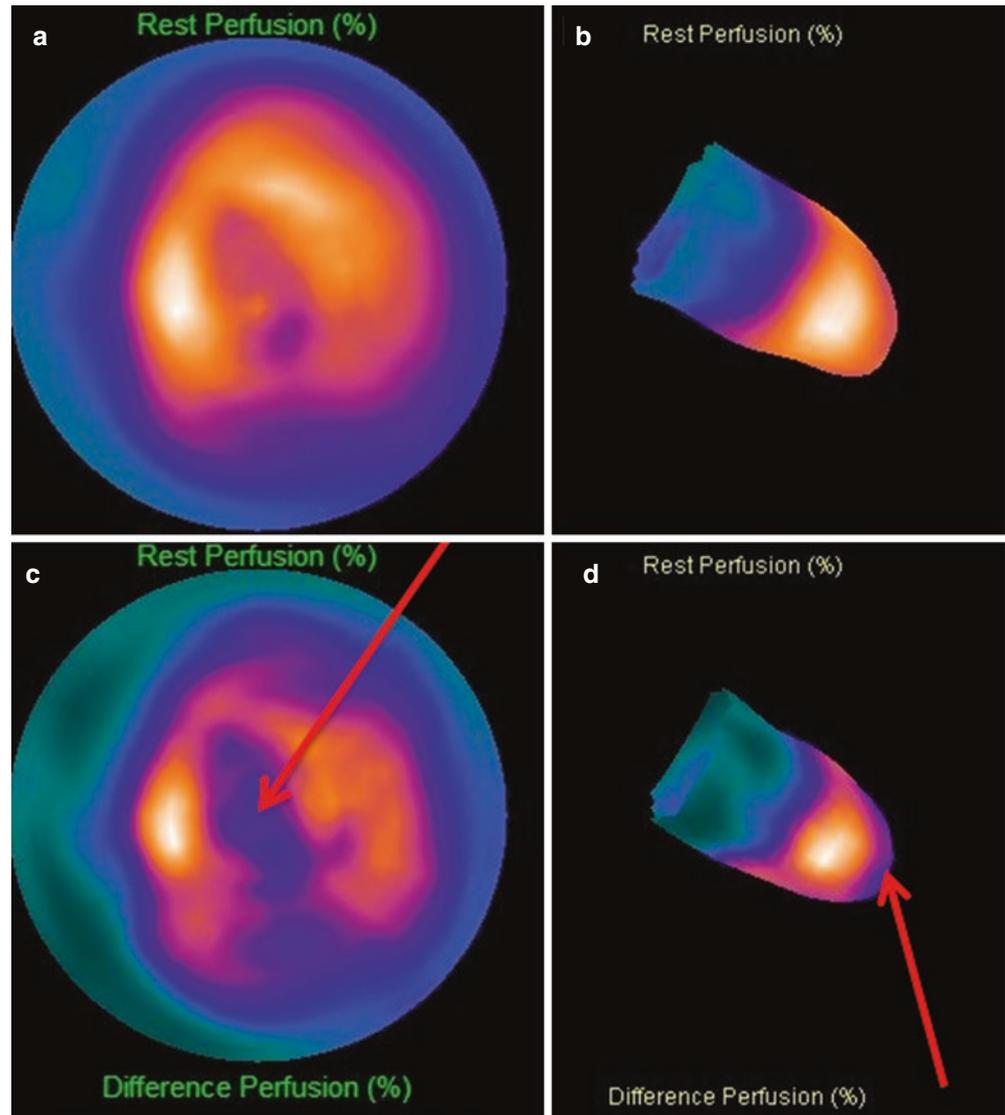
anti-apoptotic properties. Other features include increased afterload and possible diffuse coronary spasm, which altogether result in ventricular systolic dysfunction. Wall motion abnormalities are explained by regional differences in the density of β-adrenoceptors: these are higher in the apex, making this region more susceptible to circulating catecholamine levels; conversely, basal segments have higher rates of sympathetic innervation, leading to increased contractility. These findings are supported by mIBG scan findings following acute presentation, which can show reduced sympathetic innervation in the previously dysfunctional myocardial segments.

Consensus supports the definition of primary and secondary TTS [1], depending on whether TTS appears isolated (usually in the context of an emotional stressor) or triggered by another serious medical condition (phaeochromocytoma, thyrotoxicosis, neurosurgical emergencies, sepsis, cancer).

TTS is not as benign as previously reported. In the acute phase there are a variety of complications (ventricular arrhythmias, heart failure or cardiogenic shock) that require aggressive intervention, with ~50% cases having acute complications, and an inhospital mortality of ~5% across different published cohorts. Furthermore, during follow-up, survival is similar to STEMI and worse than matched population, specifically in the secondary TTS, due to additional comorbidities [5–7].

TTS in cancer patients is becoming increasingly frequent and warrants specific management [8]. This group of patients are frequently under increased levels of emotional stress that predispose to an acute event. The presence of cancer, frequently metastatic, may also be a trigger of secondary TTS via factors hitherto unknown, but may include paracrine factors. Furthermore, many cancer treatments may predispose

to developing TTS including 5-Fluorouracil, Tyrosine kinase inhibitors, Anthracyclines, HER-2 inhibitors, ablative or surgical procedures [9].

As presented in our first case, these patients are frail and many times need to discontinue their cardiac medication (betablockers in this case), which could theoretically be another potential trigger. In this clinical context, electrolytic disturbances are not uncommon and may also lead to further electrical instability. All the above may lead to increased mortality in this subgroup of patients [6–8], with non-cardiac causes being the most frequent cause of death. Finally, as described in case 2, there is a small but growing number of patients who present with a new cancer diagnosis following an episode of TTS [7, 8]. This raises the possibility that, for some patients, TTS may be a form of paraneoplastic syndrome, which highlights the importance of long term follow-up in TTS patients, particularly in those without an identifiable acute triggering event.

- The hypothesis of stimulus trafficking of the β2-AR in response to high levels of epinephrine would explain regional wall motion abnormalities.
- TTS is defined as primary (whenever an emotional stress is identified) or secondary (triggered by another serious medical condition).
- TTS is not as benign as previously reported: in the acute phase there are a variety of cardiac complications (ventricular arrhythmias, heart failure or cardiogenic shock) that lead to an in hospital mortality of ~5% across different published cohorts.
- During follow-up, TTS survival is also worse than matching cohorts, mainly in the secondary TTS group.
- Cancer can predispose to TTS through various different mechanisms.
- TTS may be a paraneoplastic syndrome in patients with no primary stressor identified, which highlights the importance of follow-up in these subgroup of patients.

Key Points

- TTS is defined by chest pain in the presence of transient regional wall motion abnormalities of left, right or both ventricles, in the absence of matching coronary disease.
- ECG abnormalities comprise ST-segment elevation or depression, acute left bundle branch block, T wave inversion and QTc prolongation. The latter is a risk factor for cardiac arrest and warrants ECG-monitoring in the acute phase.
- Given the degree of myocardial dysfunction, the troponin rise is modest, as opposed to a substantial elevation of natriuretic peptides.
- Based on cardiac imaging, there are mainly three anatomical variants of TTS: apical, midwall variant and inverted or basal variant.
- CMR will typically show absence of infarction on LGE but active oedema/inflammation on the STIR images.
- The pathophysiology of TTS is complex and only partially understood. One of the most accepted theories describes TTS as a form of catecholamine-induced cardiotoxicity.

References

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